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Beilstein Journal of Organic Chemistry

Multicomponent reactions II

Thomas J. J. Müller

Editorial

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The concept of multicomponent reactions (MCR) [1] has been around in organic chemistry since the very early days. Indeed, the first example known in literature, the Strecker synthesis of α-aminonitriles [2], has been developed into an industrial process for the production of methionine in an annual scale of several hundreds of thousand tons per year. In addition, a lot of syntheses of heterocycles from the early days are MCR, and these reaction sequences paved the way to a multitude of applications. Moreover, Ugi's groundbreaking developments in isonitrile-based chemistry and his conclusions demonstrated that MCR are not only highly practicable in the light of approaching the ideal synthesis [3,4] as one-pot methodologies, but rely on a reactivity based concept [5]. The perpetual generation of reactive functionalities and reactivity is the underlying general principle. Therefore, MCR are intriguing for industrial applications. But they are also challenging for academia, in particular for the minute and sophisticated fine-tuning of reactivity and selectivity, which is required to concatenate elementary steps to novel sequences.

This Thematic Series on multicomponent reactions is a continuation of the previously released series two years ago [6] and again presents a snap shot of this highly dynamic field. With the traditional formats of letters, full papers, and reviews it spans the broad range of modern chemistry, including organocatalytic, organometallic, transition metal-catalyzed, radical reactions, condensation and isonitrile-based MCR. Biologically active compounds and photonic properties are addressed as well as mechanistic studies and models. The interested reader – whether an expert in the field or a newcomer – will find exciting reports from the current realm of MCR chemistry.

As the guest editor of this Thematic Series I cordially thank all authors for their excellent contributions. I am also grateful to the staff of the Beilstein-Institut for their excellent and professional support.

Thomas J. J. Müller

Düsseldorf, December 2013

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Beilstein Journal of Organic Chemistry

Post-Ugi gold-catalyzed diastereoselective domino cyclization for the synthesis of diversely substituted spiroindolines

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Full Research Paper

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Abstract

An Ugi four-component reaction of propargylamine with 3-formylindole and various acids and isonitriles produces adducts which are subjected to a cationic gold-catalyzed diastereoselective domino cyclization to furnish diversely substituted spiroindolines. All the reactions run via an *exo-dig* attack in the hydroarylation step followed by an intramolecular diastereoselective trapping of the imminium ion. The whole sequence is atom economic and the application of a multicomponent reaction assures diversity.

Introduction

The importance of nitrogen containing heterocyclic molecules in chemical biology is undisputed. The synthesis of such biologically interesting heterocycles is generally target-oriented, inspired by nature or randomly directed. In all these cases the design of a synthetic sequence to produce a library of diversely substituted molecules is the first and most important step. The basic concept of diversity-oriented synthesis (DOS) involves short reaction sequences, a strong focus on bond construction, and functional group compatibility [1-3]. Reactions that involve multiple bond formation, such as multicomponent reactions [4-9] and tandem reactions [10-16], are very useful in this context.

As an efficient activator of alkynes, gold has recently attracted a lot of attention [17-36]. Many tandem approaches have been reported which utilize this coinage metal for the construction of variously substituted complex molecules [37-43]. We have recently reported a post-Ugi gold-catalyzed intramolecular

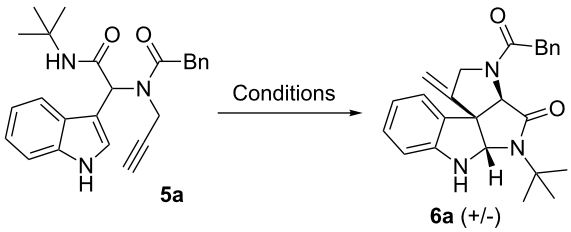
domino cyclization sequence which produces spiroindolines (Scheme 1) [44]. The first step in this sequence is an Ugi four-component reaction (Ugi-4CR) [4,5] with 2-alkynoic acid as an alkyne source. The second step is a cationic gold-catalyzed intramolecular hydroarylation tandem cyclization to produce spiroindolines with complete diastereoselectivity. This synthetic sequence is atom economic and mild conditions are applied to generate a very complex molecular structure from readily available starting materials. Based on this work and our continuous interest in transition metal catalysis [45-54], multicomponent reactions [55-57] and the chemistry of the indole core [58-60], we herein report a post-Ugi gold-catalyzed intramolecular domino cyclization sequence for the synthesis of spiroindolines with propargylamines as an alkyne source (Scheme 1).

Results and Discussion

The use of benzoic acid as an acid component in the Ugi-4CR did not produce the Ugi-adduct in good yield even after a prolonged reaction time. Therefore, we switched to phenylacetic acid. The Ugi-4CR of indole-3-carboxaldehyde (**1a**), propargylamine (**2a**), phenylacetic acid (**3a**) and *tert*-butylisonitrile (**4a**) in methanol at 50 °C gave the Ugi-adduct **5a** with an excellent yield of 94%. With compound **5a** in hand we were keen to apply the previously developed conditions for intramolecular hydroarylation [44]. Reaction of **5a** with 5 mol % of $Au(PPh_3)SbF_6$ in chloroform at room temperature produced the desired spiroindoline **6a** in a moderate yield of 55% along with some unidentified byproducts (Table 1, entry 1). The use of a protic acid with a gold catalyst is known in the literature [61-64]. To our delight, when the above reaction was carried out with 1 equivalent of trifluoroacetic acid (TFA) the yield was improved to 81% (Table 1, entry 2). Apart from being a good proton source TFA might be working as a coligand.

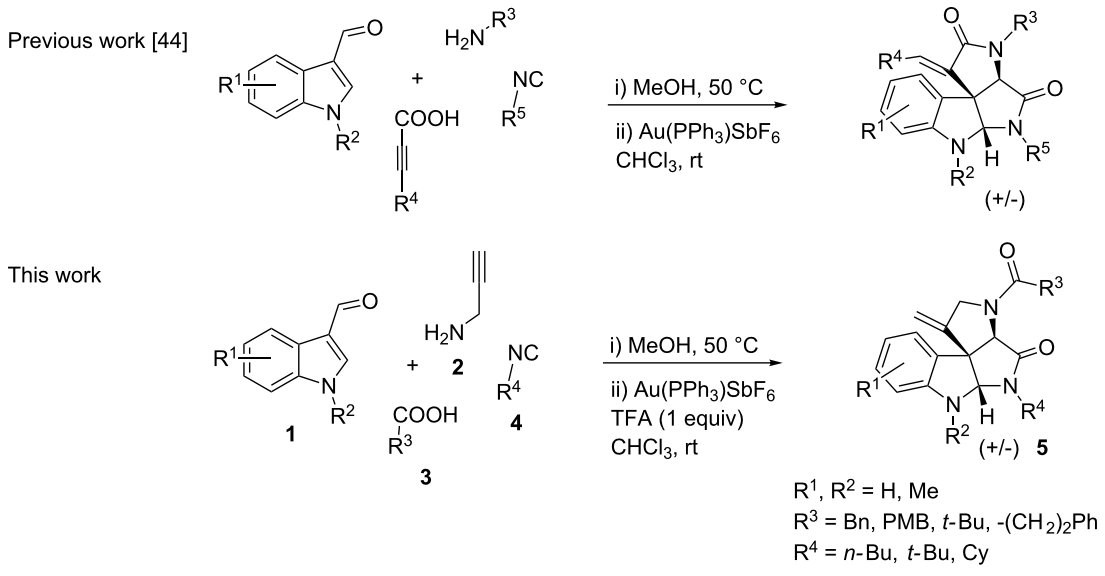
Experiments with $PtCl_2$ as a catalyst did not show any conversion and the starting material was recovered quantitatively (Table 1, entries 3 and 4). In absence of the gold catalyst no product could be observed (Table 1, entry 5). The application of *p*-toluenesulfonic acid (PTSA) instead of TFA did not improve the outcome (Table 1, entry 6).

Table 1: Optimization for the intramolecular hydroarylation.[a]



Entry	Catalyst (mol %)	Acid (1 equiv)	Time h	% Yield[b]
1	$Au(PPh_3)SbF_6$ (5)	—	2	55[c]
2	**$Au(PPh_3)SbF_6$ (5)**	**TFA**	**2**	**81**
3	$PtCl_2$ (5)	—	10	—[d]
4	$PtCl_2$ (5)	TFA	10	—[d]
5	—	TFA	10	—[d]
6	$Au(PPh_3)SbF_6$ (5)	PTSA	2	70

[a]All the reactions were run on 0.1 mmol scale of **5a** with chloroform (2 mL) as a solvent at rt. [b]Isolated yields. [c]Unidentified byproducts were formed. [d]No conversion.



Scheme 1: Gold-catalyzed approaches towards spiroindolines.

Having the optimized conditions in hand (Table 1, entry 2), various Ugi-adducts **5b–q** were synthesized and subjected to this hydroarylation domino cyclization sequence (Table 2). Different substituents are well-tolerated and the sprioindolines were obtained in good to excellent yields. A methyl substituent on the indole nitrogen did not hamper the domino cyclization (Table 2, entries 4, 6, 11, 12, 14, 15). Substituents like *tert*-butyl, cyclohexyl and *n*-butyl on the isonitrile are well-tolerated for the domino cyclization on the second position of the indole (Table 2, entries 1–16). Regarding the substituents coming from the acid part, *tert*-butyl gave a decreased yield probably due to steric hindrance (Table 2, entry 5). It is noteworthy that the gold-catalyzed intramolecular hydroarylation exclusively gives the *exo-dig* product in all cases and with complete diastereoselectivity.

A plausible mechanism [30,44] is shown in Scheme 2 with only the *R*-isomer of the Ugi-adduct **5a** to simplify the discussion. The cationic gold coordinates with the terminal alkyne which becomes activated for a nucleophilic attack. This can occur from both sides of the indole core. When the attack occurs from the back side of the indole core, spiro intermediate **B**

Table 2: Scope and limitations of intramolecular domino cyclization.[a]

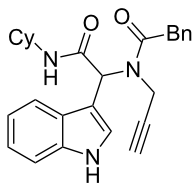
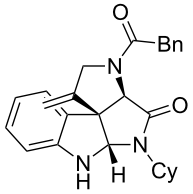
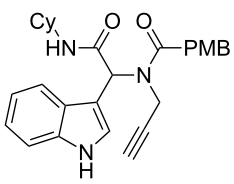
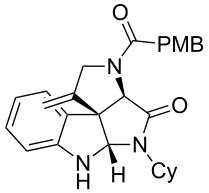
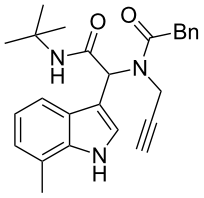
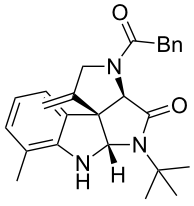
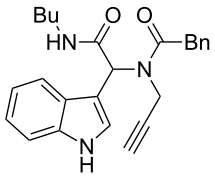
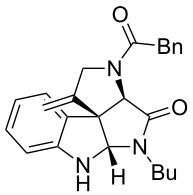
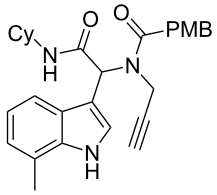
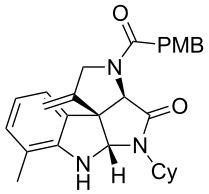
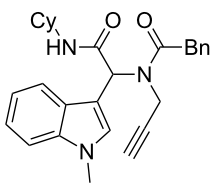
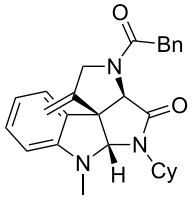
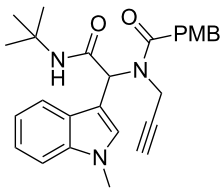
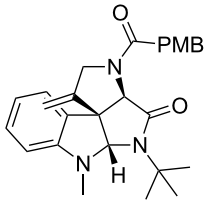
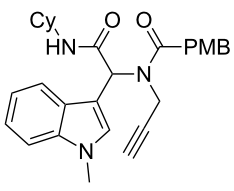
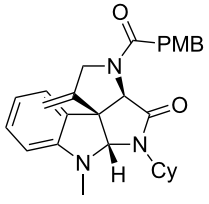
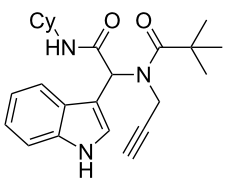
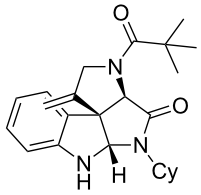
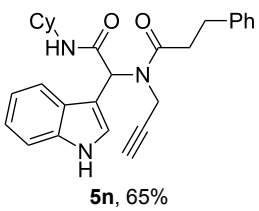
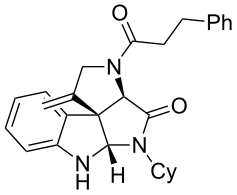
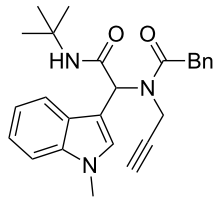
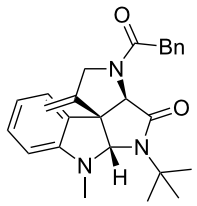
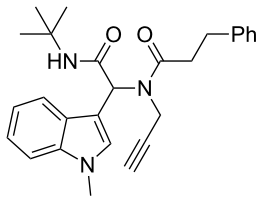
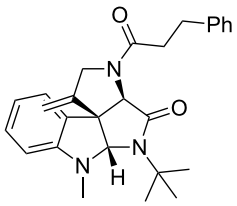
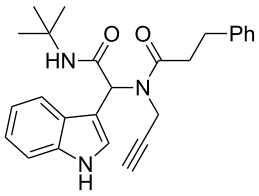
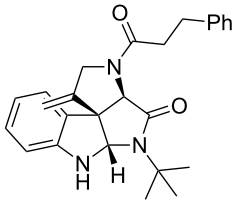
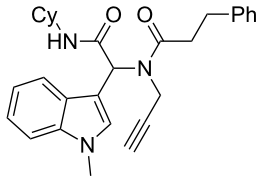
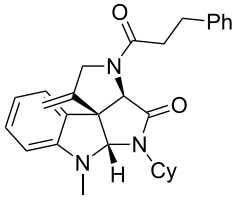
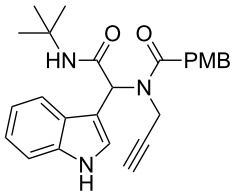
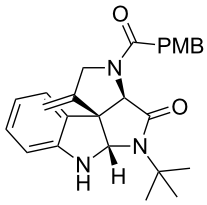
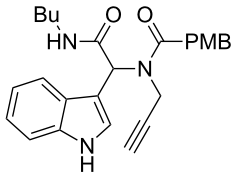
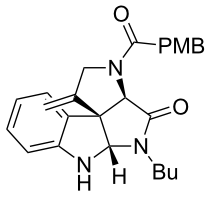
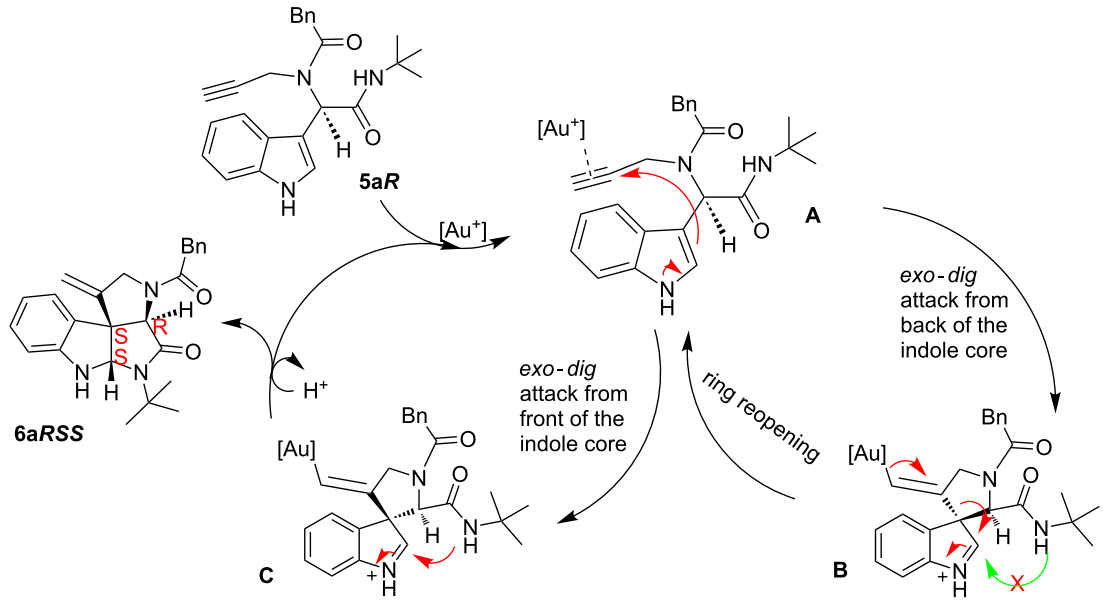
Entry	Ugi adduct **5**	Spiroindolines **6** (+/−)	Entry	Ugi adduct **5**	Spiroindolines **6** (+/−)
1	 **5b**, 87%	 **6b**, 70%	9	 **5j**, 89%	 **6j**, 75%
2	 **5c**, 86%	 **6c**, 60%	10	 **5k**, 63%	 **6k**, 80%
3	 **5d**, 69%	 **6d**, 76%	11	 **5l**, 77%	 **6l**, 74%
4	 **5e**, 72%	 **6e**, 66%	12	 **5m**, 74%	 **6m**, 68%
5	 **5f**, 68%	 **6f**, 40%	13	 **5n**, 65%	 **6n**, 72%

Table 2: Scope and limitations of intramolecular domino cyclization.[a] (continued)

6		**5g**, 77%		**6g**, 71%	14		**5o**, 68%		**6o**, 60%
7		**5h**, 79%		**6h**, 83%	15		**5p**, 58%		**6p**, 84%
8		**5i**, 67%		**6i**, 69%	16		**5q**, 59%		**6q**, 69%

[a]All the reaction were run on a 0.2 mmol scale of **5** in a screw capped vial employing the optimal conditions of Table 1. Cy = cyclohexyl, Bn = benzyl, PMB = *p*-methoxybenzyl, Bu = *n*-butyl.



Scheme 2: Plausible mechanism for the domino sequence.

will be formed. However, in this spiro intermediate the intramolecular trapping of the imminium ion by the amidic NH is sterically impossible and thus the intermediate reopens to intermediate **A**. If the attack takes place from the front side of the indole core, intermediate **C** is formed and trapping is possible. After deprotonation and protodeauration the desired spiro-

indoline **6a** is formed with the stereochemistry of two new stereocenters *S*.

Conclusion

In conclusion we have developed a diversity-oriented post-Ugi gold-catalyzed intramolecular hydroarylation domino cyclization sequence for the diastereoselective synthesis of spiroindolines. The mild reaction conditions and short synthetic sequence are the merits of this method. The flexibility given by the multicomponent reaction assures the generation of diversity.

Experimental

General procedure for the synthesis of spiroindolines **6a**–**q**

To a screw capped vial $Au(PPh_3)Cl$ (5 mol %) and $AgSbF_6$ (5 mol %) were loaded along with chloroform (2 mL). Ugi product **5** (0.2 mmol) was added followed by TFA (1 equiv), and the reaction mixture was stirred at rt. After completion, the reaction mixture was partitioned between EtOAc (100 mL) and 2 N K_2CO_3 solution (2 × 50 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (10% diethyl ether in dichloromethane) to afford compound **6a**–**q**.

Supporting Information

Supporting Information File 1

Experimental section.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-246-S1.pdf]

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Efficient synthesis of dihydropyrimidinones via a three-component Biginelli-type reaction of urea, alkylaldehyde and arylaldehyde

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Full Research Paper

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Abstract

A one-pot three-component synthesis of dihydropyrimidinones via a molecular iodine-catalyzed tandem reaction of simple readily available mono-substituted urea, alkylaldehyde, and arylaldehyde has been developed. The reaction proceeds with high chemo- and regioselectivity to give highly diverse dihydropyrimidinones in reasonable yields under mild reaction conditions. Moreover, the first catalytic enantioselective version of this reaction was also realized by using chiral spirocyclic SPINOL-phosphoric acids.

Introduction

The dihydropyrimidinones (DHPMs) have exhibited interesting and multifaceted biological activities, such as antiviral, antitumor, antibacterial, and antiflammatory properties as well as calcium channel modulating activity [1,2]. As a consequence, the synthesis of dihydropyrimidinone derivatives bearing diverse substitution patterns has attracted significant attention since its discovery 120 years ago in 1893 by the Italian chemist Pietro Biginelli [3,4]. Among them, the Biginelli multicomponent reaction, involving a multicomponent condensation of aldehyde, β-ketoester, and urea, provides an easy access to the preparation of DHPMs, because multicomponent reactions (MCRs) are considered with high facileness, efficiency and economy in organic chemistry [5-8]. Recently, many one-pot variants of Biginelli-type reactions for the preparation of novel DHPMs using various active methylene compounds [9-15], such as enaminone, cyclic β-diketones, acetophenone, benzocyclic ketones and β-oxodithioesters etc., have also been developed to be carried out in the presence of a Lewis or protic acid. It is still highly valuable to develop new direct approaches for the efficient synthesis of DHPMs due to the continued importance of the dihydropyrimidinone core in organic and medicinal chemistry.

Recently, molecular iodine has emerged as an inexpensive, low-toxic catalyst with moderate Lewis acidity and water-tolerance in organic chemistry [16]. Previously, we have developed some

molecular iodine-catalyzed organic transformations [17-21], herein we describe the first molecular iodine-catalyzed one-pot three-component Biginelli-type synthesis of DHPMs from simple readily available mono-substituted urea, alkylaldehyde, and arylaldehyde under mild reaction conditions [22-24]. The present method is suitable for a wide range of substrates, and especially for functionalized arylaldehydes. The first catalytic enantioselective version of this reaction is also presented by using chiral spirocyclic SPINOL-phosphoric acids (SPAs) as the catalyst.

Results and Discussion

Initially, the mixture of *N*-methylurea (**1a**, 2.5 mmol), phenylacetaldehyde (**2a**, 2.5 mmol) and *p*-nitrobenzaldehyde (**3a**, 3.75 mmol) in toluene (3 mL) was treated with 10 mol % of iodine under reflux for 12 hours. The functionalized dihydropyrimidinone **4a** was obtained in 56% yield and the structure of the product was clearly assigned by both abundant spectral analysis and X-ray single crystal diffraction (Figure 1).

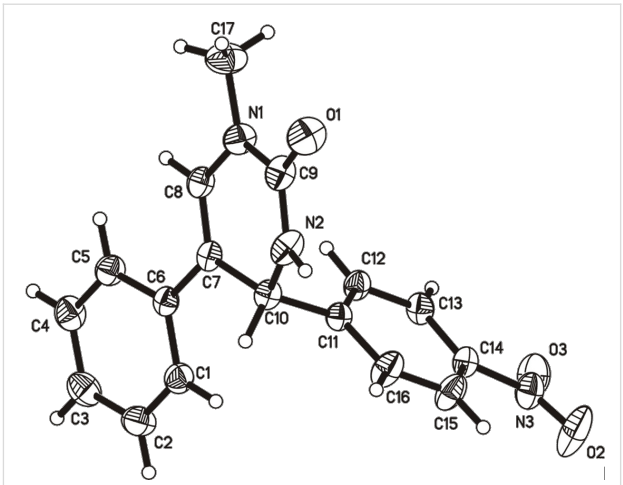
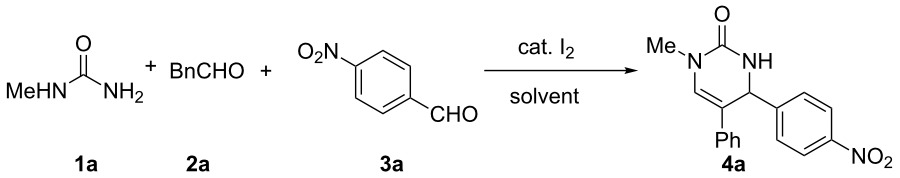


Figure 1: X-ray crystal structure of **4a**.

For optimization of the reaction conditions, various trial reactions were conducted with a combination of *N*-methylurea (**1a**), phenylacetaldehyde (**2a**) and *p*-nitrobenzaldehyde (**3a**) in order to obtain the best yield of **4a**, which is summarized in Table 1. We examined some organic solvents, and have noted that acetonitrile was the most suitable solvent among others, such as toluene, 1,4-dioxane, THF, DCE, and DCM (Table 1, entries 1–6). The catalyst loading (10%) gave the good result for the formation of the desired product (Table 1, entries 6–8).

The substrate scope of the molecular iodine-catalyzed one-pot three-component Biginelli-type reaction was then investigated, and the results were presented in Table 2. First, we examined the scope of the aromatic aldehydes **3**. Various aromatic aldehydes **3a**–**3l** and furfural (**3m**) were suitable substrates, and the expected products were obtained in moderate isolated yields (39–70%) (Table 2, entries 1–13). Electron-withdrawing as well as electron-donating groups on aromatic rings were tolerated, although the latter gave slightly reduced yields. It is noted that a halogen group on the aromatic ring was well tolerated to give the desired products, which can participate in subsequent transformations such as cross-coupling reactions (Table 2, entries

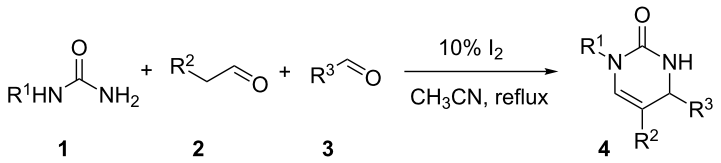
Table 1: Optimization of reaction conditions.[a]



Entry	Iodine (mol %)	Solvent	*T*	*t* (h)	Yield (%)[b]
1	10	toluene	reflux	12	56
2	10	1,4-dioxane	reflux	12	53
3	10	THF	reflux	12	58
4	10	DCE	reflux	12	52
5	10	DCM	rt	24	10
6	10	MeCN	reflux	12	70
7	15	MeCN	reflux	10	70
8	5	MeCN	reflux	24	58
9	0	MeCN	reflux	12	0

[a]All the reactions were carried out using **1a** (2.5 mmol), **2a** (2.5 mmol), and **3a** (3.75 mmol) in 3 mL solvent. [b]Isolated yields.

Table 2: One-pot synthesis of dihydropyrimidinones.[a]



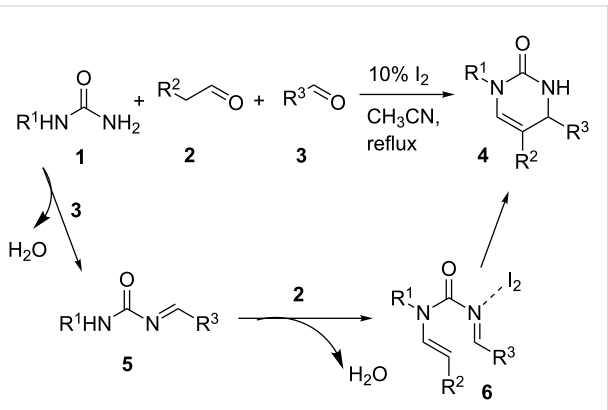
1 2 3 4

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	Me (**1a**)	Ph (**2a**)	4-$NO_2C_6H_4$ (**3a**)	**4a**	70
2	**1a**	**2a**	3-$NO_2C_6H_4$ (**3b**)	**4b**	67
3	**1a**	**2a**	4-CNC_6H_4 (**3c**)	**4c**	68
4	**1a**	**2a**	4-ClC_6H_4 (**3d**)	**4d**	63
5	**1a**	**2a**	4-BrC_6H_4 (**3e**)	**4e**	70
6[c]	**1a**	**2a**	2-BrC_6H_4 (**3f**)	**4f**	67
7	**1a**	**2a**	4-$CF_3C_6H_4$ (**3g**)	**4g**	56
8	**1a**	**2a**	Ph (**3h**)	**4h**	57
9	**1a**	**2a**	4-MeC_6H_4 (**3i**)	**4i**	53
10	**1a**	**2a**	4-$MeOC_6H_4$ (**3j**)	**4j**	46
11	**1a**	**2a**	piperonyl (**3k**)	**4k**	39
12	**1a**	**2a**	1-naphthyl (**3l**)	**4l**	49
13	**1a**	**2a**	2-furyl (**3m**)	**4m**	42
14	**1a**	**2a**	Bn (**2a**)	**4n**	81
15	**1a**	iPr (**2b**)	**3a**	**4o**	48
16	**1a**	*n*-Bu (**2c**)	**3a**	**4p**	55
17	**1a**	pentyl (**2d**)	**3a**	**4q**	54
18	Et (**1b**)	**2a**	**3a**	**4r**	72
19	Et (**1b**)	**2a**	**3b**	**4s**	66
20	Et (**1b**)	**2a**	**3c**	**4t**	67
21	Et (**1b**)	**2a**	**3d**	**4u**	58
22	Et (**1b**)	**2a**	**3e**	**4v**	63

[a]All the reactions were carried out using **1** (2.5 mmol), **2** (2.5 mmol), **3** (3.75 mmol), and iodine (0.25 mmol) in 3 mL MeCN at reflux for 12 h. [b]Isolated yields.

4–6). Furthermore, when phenylacetaldehyde (**2a**) was used instead of an aromatic aldehyde, product **4n** was isolated with good yield (81%; Table 2, entry 14). Subsequently, we investigated the scope of substituted acetaldehydes **2** (Table 2, entries 15–17). The variation of the alkyl substituent of acetaldehydes **2** is well tolerated to provide the desired products **4o**–**4q** in 48–55% isolated yields. Finally, *N*-ethylurea **1b** was also investigated in the one-pot three-component reaction, and the reactions proceeded smoothly to give the corresponding dihydropyrimidinones **4r**–**4v** in 58–72% isolated yields (Table 2, entries 18–22). Based on the experimental results above, the iodine-catalyzed Biginelli-type reaction proved to be of broad scope and provides higher yields of dihydropyrimidinones than the earlier described method with $BF_3{\cdot}Et_2O$ as the catalyst.

Molecular iodine is a mild catalyst with moderate Lewis acidity. Thus, a possible mechanism was proposed in Scheme 1. The first step is the condensation via the primary nitrogen of monosubstituted urea **1** with the aromatic aldehyde **3** to give the intermediate **5**. Then, the enamide **6** is generated through the condensation of imine **5** with substituted acetaldehyde **2**. This



Scheme 1: Possible mechanism.

could then undergo an iodine-catalytic intramolecular cyclisation to afford the final dihydropyrimidinone **4**.

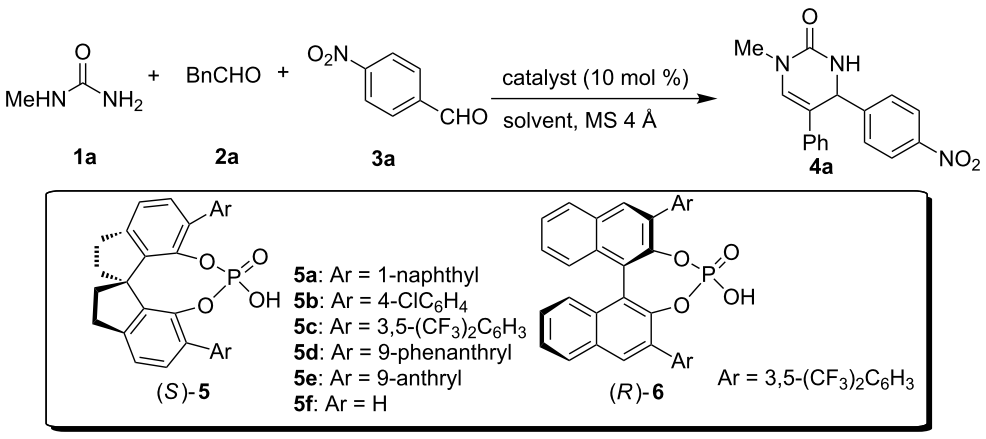
Based on the observations above, a preliminary investigation on the catalytic asymmetric version was performed. Recently, our group has developed a novel class of spirocyclic SPINOL-phosphoric acids derived from chiral 1,1'-spirobiindane-7,7'-diol, which could effectively catalyze some highly enantioselective reactions [25-31]. These previous successes led us to envision that SPINOL-phosphoric acids would effectively catalyze the enantioselective three-component reaction of mono-substituted ureas **1**, alkylaldehydes **2** and arylaldehydes **3** to generate enantioenriched dihydropyrimidinones **4** [32-35].

In our initial study, we examined the multicomponent model reaction between *N*-methylurea **1a**, phenylacetaldehyde **2a**, and *p*-nitrobenzaldehyde **3a**. As shown in Table 3, optimization of the reaction conditions revealed that toluene was the best solvent, chiral SPINOL-phosphoric acid **5a** was the best catalyst and the best temperature was room temperature, which afforded product **4a** with 77% ee in 62% yield (Table 3, entry 4). With these reaction conditions identified, the variation of the reaction substrates was well tolerated to provide the desired products with up to 77% ee (Figure 2). Although the enantioselectivity was low to moderate, it should be noted that this is the first catalytic enantioselective version of this multicomponent reaction.

Conclusion

In conclusion, we have demonstrated the first efficient, molecular iodine-catalyzed three-component synthesis of dihydropyrimidinones starting from simple readily available monosubstituted ureas, alkylaldehydes, and arylaldehydes. A significant progress was obtained with an extremely broad substrate scope, giving the corresponding DHPMs with reasonable yields under mild reaction conditions. Moreover, the catalytic asym-

Table 3: Optimization of the asymmetric reaction conditions.[a]



Entry	Catalyst	Solvent	*T* (°C)	Yield (%)[b]	ee[c]
1	**5a**	CH_3CN	rt	75	17
2	**5a**	CH_3CN	0	51	34
3	**5a**	xylene	rt	60	72
4	**5a**	toluene	rt	62	77
5	**5a**	toluene	0	0	–
6	**5a**	toluene	50	65	67
7	**5b**	toluene	50	39	34
8	**5c**	toluene	50	30	42
9	**5d**	toluene	50	41	58
10	**5e**	toluene	50	28	60
11	**5f**	toluene	50	58	12
12	**6**	toluene	50	0	–

[a]Reaction conditions: Catalyst (10 mol %, 0.02 mmol), **1a** (0.2 mmol), **2a** (0.2 mmol), **3a** (0.3 mmol), MS 4 Å (0.1 g), solvent (1 mL), 2 days. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

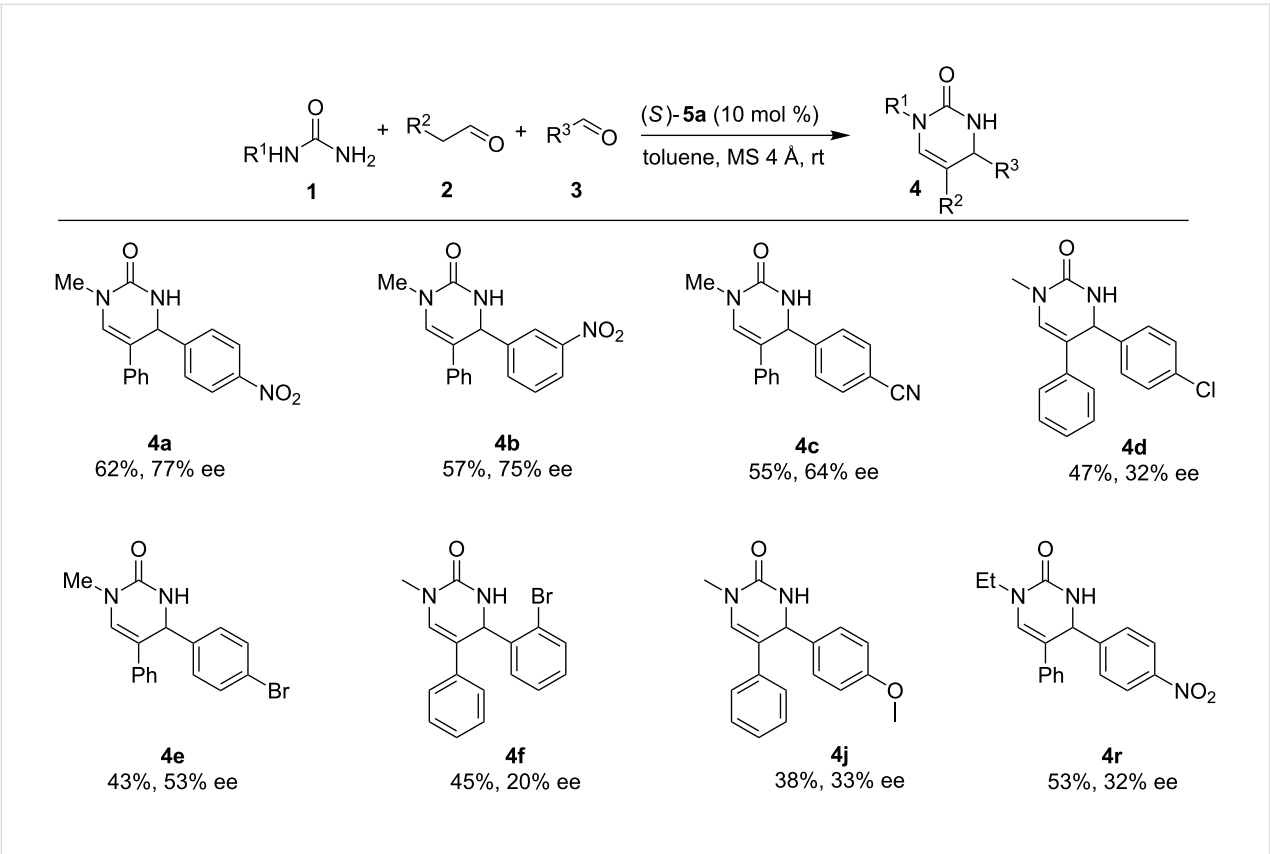


Figure 2: Scope of the enantioselective reaction. Reaction conditions: **5a** (10 mol %, 0.02 mmol), **1** (0.2 mmol), **2** (0.2 mmol), **3** (0.3 mmol), MS 4 Å (0.1 g), toluene (1 mL), rt, 2 days. Isolated Yields were given. The ee's were determined by chiral HPLC.

metric version of this multicomponent reaction has also been developed to a straightforward synthesis of enantiomerically enriched DHPMs by using a chiral SPINOL-phosphoric acid as the catalyst.

Crystallographic Data

Single crystal data for compound **4a** (CCDC 918944) has been deposited in the Cambridge Crystallographic Data Centre. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information

Supporting Information File 1

Experimental details and spectroscopic data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-320-S1.pdf]

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Four-component reaction of cyclic amines, 2-aminobenzothiazole, aromatic aldehydes and acetylenedicarboxylate

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Full Research Paper

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Abstract

The four-component reaction of 2-aminobenzothiazole, aromatic aldehydes, acetylenedicarboxylate and piperidine or pyrrolidine in ethanol afforded the functionalized 2-pyrrolidinones containing both benzothiazolyl and piperidinyl (or pyrrolidinyl) units in good yields. On the other hand, the similar four-component reactions resulted in the functionalized morpholinium or piperidinium 2-pyrrolidinon-3-olates in the presence of *p*-toluenesulfonic acid.

Introduction

Over fifty years ago, Huisgen firstly described the addition reactions of nitrogen-containing heterocycles to electron-deficient alkynes to form 1,4-dipolar intermediates, which can reacted sequentially with other reagents to give cycloaddition products [1,2]. From then on much developments on the chemistry of Huisgen 1,4-dipoles have been achieved [3,4]. In the past few years, Huisgen 1,4-dipoles have been recognized as key components for designing practical multicomponent reactions and domino reactions, mainly due to their easy generation and versatile reactivity [5-10]. On the other hand, the similar reactive Huisgen 1,4-dipoles derived from the addition of primary or secondary amines to electron-deficient alkynes also provided many elegant procedures for the synthesis of various nitrogen-containing heterocycles [11-16]. In this hot research field, we also successfully developed a series of domino reactions containing primary amine, electron-deficient alkynes and the other components, and found several efficient synthetic protocols for versatile heterocycles and spiro compounds by using the in situ generated Huisgen 1,4-dipoles [17-24]. During these research works, we noticed that even through the cyclic secondary amines such as pyrrolidine, piperidine and morpholine also reacted with electron-deficient alkynes to give the Huisgen 1,4-dipoles very fast and in nearly quantitative yields [25,26]. But until now it seems that this kind of easily generated Huisgen 1,4-dipoles have not been utilized for the design of domino reactions. In continuation of our efforts to explore

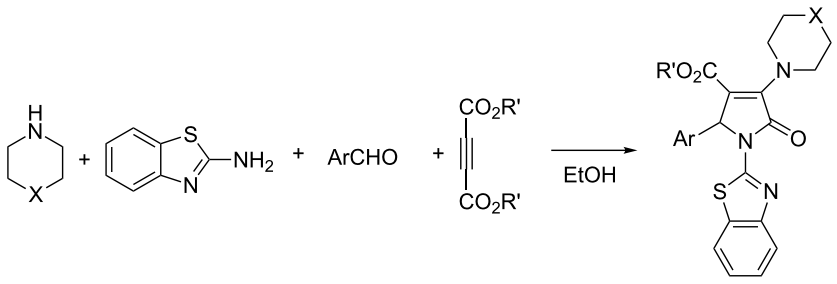
the practical applications of Huisgen 1,4-dipoles for the synthesis of a versatile heterocyclic system, herein we wish to report the interesting results of the four-component reaction of secondary cyclic amines, acetylenedicarboxylate, 2-aminobenzothiazole and aromatic aldehydes and the efficient synthesis of the complex 2-pyrrolidinones containing both benzothiazolyl and piperidinyl (or pyrrolidinyl) units.

Results and Discussion

Initially, we set out to investigate the reaction conditions by using piperidine to react with dimethyl acetylenedicarboxylate to give the expected β-enamino ester. It is interesting to find that the reaction of piperidine with acetylenedicarboxylate in ethanol at room temperature proceeded very quickly and could be finished to give the expected β-enamino ester in less than twenty minutes [27], while the reaction of normal primary arylamine with acetylenedicarboxylate or propiolate in ethanol at room temperature usually needed more than one day [28]. Thus we chose to employ a one-pot multicomponent reaction procedure to investigate our reaction. A mixture of dimethyl acetylenedicarboxylate, benzaldehyde, 2-aminobenzothiazole and excess piperidine in ethanol was stirred at room temperature for about twenty minutes and then was heated at 50–60 °C for about 48 hours. In this reaction the excess piperidine acted as base catalyst. After work-up, the expected polyfunctionalized 2-pyrrolidinone **1a** was obtained in good yield (Table 1, entry 1). Under similar reaction conditions, various aromatic aldehydes were utilized in the reaction to give the polyfunctionalized 2-pyrrolidinone **1b**–**1f** (Table 1, entries 2–6) in 53–72% yields, respectively. The four-component reaction containing diethyl acetylenedicarboxylate also successfully afforded the expected 2-pyrrolidinone **1g** in 63% (Table 1, entry 7).

In view of the success of the above reaction, we explored the scope of this promising reaction by varying the structure of the secondary cyclic amines. When excess pyrrolidine was used in the reaction by using the above reaction procedure, it was surprising to find that only very low yields of 3-(pyrrolidin-1-yl)-2-pyrrolidinones were produced. After carefully optimizing the reaction conditions, we were pleased to find that the

Table 1: Synthesis of pyrrolidinones **1a**–**1n** via four-component reactions[a].



1a–1n

Entry	Compd	X	R'	Ar	Yield[b] (%)
1	**1a**	CH_2	CH_3	C_6H_5	58
2	**1b**	CH_2	CH_3	*m*-$CH_3C_6H_4$	72
3	**1c**	CH_2	CH_3	*p*-$CH(CH_3)_2C_6H_4$	55
4	**1d**	CH_2	CH_3	*p*-ClC_6H_4	53
5	**1e**	CH_2	CH_3	*m*-ClC_6H_4	67
6	**1f**	CH_2	CH_3	*m*-$NO_2C_6H_4$	70
7	**1g**	CH_2	CH_2CH_3	*p*-$CH_3C_6H_4$	63
8	**1h**	O	CH_3	C_6H_5	66[c]
9	**1i**	O	CH_3	*p*-$CH_3OC_6H_4$	55[c]
10	**1j**	O	CH_3	*p*-ClC_6H_4	58[c]
11	**1k**	O	CH_3	*m*-ClC_6H_4	63[c]
12	**1l**	O	CH_3	*m*-$NO_2C_6H_4$	68[c]
13	**1m**	O	CH_3	*p*-$NO_2C_6H_4$	52[c]
14	**1n**	O	CH_3	*p*-$CH_3OC_6H_4$	10[c]

[a]Reaction conditions: 2-aminobenzothiazole (2.0 mmol), acetylenedicarboxylate (2.0 mmol), aromatic aldehyde (2.0 mmol), piperidine (3.0 mmol) in EtOH (10.0 mL), rt, 20 min, 50–60 °C, 48 h; [b]Isolated yield; [c]Pyrrolidine or morpholine (2.0 mmol) and DABCO (0.5 mmol) were used.

expected 3-(pyrrolidin-1-yl)-2-pyrrolidinones **1h**–**1m** could be prepared in the satisfactory yields by adding the stronger base DABCO into the reaction as base catalyst (Table 1, entries 8–13). Another common cyclic amine morpholine still gave a very low yield of the desired 3-morpholinyl-2-pyrrolidinone **1n** (Table 1, entry 14). It is known that pyrrolidine (pK_b = 2.73) and piperidine (pK_b = 2.88) have near similar basicity, while morpholine has a relative weak basicity (pK_b = 5.64). At present, the exact reason for the different reactivity of piperidine, pyrrolidine and morpholine in this reaction is not very clear. The structures of the prepared 2-pyrrolidinones **1a**–**1n** were fully characterized by ^{1}H and ^{13}C NMR, HRMS, IR spectra, and were further confirmed by single crystal structure determination of compound **1f** (Figure 1). In ^{1}H NMR spectra of compounds **1a**–**1n**, the proton at the 5-position of the newly-formed 2-pyrrolidonyl ring usually displays a singlet at about 6.15 ppm. The piperidin-1yl or pyrrolidin-1-yl groups usually show two or three characteristic mixed peaks.

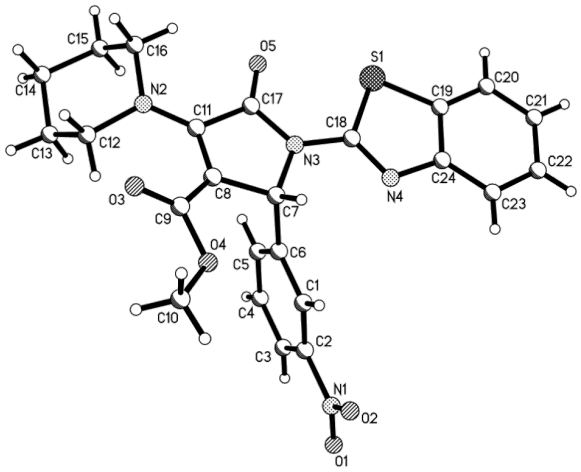
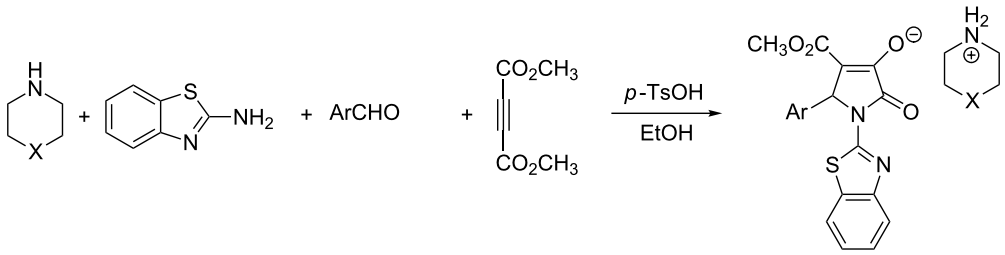


Figure 1: Molecular structure of compound **1f**.

Two years ago, we reported that a *p*-toluenesulfonic acid-catalyzed three-component reaction of arylamine, aromatic aldehyde and acetylenedicarboxylate afforded 3-hydroxy-2-pyrrolidinone as main product [28]. In order to improve the reactivity of morpholine in this four-component reaction, *p*-toluenesulfonic acid was added in the four-component reaction of morpholine, *p*-methoxybenzaldehyde, 2-aminobenzothiazole and dimethyl acetylenedicarboxylate. After work-up, we found that the reaction afforded unexpected morpholinium 2-pyrrolidinon-3-olate **2a** in 75% yield (Table 2, entry 1). Under similar conditions, the reactions with other aromatic aldehydes also gave the morpholinium 2-pyrrolidinon-3-olates **2b**–**2e** (Table 2, entries 2–5) in 65–87% yields, respectively. The formation of morpholinium 2-pyrrolidinon-3-olates **2a**–**2e** clearly indicated that the reaction initially gave the expected

Table 2: Synthesis of pyrrolidinones **2a–2h** via four-component reactions[a].



2a–2h

Entry	Compd	X	Ar	Yield[b] (%)
1	**2a**	O	*p*-$CH_3OC_6H_4$	75[c]
2	**2b**	O	*p*-$CH(CH_3)_2C_6H_4$	73
3	**2c**	O	*p*-$CH_3C_6H_4$	65
4	**2d**	O	C_6H_5	87
5	**2e**	O	*m*-$NO_2C_6H_4$	79
6	**2f**	CH_2	*p*-$CH_3C_6H_4$	75
7	**2g**	CH_2	*m*-$CH_3C_6H_4$	72
8	**2h**	CH_2	*p*-$(CH_3)_3CC_6H_4$	80

[a]Reaction condition: 2-aminobenzothiazole (2.0 mmol), acetylenedicarboxylate; (2.0 mmol), aromatic aldehyde (2.0 mmol), piperidine or piperidine (2.0 mmol), *p*-TsOH (0.5 mmol), in EtOH (10.0 mL), rt, 20 min., 50–60 °C 48 h; [b]Isolated yield.

3-hydroxy-2-pyrrolidinone, which in turn converted to enolate by deprotonation of basic morpholine. This result also showed that this four-component reaction has an interesting molecular diversity in basic or acidic solution. We also utilized piperidine in this acid-catalyzed four component reaction and obtained the corresponding piperidinium 2-pyrrolidinon-3-olates **2f**–**2h** in good yields (Table 2, entries 6–8). The prepared piperidinium and morpholinium 2-pyrrolidinon-3-olates **2a**–**2h** are very stable compounds. Their structures were fully characterized by ^{1}H and ^{13}C NMR, HRMS, IR spectra, and were also confirmed by single crystal structure determination of compounds **2a** (Figure 2) and **2h** (Figure 3).

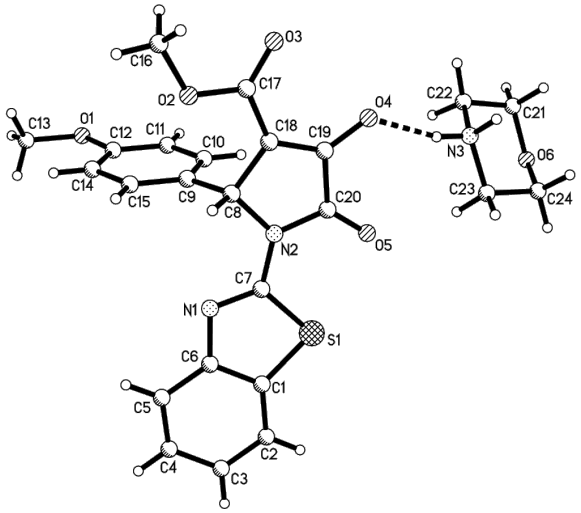


Figure 2: Molecular structure of compound **2a**.

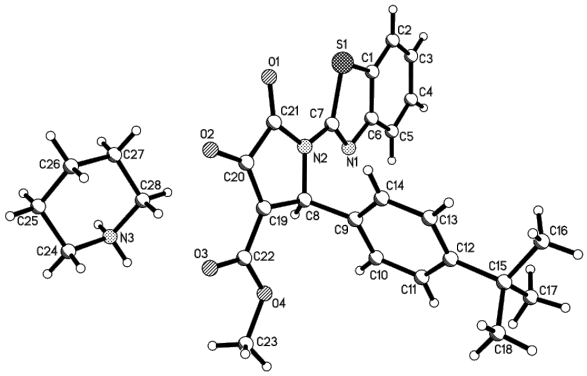


Figure 3: Molecular structure of compound **2h**.

A plausible reaction mechanism for this four-component reaction both in basic media and in acid solution was proposed based on the previous reported similar reactions (Scheme 1) [29-34]. At first, piperidine adds to acetylenedicarboxylate to give 1,3-dipolar intermediate **A**. In the meantime, the condensation of the aromatic aldehyde with 2-aminobenzothiazole affords an aldimine **B**. Secondly, the nucleophilic addition of 1,3-dipole intermediate **A** to aldimine **B** gives an addition intermediate **C**. Thirdly, the intramolecular nucleophilic attack of the amino group to the carbonyl group produces the polyfunctionalized 2-pyrrolidinone **1**. There is one reactive enamine unit in the obtained 2-pyrrolidinone **1**. Under the catalysis of *p*-toluenesulfonic acid, the enamine moiety in 2-pyrrolidinone **1** was easily hydrolyzed to yield a 2, 3-pyrrolidinedione (**D**) and piperidine. Then 2,3-pyrrolidinedione **D** transforms to the more stable enol-form through the keto–enol tautomerism. Because the enol connects to both ester and amide groups, it has much stronger acidity and is deprotonated by piperidine in the solution to give the piperidinium 2-pyrrolidinon-3-olate **2** as the final product.

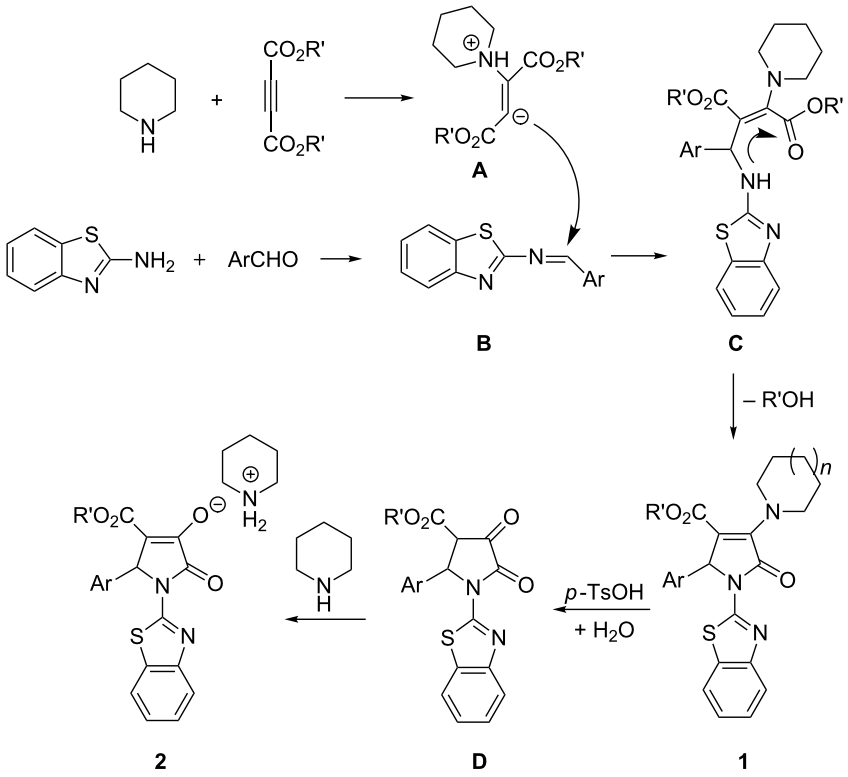
Conclusion

In summary, we have successfully developed a four-component reaction of an aromatic aldehyde, 2-aminobenzothiazole, secondary cyclic amines and acetylenedicarboxylate in basic or acidic soution. This four-component reaction provides a convenient procedure for the preparation of the mixed heterocyclic compounds containing units of benzothiazole, piperidine and 2-pyrrolidinone in satisfactory yields. The range of substrates and the reaction mechanism for this reaction were briefly discussed. This convenient synthetic reaction might be potentially used for complex heterocyclic systems in synthetic and medicinal chemistry.

Experimental

Reagents and apparatus: Melting points were taken on a hot-plate microscope apparatus. IR spectra were obtained on a Bruker Tensor 27 spectrometer (KBr disc). NMR spectra were recorded with a Bruker AV-600 spectrometer with DMSO-d_6 as solvent and TMS as internal standard (600 and 150 MHz for ^{1}H and ^{13}C NMR spectra, respectively). HRMS were measured at UHR-TOF maXis instrument. X-ray data were collected on a Bruker Smart APEX-2 diffractometer. 2-Aminobenzothiazole, dimethyl or diethyl acetylenedicarboxylate, aromatic aldehyde and other reagents are commercial reagents and used as received. Solvents were purified by standard techniques. All reactions were monitored by TLC.

General procedure for the preparation of the functionalized 2-pyrrolidinones 1a–1n as a one-pot four-component reaction: A mixture of 2-aminobenzothiazole (2.0 mmol), acetylenedicarboxylate (2.0 mmol), aromatic aldehyde (2.0 mmol), piperidine (3.0 mmol) (in cases of pyrrolidine or morpholine was used in the reaction, pyrrolidine or morpholine (2.0 mmol), DABCO (0.5 mmol)) in ethanol (10.0 mL) was



Scheme 1: The proposed reaction mechanism for the four-component reaction.

stirred at room temperature for about twenty minutes and then was heated at about 50–60 °C for about two days. After cooling to room temperature, the resulting precipitates were collected by filtration and washed with cold ethanol to give the crude product, which was recrystallized in ethanol to give the pure products **1a**–**1n** for analysis.

General procedure for the preparation of functionalized 2-pyrrolidinon-3-olates 2a–2h as a one-pot reaction: A mixture of 2-aminobenzothiazole (2.0 mmol), acetylenedicarboxylate (2.0 mmol), aromatic aldehyde (2.0 mmol), morpholine or piperidine (3.0 mmol) and *p*-toluenesulfonic acid (0.5 mmol) in ethanol (10.0 mL) was stirred at room temperature for about twenty minutes and then was heated at about 50–60 °C for about two days. After cooling to room temperature, the resulting precipitates were collected by filtration and washed with cold ethanol to give the products **2a**–**2h**.

X-ray crystallographic data: Single crystal data for compounds **1f** (CCDC 950634), **2a** (CCDC 950635) and **2h** (CCDC 952039) have been deposited in the Cambridge Crystallographic Data Center. These data can be obtained free of charge via http://www.ccdc.ac.ck./data_request/cif .

Supporting Information

Supporting Information File 1

Analytical data and ^{1}H and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-330-S1.pdf]

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Studies on the interaction of isocyanides with imines: reaction scope and mechanistic variations

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Letter

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Abstract

The interaction of imines with isocyanides has been studied. The main product results from a sequential process involving the attack of two units of isocyanide, under Lewis acid catalysis, upon the carbon–nitrogen double bond of the imine to form the 4-membered ring system. The scope of the reaction regarding the imine and isocyanide ranges has been determined, and also some mechanistic variations and structural features have been described.

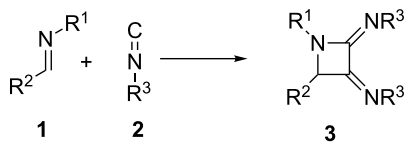
Introduction

The interaction of imines with isocyanides is mainly focused on to the well-known Ugi multicomponent reaction (MCR) [1]. This fundamental process features the participation of a carboxylic acid group which attacks the intermediate nitrilium ion thus leading, after the Mumm rearrangement, to α-amidoamides. However, the direct reaction of imines and isocyanides has been considerably less studied and, in the absence of a carboxylate, the mechanistic outcome is considerably modified [2]. A relevant precedent was described by Deyrup in the late sixties, demonstrating the double incorporation of an isocyanide moiety to an imine [3,4]. Interestingly, the 3CR between a carbonyl, an amine and an isocyanide, taking place through the intermediacy of the in situ generated imine, leads to α-aminoamidines, resulting from the trapping of the nitrilium cation by the remaining amine [5-8]. Taking into account the intrinsic interest in the azetidine scaffold in medicinal chemistry [9], we decided to study in detail the formation of bis(imino)azetidines **3** from the interaction of imines **1** and isocyanides **2** (Scheme 1), including the scope of the reaction and mechanistic features of this interesting ABB' process [10].

Results and Discussion

Reaction scope

In this section we analyze the reaction conditions, the structural features of the products and the scope of the reactants.



Scheme 1: Azetidine formation from the interaction of imines with isocyanides.

Reaction conditions

We began our studies with the experimental screening of the solvents, catalysts and temperatures suitable for this transformation. In this respect, taking imine **1a** (R^1 = *p*-$MeOC_6H_4$; R^2 = *p*-ClC_6H_4) and isocyanide **2a** (R^3 = *t*-Bu), we tested the standard reaction in THF, MeCN, and CH_2Cl_2 as solvents using a variety of Lewis and Brønsted acid activating agents (20–100 mol %) including: $InCl_3$, $Sc(OTf)_3$, $AuCl_3$, AgOTf, $GaCl_3$, $NbCl_5$, camphorsulfonic acid, I_2, $Br_2{\cdot}SMe_2$ and $BF_3{\cdot}OEt_2$, at temperatures ranging from rt to 80 °C. The transformations were tested under standard heating or microwave irradiation, with reaction times lasting form 30 min to 48 h. The imine **1a** was generated in situ, using MS 4 Å, or previously prepared by condensation of the corresponding aldehyde and aniline. It was found that the best conditions were obtained using $BF_3{\cdot}Et_2O$ as the activating agent in stoichiometric amounts in THF, at rt for 24 hours or under MW irradiation for 30 min at 65 °C, allowing the formation of the expected azetidine **3a** in 43% and 48%, respectively. Compounds **4** and **5** could not be detected (Scheme 2). When the process was run as a true MCR (mixing the amine, the aldehyde and two equivalents of isocyanide **2a**), the adduct **3a** was produced in trace amounts and the main product was the α-amino-amidine **4**, in good agreement with previous reports [5-8]. In a different experiment, the addition of a 9-fold excess of isocyanide **2a** to the imine **1a** under the usual conditions led to detection of tris(imino)pyrrolidine **5** (9%) as the minor product, and azetidine **3a** as the major component (24%, Scheme 2).

Structural elucidation

Although we could confirm the constitution of the azetidine **3a** by spectroscopic methods (NMR, MS), the stereochemistry of the C=N bonds present in the structure remained unsolved. Furthermore, no conclusive nOe's were observed to assign these stereogenic centers, and there were no reports in the literature regarding this point. A monocrystal of the bis(imino)azetidine **3a** was subjected to X-ray diffraction analysis and the solid state structure is depicted in Figure 1 [11].

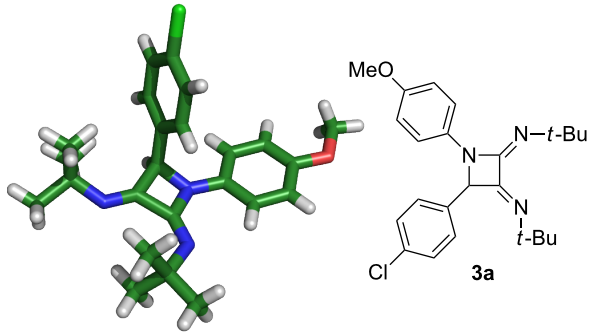
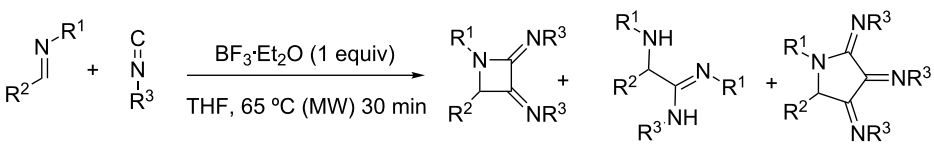
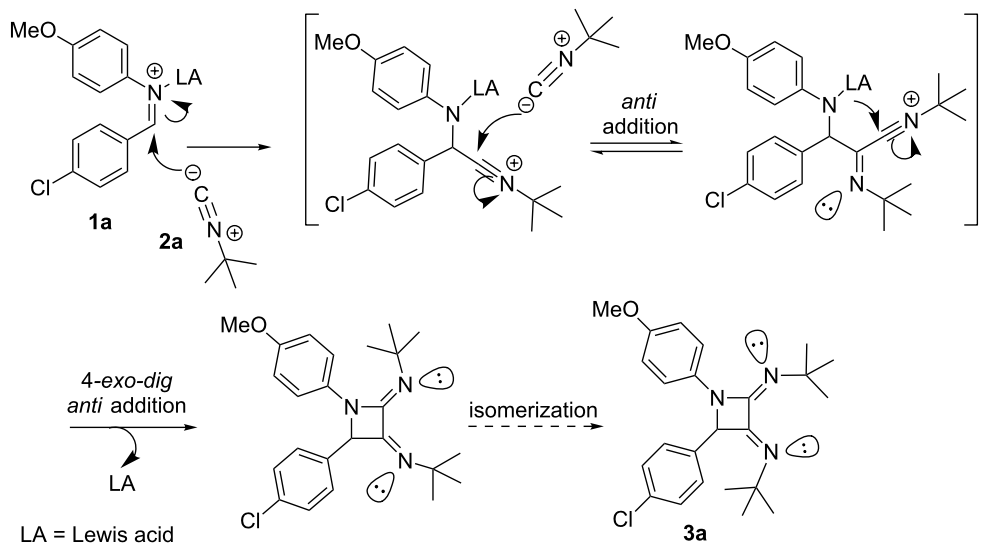


Figure 1: X-ray diffraction analysis of azetidine **3a**.

This result confirms the structural features associated to this scaffold, and also raises some questions on the origin of the stereochemistry associated to the C=N moieties. First of all, the process can be explained by an attack of one isocyanide equivalent to the Lewis acid (LA)-activated imine, leading to a first nitrilium intermediate (Scheme 3), then a subsequent attack would give raise to a second nitrilium ion [12-15], which is trapped by the nucleophilic nitrogen of the imine. This last step is formally a disfavoured nucleophilic 4-*exo*-*dig* process [16], although recent results and calculations show that it should be feasible and some examples have been disclosed [17]. Interestingly, the expected *anti*-addition mode towards the carbon–nitrogen triple bonds should generate *Z* configurations [18,19], which are not observed in the solid-sate, thus suggesting isomerization processes affecting the C=N moieties,



Scheme 2: Reaction conditions.



Scheme 3: Stepwise mechanism for the formation of azetidine **3a**.

likely mediated by acid-catalyzed prototropy or other tautomerization steps. Computational calculations (MMFF, AM1 and BL3YP/6-31G* performed in a Spartan suite) suggest that the differences in the heat of formation among some geometrical isomers are small. Furthermore, NMR spectra nearly always display a single set of signals, thus discarding further isomerization events once the compounds are detected or isolated.

Reactant scope

Next, the scope of the reaction was investigated, and a variety of imines was subjected to the interaction with a range of isocyanides under the optimized conditions to determine the generality of the process and to detect possible restrictions. Results are depicted in Table 1.

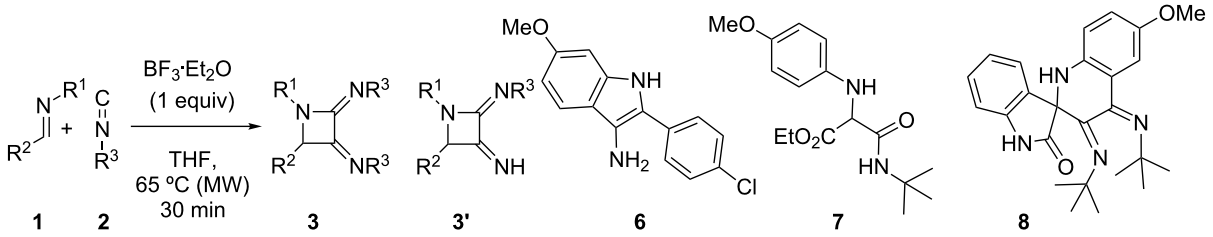
The scan of isocyanides shows that their nucleophilicity plays a determining role in the reactivity, since *tert*-butyl, cyclohexyl and benzyl isocyanides (Table 1, entries 1–3, 5–12) show a relatively high conversion, whereas the aromatic isocyanide was less reactive (entry 4) and the weaker nucleophiles TOSMIC and methyl isocyanoacetate were not productive (Table 1, entries 13 and 14) [20]. Additionally, with respect to imines, the reaction works well for substrates generated from aromatic aldehydes and anilines displaying *o*-, *m*- and *p*-substituents (Table 1, entries 1–7). Moreover, in one case the 3-aminoindole **6** was detected (27%), in agreement with a recent report (Table 1, entry 5) [21].

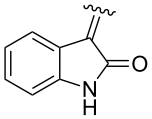
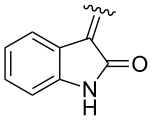
N-Alkylimines seem to react appropriately (Table 1, entry 8). Furthermore, we have observed some *tert*-butyl eliminations, probably due to competing reactions under the acidic conditions (Table 1, entries 5, 6 and 8). In general, imines containing electron-rich *N*-aryl moieties showed higher reactivities, and we were not able to isolate azetidine adducts **3** from the reaction of arylimines containing strong electron-withdrawing groups at the aniline moiety (*p*-CF_3, *p*-F and *p*-COOEt), likely because of their low conversions. However, the presence of such groups linked to the carbon of the imine did not seem to disturb their reactivity (Table 1, entries 1–8). Interestingly, the reaction of glyoxylate imine (Table 1, entry 9) with *tert*-butyl isocyanide led to the formation of minor amounts of the azetidine adduct **3i** (9%) whereas the α-aminoamide **7** (34%) was the major component. The formation of amidoamides has been reported in the *p*-toluenesulfonic acid-catalyzed interaction of anilines, amines and isocyanides [8]. On the other hand, the reaction of the same imine with cyclohexyl isocyanide gave azetidine **3j** (34%) in a selective manner (Table 1, entry 10), without traces of the corresponding α-aminoamide. Different types of activated substrates displaying C=N bonds (*N*-sulfinylimines, oximes and hydrazones) were studied, but none of them reacted productively with isocyanides under the described conditions. Finally, the reaction with isatinimines led to the formation of the spiroazetidines **3k** (14%) and **3l** (28%, Table 1, entries 11 and 12). Remarkably, in the former case an intramolecular cyclization of the nitrilium ion upon the electron rich *p*-methoxyphenyl group took place and led to the formation of the bis(imino)tetrahydroquinoline **8** (17%, Table 1, entry 11).

Mechanistic analysis

Taking into account the structural variety observed in this family of reactions, a rational explanation is needed to understand the formation of such products. Here we describe a

Table 1: Scope of the imine and isocyanide starting materials.



entry	R^1	R^2	R^3	yield
1	4-$MeOC_6H_4$	4-ClC_6H_4	*t*-Bu	**3a** (48%)
2	4-$MeOC_6H_4$	4-ClC_6H_4	*c*-C_6H_{11}	**3b** (41%)[a]
3	4-$MeOC_6H_4$	4-ClC_6H_4	Bn	**3c** (63%)[a]
4	4-MeC_6H_4	4-ClC_6H_4	4-$MeOC_6H_4$	**3d** (19%)[b]
5	3-$MeOC_6H_4$	4-ClC_6H_4	*t*-Bu	**3e** (19%) + **6** (27%)
6	4-$MeOC_6H_4$	2-ClC_6H_4	*t*-Bu	**3f** (12%) + **3f'** (15%)
7	2-MeC_6H_4	4-ClC_6H_4	*t*-Bu	**3g** (31%)
8	*n*-C_3H_7	4-ClC_6H_4	*t*-Bu	**3h'** (32%)
9	4-$MeOC_6H_4$	EtOCO	*t*-Bu	**3i** (9%)[a] + **7** (34%)
10	4-$MeOC_6H_4$	EtOCO	*c*-C_6H_{11}	**3j** (34%)[a]
11	4-$MeOC_6H_4$		*t*-Bu	**3k** (14%)[b] + **8** (17%)
12	4-MeC_6H_4		*t*-Bu	**3l** (28%)
13	4-$MeOC_6H_4$	4-ClC_6H_4	Ts-CH_2	–
14	4-$MeOC_6H_4$	4-ClC_6H_4	MeO_2C-CH_2	–

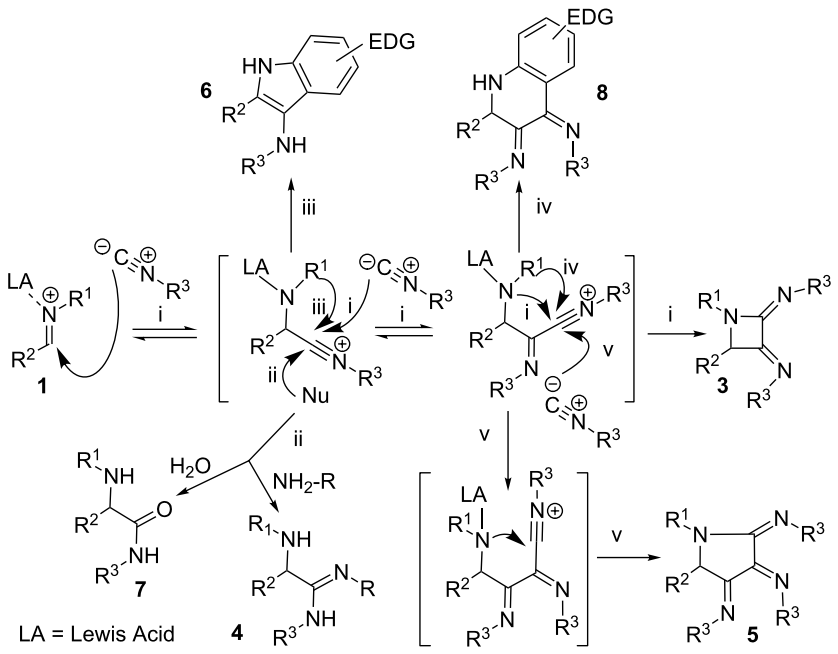
[a]The reaction was performed at rt. 20% of catalyst was used. [b]The adduct could not be isolated in pure form.

simplified hypothesis based on the well-known nucleophilic addition of isocyanides to Lewis acid-activated imines (Scheme 3). The first nitrilium intermediate can evolve through a second addition and ring-closure to yield the azetidine adduct **3** (Scheme 4, route i), or can also be trapped by water or amine/imine nucleophiles leading to α-aminoamides **7** and α-aminoamidines **4**, respectively (Scheme 4, route ii). The formation of aminoamide **7** was restricted to the use of glyoxylate imines, and happens only with *tert*-butyl isocyanide, but not with cyclohexyl isocyanide. On the other hand, the aminoamidines **4**, the standard adducts from the amine–aldehyde–isocyanide 3CR were observed in some occasions [5-7] under our conditions presumably by attack of the unreacted imine upon the nitrilium cation. These facts suggest that either a good nucleophile (amines, imines) may act intermolecularly to undergo fast addition to this intermediate or, when an alkyl carboxylate group is present it may stabilize the nitrilium intermediate precluding further addition events and leading to the aminoamides **7** after the final aqueous treatment.

Furthermore, we have detected indole **6** arising from the cyclization of electron-rich aromatic rings linked to the imine nitrogen upon the electrophilic nitrilium intermediate, in agreement with a Sorensen report (Scheme 4, route iii) [21]. Finally, the imino-nitrilium cation can be trapped by an aromatic ring when using isatin imines, leading to bis(imino)tetrahydroquinoline **8**, (Scheme 4, route iv). In a reaction using a large isocyanide excess, a triple insertion of the isocyanide moiety has been observed, the adduct being the tris(imino)pyrrolidine **5** (Scheme 4, route v).

Conclusion

As a summary, we have described structural and mechanistic features for the bis(imino)azetidines arising from the



Scheme 4: Manifold reaction mechanism.

imine–isocyanide interaction, finding that the process involves a sequential double isocyanide incorporation into the C=N bond. The final step is a nucleophilic 4-*exo*-*dig* cyclization, and the anti addition modes likely lead to less stable stereoisomers which spontaneously isomerize to the observed compounds. Furthermore, we have determined the scope of the reaction, according to the imine and isocyanide starting materials, and a small collection of multicomponent adducts has been prepared. These structures bear a novel azetidine scaffold of potential interest in medicinal chemistry [22,23]. Although the yields are modest, the compounds can be conveniently prepared in a straightforward manner. A part of the azetidine structure distinct scaffolds have been obtained from the interaction of different reactant combinations: α-aminoamides, α-aminoamidines, indoles, bis(imino)tetrahydroquinolines and tris(imino)pyrrolidines. Finally, a unified reaction mechanism that can account for the production of this rich structural outcome has been proposed.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, copies of the NMR spectra for all new compounds and X-ray views of azetidine **3a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-3-S1.pdf]

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The regioselective synthesis of spirooxindolo pyrrolidines and pyrrolizidines via three-component reactions of acrylamides and aroylacrylic acids with isatins and α-amino acids

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Abstract

The regioselective three-component condensation of azomethine ylides derived from isatins and α-amino acids with acrylamides or aroylacrylic acids as dipolarophiles has been realized through a one-pot 1,3-dipolar cycloaddition protocol. Decarboxylation of 2'-aroyl-2-oxo-1,1',2,2',5',6',7',7a'-octahydrospiro[indole-3,3'-pyrrolizine]-1'-carboxylic acids is accompanied by cyclative rearrangement with formation of dihydropyrrolizinyl indolones.

Introduction

The design of new spirocyclic compounds is intriguing due to their unique non-planar structure and great potential for binding to biomolecules due to their inherent rigid chiral structure. The spirooxindolo pyrrolidine and pyrrolizidine frameworks form core units of many naturally occurring molecules possess significant pharmacological activities. Among them are alka-

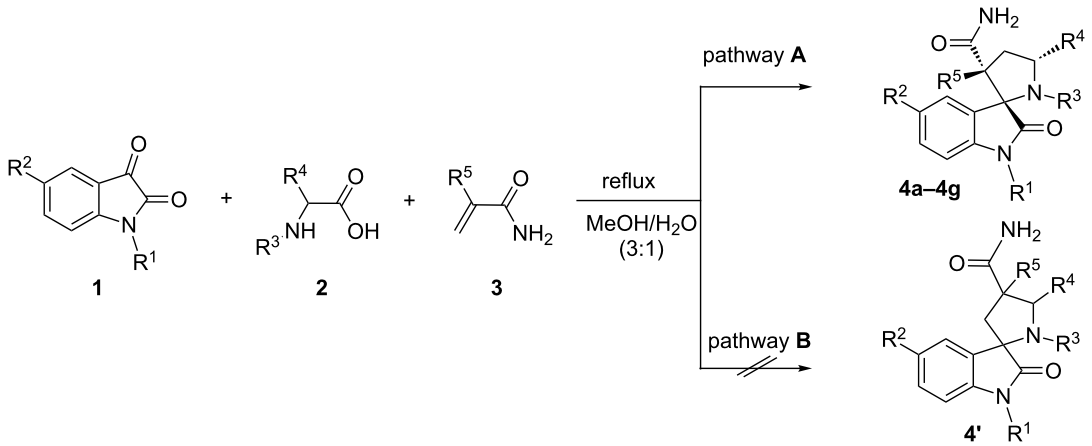
loids such as horsfiline from *Horsfieldia superba* [1-3], elacomine from *Elaeagnus commutata* [4], mitraphylline from *Uncaria tomentosa* [5] and spirotryprostatines A and B from the secondary metabolites of *Aspergillus fumigatus* [6-8]. In particular, oxindole derivatives are well known as powerful antitumor agents due to their kinase inhibitory properties, especially as tyrosine kinase inhibitors [9,10]. The multicomponent 1,3-dipolar cycloaddition of azomethine ylides, generated in situ via decarboxylative condensation of isatins and α-amino acids with olefinic and acetylenic dipolarophiles, represents a key approach for the regio- and stereoselective construction of a variety of complex spirooxindoles. Recently, this route has become significant in combinatorial chemistry due to its process simplicity, mild conditions, atomic economy and extension of the scope of substrates. A large number of focused libraries of spirooxindolo pyrrolidines and pyrrolizidines containing a wide set of natural and nonnatural α-amino acids [11-13], more than fifteen isatins [14], and 1,3-dipolarophiles, e.g. α,β-unsaturated ketones [15-17], maleimides [18,19], benzo[*b*]thiophene-1,1-dioxide [20], bis(arylmethylidene)acetones and -cycloalkanones [21,22], 1,4-naphthoquinone [23], arylidenemalonodinitriles [24], arylidenerhodanines [25,26], α,β-unsaturated lactones [27], nitrostyrenes [28], acrylic and propiolic esters [29], acrylonitriles [30] and arylidene-1,3-dimethylpyrimidine-2,4,6-triones [31] have been reported. However, the molecular diversity of suitable building blocks for construction of spirooxindoles is by far not exhausted with the above mentioned substances. Our interest to spirooxindoles is inspired by the search of new antidiabetic substances that might inhibit 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) in metabolically relevant tissues such as liver and adipose tissue. Recent studies have demonstrated that 11β-HSD1 is a novel molecular target for treating the "metabolic syndrome" and type 2 diabetes mellitus, and that compounds inhibiting the activity of this enzyme provide promising opportunities for the development of therapeutic interventions [32,33]. Among the large class of 11β-HSD1 inhibitors there are compounds containing a pyrrolidine-2-one as a part of the spirocyclic system [34].

In the present work we report the synthesis of spirooxindolo pyrrolidines and pyrrolizidines by utilizing a 1,3-dipolar cycloaddition of hitherto uninvestigated acrylamides and aroylacrylic acids with azomethine ylides, generated in situ via decarboxylative condensation of isatins and N-substituted α-amino acids (sarcosine, proline and thiazolidine-4-carboxilic acid) in a three-component fashion.

Results and Discussion

The three-component condensation of equimolar amounts of isatins **1**, α-amino acids **2** and acrylamides **3** in boiling aqueous methanol (1:3) afforded the spirooxindoles **4a–4g** in moderate to excellent yields (Table 1). The reaction times largely depend

Table 1: Three-component synthesis of spirooxindoles **4a–4g**.



entry	compound	R^1	R^2	R^3	R^4	R^5	yield (%)	time
1	**4a**	H	Br	CH_3	H	H	31	7 h
2	**4b**	H	NO_2	$CH_2CH_2CH_2$		H	85	3 h
3	**4c**	H	NO_2	$CH_2CH_2CH_2$		CH_3	37	40 min
4	**4d**	H	Br	CH_2SCH_2		H	42	1 h
5	**4e**	H	NO_2	CH_2SCH_2		H	60	6 h
6	**4f**	4-$CH_2C_6H_4Cl$	H	CH_2SCH_2		H	38	2 h
7	**4g**	CH_3	Br	$CH_2CH_2CH_2$		CH_3	58	2 h

on the reactivity of the employed α-amino acid. The longest reaction time (7 h) was found for sarcosine, while the fastest reaction (40 min) was found for proline as a substrate (Table 1, entries 1 and 3).

The 1,3-dipolar cycloaddition of unsymmetrical dipolarophiles such as acrylamides can occur via the two pathways **A** and **B** leading to the formation of the regioisomers **4** and **4'**. In our case, spirooxindol **4** is exclusively formed. All new cycloadducts obtained by the above method were characterized by mass spectrometry, ^{1}H and ^{13}C NMR, and elemental analyses. The regiochemical outcome of the cycloaddition was unambiguously confirmed by NOE experiments in ^{1}H NMR as well as later by a single crystal X-ray structure analysis of the cycloadduct **4a**.

The ^{1}H NMR spectra of compounds **4b–4d** have two multiplets at 4.07–3.72 ppm for 7a'-CH and 3.50–3.35 ppm for 2'-CH (compound **4b**) or 6'-CH (compound **4d**) and a singlet at 1.45 ppm for 2'-CCH_3 of compound **4c**. The relative stereochemistry of compounds **4b–4d** was established by NOE cross peaks between 7a'-CH and 2'(6'-CH) and 2'-CCH_3. Also, multiplets for 7a'-CH and 2'-(6'-CH) and singlet for 2'-CCH_3 show correlation signals to the neighboring methylene groups. Additionally, the absence of the NOE cross peak of 4-CH of the isatin nucleus and 2'(6'-CH) or 2'-CCH_3 of the pyrrolizidine moiety was indicative for the assigned relative stereochemistry. Therefore, the relative stereochemistry could be as shown in Figure 1.

The NH-proton of the oxindole moiety appeared as a singlet between 10.38–10.86 ppm. The ^{13}C NMR spectra of compounds **4a–4g** showed characteristic peaks at 71–73 ppm due to the spiro carbon nucleus.

The structure of compound **4a** was determined by an X-ray diffraction study of a single crystal and supports the structure deduced from NMR spectroscopy (Figure 2).

Dipolarophiles, such as aroylacrylic acids **5**, can also be successfully used in this three-component reaction. The cycloaddition of dipolarophiles **5** with non-stabilized azomethine ylides generated from isatins **1** and sarcosine/proline has led to spiropyrrolidines **6a,6b** and spiropyrrolizidines **6c–6h** in moderate to good yields. In this reaction also two regioisomers can be expected, but in all experiments solely the regioisomer **6** is isolated without detectable trace amounts of other isomers.

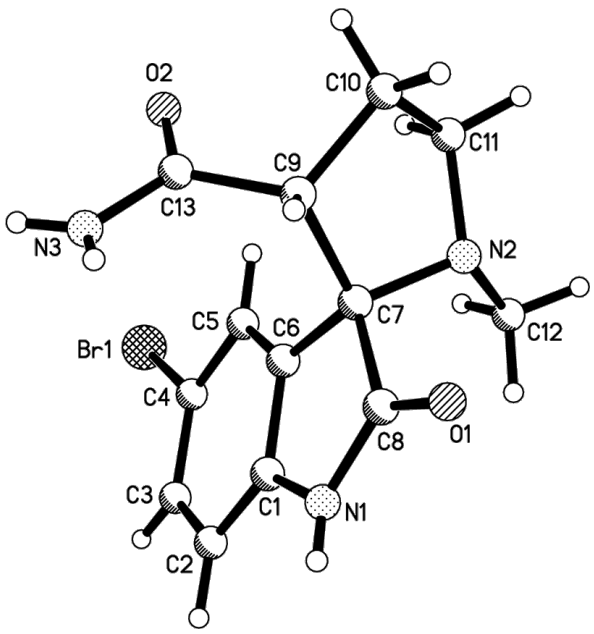


Figure 2: Molecular structure of spirooxindole **4a** according to X-ray diffraction data.

The higher reactivity of aroylacrylic acids induces remarkable rate acceleration and decreases the reaction time to only 10–15 min in a boiling mixture of methanol and water. The low to moderate yields of the target compounds **6c–6h** can be explained by considerable resinification of the reaction mixture and by formation of byproducts. To suppress these negative adverse processes we carried out the reaction under stirring at room temperature. The results are shown in Table 2.

All compound structures are fully supported by spectroscopic data and elemental analysis as illustrated for compound **6c**. The

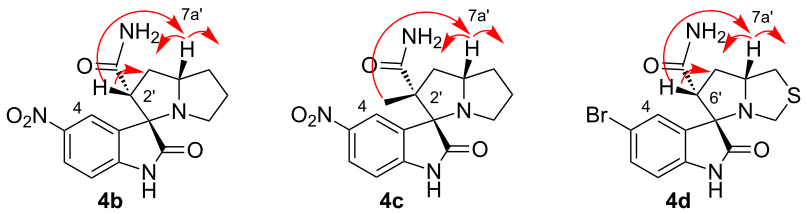
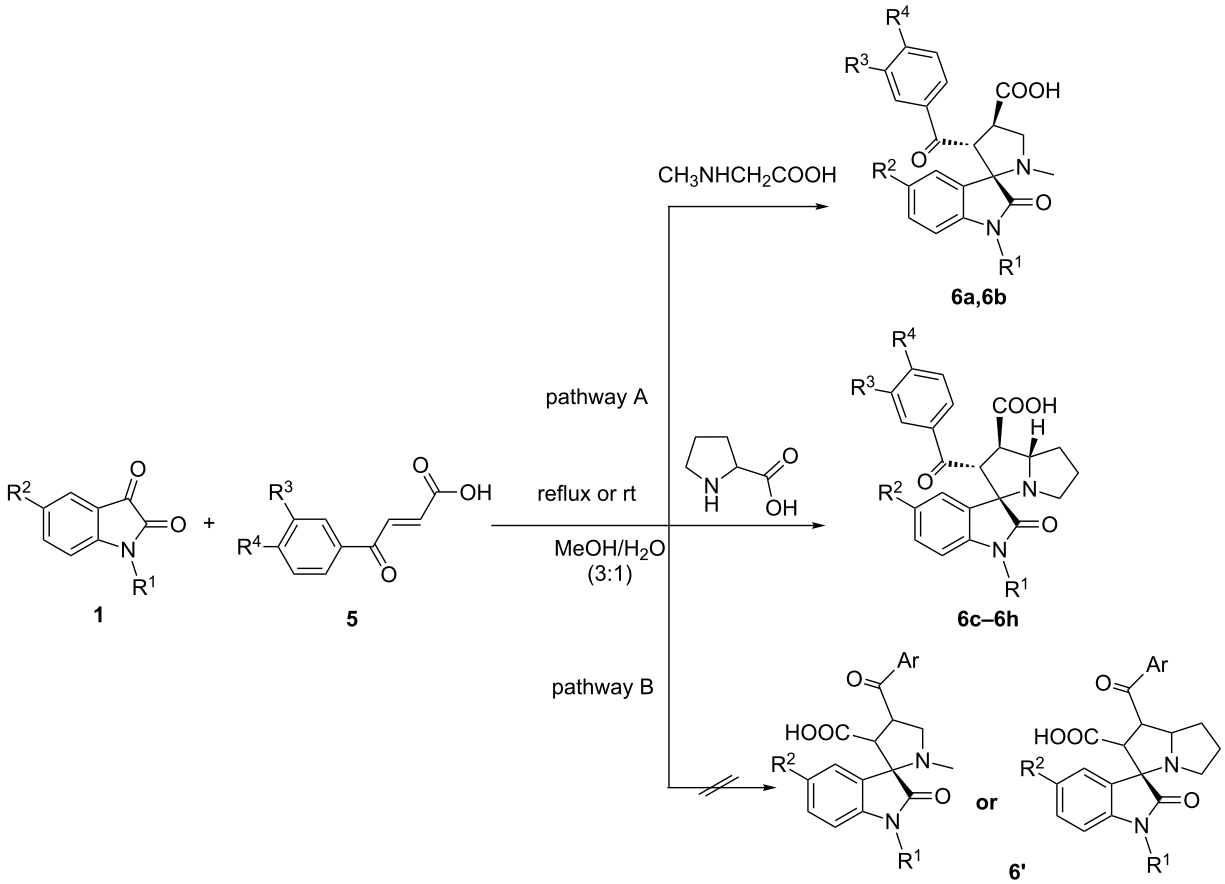


Figure 1: The NOE correlations of the signals in ^{1}H NMR spectra of compounds **4b–4d**.

Table 2: Synthesis of spirooxindoles **6a–6h** from the three-component reaction.



entry	compound	R^1	R^2	R^3	R^4	reflux		room temperature (rt)	
						yield (%)	time	yield (%)	time
1	**6a**	H	Br	Cl	Cl	50	6 h	–	–
2	**6b**	CH_3	Br	H	Br	34	8 h	–	–
3	**6c**	H	H	Cl	Cl	27	30 min	67	12 h
4	**6d**	CH_3	CH_3	Cl	Cl	30	1 h	–	–
5	**6e**	H	H	H	Br	15	1 h	57	25 min
6	**6f**	H	H	H	NO_2	74	10 min	76	3 h
7	**6g**	H	CH_3	H	NO_2	30	20 min	74	3 h
8	**6h**	H	Br	H	NO_2	50	15 min	76	5 h

^{1}H NMR spectrum of compound **6c** shows a doublet at 4.66 ppm (J =11.4 Hz) for 2'-CH and two multiplets at 3.77–3.93 ppm for 7a'-CH and 3.60–3.43 ppm for 1'-CH. The stereochemistry of compound **6c** was assigned by NOE cross peaks between 7a'-CH and 2'-CH and as well as the neighboring 7'-CH_2 with a multiplet at 1.91–2.12 ppm. Although a week NOE correlation was found between 1'-CH and 2'-CH, the *trans*-configuration of the mentioned protons is predetermined by the *trans*-configuration of the initial aroyl acrylic acid. Also, a NOE correlation is found between signals of 2'-CH and doublet at 7.30 ppm (J =1.8 Hz) for 2-CH of the aroyl acrylic acid moiety. In addition, the absence of NOE cross peaks between 4-CH of the isatin core and 2'-CH of the pyrrolizidine fragment supports the assignment. The NH-proton of the oxindole moiety and the 1'-COOH proton of the pyrrolidine/pyrrolizidine ring give singlets at 10.25 and 12.67 ppm, respectively. Therefore, the correct stereochemistry can be drawn as shown in Figure 3. The ^{13}C NMR spectrum of compound **6c** shows a characteristic peak at 73 ppm due to the spiro carbon nucleus.

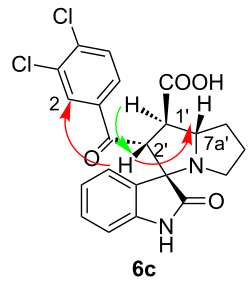


Figure 3: The NOE correlations of the signals in ^{1}H NMR spectrum of compound **6c**.

A single crystal X-ray study of compound **6a** provided a conclusive support for the assigned structure (Figure 4). Interesting feature of this structure is a pincers-like conformation of the molecule. The substituent at the C9 atom has equatorial orientation (the N2–C7–C9–C14 torsion angle is 122.7(2)°) and its carbonyl group is almost coplanar to the C9–C10 endocyclic bond (the C10–C9–C14–O4 torsion angle is 10.2(4)°). Such an orientation of this substituent creates conditions for appearance of intramolecular stacking interactions between the aromatic rings of the indole fragment and the aryl substituent (angle between planes of aromatic rings is 22.9° and the shortest distance between carbon atoms (C6…C15) is 3.04 Å).

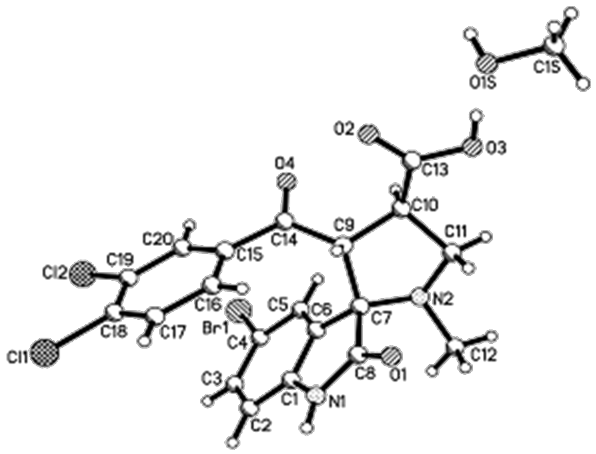
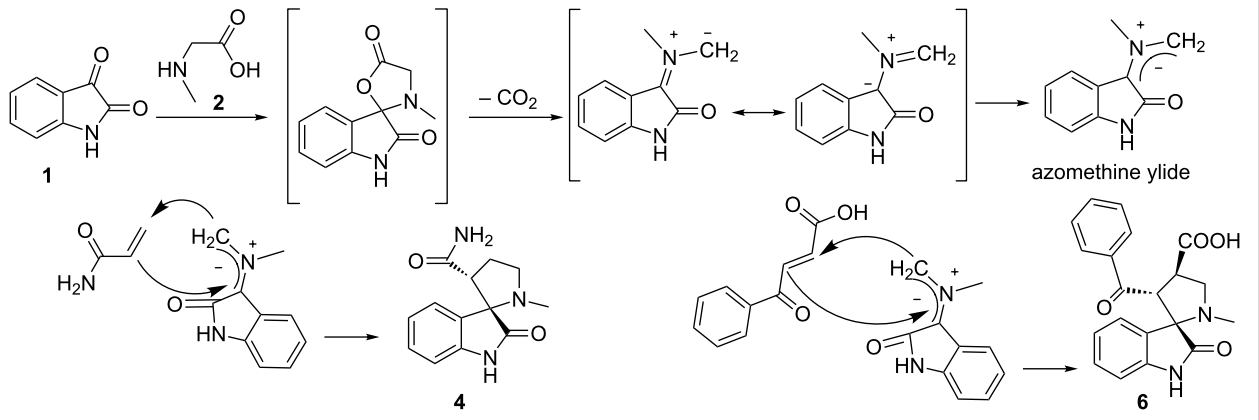


Figure 4: Molecular structure of spirooxindole **6a** observed in crystal phase as solvate with methanol according to X-ray diffraction data.

The mechanism of the azomethine ylide formation by a decarboxylative route has been repeatedly described by a number of authors and is depicted in Scheme 1 [35,36]. The reaction between isatin and the α-amino acid affords the azomethine ylide, which regioselectively adds to the C=C bond of acrylamide or aroylacrylic acid.

Since the stereochemistry of the cycloadducts **4a** and **6a** was clarified by a single-crystal X-ray analysis, the structures of the reacting systems – the azomethine ylide and dipolarophiles (acrylamide and benzoylacrylic acid) – were investigated computationally. The geometrical structures of all possible conformers of the reacting systems were optimized using M06-2X [37] theory with the cc-pVTZ basis set [38] in the GAUSSIAN09 program [39]. The character of stationary points on the potential energy surface was verified by calculations of vibrational frequencies within the harmonic approximation, using analytical second derivatives at the same level of theory. All stationary points possess zero imaginary frequencies. It was found that the acrylamide conformer **I** was more stable than conformer **II** by 1.24 kcal/mol. The most stable conformation of benzoylacrylic acid possesses the benzoyl and carboxylic groups *trans* to each other (Figure 5).



Scheme 1: The mechanism of the regioselective synthesis of compounds **4** and **6**.

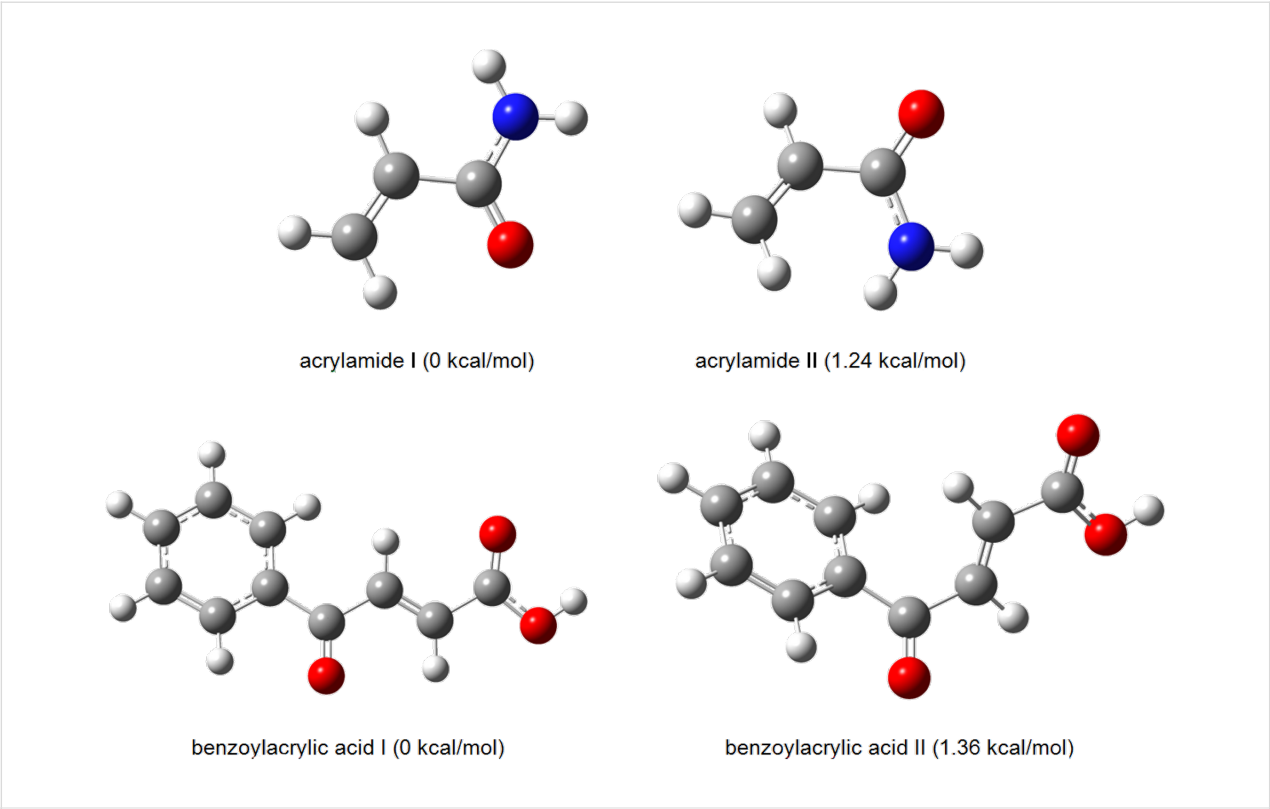


Figure 5: Conformations of acrylamide and benzoylacrylic acid.

The atom charges for the analysis of the Fukui function indices were calculated within the Natural Bonding Orbitals theory [40] with the NBO 5.0 program [41], that revealed the most reactive sites of the reagents. The reaction proceeds regioselectively with the addition of the most nucleophilic methylene group carbon of the azomethine ylide to the most electrophilic sites of the acrylamide and benzoylacrylic acid, which affords only one stereoisomer of cycloadducts **4** and **6** stereoselectively despite the presense of several stereocenters in the molecules (Figure 6).

For assigning structures of byproducts we carried out the reaction of isatins **1**, aroylacrylic acids **5** and proline in a boiling mixture of EtOH and water, which resulted in the formation and isolation of compounds **7a–7c** (Scheme 2). The unexpected structure of rearranged product **7a** was confirmed by ^{1}H, ^{13}C and 2D NMR spectroscopy (Table 3).

The main feature of the ^{13}C spectra of compounds **7a–7c** is the absence of the signal of the 3C-spiro nucleus. The ^{1}H NMR spectrum of compound **7a** displays a singlet at 5.30 ppm for the 7-CH of the dihydropyrrolizinyl moiety, which shows a H,H-NOESY correlation with a singlet at 4.56 ppm (3-CH of the oxindole ring) and HMBCs with 7a-C at 138.34 ppm. The singlet at 4.56 ppm of 3-CH of the oxindole ring shows H,H-COSY and H,H-NOESY correlations with a singlet at 7.05 ppm of 4-CH (oxindole ring) and HMBCs with 2-CO at 178.09 ppm, 4-C at 127.55 ppm and 6-C at 120.38 ppm (Figure 7). The NH proton of the oxindole ring gives a singlet at 10.59 ppm.

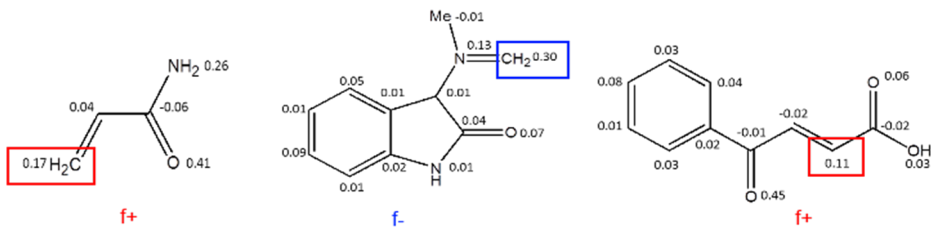
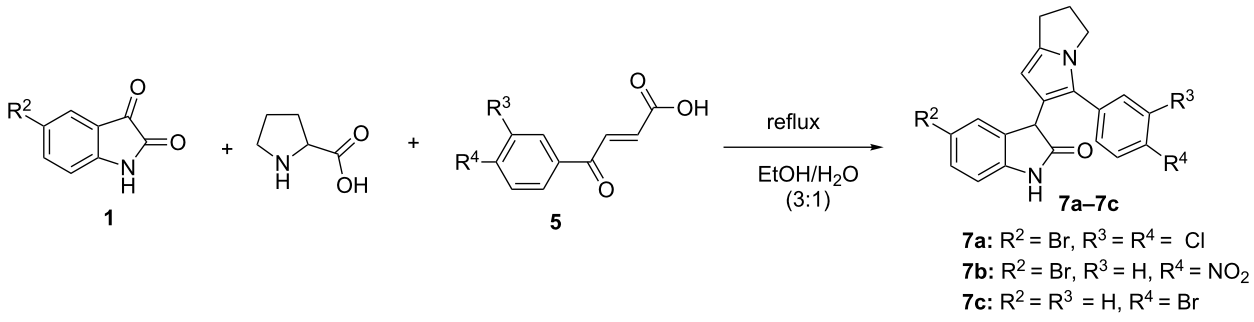


Figure 6: The Fukui function indices of acrylamide, azomethine ylide and benzoylacrylic acid.



Scheme 2: The synthesis of compounds **7a–7c**.

Table 3: ^{13}C and ^{1}H spectral data for compound **7a**.

entry	functional group	^{13}C	^{1}H		
		δ, ppm	δ, ppm	multiplicity	*J*, Hz
1	1-NH	–	10.59	s	–
2	2-CO	178.09	–	–	–
3	3-CH	45.33	4.56	s	–
4	3a-C (oxindole)	134.06	–	–	–
5	4-CH (oxindole)	127.55	7.05	s	–
6	5-C (oxindole)	113.56	–	–	–
7	6-CH (oxindole)	130.77	7.33	dd	8.1; 2.2
8	7-CH (oxindole)	111.57	6.80	d	8.1
9	7a-C (oxindole)	142.21	–	–	–
10	5-C	124.67	–	–	–
11	6-C	120.38	–	–	–
12	7-CH	99.69	5.30	s	–
13	7a-C	138.34	–	–	–
14	1-CH_2	24.43	2.85–2.63	m	–
15	2-CH_2	27.31	2.43–2.27	m	–
16	3-CH_2	46.26	4.20–4.02, 3.90–3.70	m	–
17	1-C Ar	129.50	–	–	–
18	2-CH Ar	129.87	7.82	d	1.8
19	3-C Ar	133.12	–	–	–
20	4-C Ar	131.63	–	–	–
21	5-CH Ar	130.95	7.65	d	8.1
22	6-CH Ar	128.44	7.55	dd	8.2; 1.8

The tentative mechanism for the formation of **7a** is outlined in Scheme 3. First, the initially formed spiropyrrolizidine undergoes decarboxylation via ring opening of the spiro cycle. The subsequent enolization of the intermediate leads to the formation of the dihydropyrrolizinyl oxindole system.

Conclusion

The 1,3-dipolar cycloaddition of azomethine ylides generated in situ from isatins and sarcosine or cyclic amino acids to acrylamides or aroylacrylic acids afforded regio- and stereoselectively the spirooxindoles **4** and **6** in moderate to good yields. The selectivity of the three-component condensation of isatins and α-amino acids with aroylacrylic acids can be controlled by the reaction temperature and the reaction medium. While spiro cycloadducts can be obtained in methanol dihydropyrrolizinyl oxindoles are formed in aqueous ethanol media at higher temperatures. Therefore, reactions involving aroylacrylic acids as substrates can afford the product in a regiocontrolled manner.

Experimental

Reagents and analytics: The ^{1}H NMR spectra were recorded on Varian Mercury VX-200 (200 MHz) and Bruker Avance

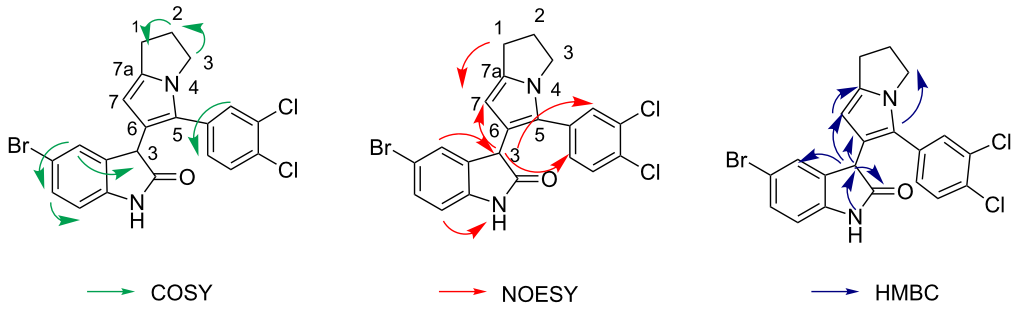
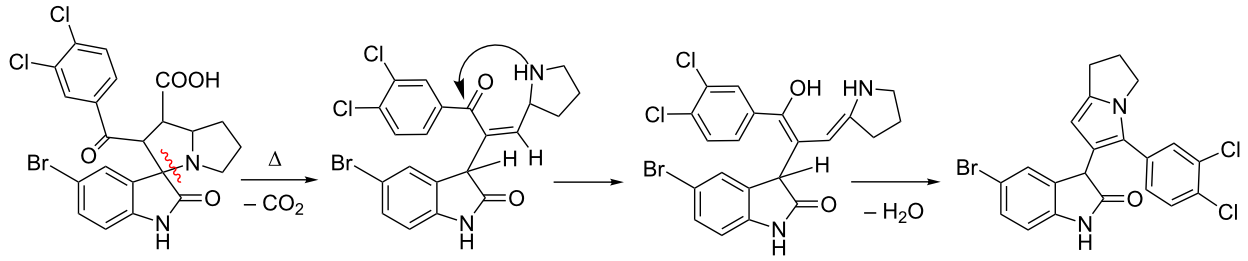


Figure 7: The selected COSY, NOESY and HMBC correlations of the signals in the ^{1}H and ^{13}C NMR spectra of compound **7a**.



Scheme 3: Tentative reaction mechanism for the decarboxylative cyclative rearrangement of the initial three-component product.

DRX-500 (500 MHz) instruments in DMSO-d_6 with TMS as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (125 MHz) and Bruker AM-300 (75 MHz) instruments in DMSO-d_6 with TMS as an internal standard. The COSY, NOESY, HSQC, and HMBC spectra were recorded using the standard procedure with gradient separation of the signal. The mass spectra were recorded on a Varian 1200L GC–MS instrument, ionization by EI at 70 eV. Elemental analysis was carried out on an EA 3000 Eurovector elemental analyzer. Melting points were determined on a Kofler hot bench. The progress of reactions and also the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates with acetone/heptane (4:1) as an eluent. Commercially available reagents and solvents were used without further purification. The aroylacrylic acids **5** were prepared according to the previously reported procedure [42].

General procedure for the synthesis of spirooxindoles 4a–4g from the three-component reaction of isatins, sarcosine or cyclic α-amino acids and acrylamides: A mixture of isatin (1.0 mmol), α-amino acid (1.0 mmol) and acrylamide (1.0 mmol) in 4.0 mL aqueous methanol (1:3) was heated in an oil bath to reflux temperature for 40 min to 7 hours. The resulting precipitates were collected by filtration and washed with cold methanol to give the analytically pure products **4**. **4a:** colorless solid, 31%, mp 260–262 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.42 (s,1H, 1-NH), 7.32 (dd, J = 8.2, 1.8 Hz, 1H, 6-CH), 7.21 (d, J = 1.8 Hz, 1H, 4-CH), 7.11 (s, 1H, NH-amide), 6.74 (s, 1H, NH-amide), 6.70 (d, J = 8.1 Hz, 1H, 7-CH), 3.11–2.99 (m, 2H, 4'-CH_2), 2.99–2.89 (m, 1H, 3'-CH), 2.38–2.26 (m, 1H, 5'-CH_2), 2.13–1.98 (m, 1H, 5'-CH_2), 1.91 (s, 3H, 1'-NCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.03 (2-CO), 170.35 ($CONH_2$), 142.38, 131.75, 129.77, 127.23, 112.27, 111.06, 72.26 (C-spiro), 56.51, 48.56, 34.38, 25.44; MS (m/z) (%): 325/323 (M^+, 19/20), 295/292 (59/78), 280/278 (97/100), 252/250 (54/38), 131/129 (15/43), 57 (78); anal. calcd for $C_{13}H_{14}BrN_3O_2$ (324.17): C 48.17, H 4.35, N 12.96; found: C 48.19, H 4.40, N 12.99.

General procedure for the synthesis of spirooxindoles 6a–6h from the three-component reaction of isatins, sarcosine or proline and aroylacrylic acids: A mixture of isatin (1.0 mmol), α-amino acid (1.0 mmol) and aroylacrylic acid (1.0 mmol) in 4.0 mL aqueous methanol (1:3) was heated in an oil bath to reflux temperature for about 20 min or stirred at room temperature for 25 min to 12 hours. The resulting precipitates were collected by filtration and washed with cold methanol to give the analytically pure products **6**. **6a:** colorless solid, 50%, mp 240–242 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.81 (s, 1H, 4'-COOH), 10.65 (s, 1H, 1-NH), 7.63 (d, J = 8.4 Hz, 1H, 5-CH (dichlorobenzoyl)), 7.44 (s, 1H, 2-CH (dichlorobenzoyl)), 7.36 (d, J = 8.4 Hz, 1H, 6-CH (dichlorobenzoyl)), 7.21 (d, J = 8.1 Hz, 1H, 6-CH), 6.96 (s, 1H, 4-CH), 6.44 (d, J = 8.4 Hz, 1H, 7-CH), 4.51 (d, J = 9.2 Hz, 1H, 3'-CH),

3.99 (q, J = 8.4 Hz, 1H, 4'-CH), 3.32–3.12 (m, 2H, 5'-CH_2), 1.96 (s, 3H, 1'-NCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 195.09 (CO-benzoyl), 177.42 (2-CO), 173.16 (4'-COOH), 141.26, 136.44, 132.08, 131.70, 130.95, 130.32, 129.02, 128.55, 128.20, 127.13, 113.55, 111.33, 72.27 (C-spiro), 56.54, 54.66, 42.96, 34.40; anal. calcd for $C_{20}H_{15}BrCl_2N_2O_4$ (498.15): C 48.22, H 3.04, N 5.62; found: C 48.17, H 3.10, N 5.67.

General procedure for synthesis of compounds 7a–7c from the three-component reaction of isatins, proline and aroylacrylic acids: A mixture of isatin (1.0 mmol), proline (1.0 mmol) and aroylacrylic acid (1.0 mmol) in 4.0 mL aqueous ethanol (1:3) was heated in an oil bath to reflux temperature for 15 min. The resulting precipitates were collected by filtration and washed with cold ethanol to give analytically pure products **7**. **7a**: orange powder, 22%, mp 215–216 °C. ^{1}H (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) data are given in Table 3. MS (m/z) (%): 462 (M^+, 52), 435 (45), 405 (8), 353 (12), 317 (18), 289 (52), 208 (30), 173 (33), 127 (46), 75 (30), 41 (100); anal. calcd for $C_{21}H_{15}BrCl_2N_2O$ (462.17): C 54.57; H 3.27; N 6.06; found: C 54.48; H 3.19; N 6.10.

Experimental part of X-ray diffraction study

The colourless crystals of **4a** ($C_{13}H_{14}N_3O_2Br$) are triclinic. At 293 K, a = 6.9659(3), b = 7.5441(4), c = 13.4092(5) Å, α = 90.994(4)°, β = 90.947(4)°, γ = 106.218(5)°, V = 676.36(5) Å^3, M_r = 324.18, Z = 2, space group $P\bar{1}$, d_{calc} = 1.592 g/cm^3, μ(Mo K_α) = 3.040 mm^{-1}, F(000) = 328. Intensities of 6411 reflections (3942 independent, R_{int} = 0.018) were measured on an «Xcalibur-3» diffractometer (graphite monochromated Mo K_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°).

The colourless crystals of **6a** ($C_{21}H_{19}N_2O_5BrCl_2$) are triclinic. At 293 K, a = 8.8751(7), b = 10.5764(9), c = 12.352(1) Å, α = 75.858(5)°, β = 84.297(5)°, γ = 76.237(5)°, V = 1091.0(2) Å^3, M_r = 530.19, Z = 2, space group $P\bar{1}$, d_{calc}= 1.614 g/cm^3, μ(Mo K_α) = 2.165 mm^{-1}, F(000) = 536. Intensities of 15460 reflections (3842 independent, R_{int} = 0.043) were measured on an «Xcalibur-3» diffractometer (graphite monochromated Mo K_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 50°).

The structures were solved by direct methods using the SHELXTL package [43]. The absorption correction was performed using the multi-scan method (T_{min} = 0.582, T_{max} = 0.751 for **4a** and T_{min} = 0.563 T_{max} = 0.671 for **6a**). Position of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for methyl and hydroxy groups and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for non-hydrogen atoms using 3908 (**4a**), 3801 (**6a**) reflections was converged to: wR_2 = 0.111 (R_1 = 0.046 for 2795 reflections with F>4σ(F), S = 1.049) for structure **4a** and wR_2 = 0.110 (R_1 = 0.043 for 2435 reflections with F>4σ(F), S = 1.055) for structure **6a**. The final atomic coordinates, and crystallographic data for molecules **4a** and **6a** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 964021 for **4a** and CCDC 972494 for **6a**).

Supporting Information

Supporting Information File 1

Spectroscopic and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-8-S1.pdf]

Supporting Information File 2

X-ray diffraction data description for compounds **4a** and **6a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-8-S2.pdf]

Supporting Information File 3

Crystallographic information file for compound **4a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-8-S3.cif]

Supporting Information File 4

Crystallographic information file for compound **6a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-8-S4.cif]

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Organobase-catalyzed three-component reactions for the synthesis of 4*H*-2-aminopyrans, condensed pyrans and polysubstituted benzenes

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Full Research Paper

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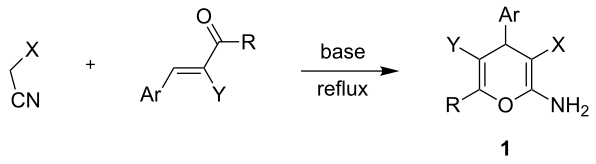
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Abstract

Novel routes for the preparation of 2-amino-4*H*-pyran-3-carbonitrile **9**, amino-arylbenzoic acid ester derivatives **13a**,**b**, 2-aminotetrahydro-4*H*-chromene-3-carbonitrile **18**, 3-amino-4-cyanotetrahydronaphthalene-2-carboxylic acid ester **26** and 4-amino-3,5-dicyanophthalic acid ester derivatives **37a–c** were developed. The synthetic methods utilize one-pot reactions of acetylene carboxylic acid esters, α,β-unsaturated nitriles and/or active methylenenitriles in the presence of L-proline or DABCO. Plausible mechanisms are suggested for the formation of the products. Finally, these compounds were used for the efficient synthesis of 6-amino-5-cyanonicotinic acid ester derivatives **31a**,**b**, ethyl 4-amino-5*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylates **33a**,**b**, 4-amino-6*H*-pyrrolo[3,4-*g*]quinazoline-9-carbonitrile **39**, and 1,7-diamino-6-(*N*'-hydroxycarbamimidoyl)-3-oxo-5-phenyl-3*H*-isoindole-4-carboxylate (**40**).

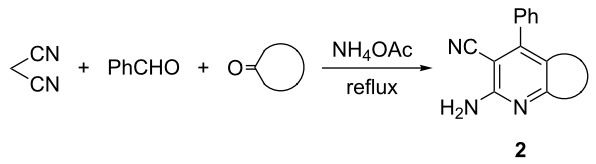
Introduction

The reaction of arylidenemalononitriles with active methyl and methylene compounds was extensively utilized for the syntheses of otherwise non-readily obtainable pyrans [1-3], pyridines [3-5] and polysubstituted aromatics [6,7]. The synthesis of 2-amino-4*H*-pyrans by these reactions has recently been surveyed. Since the first report describing the preparation of 2-amino-4*H*-pyrans by the addition of active methylenenitriles to α,β-unsaturated ketones [8], 2-amino-4*H*-pyrans **1** (Scheme 1) have become the central focus of a number of chemical and biological investigations [9,10].



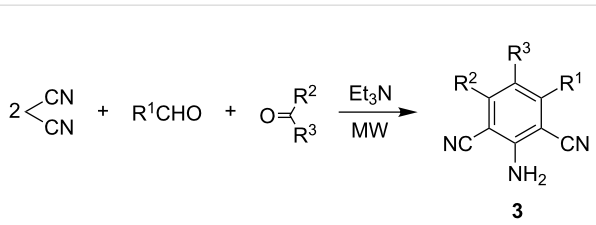
Scheme 1: Reaction of active methylenenitriles with α,β-unsaturated ketones **1**.

Perez et al. recently reported an interesting method for the synthesis of condensed pyridines **2** through a three-component reaction of malononitrile with benzaldehyde and cyclic ketones [11] (Scheme 2).



Scheme 2: Synthesis of 2-amino-4-phenyl-3-cyanopyridines **2**.

In contrast, MW-irradiation-promoted reactions of ketones, aldehydes and malononitrile are known to afford polysubstituted benzenes **3** (Scheme 3) [12].



Scheme 3: Synthesis of polysubstituted benzenes **3**.

Elnagdi et al. reported [13] that reaction of alkyl azenyl carbonitrile with arylidene malononitrile afforded benzo-fused azenes. Based on these studies several surveys were published during the last decade [10,14-19].

Results and Discussion

Very recently we reported that the reaction of dimethylacetylene dicarboxylate (DMADC) with benzylidenemalononitrile afforded 2-amino-4*H*-pyran **9** and that the yield of the process can be improved if equimolar amounts of DMADC, benzylidenemalononitrile and malononitrile are used [20]. Similar observations have been made in previous studies of these reactions using 1-methylimidazole [21]. Recently we observed that 2-amino-4*H*-pyran **9** can be generated using a one-pot reaction involving condensation of ethyl propiolate (**4a**) with benzylidenemalononitrile (**7a**) in the presence of L-proline (**5**) (Scheme 4) [4].

It is believed that the pathway followed in this process involves conjugate addition of proline to the propiolate to yield adduct **6** which then reacts with **7a** to form the enamino ester **8a**. Hydrolysis of **8a** followed by cyclization affords **9** in 85% yield. The structure of **9** was unambiguously assigned by X-ray crystallographic methods (Figure 1).

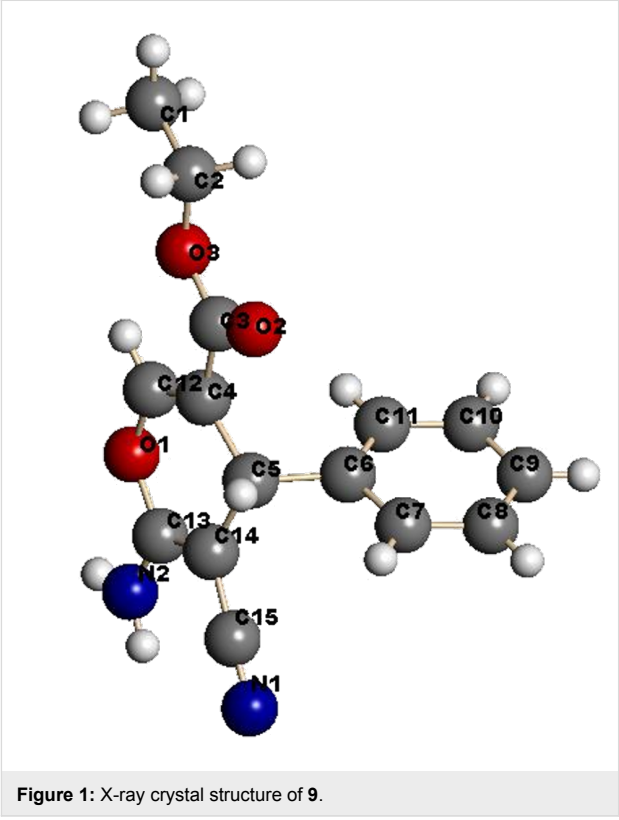
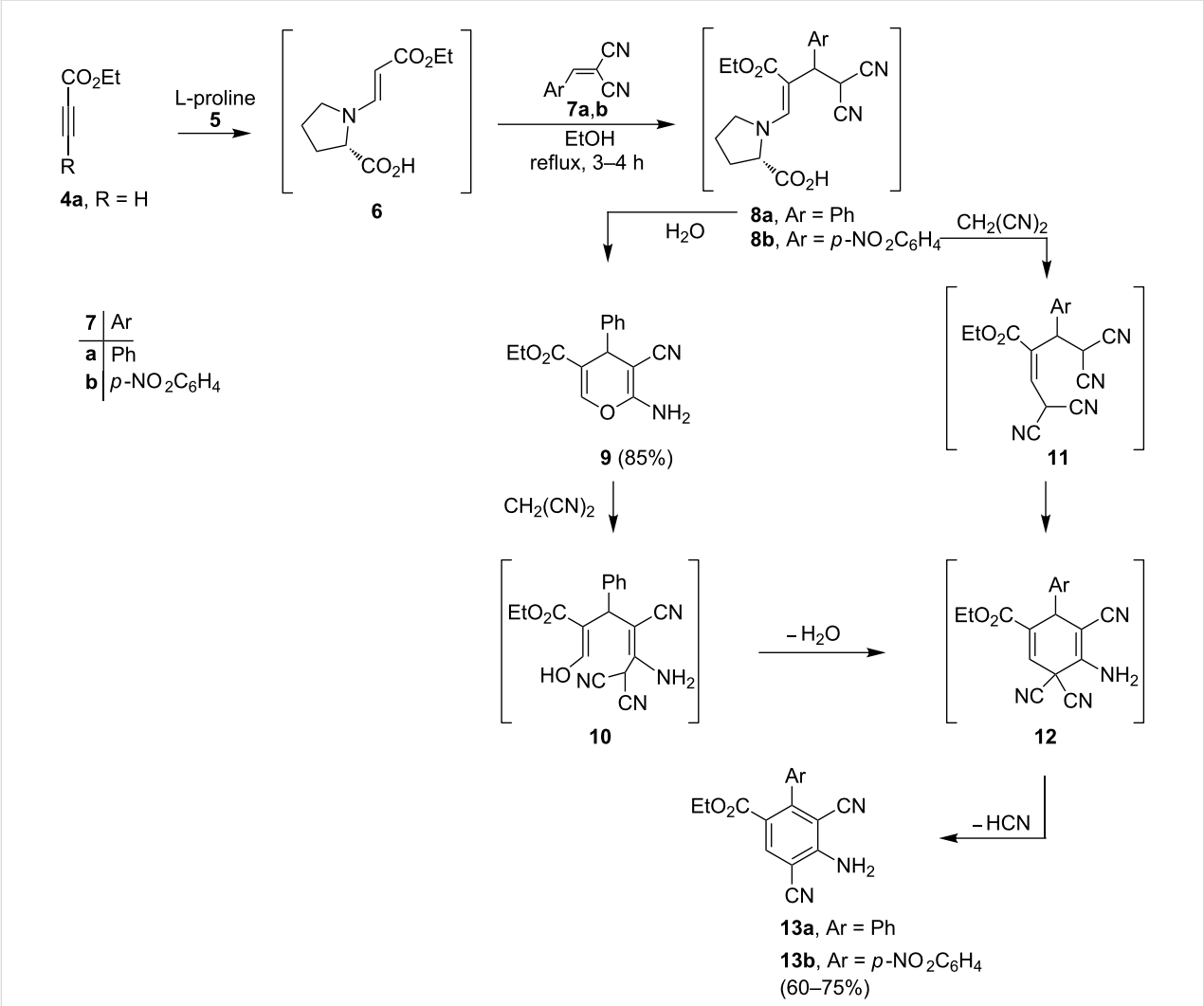


Figure 1: X-ray crystal structure of **9**.

In contrast, we found that the *p*-nitrophenyl-substituted analogue **7b** reacts with ethyl propiolate (**4a**) in the presence of L-proline to produce the penta-substituted benzene derivative **13b** in 60% yield (Scheme 4). In order to explain this unusual finding, we proposed that malononitrile, perhaps formed under the reaction conditions by C–C bond cleavage promoted fragmentation of **8**, adds to **9** to generate **10** that cyclizes to form **12**. Subsequent aromatization of **12** produces the benzoate derivative **13b**. Alternatively, **8** could react with malononitrile to yield **11** that then serve as a precursor to **13** (Scheme 4). In support of the former mechanistic proposal, it was observed that 2-amino-4*H*-pyran **9** reacts with malononitrile to yield **13a** (Scheme 4), whose structure was unambiguously assigned by X-ray crystallographic analysis (Figure 2).



Scheme 4: Syntheses of compound **9** and compounds **13a**,**b**.

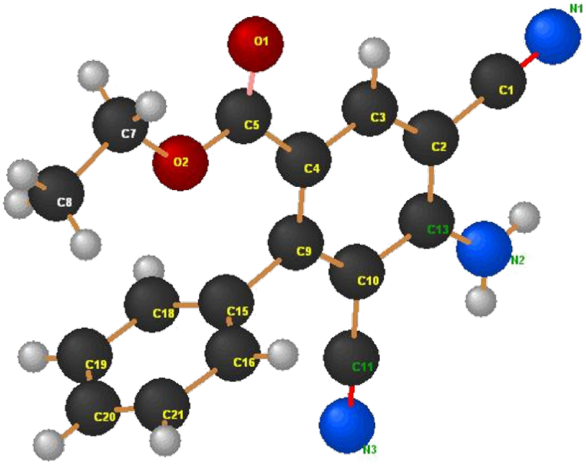


Figure 2: X-ray crystal structure of **13a**.

This finding led to the development of a procedure for the high yielding preparation of **13b** that involves the addition of one equivalent of malononitrile to the reaction mixture containing ethyl propiolate (**4a**) and **7b**.

The observations described above prompted us to extend the synthetic potential of these types of condensation reactions. In the following studies, we found that 5,5-dimethylcyclohexane-1,3-dione (**14**) reacts with enaminonitrile **15** and malononitrile in the presence of L-proline or DABCO to yield the 2-amino-4*H*-pyran **18** whose structure was assigned by X-ray crystallographic methods (Figure 3).

We assumed that in this process **14** and **15** undergo an initial condensation to yield dione **16** that reacts with malononitrile to afford adduct **17**, which subsequently cyclizes to produce **18**. It is of value to note that, when the reaction of **14** and **15** is

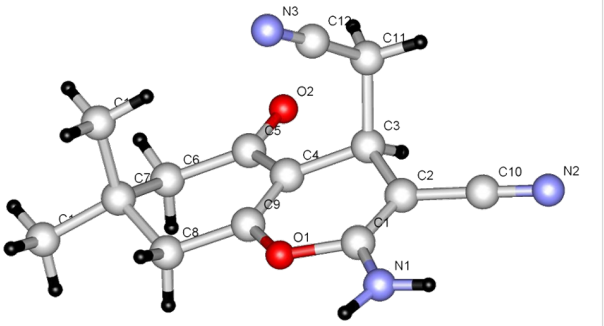
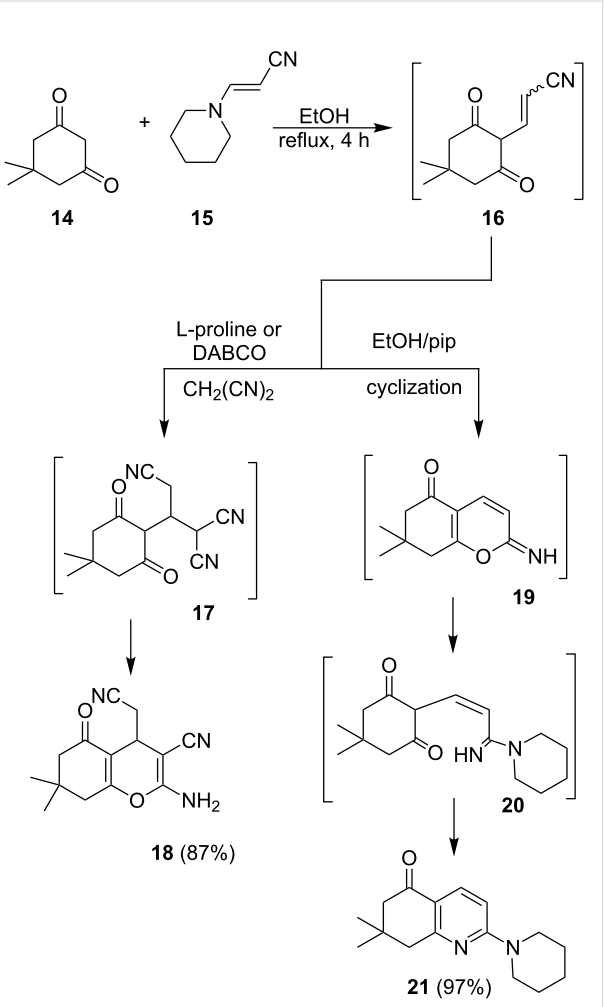


Figure 3: X-ray crystal structure of **18**.

conducted in the absence of malononitrile, dihydroquinolinone **21** is generated through a pathway involving the intermediate imines **19** and **20** (Scheme 5). The structure of **21** was determined by X-ray crystallographic methods (Figure 4).



Scheme 5: Syntheses of compounds **18** and **21**.

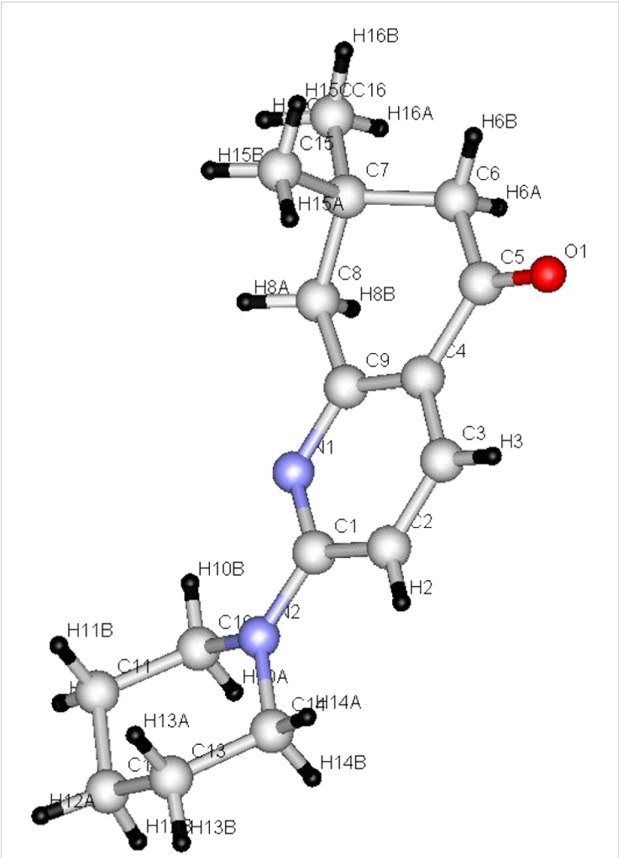


Figure 4: X-ray crystal structure of **21**.

An attempt to prepare the bicyclic 2-amino-4*H*-pyran **24** by the reaction of dione **14** with ethyl propiolate (**4a**) in the presence of malononitrile and L-proline or DABCO was not successful. Instead, these substances reacted to the fused benzoic acid ester **26**, which was characterized by X-ray crystallography (Figure 5).

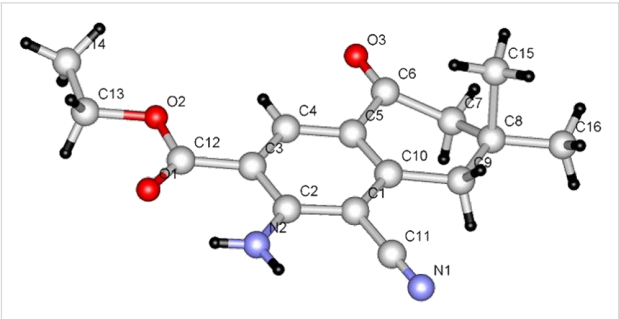
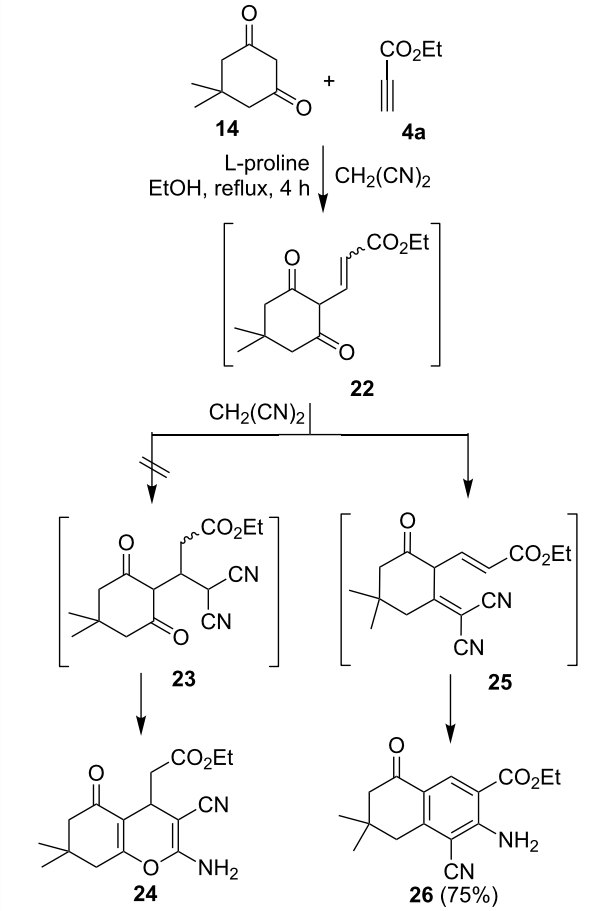


Figure 5: X-ray crystal structure of **26**.

It appears that in this process, ethyl propiolate (**4a**) reacts with dione **14** initially to form adduct **22** which then adds to malononitrile to produce **25**. The latter undergoes cyclization to afford **26** (Scheme 6).



Scheme 6: Syntheses of compound **26**.

It is interesting that the 2-amino-4*H*-pyrans, generated in the reactions described above, serve as excellent precursors to uniquely substituted nicotinate derivatives. For example, both pyrans **9a** and **9b** [22] react with hydroxylamine hydrochloride in ethanolic solutions containing sodium acetate to yield the respective amidoximes **27a** and **27b**. The structures of these compounds were assigned by X-ray crystallographic methods (Figure 6). In addition, these substances can be transformed to the corresponding ethyl 6-amino-5-carbamoyl-4-phenylnicotinate derivatives **28a** and **28b** by stirring in refluxing DMF (Scheme 7, Figure 7).

Furthermore, **9a** and **9b** rearrange to the corresponding nicotinic acid derivatives **31a** and **31b** when they are stirred in refluxing acetic acid containing ammonium acetate. The structures of both of the products were assigned by employing X-ray crystallographic methods (Figure 8 and Figure 9).

We believe that the nicotinic acid esters are generated in these reactions by ring opening of **9a** and **9b** to yield the respective amidines **29a** and **29b**, which then cyclize to produce **30a** and

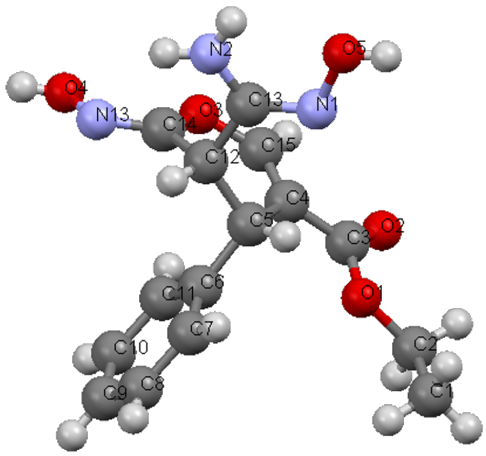
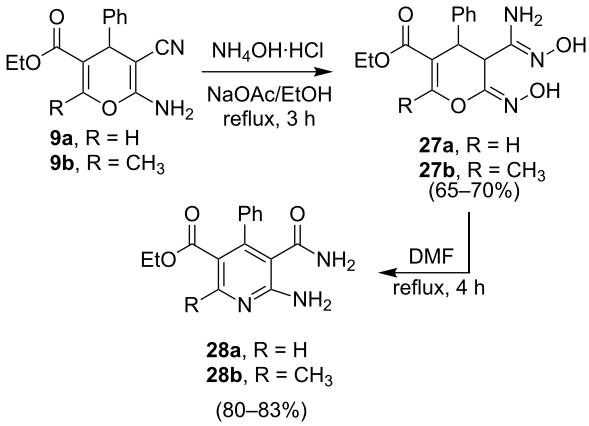


Figure 6: X-ray crystal structure of **27a**.



Scheme 7: Syntheses of compound **28a**,**b**.

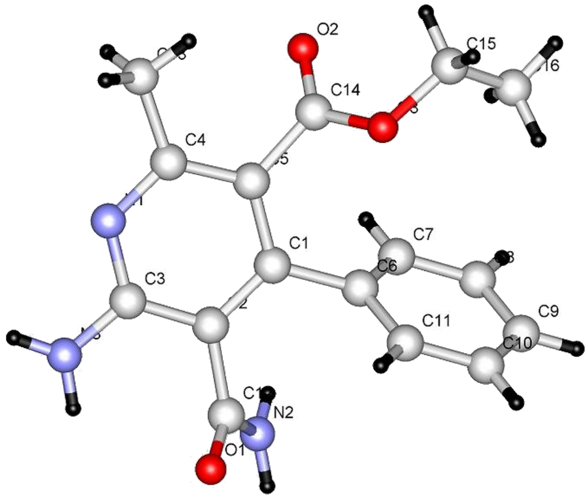


Figure 7: X-ray crystal structure of **28b**.

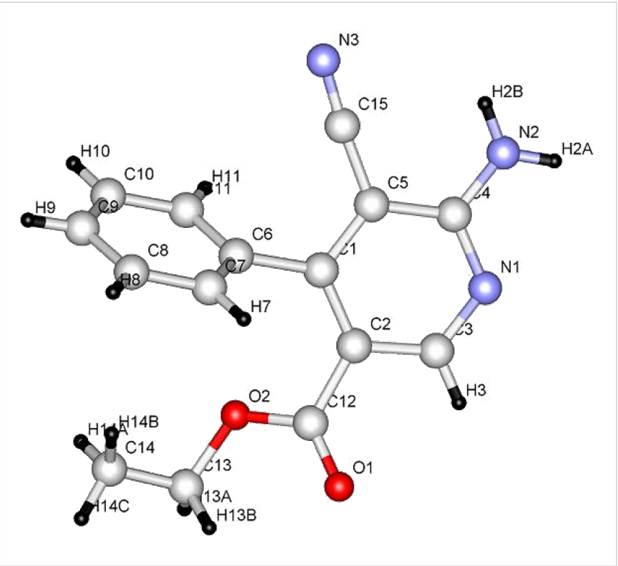


Figure 8: X-ray crystal structure of **31a**.

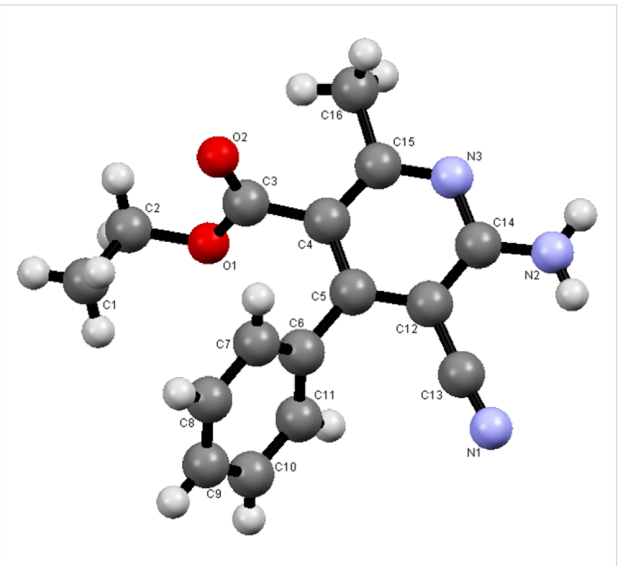
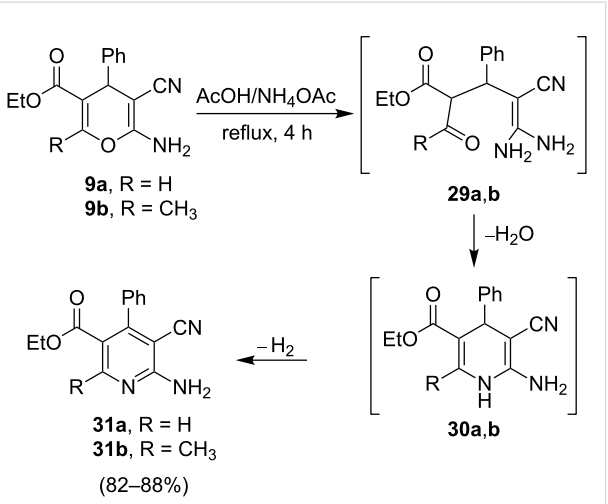


Figure 9: X-ray crystal structure of **31b**.

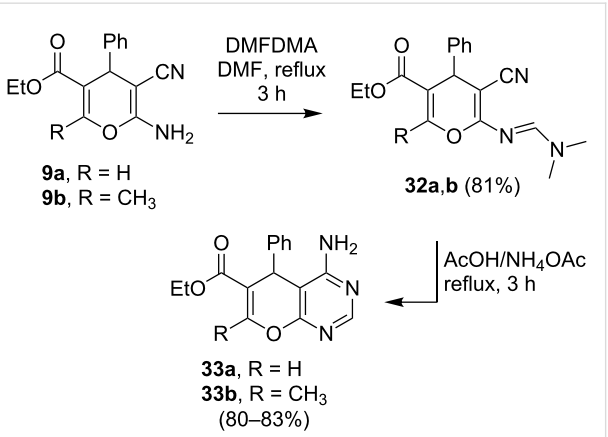
30b. The latter compounds readily undergo autooxidation to form **31a** and **31b** (Scheme 8).

Finally, the pyranopyrimidines **33a** and **33b** were efficiently produced by a sequence including an initial condensation reaction of the 2-amino-4*H*-pyrans **9a** and **9b** with dimethylformamide dimethylacetal (DMFDMA) to yield the amidine-substituted derivatives **32a** and **32b**. Stirring solutions of these substances in refluxing AcOH/NH_4OAc gave the respective pyranopyrimidines **33a** and **33b** (Scheme 9, Figure 10).

In an exploratory study aimed at expanding the chemistry shown in Scheme 4, we observed that diethyl acetylenedicar-



Scheme 8: Syntheses of compound **31a**,**b**.



Scheme 9: Syntheses of compound **33a**,**b**.

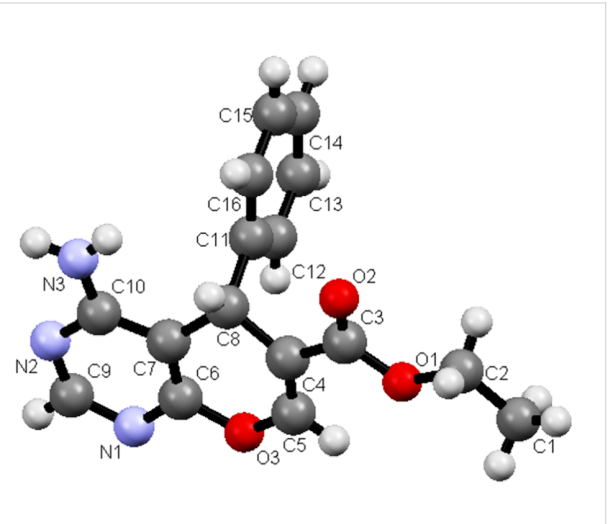
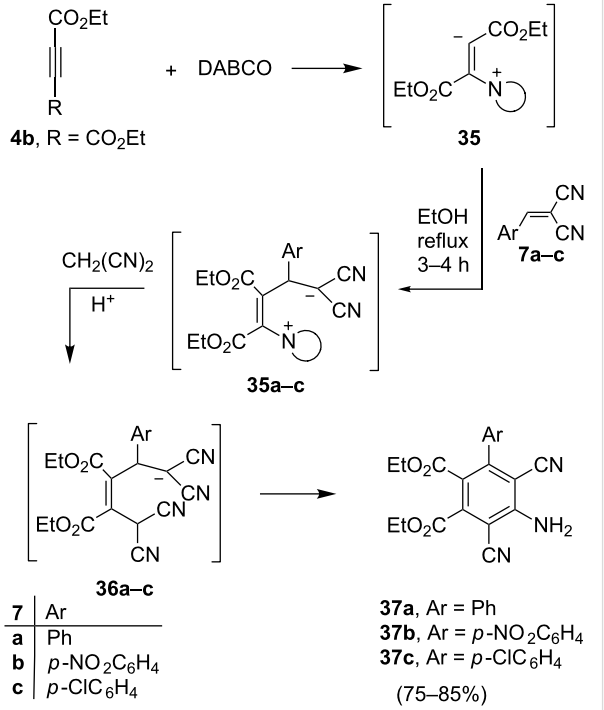


Figure 10: X-ray crystal structure of **33a**.

boxylate (DEAD, **4b**) does not react with benzylidenemalononitrile (**7a**) in the presence of L-proline. However, when DABCO was employed as the amine nucleophile, reaction of DEAD with **7a** readily took place and the substituted phthalate diester **37a** was obtained in 80% yield. The structure of **37a** was determined by X-ray crystallographic analysis (Scheme 10 and Figure 11).



Scheme 10: Syntheses of compound **37a–c**.

In a similar fashion, DEAD was observed to react with the *p*-nitro- and *p*-chloro-benzylidenemalononitriles **7b** and **7c** in the presence of DABCO to yield the corresponding phthalate diesters **37b** and **37c** (Figure 12).

A plausible mechanistic route for the formation of **37a** involves an initial addition of DABCO to DEAD to yield the intermediate zwitterionic enammonium diester **34**, which then adds to **7a** to produce zwitterion **35a**. Reaction of **35a** or its protonated form with malononitrile, which is likely generated by hydrolysis of **7a**, then forms **36a** that cyclizes and aromatizes by loss of HCN to yield **37a**. This sequence is closely related to the one described above for the formation of benzoic acid derivatives **13a** and **13b** (Scheme 6). Although they have potential utility in the field of polymer chemistry, to the best of our knowledge the preparation and chemical reactivity of only a few tetrasubstituted phthalic acid diesters have been described previously. In this effort, we observed that phthalate **37a** reacts with

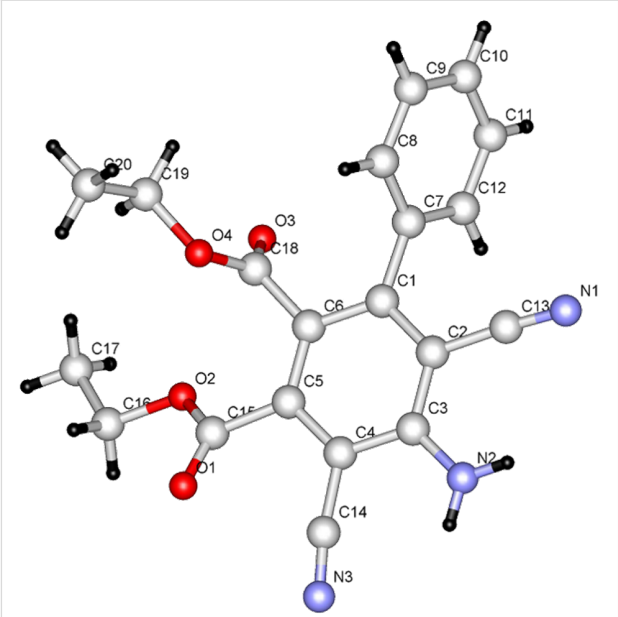


Figure 11: X-ray crystal structure of **37a**.

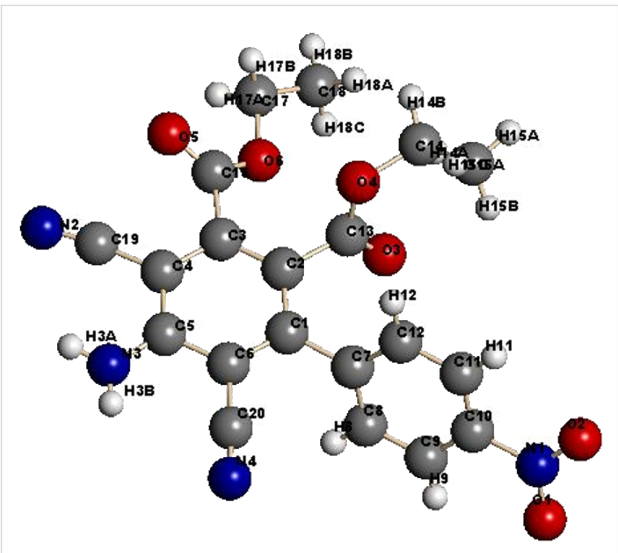
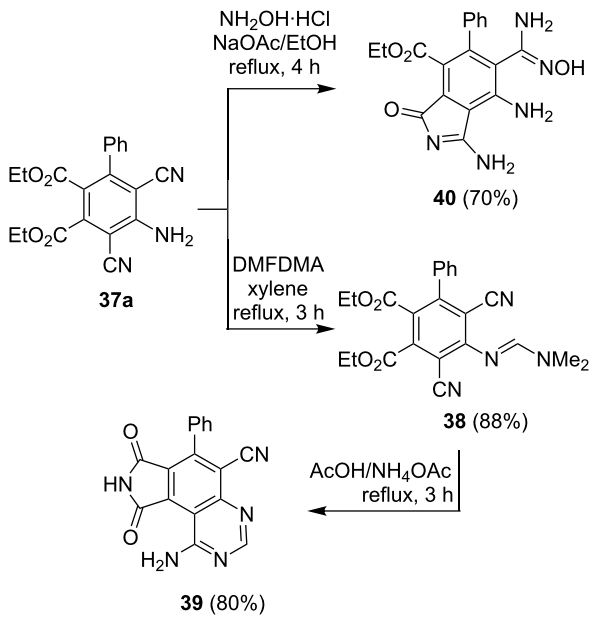


Figure 12: X-ray crystal structure of **37b**.

DMFDMA to form amidine **38**, which undergoes cyclization in refluxing AcOH/NH_4OAc to form the 1-amino-pyrrolo[3,4-*f*]quinazoline **39**. We also found that **37a** reacts with hydroxylamine hydrochloride in ethanolic sodium acetate solution to form isoindolone derivative **40** (Scheme 11 and Figure 13).

Conclusion

In the current investigation, we have developed new and efficient methods for the synthesis of polyfunctionalized 2-amino-4*H*-pyrans and aminobenzoic acids. In addition, we have explored the preparative potential of these substances as inter-



Scheme 11: Syntheses of compounds **38–40**.

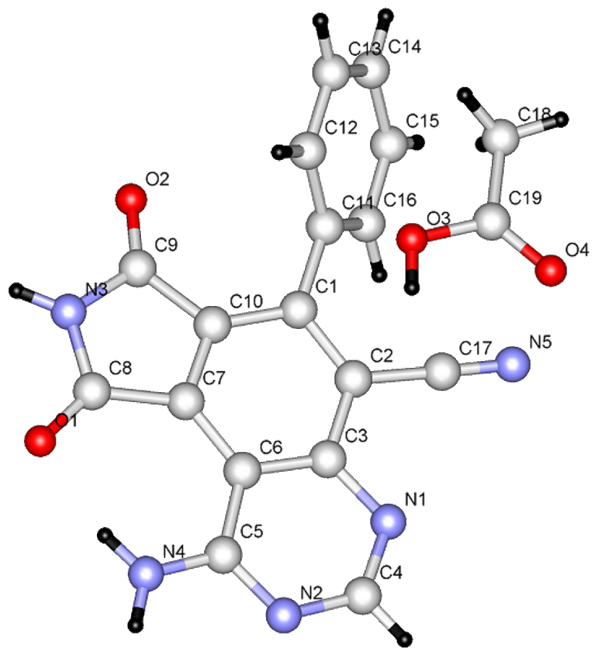


Figure 13: X-ray crystal structure of **39**.

mediates for the synthesis of 6-amino-5-cyanonicotinic acid derivatives **31a**,**b**, ethyl 4-amino-5*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylates **33a**,**b**, 4-amino-6*H*-pyrrolo[3,4-*g*]quinazoline-9-carbonitrile **39**, and 1,7-diamino-6-(*N*'-hydroxycarbamimidoyl)-3-oxo-5-phenyl-3*H*-isoindole-4-carboxylate **40**.

Supporting Information

Supporting Information File 1

Experimental.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-11-S1.pdf]

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One-pot synthesis of cyanohydrin derivatives from alkyl bromides via incorporation of two one-carbon components by consecutive radical/ionic reactions

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Letter

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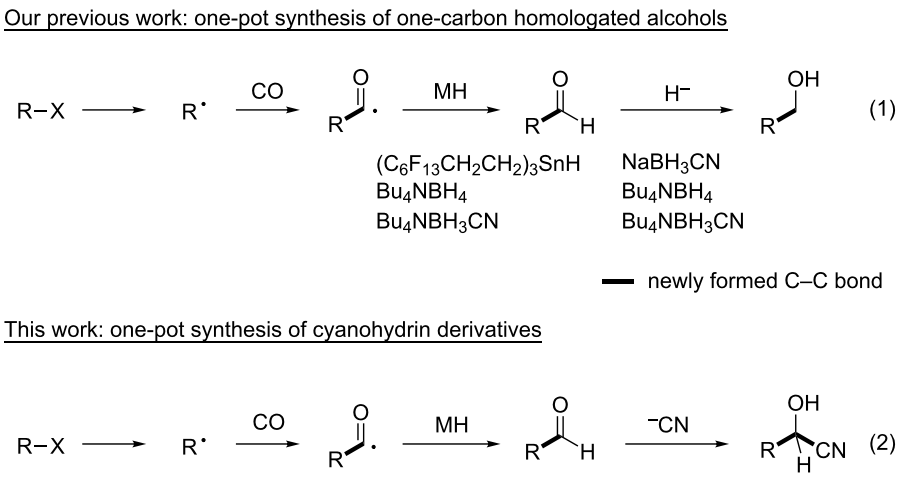
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Abstract

The consecutive radical/ionic reaction consisting of radical formylation of alkyl bromides and nucleophilic addition of a cyanide ion was investigated, which gave moderate to good yields of cyanohydrin derivatives in one-pot.

Introduction

Radical carbonylation reactions have been recognized as a versatile tool for the synthesis of a wide variety of carbonyl compounds [1-4]. In 1990, we demonstrated that aldehydes can be prepared from alkyl or aromatic halides and CO under typical radical chain reaction conditions using tributyltin hydride and AIBN [5,6]. Under the reaction conditions where a catalytic amount of fluorous tin hydride and an excess amount of sodium cyanoborohydride were used, initially formed aldehydes can be converted into hydroxymethylated compounds in one-pot [7-9], since borohydride acts not only as the reagent for the regeneration of tin hydride [10-13] but also as the reagent for aldehyde reduction. Later on we found that borohydride reagents can also serve as radical mediator delivering hydrogen to the radical centre [14], thus we developed a hydroxymethylation method using Bu_4NBH_4 and a radical initiator [15-17]. Recent work in collaboration with Dennis Curran has revealed that, with the use of NHC-borane [18], hydroxymethylation of aromatic iodides can be attained [19]. All these reactions consist of the combination of radical formylation with CO and ionic hydride reduction by hydride reagents (Scheme 1, reaction 1). During the course of our study on borohydride-mediated radical hydroxymethylation of alkyl halides with CO, we found that cyanohydrin was obtained as a byproduct when Bu_4NBH_3CN was used as a radical mediator [15], which led us to investigate the one-pot synthesis of cyanohydrins based on radical formylation. Thus, we thought that the two step radical/ionic reactions



Scheme 1: Sequential radical formylation and derivatization.

can be extended to the consecutive C–C bond forming reactions.

Cyanohydrins are important subunits frequently found in biologically active compounds and are also versatile building blocks for further synthetic transformations [20,21]. The common method to obtain cyanohydrins is the reaction of aldehydes with a cyanide sources such as TMSCN [22,23], ethyl cyanoformate [24-26] or acyl cyanide [27,28]. We provide here an efficient one-pot method for the synthesis of cyanohydrin derivatives via consecutive radical/ionic C–C bond forming reaction of alkyl bromides, CO and ethyl cyanoformate (Scheme 1, reaction 2).

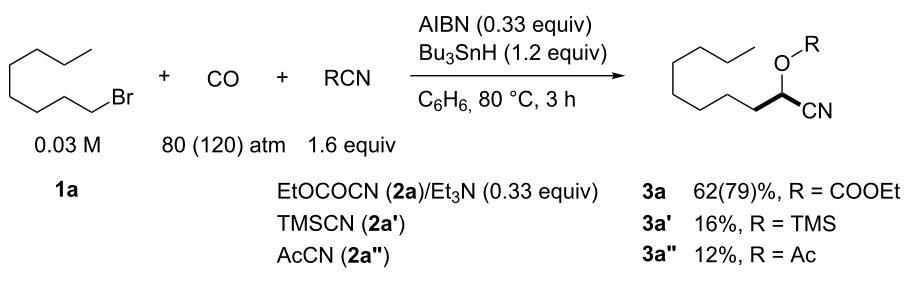
Results and Discussion

We examined AIBN-induced radical formylation of 1-bromooctane (**1a**) with Bu_3SnH under 80 atm of CO pressure in the presence of a cyanide source (Scheme 2). Under the employed conditions, the reaction using TMSCN (**2a'**) was slow, which gave 16% of **3a'** and 51% of nonanal. The use of AcCN (**2a''**) also gave **3a''** but only in 12% yield. However, when ethyl cyanoformate (**2a**) was used together with Et_3N [29], the cyanohydrin **3a** was obtained in 62% yield. When we used higher CO pressure such as 120 atm, the yield of **3a** increased to 79%.

We examined various alkyl bromides **1** in the present radical/ionic three-component coupling reaction (Table 1). Primary alkyl bromides **1b–e** containing a chlorine atom, an ester group, a cyano group, or a phenyl group worked well to give the corresponding cyanohydrin derivatives **3b–e** in good yields (Table 1, entries 2–5). The reaction of secondary and tertiary alkyl bromides **1f–i** also proceeded well to give the corresponding cyanohydrins **3f–i** in good yields (Table 1, entries 6–9). The reaction using cyclopropylmethyl bromide (**1j**) afforded the lowest yield of cyanohydrin **3j**, which possessed an olefin structure arising from the ring-opening of a cyclopropylcarbinyl radical (Table 1, entry 10) [30,31].

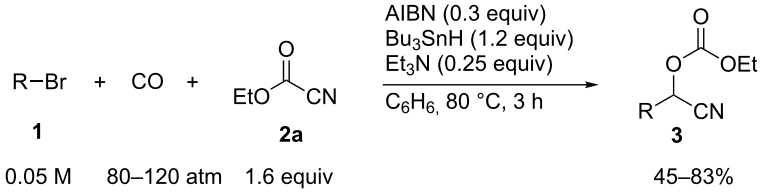
Conclusion

In summary, we have demonstrated a three-component coupling reaction comprising alkyl bromides **1**, CO and ethyl cyanoformate (**2a**) in the presence of Bu_3SnH, AIBN, and Et_3N, which



Scheme 2: Examination of cyanide source.

Table 1: Three-component coupling reaction leading to cyanohydrin derivatives.



1 **2a** **3**

0.05 M 80–120 atm 1.6 equiv 45–83%

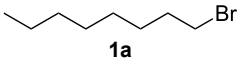
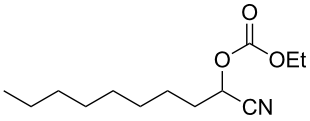
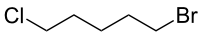
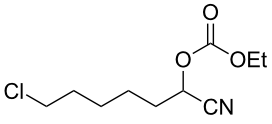
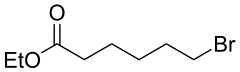
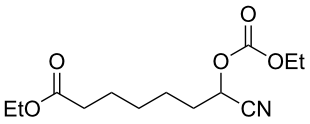
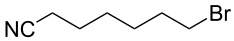
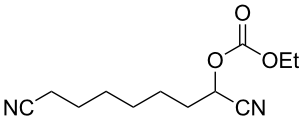
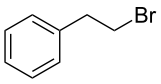
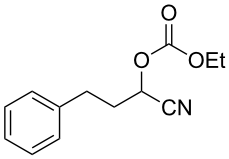
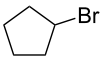
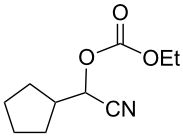
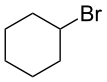
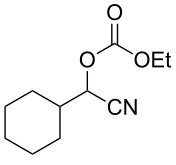
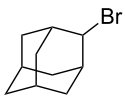
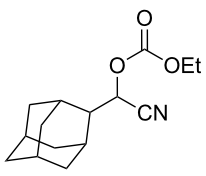
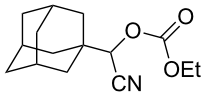
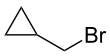
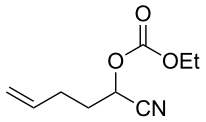
entry	alkyl bromide	CO (atm)	product	yield[a] (%)
1[b]	 **1a**	120	 **3a**	79
2	 **1b**	80	 **3b**	60
3	 **1c**	80	 **3c**	83
4	 **1d**	120	 **3d**	76
5	 **1e**	120	 **3e**	61
6	 **1f**	120	 **3f**	61
7	 **1g**	120	 **3g**	74
8	 **1h**	120	 **3h**	73

Table 1: Three-component coupling reaction leading to cyanohydrin derivatives. (continued)

9	 **1i**	110	 **3i**	82
10	 **1j**	110	 **3j**	45

[a]Isolated yield after flash chromatography on SiO_2. [b]0.03 M.

gave moderate to good yields of cyanohydrin derivatives **3**. This protocol represents a one-pot method [32,33] based on radical carbonylation and ionic cyanation.

Experimental

Typical procedure for radical/ionic three-component coupling reaction leading to cyanohydrin derivatives 1-cyanononyl ethyl carbonate (**3a**) [34] (Table 1, entry 1): A mixture of 1-bromooctane (**1a**, 96.6 mg, 0.5 mmol), ethyl cyanoformate (**2a**, 79.3 mg, 0.8 mmol), tributyltin hydride (174.6 mg, 0.6 mmol), triethylamine (13.2 mg, 0.13 mmol), and AIBN (24.6 mg, 0.15 mmol) in C_6H_6 (17 mL) were placed in a 100 mL stainless steel autoclave. The reaction mixture was degassed 3 times with 10 atm of CO and charged with 90 atm of CO at −40 °C (MeCN–dry ice bath). Then the autoclave was allowed to warm to room temperature, which caused the pressure gauge to indicate 120 atm. Then the reaction was conducted at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated and purified by silica gel flash chromatography (hexane/EtOAc 97:3) to afford **3a** (95.3 mg, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.18 (t, J = 6.8 Hz, 1H), 4.4–4.2 (m, 2H), 2.0–1.9 (m, 2H), 1.6–1.5 (m, 2H), 1.4–1.2 (m, 13H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.56, 116.51, 65.27, 64.66, 32.31, 31.68, 29.12, 28.99, 28.71, 24.34, 22.53, 14.05, 13.93.

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Synthesis and biological activity of *N*-substituted-tetrahydro-γ-carbolines containing peptide residues

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Abstract

The synthesis of novel peptide conjugates of *N*-substituted-tetrahydro-γ-carbolines has been performed using the sequence of the Ugi multicomponent reaction and Cu(I)-catalyzed click chemistry. The effect of obtained γ-carboline–peptide conjugates on the rat liver mitochondria was evaluated. It was found that all compounds in the concentration of 30 μM did onot induce depolarization of mitochondria but possessed some inhibitory effect on the mitochondria permeability transition. The original *N*-substituted-tetrahydro-γ-carbolines containing an terminal alkyne group demonstrated a high prooxidant activity, whereas their conjugates with peptide fragments slightly inhibited both autooxidation and the *t*-BHP-induced lipid peroxidation.

Introduction

The design and synthesis of new efficient pharmaceutical drugs for the treatment and prevention of a wide range of neurodegenerative diseases, such as Alzheimer's dementia, Parkinsonism and the amyotrophic lateral sclerosis, is of considerable interest in modern medicinal chemistry. Mitochondrial dysfunction was found to play a crucial role in the pathogenesis of these diseases [1-3]. Thus, one of the specific symptoms of such pathologies is a decrease in the ability of mitochondria to regulate the calcium homeostasis in cells and malfunction of mitochondrial permeability transition (MPT) that represents a key step in the

cascades of cell death. From this point of view, mitochondria and the MPT process are very attractive targets for the search of new neuroprotective agents [4,5].

Several promising mitochondria-targeting neuroprotectors have been reported in the literature. Thus, the antihistaminic drug dimebon [6,7], which relates to tetrahydro-γ-carboline derivatives, has been found to stabilize and improve mitochondrial functions in different in vivo and in vitro models [8,9] (Figure 1). Another promising class of neuroprotectors are cell-permeable mitochondria-targeting synthetic small peptides, for example, the SS (Szeto–Schiller) peptide antioxidants [10] (Figure 1). These peptides were found to scavenge hydrogen peroxide and peroxynitrite and inhibit lipid peroxidation in vitro. By reducing mitochondrial reactive oxygen species, they inhibit MPT and cytochrome c release, thus protecting cells from oxidative cell death [11].

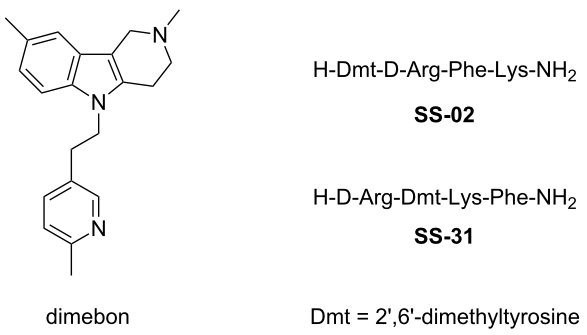


Figure 1: Structures of dimebon and SS peptides.

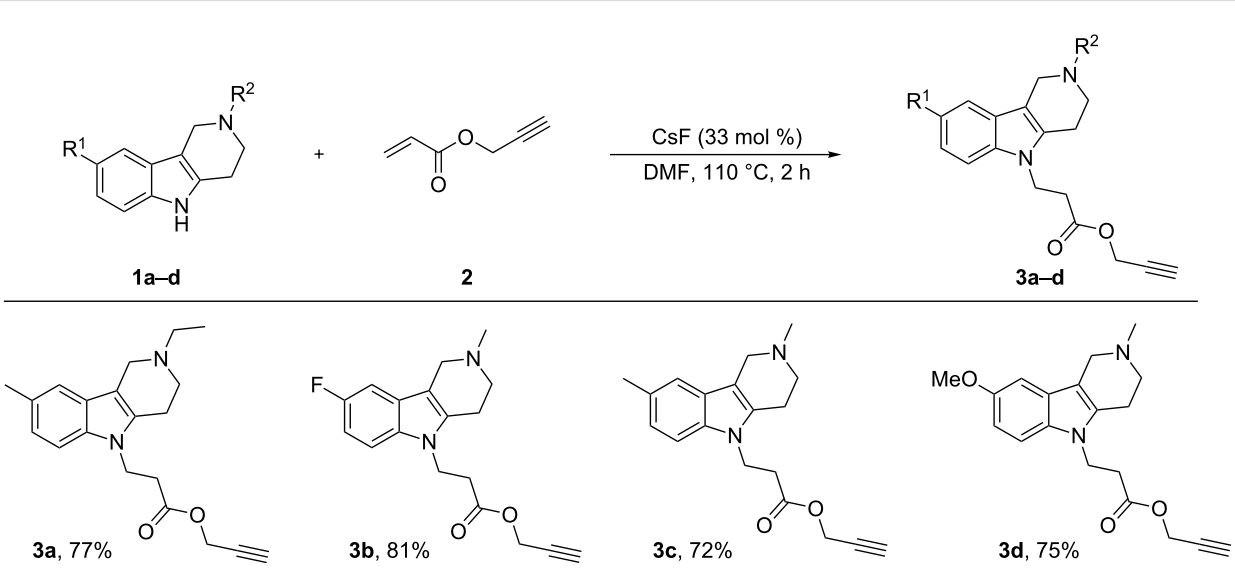
We expected that the conjugation of tetrahydro-γ-carbolines with synthetic peptides could lead to a new class of promising neuroprotectors affecting brain mitochondria. Thus, we synthesized N-substituted tetrahydro-γ-carbolines and their peptide conjugates and investigated the action of the obtained compounds on the mitochondria membrane potential, mitochondrial permeability transition and lipid peroxidation.

Results and Discussion

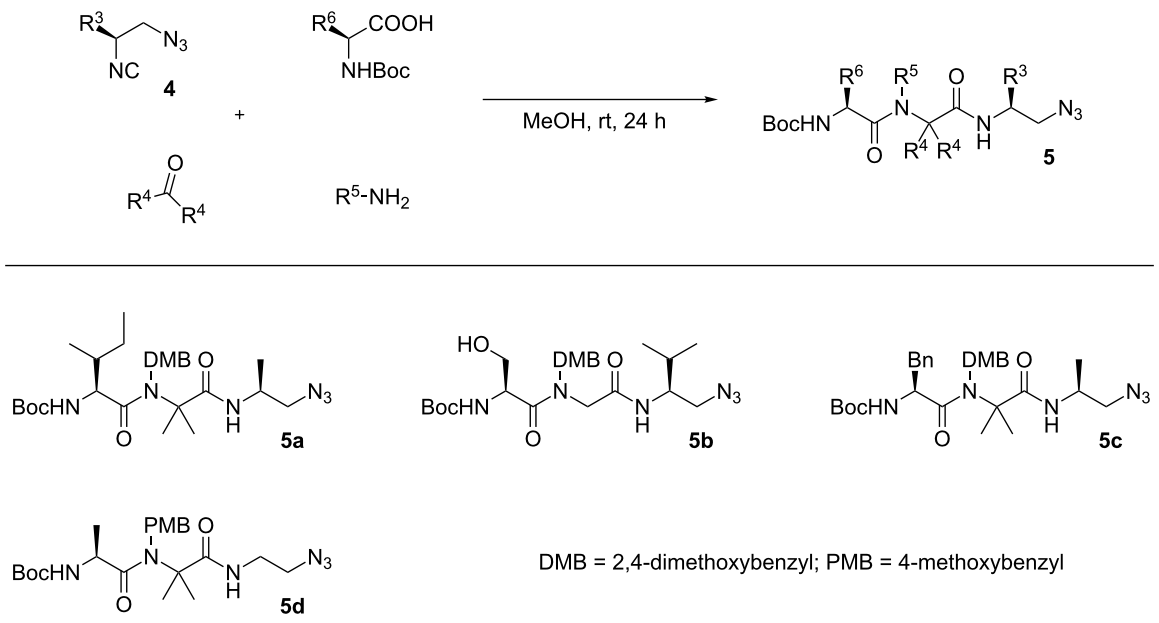
The starting N-substituted tetrahydro-γ-carbolines **3a–d** containing a terminal alkyne group were prepared in good yields by heating compounds **1a–d** [12,13] with propargyl acrylate (**2**) in the presence of catalytic amounts of CsF (Scheme 1).

The corresponding protected azidopeptides **5** [14,15] are accessible by the Ugi multicomponent reaction [16-19] of chiral isocyanoazides **4** [20] with carbonyl compounds, amines and Boc-protected amino acids (Scheme 2). As we showed before, the racemization of the chiral centre of the isocyanoazide does not occur under the conditions of the Ugi reaction [20]. This approach permits to prepare a broad variety of azidopeptides using multicomponent methodology.

The modification of N-substituted tetrahydro-γ-carbolines **3a–d** by peptide fragments was performed using Cu(I)-catalyzed click chemistry – one of the most effective conjugation methods [21,22]. Thus, heating the educts with Cu(II)/sodium ascorbate in a biphasic mixture of CH_2Cl_2/H_2O during 1 h provided compounds **6a–g** (Scheme 3). According to the ^{13}C NMR spectra, the click reaction proceeds regioselective in all cases affording the desired conjugates **6a–g** in good yields.



Scheme 1: Synthesis of starting N-substituted tetrahydro-γ-carbolines **3a–d**.



Scheme 2: Synthesis of peptides **5** through the Ugi reaction.

Next, we turned our attention to the deprotection of the amine function in the peptide residues, in order to obtain water-soluble conjugates. Thus, *N*-Boc protecting groups were removed from compounds **6a–g** with 2 M HCl in methanol to give the corresponding dihydrochloride salts **7a–g** in nearly quantitative yields (Scheme 4).

The final dihydrochloride salts **7a–g** were tested on rat liver mitochondria (RLM) using standards tests: lipid peroxidation (LP), mitochondrial membrane potential ($\Delta\Psi_m$) and Ca^{2+}-induced mitochondrial permeability transition (MPT).

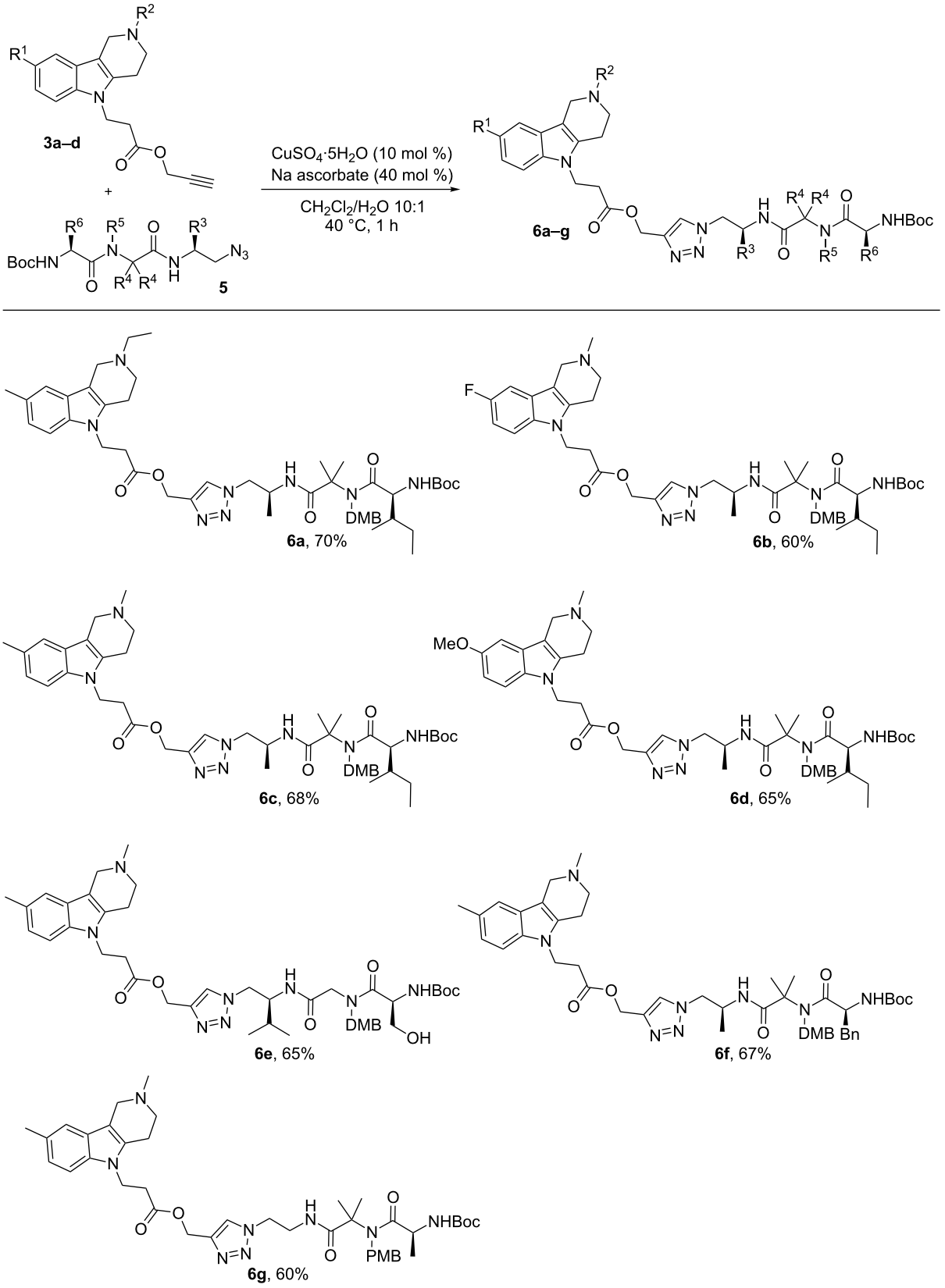
On the day of the experiment, adult male Wistar rats fasted overnight were euthanized in a CO_2 chamber followed by decapitation. The procedure is in compliance with the Guidelines for Animal Experiments at IPAC RAS. Rat liver mitochondria were isolated by conventional differential centrifugation as previously described [23]. All experiments were provided with mitochondria energized by succinate in the presence of rotenone.

The influence of compounds on spontaneous or induced by *tert*-butylhydroperoxide (*t*-BHP) LP was studied by the standard assay [24]. The extent of LP was measured spectrophotometrically (λ_{max} = 532 nm) and malondialdehyde–thiobarbituric acid adduct concentrations (MDA, expressed in nmol/mg protein) were obtained by interpolation with a MDA standard curve from commercially available 1,1,3,3-tetramethoxypropane. All experiments were repeated using three different preparations of isolated rat liver mitochondria.

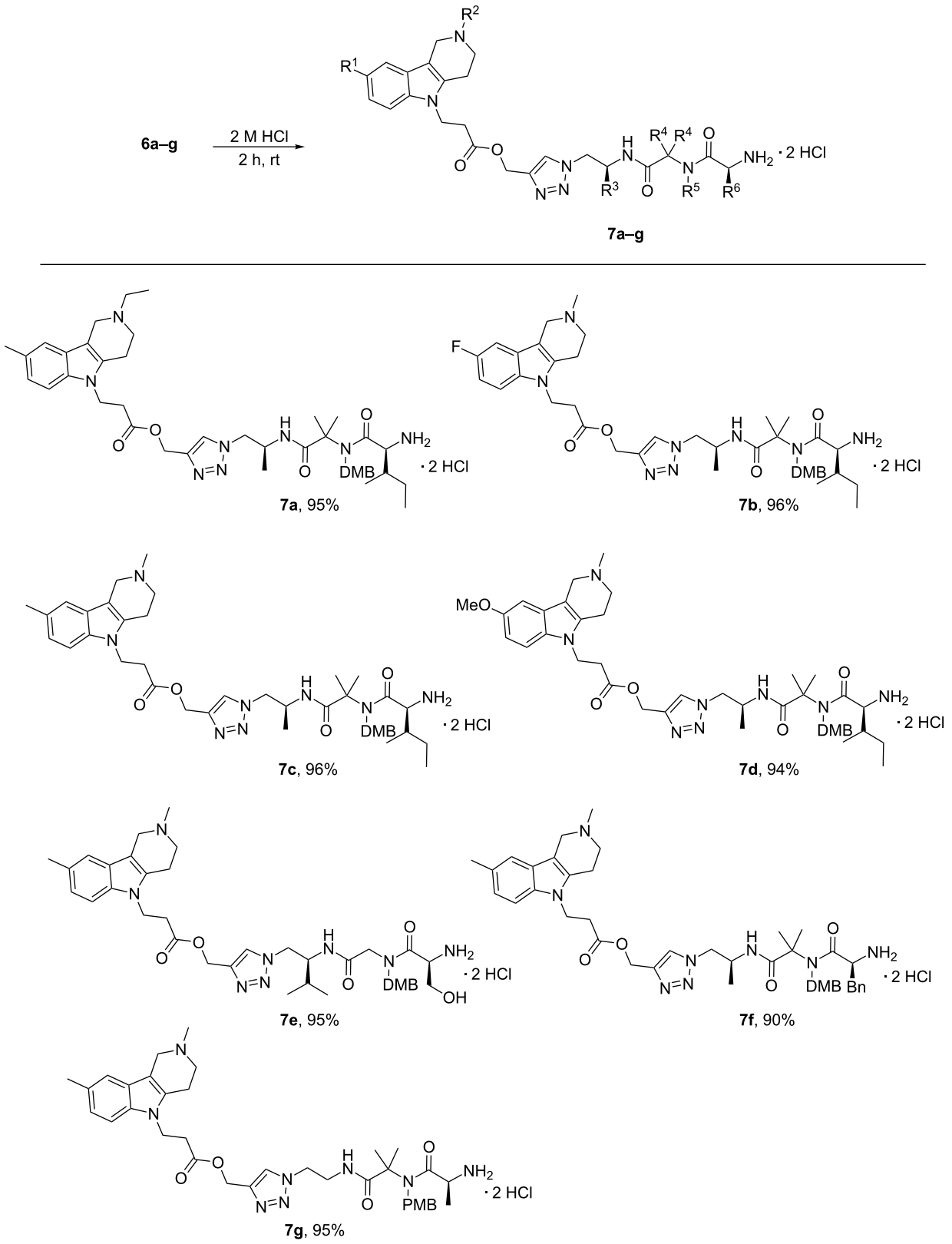
Mitochondrial membrane potential was monitored using safranine O [23]. The ability of the compounds to affect MPT was assessed by monitoring mitochondria swelling caused by calcium chloride addition in a plate reader (Victor3, Perkin Elmer). Swelling rate (V_{max}) was calculated as a slope of the steepest portion of the plot of swelling (light scattering) versus time ($dA_{530} \times 1000 \times min^{-1}$).

N-substituted tetrahydro-γ-carbolines **3a–d** possessed a pro-oxidant activity. These compounds potentiated the *t*-BHP-induced LP and also induced LP of liver mitochondria. Their peptide conjugates not only lost pro-oxidant activity but, moreover, some of these compounds could inhibit both mitochondrial lipid auto-oxidation and the *t*-BHP-induced LP (Table 1).

At the concentration of 100 μM (200 nmol/mg mitochondria) the studied compounds caused a week decrease of $\Delta\Psi_m$ and demonstrated no significant influence on mitochondrial swelling (data not shown). But at higher pharmacologically relevant concentration of 30 μM (60 nmol/mg mitochondria) all compounds did not affect the $\Delta\Psi_m$ and increased the resistance of mitochondria to calcium-induced MPT (Table 2). The results of biological evaluation revealed an antioxidant and mitoprotective potential of the new synthesized peptide-modified N-substi-



Scheme 3: Synthesis of N-substituted tetrahydro-γ-carbolines containing protected peptide residues.



Scheme 4: Synthesis of dihydrochloride salts **7a–g**.

Table 1: The influence of N-substituted tetrahydro-γ-carbolines and their peptide conjugates on LP of rat liver mitochondria.

Compound	LP in the presence of 0.1 mM compound, nmol MDA/mg protein	Influence of 0.1 mM compound on 1.6 mM *t*-BHP-induced LP, nmol MDA/mg protein
no compounds	0.48 ± 0.01	0.91 ± 0.02
3a	1.72 ± 0.05	7.63 ± 0.05
3b	1.96 ± 0.04	6.09 ± 0.08
3c	1.72 ± 0.08	6.05 ± 0.16
3d	1.81 ± 0.08	7.64 ± 0.09
7a	0.39 ± 0.02	0.86 ± 0.04
7b	0.41 ± 0.02	0.87 ± 0.06
7c	0.39 ± 0.02	0.79 ± 0.01
7d	0.38 ± 0.02	0.81 ± 0.02
7e	0.4 ± 0.03	0.92 ± 0.04
7f	0.37 ± 0.01	0.75 ± 0.02
7g	0.62 ± 0.02	0.95 ± 0.05

tuted tetrahydro-γ-carbolines. Further investigations of this class of compounds may allow finding a promising approach to cytoprotection, in particularly, neuroprotection.

Table 2: The influence of the peptide conjugates of N-substituted tetrahydro-γ-carbolines on rat liver mitochondria swelling.[a]

Compounds	ΔA530/min (% of control)
7a	70.5 ± 4.6
7b	79.9 ± 8.1
7c	80.9 ± 8.0
7d	76.2 ± 7.5
7e	72.4 ± 2.7
7f	70.2 ± 8.6
7g	79.0 ± 6.7

[a]Quantification of swelling was measured as the maximal velocity of A530 change after $CaCl_2$ addition. The values were normalized against the control values, set to 100%. Data are expressed as means ± SD (*n* = 3 or 4).

Conclusion

In summary, we described the conjugation of N-substituted tetrahydro-γ-carbolines containing a terminal alkyne group **3a–d** with various azidopeptides **5** (prepared by Ugi multicomponent reaction) through the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition. The activity of the obtained compounds on rat liver mitochondria functional characteristics, such as mitochondrial transmembrane potential, calcium-induced mitochondrial permeability transition and lipid peroxidation of mitochondrial membrane was evaluated. It was found that all compounds at a concentration of 30 μM did not induce depolarization of mitochondria but possessed some inhibitory effect on the mitochondria permeability transition. The starting N-substituted tetrahydro-γ-carbolines **3a–d** demonstrated a high pro-oxidant activity, whereas their peptide conjugates inhibited both auto-oxidation and the *t*-BHP-induced lipid peroxidation.

Experimental

General Information

^1H and ^{13}C NMR spectra were recorded in deuterated solvents on a Bruker Avance 400 MHz spectrometer. ^{19}F NMR spectra were recorded on a Bruker DXP 200 MHz spectrometer. ^1H and ^{13}C chemical shifts are reported in parts per million (ppm) or δ values downfield from TMS as internal standard. Deuterated solvent peaks were used as internal references: $CDCl_3$ at 7.25 and 77.00 ppm. ^{19}F chemical shifts are reported on δ scale (in ppm) downfield from CF_3COOH. Liquid chromatography was performed using Fluka silica gel 60 (0.063–0.200 mm). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter at 589 nm. High-resolution mass spectra (HRMS) were measured on a MicrOTOF II (Bruker Daltonics) spectrometer.

Compounds **1a–d** were obtained from the respective arylhydrazine hydrochlorides and N-substituted 4-piperidones using Fischer indole synthesis [12,13]. Propargyl acrylate (**2**) was obtained from propargyl alcohol and acryloyl chloride according to procedure described in [25].

General procedure for the synthesis of compounds 3a–d: A mixture of correspondingly substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole **1a–d** (2 mmol), 0.22 g (2 mmol) acrylic acid propyn-2-yl ester (**2**) and 0.1 g (0.66 mmol) of CsF in 1 mL of DMF was stirred at 110 °C during 2 h. The solvent was removed in vacuo (~3 mmHg) and the product was extracted from the residue with CH_2Cl_2. The solvent was removed in

vacuo and the residue was purified by column chromatography (MeOH/$CHCl_3$ 1:5).

General procedure for the Ugi-4CC synthesis of peptides 5: As described in [14], the corresponding amine (1 mmol) and acetone or CH_2O (40% in H_2O, 1 mmol) were dissolved in 5 mL of MeOH and *N*-Boc-protected amino acid (1 mmol) and isocyanide **4** (1 mmol) were added at room temperature. The mixture was stirred for 24 h. The solvent was removed in vacuo and the residue was purified by column chromatography (hexanes/ethyl acetate) to give compounds **5**.

General procedure for the synthesis of compounds 6a–g: To a solution of acetylene **3** (0.5 mmol) in 5 mL of CH_2Cl_2 was added the peptide **5** (0.5 mmol), 0.012 g (0.05 mmol) of $CuSO_4{\cdot}5H_2O$ in 0.25 mL of H_2O and 0.04 g (0.2 mmol) of sodium ascorbate in 0.25 mL of H_2O. The reaction mixture was stirred at 40 °C for 1 h. After the reaction was completed 10 mL of CH_2Cl_2 was added and the reaction mixture was washed with aq NH_3 and then with water. The organic layer was separated and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography (CH_2Cl_2/MeOH 10:1).

General procedure for the synthesis of dihydrochlorides 7a–g: The corresponding compound **6a–g** (0.12 mmol) was dissolved in 1 mL (2 mmol) of a 2 M solution of HCl in MeOH. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue was dissolved in 5 mL of EtOH. Then the solvent was evaporated and 5 mL of acetonitrile were added to the residue. After evaporation of the solvent the corresponding dihydrochlorides **7a–g** were obtained.

Supporting Information

Supporting Information File 1

General information and characterization data for all compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-13-S1.pdf]

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Diversity-oriented synthesis of dihydrobenzoxazepinones by coupling the Ugi multicomponent reaction with a Mitsunobu cyclization

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Letter

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Abstract

An operationally simple protocol for the synthesis of 2,3-dihydrobenzo[*f*][1,4]oxazepin-3-ones, based on an Ugi reaction of an *ortho*-(benzyloxy)benzylamine, glycolic acid, an isocyanide and an aldehyde, followed by an intramolecular Mitsunobu substitution was developed. The required *ortho*-(benzyloxy)benzylamines have been in situ generated from the corresponding azides, in turn prepared in high yields from salicylic derivatives.

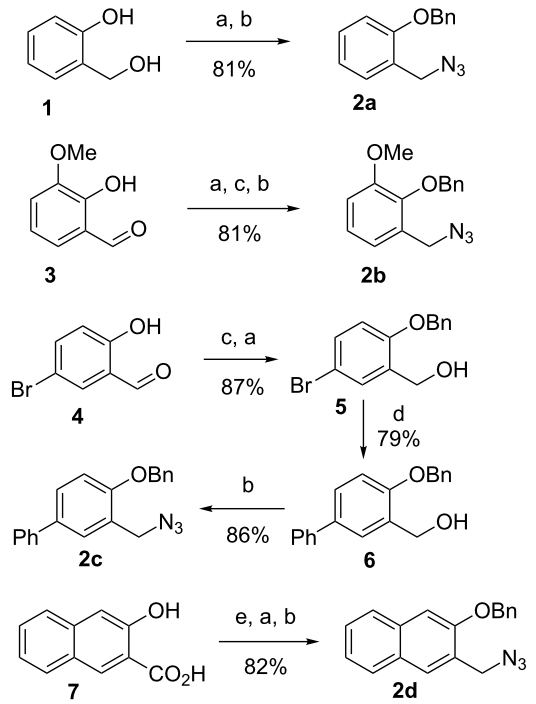
Introduction

Although the classical Ugi 4-component reaction (U-4CR) leads to acyclic peptide-like compounds, post-condensation cyclizations can afford a huge variety of drug-like heterocycles [1]. This is usually accomplished by introducing additional orthogonal functional groups in the starting components, taking advantage of the high tolerance of the U-4CR. In particular our group has been quite active in the last seven years in coupling the U-4CR with acyl or aliphatic substitution reactions [2], especially the intramolecular Mitsunobu reaction of alcohols with phenols or sulfonamides. By exploiting a single post-MCR transformation (the Mitsunobu reaction) it is possible to obtain several diverse heterocyclic scaffolds by installing the two additional groups in any of the four components and by varying the length of the spacers that connect them to the parent Ugi structure. In a previous paper [3] we have described an efficient access to dihydrobenzoxazinones by installing the alcohol moiety into the carboxylic acid and the nucleophile (a phenol) into the amine component. Our continuous interest in the use of isocyanide based MCRs in the synthesis of seven-membered heterocycles [4-7] has now prompted us to extend the methodology to the synthesis of 2,3-dihydrobenzo[*f*][1,4]oxazepin-3-ones **10**, which represent a typical drug-like scaffold, already demonstrated to be useful in medicinal chemistry [8-10].

Results and Discussion

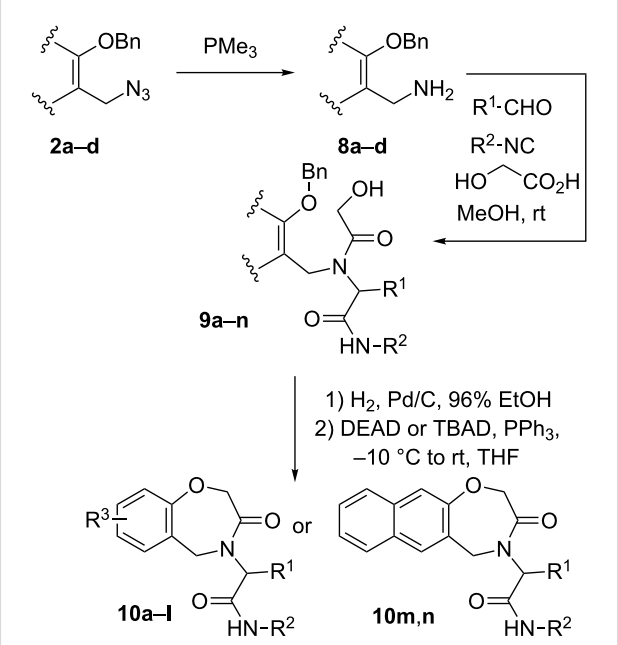
Towards this goal we needed, as key components, *ortho*-hydroxybenzylamines. However, very few members of this family are commercially available, in contrast to the 2-hydroxy-

anilines employed in our previous synthesis of six-membered oxaza heterocycles [3]. On the other hand, various *ortho*-hydroxybenzyl alcohols are on the market or can be easily prepared from the corresponding salicylaldehydes or salicylic acids. Thus we decided to set up a general and efficient strategy to access the desired amines, through conversion of the benzyl alcohols into benzyl azides by nucleophilic substitution, followed by azide reduction. This strategy required in any case protection of the phenol moiety. As a matter of fact, in preliminary attempts, we found out that Ugi reactions employing free *para*-hydroxybenzylamines proceed in very poor yields (<25%), probably because of interference of the phenol moiety, which can act as internal nucleophile. For these reasons we decided to use the *O*-benzylated benzylamines as starting materials for the U-4CR, postponing the hydrogenolytic removal of the protecting group after the condensation. Four different benzyl azides **2a–d** were straightforwardly prepared in excellent yields from low cost starting materials **1**, **3**, **4**, and **7**, in all cases passing through the benzyl alcohols (Scheme 1). Apart from **2a** [11], they are all new compounds.



Scheme 1: Synthesis of benzyl azides. a) BnBr, K_2CO_3, acetone or DMF, rt or 60 °C (for **2d**); b) 1) MsCl, Et_3N, CH_2Cl_2, −10 °C; 2) NaN_3, DMF, rt; c) $NaBH_4$, MeOH, rt; d) $PhB(OH)_2$, Cs_2CO_3, $Pd(OAc)_2$, PPh_3, 80 °C, 4.5 h; e) 1) MeOH, H_2SO_4, reflux; 2) $LiAlH_4$, THF, rt.

Initially we reduced azide **2a** with PPh_3 and separated the amine from triphenylphosphine oxide by extracting it into acidic water. However, the amine recovery, after basification and a second extraction with an organic solvent, was never complete and the yields were poorly reproducible. This can be due to the sluggish and unpredictable hydrolysis of the intermediate phosphazene, and to the easy reaction of this electron-rich benzylamine with CO_2 to give an insoluble carbamate. Skipping the extractive purification and directly using the crude amine in the ensuing sequence gave again erratic yields and was troublesome because of the difficult separation of the Ugi adducts **9** from triphenylphosphine oxide. We eventually found that the easiest and most efficient protocol involved reduction with Me_3P, followed by evaporation of the solvent and by subsequent Ugi reaction on the crude. With Me_3P, phosphazene hydrolysis was much faster and the phosphine oxide was much more easily separated by chromatography at the level of **9**. With these optimized conditions in hand, we performed a series of Ugi reactions using azides **2a–d**, glycolic acid, various aldehydes and isocyanides (Scheme 2). After a fast purification through a short silica gel column, the Ugi adducts **9a–n** were submitted to hydrogenolysis and, after catalyst removal and evaporation, to the final Mitsunobu cyclization. The overall sequence from starting benzyl azides **2a–d** to the heterocyclic products **10a–n** required just two evaporations, a filtration, and two chromatographic purifications.



Scheme 2: Synthesis of dihydrobenzoxazepinones **10**.

Table 1 reports the results. Three diversity inputs have been varied and the overall yields are generally good (>45% overall yield from azides **2** to dihydrobenzoxazepinones **10**). In general diethyl azodicarboxylate (DEAD) or di-*t*-butyl azodicarboxylate gave similar results and the choice of the reagent was made only on the basis of the easiness of separation from the

Table 1: Scope of the synthesis of 2,3-dihydrobenzo[*f*][1,4]oxazepin-3-ones **10**.

Starting azide	R^1	R^2	R^3	Ugi time	Yield (**9**)[a]	Mitsunobu reagent[b]	Yield (**10**)[c]	Final product	Overall yield
2a	*c*-Hex	*t*-Bu	H	22 h	92%	DEAD	82%	**10a**	75%
2a	Ph	*c*-Hex	H	24 h	82%	DEAD	70%	**10b**	57%
2a	3,4-$(OCH_2O)C_6H_4$	*t*-Bu	H	24 h	92%	DEAD	80%	**10c**	74%
2a	3,4,5-$(OMe)C_6H_3$	EtO_2C-CH_2	H	40 h	46%[d]	DEAD	59%	**10d**	27%
2a	Ph	*n*-Bu	H	48 h	63%	DEAD	85%	**10e**	54%
2a	iBu	*c*-Hex	H	67 h	86%	DEAD	80%	**10f**	69%
2b	Et	Me	6-OMe	19 h	54%	DEAD	98%	**10g**	53%
2b	*t*-Bu	Bn	6-OMe	120 h	74%	TBAD	92%	**10h**	68%
2b	Ph	*t*-Bu	6-OMe	42 h	84%	TBAD	93%	**10i**	78%
2b	Ph	2,6-MeC_6H_4	6-OMe	48 h	89%	TBAD	66%	**10j**	59%
2c	*c*-Hex	*t*-Bu	4-Ph	144 h	77%	DEAD	93%	**10k**	72%
2c	iBu	2,6-MeC_6H_4	4-Ph	96 h	89%	DEAD	54%	**10l**	48%
2d	3,4,5-$(OMe)C_6H_3$	*n*-Bu		72 h	66%	TBAD	92%	**10m**	61%
2d	*t*-Bu	Bn		72 h	68%	TBAD	65%	**10n**	45%

[a]Isolated yields (after chromatography) from azides **2a–d**. [b]DEAD = diethyl azodicarboxylate; TBAD = di-*tert*-butyl azodicarboxylate. [c]Isolated yields (after chromatography) from Ugi adducts **9a–n**. [d]In this case trifluoroethanol was used as solvent.

hydrazinocarboxylate side product. Only in the case of compound **10d** the overall yield was slightly lower. This was due to the concurrent formation of a 2-imidazoline through the 3-component Orru's reaction [12]. The imidazoline was even the major product when the reaction was carried out in methanol. Shifting to trifluoroethanol this side reaction was mostly, but not totally, suppressed.

Conclusion

In conclusion, we have reported a further example of a synthesis of seven-membered heterocycles by coupling the Ugi multicomponent reaction with an intramolecular Mitsunobu reaction. This operationally simple protocol opens a straightforward route to 2,3-dihydrobenzo[*f*][1,4]oxazepin-3-ones **10** starting from 2-(benzyloxy)benzyl azides, in turn accessible from variously substituted salicylic aldehydes or acids. We were able to use directly the azides as input in the Ugi reaction without the need to isolate the intermediate amine. Since complex amines are often synthesized from the corresponding alcohols via substitution with an azide anion, this one-pot procedure can be useful in further expanding the scope of the Ugi reaction, in addition to the recently reported in situ generation of aldehydes/imines [13-15] and isocyanides [16,17].

Experimental

Typical procedure for the synthesis of dihydrobenzoxazepinones 10a–n. A solution of benzyl azide **2** (1 mmol) in dry THF (3 mL) was treated with trimethylphosphine (1 M solution in toluene, 1.1 mmol) and stirred for 2 h at room temperature. Then water (4 mmol, 68 μL) was added and the mixture was further stirred for 1 h. The solvent was evaporated and the crude taken up in dry methanol (2.5 mL) and treated with 3 Å powdered molecular sieves (50 mg). Glycolic acid (1.2 mmol) and the appropriate aldehyde and isocyanide (1.2 mmol each) were added, and the solution was stirred at room temperature for the time reported in Table 1. After evaporation, the residue was chromatographed with 220–400 mesh silica gel and PE/EtOAc (the ratio depends on the polarity of **9**). The fractions containing the Ugi product **9** were evaporated to dryness and weighted. afterwards **9** was taken up in 96% ethanol (5 mL/mmol), treated with 10% Pd/C (130 mg/mmol) and hydrogenated at 1 atm and room temperature for 20–40 h (until the reaction was complete (tlc control)). After filtration of the catalyst and evaporation of the solvent, the crude was taken up in dry THF (5 mL/mmol), cooled to −10 °C, and treated with PPh_3 (1.5 equiv) and DEAD or TBAD (1.5 equiv). After stirring for 1 h, the temperature was allowed to rise to rt, and the solution stirred overnight. After evaporation the crude was chromatographed with 220–400 mesh silica gel and PE/EtOAc (the ratio depends on the polarity of **10**) to give the pure final product.

Supporting Information

Supporting Information File 1

Experimental procedure, characterization data and copies of ^1H and ^{13}C spectra of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-16-S1.pdf]

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Beilstein Journal of Organic Chemistry

Boron-substituted 1,3-dienes and heterodienes as key elements in multicomponent processes

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Review

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Abstract

In the last few years, multicomponent reactions involving boron substituted 1,3-dienes have emerged as important tools in synthetic organic chemistry. The most significant recent results and developments obtained in this area are reported in this review.

Introduction

Multicomponent reactions involving catalytic or non-catalytic step(s) have become essential tools in the field of synthetic organic chemistry [1-9]. Several of these, which now bear the name of their inventors: Strecker, Hantzsch, Biginelli, Mannich, Passerini or Ugi, have been known and widely used for many years, and the development of new multicomponent processes still receives considerable attention. Indeed, these reactions offer a number of attractive advantages including simple experimental procedures, high convergence, and access to diverse structural and functional systems, often with high levels of atom economy. Boron compounds have long been ignored in this attractive area of research despite their wide range of reactivity [10,11]. In 1993, however, Petasis and co-workers reported a new synthesis of allylamines via stepwise condensation of a secondary amine, paraformaldehyde and (*E*)-styrylboronic acid [12]. This was the first report of this type of transformation, which is now referred as the Petasis borono–Mannich reaction, and was later extended to a wide variety of other aldehydes, such as glyoxylic acid (for example), boronic acids, esters or trifluoroborates and other amine partners [13-15]. Subsequently, other multicomponent reactions involving trialkylborane [16,17], alkenyl- [18,19], aryl- [20,21], allyl- [22], allenyl- [23],

and alkynylboronic acids or esters [24-26] have been reported in the literature. Boron-substituted 1,3-dienes and heterodienes have also been successfully used as key elements in such strategies. In this review, we focus on the most significant results and recent contributions obtained in this area [27,28].

Review

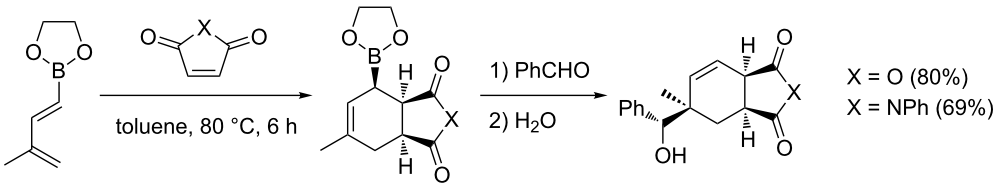
1-Boron-substituted 1,3-dienes

The first Diels–Alder reaction involving a 1-boron-substituted 1,3-diene was described in 1972 by Mikhailov and co-workers [29], and it was only fifteen years later that the groups of Vaultier and Hoffmann highlighted the real potential of these compounds in tandem cycloaddition [4 + 2]/allylboration processes [30]. These dienes reacted with activated dienophiles, such as maleic anhydride or maleimides, at relatively high temperatures (80 °C in toluene) to afford exclusively the *cis*-isomers (Scheme 1). The resulting cycloadducts, which contain an allylboronate functionality, then reacted with aldehydes to afford the corresponding homoallylic alcohols with high diastereoselectivity.

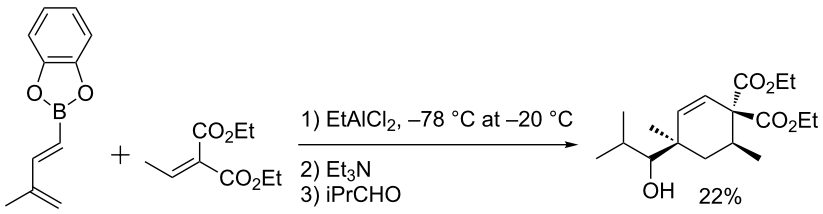
In the case of methyl acrylate or acrylonitrile, a mixture of *cis* diastereomers was obtained regioselectively at higher temperature, in a 1:1.6 to 1:1.8 ratio. By contrast, the [4 + 2]-cycloaddition proved to be completely regioselective when performed on the catechol derivative in the absence of solvent [31]. The use of a stoichiometric amount of $EtAlCl_2$ as Lewis acid catalyst allowed a lowering of the reaction temperature, a shortening of the reaction time and good stereocontrol (Scheme 2) [32].

Alternatively, the simple heating of a mixture of a 1-bora-1,3-diene, a dienophile and an aldehyde gave direct access to polysubstituted cyclohexenes that were difficult to prepare using the previously reported two step methodology [33]. A concise and efficient synthesis of an advanced precursor of Clerodin, a powerful antifeedant natural product, has been reported using a strategy based on this three-component process (Scheme 3) [34].

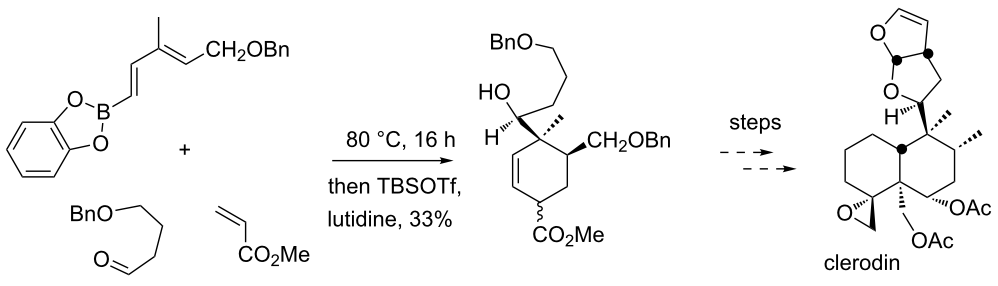
Extension of this work to the intramolecular version is depicted in Scheme 4. The bicyclic lactone **1** was obtained stereoselec-



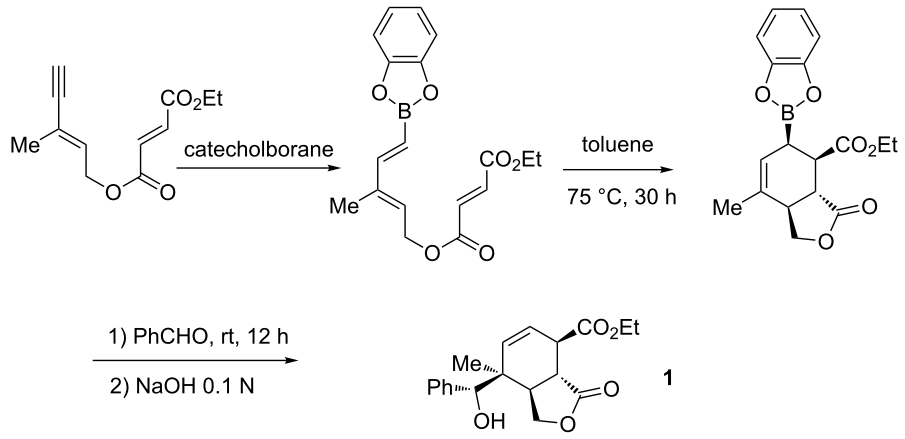
Scheme 1: 1-Boron-substituted 1,3-diene in a tandem cycloaddition [4 + 2]/allylboration sequence.



Scheme 2: Lewis acid catalyst in the tandem cycloaddition [4 + 2]/allylboration sequence.



Scheme 3: Synthesis of an advanced precursor of clerodin.



Scheme 4: Intramolecular Diels–Alder/allylboration sequence.

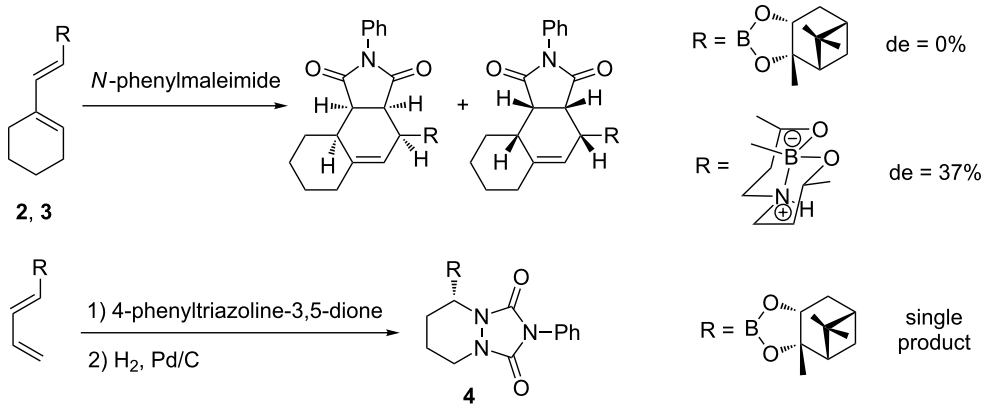
tively from a diene-yne in a one-pot process with control of the relative stereochemistry of the five stereogenic centers [35].

Concerning the access to enantioenriched compounds by using chiral boron substituents, no diastereoselectivity was observed with the (+)-pinanediol ester **2** and *N*-phenylmaleimide [36]. 1,3-Dienyldioxazaborecane **3**, derived from a chiral aminodiol of C_2 symmetry, underwent a faster cycloaddition, as already observed for similar tetracoordinated boron species [37,38], but giving only a modest 2.2:1 ratio of diastereoisomers. By contrast, the cycloadduct **4** was obtained as a single product with excellent stereoselectivity in 84% yield, however, this could probably be attributed to the special structure of the dienophile used (Scheme 5) [39].

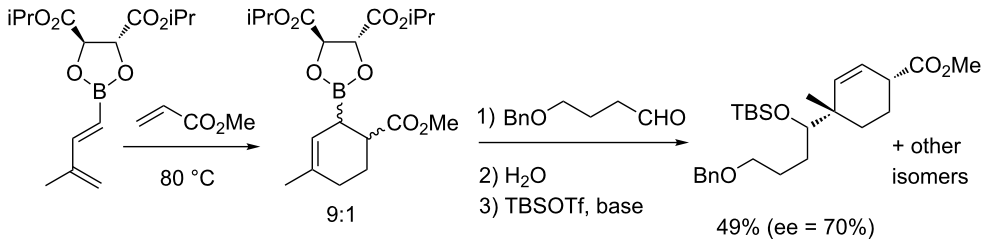
Finally, interesting results were reported with methyl acrylate and dienes derived from tartrate esters (9/1 de, 70% ee for the major isomer) (Scheme 6) [40].

In 2003, Hall and co-workers reported the application of electron-rich dienylboronates in one-pot tandem Diels–Alder/allylboration reactions [41]. In the case of the 4-methoxy-substituted diene, if the first step occurred at 80 °C in toluene, it was impossible to obtain the allylation products, even by heating at higher temperature or by activation with $EtAlCl_2$. By contrast, with the 3-OTES derivative, bicyclic, three-component adducts were isolated in good yields up to 92%. A single diastereomer was detected with maleimides; the diastereoselectivity being lower with methyl acrylate and vinyl oxazolidinone (Scheme 7).

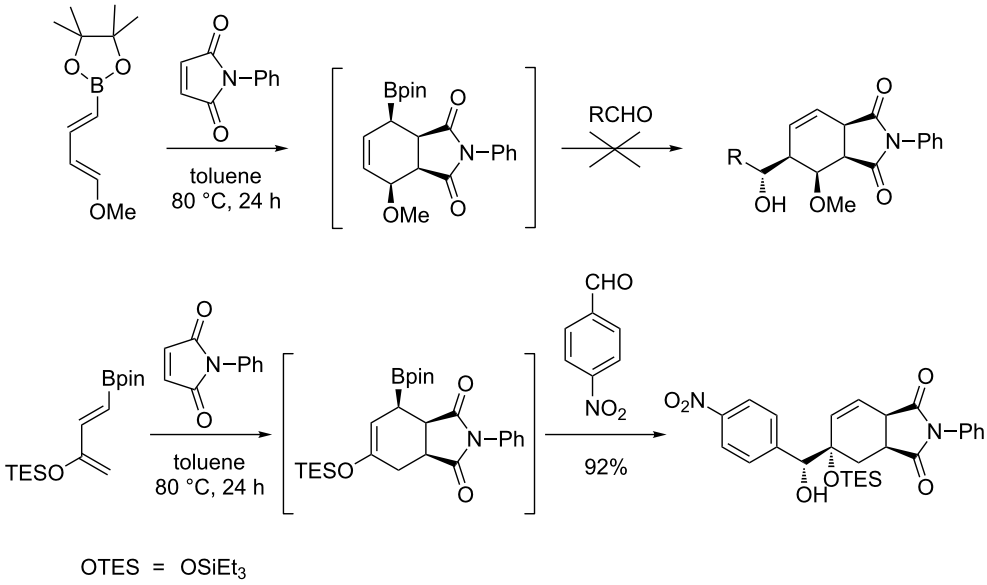
A one-pot, palladium-mediated cycloisomerization of ene-ynes **5** was applied to the synthesis of the boronated dienes **6**, which were not isolated, but directly used in a one-pot Diels–Alder reaction/allylboration sequence. This efficiently generated, in high yields, tricyclic structures **7** with control of four stereogenic centers created (Scheme 8). In the presence of Grubbs II catalyst, a skeletal isomer **8** was produced from **5**. If the



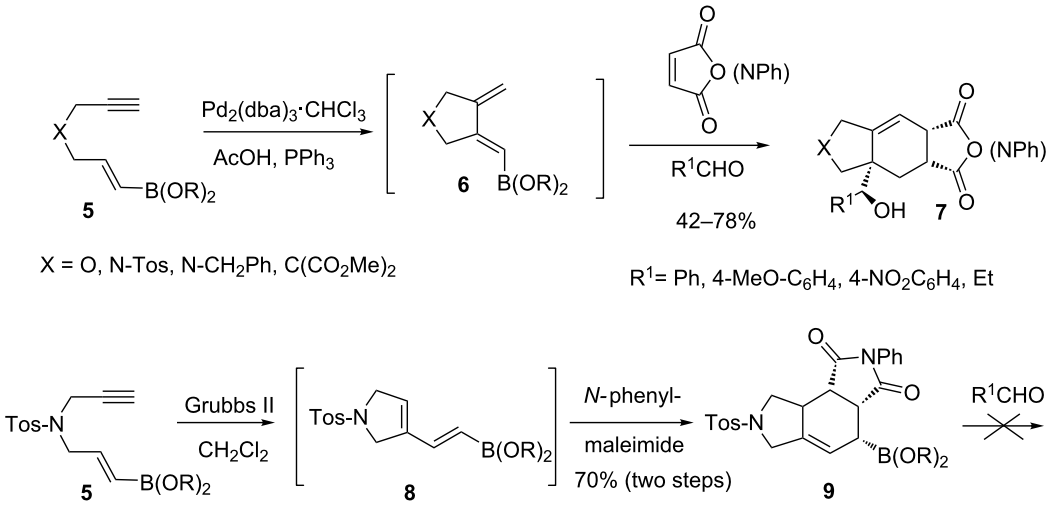
Scheme 5: Diastereoselective Diels–Alder reaction with *N*-phenylmaleimide and 4-phenyltriazoline-3,5-dione.



Scheme 6: Asymmetric synthesis of a α-hydroxyalkylcyclohexane.



Scheme 7: Tandem [4 + 2]-cycloaddition/allylboration of 3-silyloxy- and 4-alkoxy-dienyl boronates.



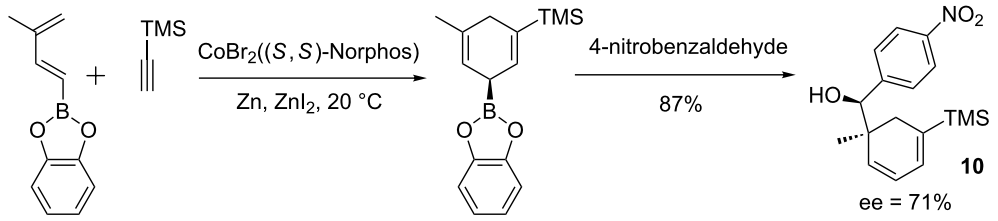
Scheme 8: Metal-mediated cycloisomerization/Diels–Alder reaction/allylboration sequence.

[4 + 2]-cycloadduct **9** was obtained with *N*-phenylmaleimide, it failed to give homoallylic alcohols, probably due to steric hindrance [42].

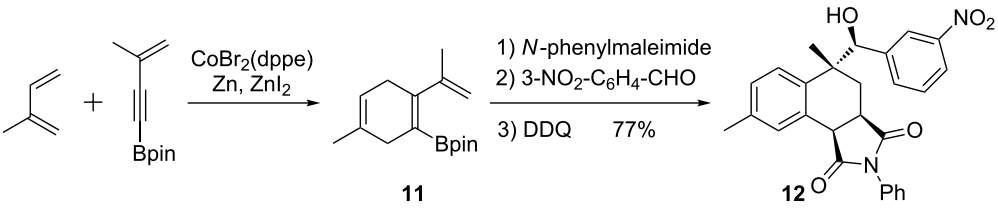
An elegant three-component process was developed by Hilt and co-workers using a cobalt-catalyzed Diels–Alder reaction as the key step in a one-pot, cycloaddition/allylboration sequence [43,44]. With (*S,S*)-Norphos as chiral ligand, the desired alcohol **10** was isolated in 87% yield and 71% ee (Scheme 9).

In a related process, the same group reported a two-step reaction cascade interconnecting four components to afford dihydroaromatic compounds **11** with a high degree of diastereoselectivity and good yields. After cycloaddition and allylboration, the resulting product was oxidized to afford the corresponding tetrahydronaphthalenes **12** (Scheme 10) [45].

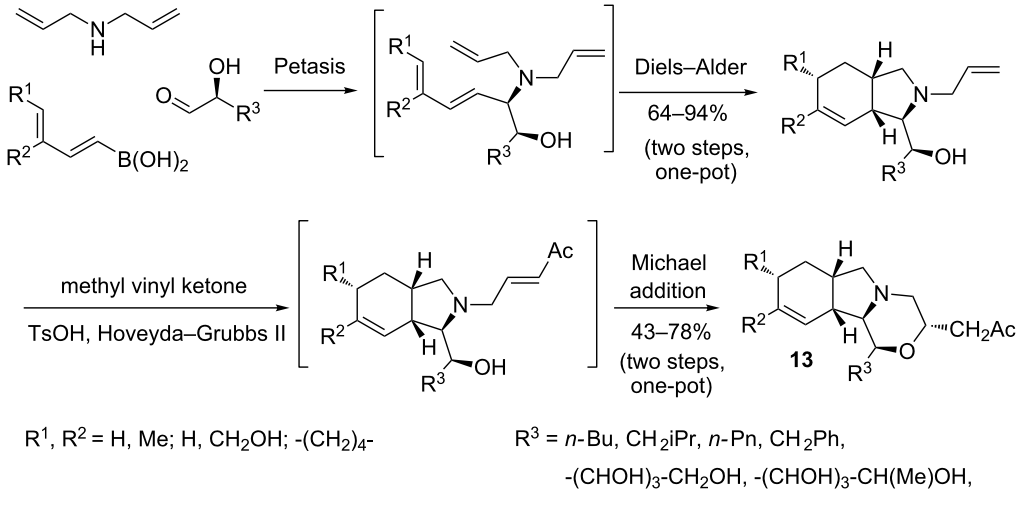
Most of the tandem sequences, in which boron-substituted 1,3-dienes were involved, were based on a first Diels–Alder cycloaddition, as shown above. However, a recent report of Norsikian, Beau and co-workers described a novel sequence of tandem transformations which combined the Petasis reaction, intramolecular [4 + 2]-cycloaddition, cross metathesis and Michael reaction. This process gave access to new polycyclic heterocyclic scaffolds **13** with good yields and complete stereocontrol (Scheme 11) [46].



Scheme 9: Cobalt-catalyzed Diels–Alder/allylboration sequence.



Scheme 10: A two-step reaction sequence for the synthesis of tetrahydronaphthalenes **12**.



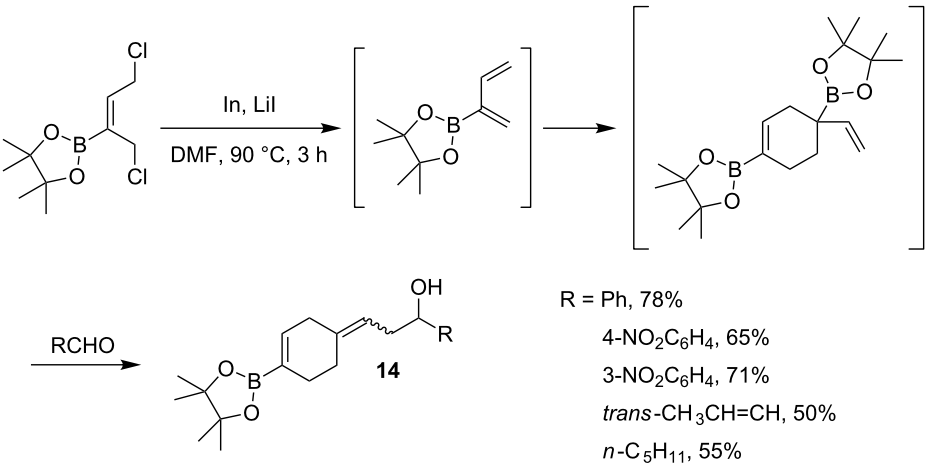
Scheme 11: Tandem sequence based on the Petasis borono–Mannich reaction as first key step.

2-Boron-substituted 1,3-dienes

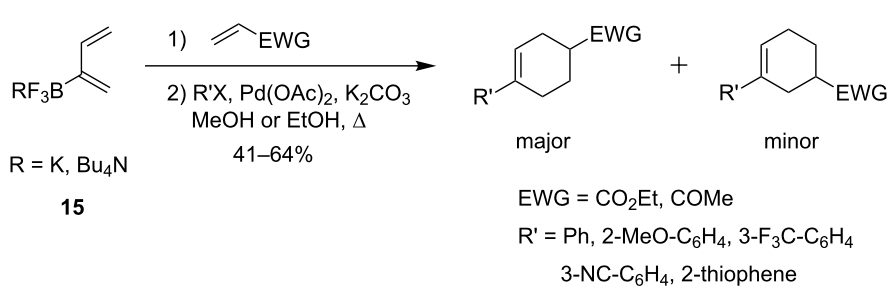
In contrast to 1,3-dienes functionalized with a boron atom in position 1, only a few studies have been reported on the related dienes substituted in position 2. These compounds are often difficult to synthesize and have, at least for the less-substituted derivatives, a strong tendency to undergo Diels–Alder dimerization even at room temperature [47,48]. This process was carefully investigated by Carreaux, Cossio and co-workers with regard to theoretical and experimental aspects [49]. When the dechlorination was carried out in the presence of an aldehyde, the dimer was immediately converted to the expected corresponding homoallylic alcohols **14** in moderate to good yields as mixtures of *E*/*Z* isomers (Scheme 12).

In 2005, Welker and co-workers started a series of studies on the synthesis of 2-boron-substituted 1,3-dienes and their reactivity in tandem reactions, concentrating mainly upon [4 + 2]-cycloadditions followed by cross-coupling reactions. Potassium and tetra-*n*-butylammonium buta-1,3-dienyl-2-trifluoroborates **15** were synthesized in good yields from chloroprene and showed no propensity to dimerize [50,51]. Exploration of the reactivity of these dienyl trifluoroborates began with Diels–Alder reactions with ethyl acrylate, methyl vinyl ketone and *N*-phenylmaleimide. The boron-containing cycloadducts, isolated with high yields, were subsequently cross-coupled using palladium catalysis. A one-pot sequence was also developed, first heating the boron diene with the dienophile, then adding an aryl halide, $Pd(OAc)_2$ (5 mol %), K_2CO_3 (3 equiv) and finally refluxing the mixture in EtOH or MeOH for 5 h (Scheme 13). Reactions with various aryl halides, substituted by electron-donating or -withdrawing groups and heteroaromatic halides occurred in moderate to good yields (41% to 64% over two steps) with a preference for the *para*- over *meta*-regioisomers (2.3:1 to 5.7:1 ratio).

Using the same methodology, the preparation and reactivity in tandem Diels–Alder/palladium cross-coupling sequences of a 2-diethanolaminoboron-substituted 1,3-diene **16** were investigated [52]. This diene has proved to be significantly more reactive and more regioselective in [4 + 2]-cycloadditions compared to the corresponding trifluoroborate. The cycloadducts were then efficiently cross-coupled to iodobenzene, 4-trifluoro-



Scheme 12: One-pot tandem dimerization/allylboration reaction of 1,3-diene-2-boronate.



Scheme 13: Tandem Diels–Alder/cross-coupling reactions of trifluoroborates **15**.

methyl-1-iodobenzene and 4-iodoanisole. The regioselectivities observed in the initial Diels–Alder reactions were maintained after cross-coupling (Scheme 14).

More recently, new 2-boron-substituted 1,3 dienes containing diol and triol ligands were prepared under basic conditions that prevent the dimerization by-product formation. These four-coordinate boron complexes participated in the same tandem Diels–Alder/Suzuki cross-coupling sequence, which appeared to be palladium- catalysed. The final cycloadducts were obtained in good yields (63% to 83%) [53].

Finally, Welker and co-workers described metal-catalysed tandem Diels–Alder/hydrolysis reactions of 2-boron-substituted 1,3-dienes [54,55]. Boron-dienes containing various ligands reacted with maleimides in the presence of rhodium and copper catalysts using BINAP as ligand (Scheme 15). NMR analysis of the crude product showed traces of the boron cycloadduct, highlighting that this mechanism proceeds, first with a Lewis-acid catalysed [4 + 2]-cycloaddition, and then by Lewis acid-assisted C–B bond protonation.

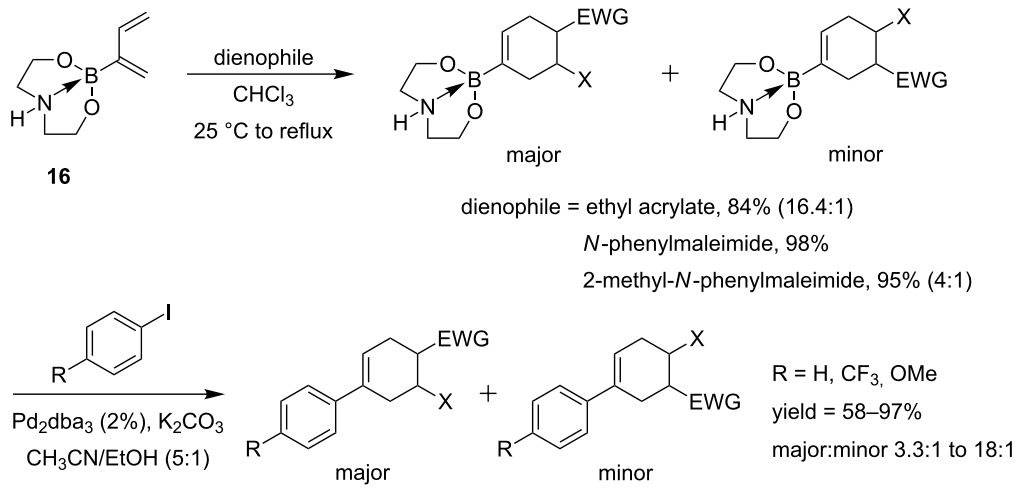
In a different approach which exploited another aspect of the reactivity of boron-substituted dienes, 2,3-bis[(pinacolato)boryl]-1,3-diene **17**, synthesized by treatment of 1,1-[bis(pinacolato)boryl]alkenes with excess of 1-bromo-1-lithioethene [56,57], were engaged in a triple aldehyde addition. 1,5-*anti*-Diols **18** were produced via successive Pt-catalyzed 1,4-diboration, allylboration reactions and finally elimination of boryl and boroxy groups. Four C–B bonds were converted into two C–C and one C=C bonds with total stereocontrol in each step (Scheme 16) [58].

1-Boron-substituted 1,3-heterodienes

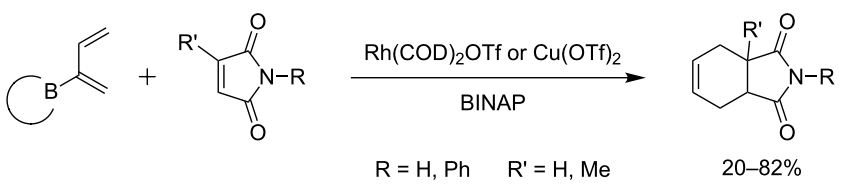
1-Oxo-4-borono-1,3-dienes

In 2003, first examples of a novel diastereoselective routes to α-hydroxyalkyldihydropyrans were reported; a substructure frequently encountered in the core of a wide range of natural products [59-61]. As in the carbocylic variant, the intermediate cyclic allylboronate (+)-**19**, prepared from 3-boronoacrolein, was the key element of a sequential Diels–Alder/allylation. In this case, the catalytic asymmetric version was carried out efficiently in the presence of the Jacobsen's tridentate chromium(III) complex **20** catalyst with high diastereo- and enantioselectivity (Scheme 17).

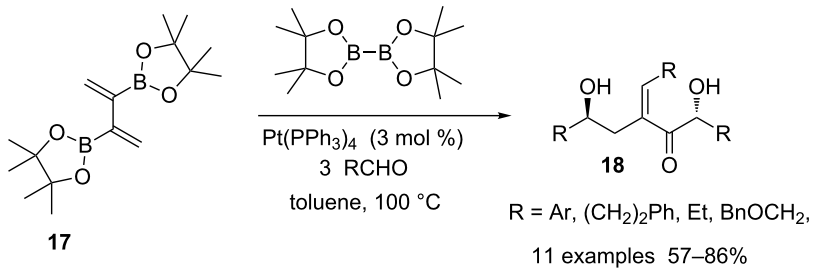
The first application of this strategy in the synthesis of natural products and analogues concerned (*5R,6S*)-6-acetoxy-5-hexa-



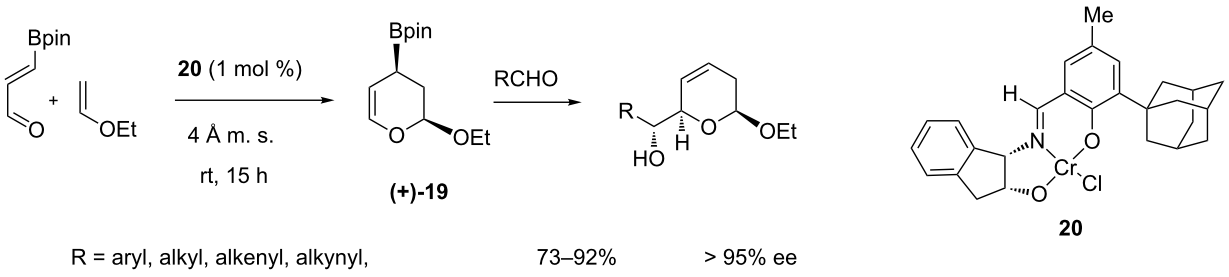
Scheme 14: Diels–Alder/cross-coupling reactions of **16**.



Scheme 15: Metal catalyzed tandem Diels–Alder/hydrolysis reactions.



Scheme 16: Synthesis of *anti*-1,5-diols **18** by triple aldehyde addition.



Scheme 17: Catalytic enantioselective three-component hetero-[4 + 2]-cycloaddition/allylboration sequence.

decanolide **21**, the oviposition attractant pheromone of a mosquito capable of transmitting the West Nile virus [59]. Thereafter, several members of the natural styryllactone family **21**–**25**, displaying cytotoxic and antitumor activities, have been also prepared according to this methodology [62-64]. The combination of the catalytic hetero-Diels–Alder/allyboration sequence with a ruthenium-catalyzed isomerization gave access to the 6,8-dioxabicyclo[3.2.1]octane skeleton of (+)-iso-*exo*-brevicomin (**26**, Scheme 18) [65].

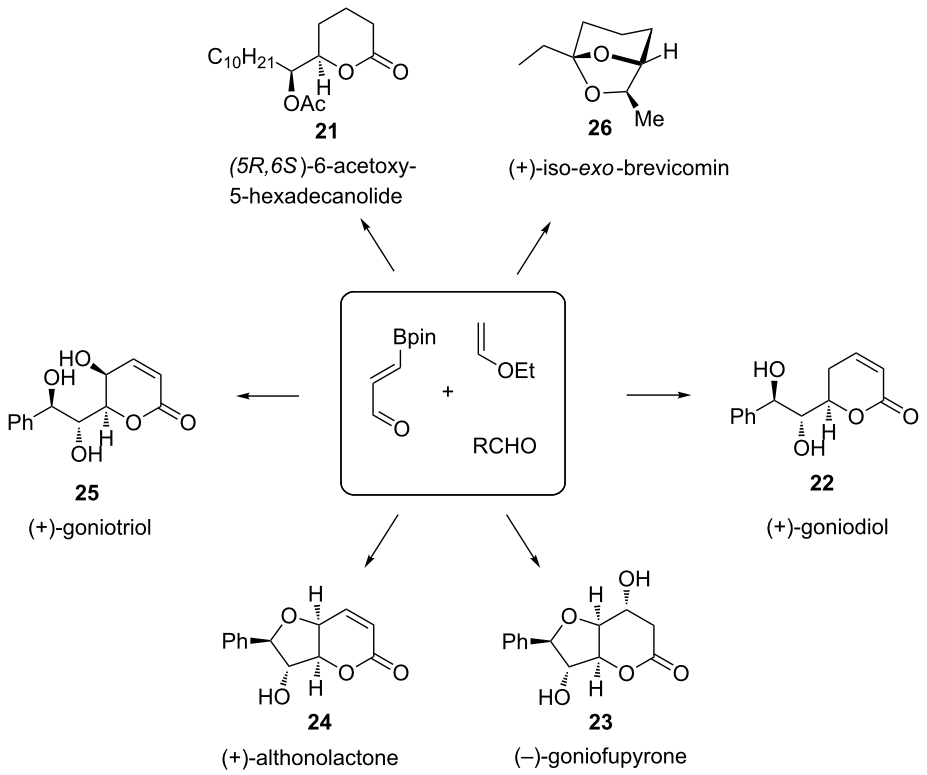
When a *Z*/*E* mixture of 2-substituted enol ethers was used as dienophile, only cycloadducts resulting from a selective reaction of the *Z*-isomer were present in the final product that prevented the tedious preparation of an isomerically pure starting material. While the second allylboration step required conditions more severe than those employed in the case of ethyl vinyl ether, this approach was successfully applied in the key steps of the total synthesis of a member of the thiomarinol class of marine antibiotics (Scheme 19) [66,67].

More recently, Hall and co-workers described the total synthesis of a complex 20-membered marine macrolide, palmerolide A, a potent and unusually selective antitumor agent [68]. In this case, the cyclic allylboronate (−)-**19** prepared from the [4 + 2]-cycloaddition reacted with the starting 3-boronoacrolein which then played the role of the aldehyde partner. The hydroxy group of the resulting homoallylic alcohol was then engaged in a Claisen–Ireland rearrangement to afford an advanced intermediate **27** for the completion of the total synthesis (Scheme 20).

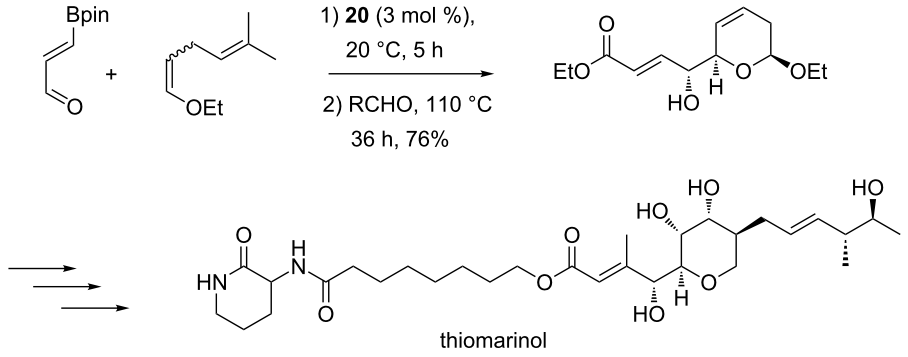
1-Aza-4-borono-1,3-dienes

A few years before the description of the tandem process concerning the 3-boronoacrolein, Hall and co-workers realized a multicomponent reaction involving 1-aza-4-borono-1,3-dienes **28** as key starting materials for the preparation of α-hydroxyalkylpiperidines. These scaffolds are present in several natural products, particularly in the alkaloid family of palustrine. The tandem process started with the hetero-[4 + 2]-cycloaddition of an hydrazonodiene with maleimides, as electron-poor dienophiles, followed by an allylboration (Scheme 21) [69]. This sequence proceeded with high stereocontrol, as already observed with the carbon and oxygen analogues. In addition, the absolute stereochemistry of the four new created stereogenic centers was controlled by using a chiral auxiliary (>95% de in the case of an L-proline-derived diene).

Diversification on the different units, diene, dienophile and aldehyde, has been described. Concerning the maleimide material, substituent R^3 did not exert any significant effect on the process. Other dienophiles have also been tested (acrylates, maleic anhydride) giving no products or unsatisfactory results. A large range of aldehydes, as aliphatic, electron-rich or electron-poor benzaldehyde, could be used. Only very hindered



Scheme 18: Synthesis of natural products using the catalytic enantioselective HDA/allylboration sequence.

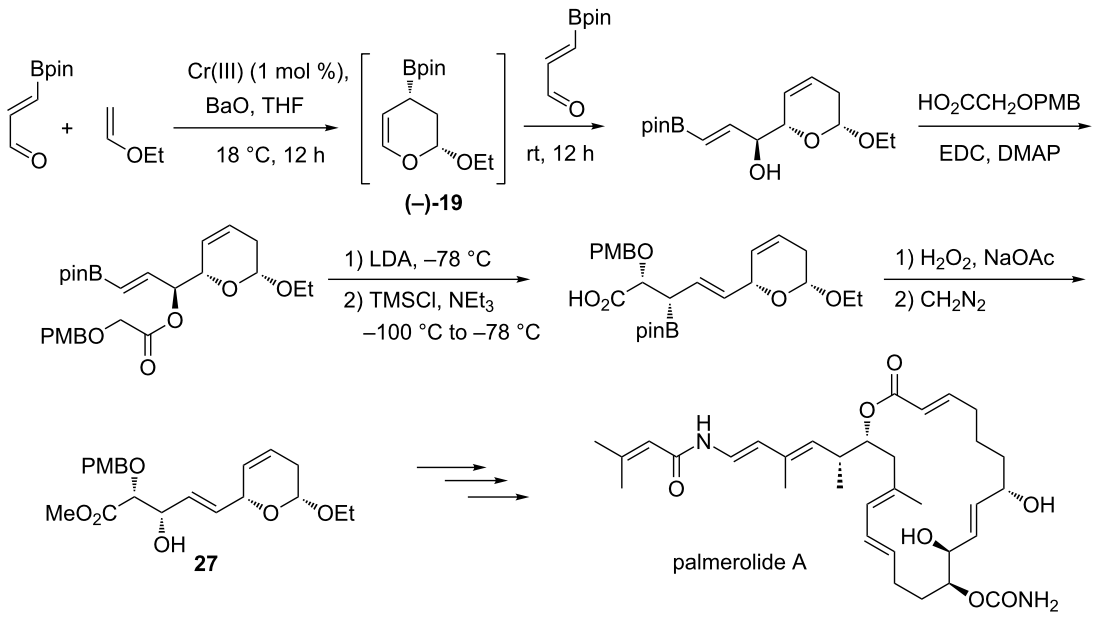


Scheme 19: Total synthesis of a thiomarinol derivative.

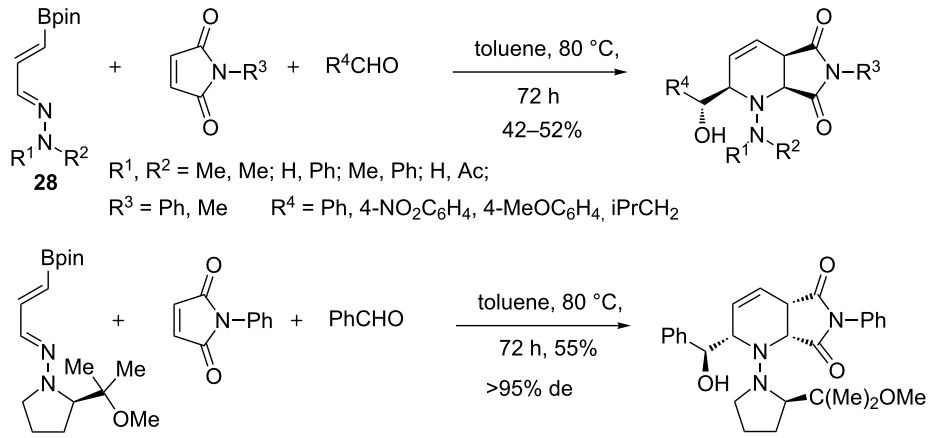
aldehydes did not afford any product and both mono- and disubstituted arylhydrazines have proved to give the best yields, probably due to the higher reactivity of the corresponding hydrazones. Furthermore, the double bond of **29** was selectively hydrogenated under palladium on charcoal, while hydrogenolysis of the hydrazine moiety occurred in the presence of Raney nickel (Scheme 22).

Following these results obtained in the liquid phase, Hall and co-workers also examined the suitability of a solid-phase strategy. Finally, due to problems of purity encountered with an *N*-arylmaleidobenzoic acid-functionalized resin [70], or availability of the supported aldehyde partner, a four-component variant of this chemistry was developed in solution phase. The pre-formation of the azabutadiene component was not necessary and this gave access to a library of 944 polysubstituted piperidines with sufficient purity suitable for biological screening after purification by HPLC with mass-based fraction collection [71].

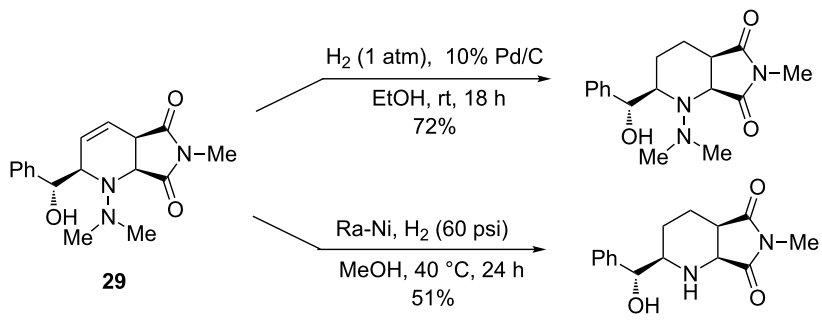
The flexibility and usefulness of this chemistry was also demonstrated in target-oriented synthesis with the synthesis of



Scheme 20: Synthesis of an advanced intermediate **27** for the east fragment of palmerolide A.



Scheme 21: Bicyclic piperidines from tandem aza-[4 + 2]-cycloaddition/allylboration.



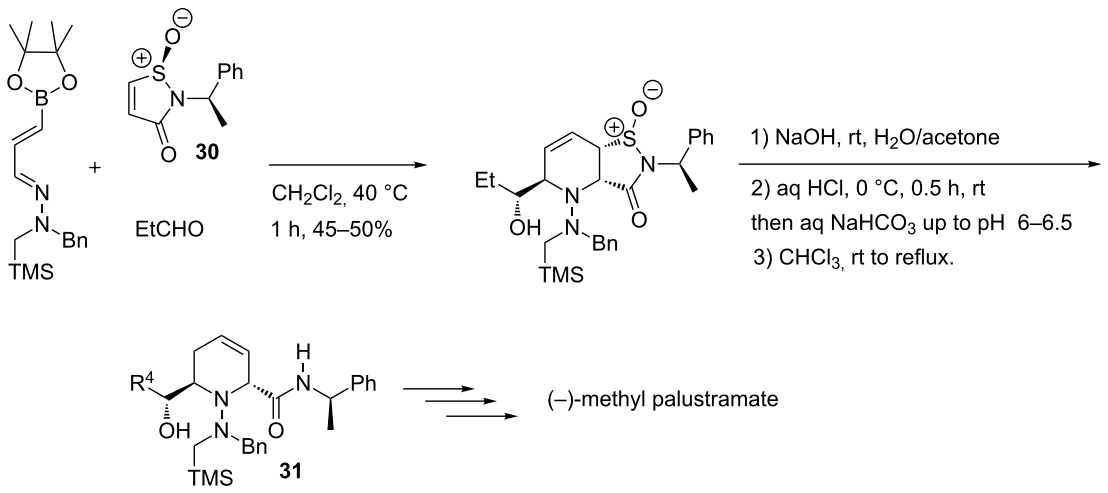
Scheme 22: Hydrogenolysis reactions of hydrazinopiperidines.

(−)-methyl palustramate and other 2,6-disubstituted piperidines [72,73]. A chiral sulfinimide **30** was used as dienophile and a sequential three component aza-[4 + 2]-cycloaddition/allylboration/retro-sulfinyl-ene sequence was performed to afford 1,2,5,6-tetrahydropyridine **31** with high regio- and diastereoselectivity (Scheme 23).

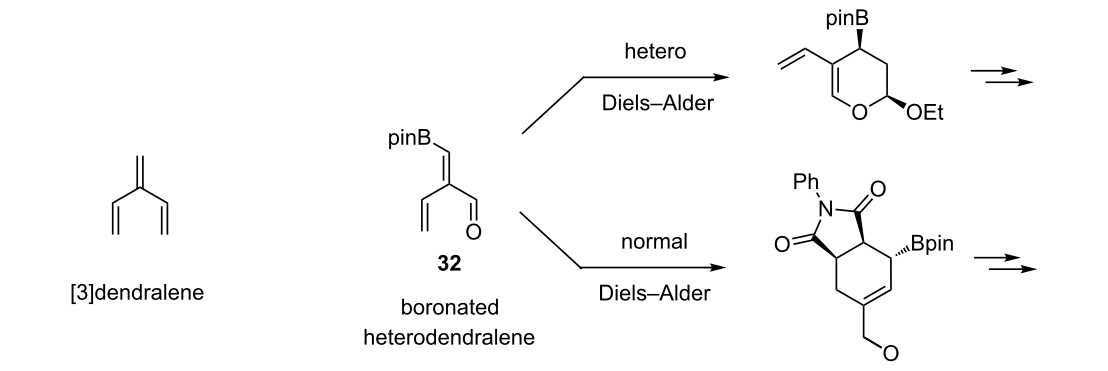
Boron-substituted heterodendralene

On the basis of these precedents, boronated 2-vinyl-α,β-unsaturated aldehydes **32** were designed to fully exploit the synthetic potential of these classes of organoboranes. These compounds, named boronated [3]-1-heterodendralenes by analogy with the corresponding carbotrienes [74], have been used to synthesize polycyclic heterocycles with control of multiple stereocenters [75]. Based on the intrinsic reactivity of each 1,3-dienyl system, sequential hetero-Diels–Alder/Diels–Alder reactions (or vice versa if the order of introduction of the reagents was inversed) were carried out chemoselectively. The allylboronic ester moiety, generated in the first cycloaddition step or after the two consecutive [4 + 2]-cycloadditons, can further be engaged in an allylation reaction that significantly increased the structural diversity of the final products (Scheme 24).

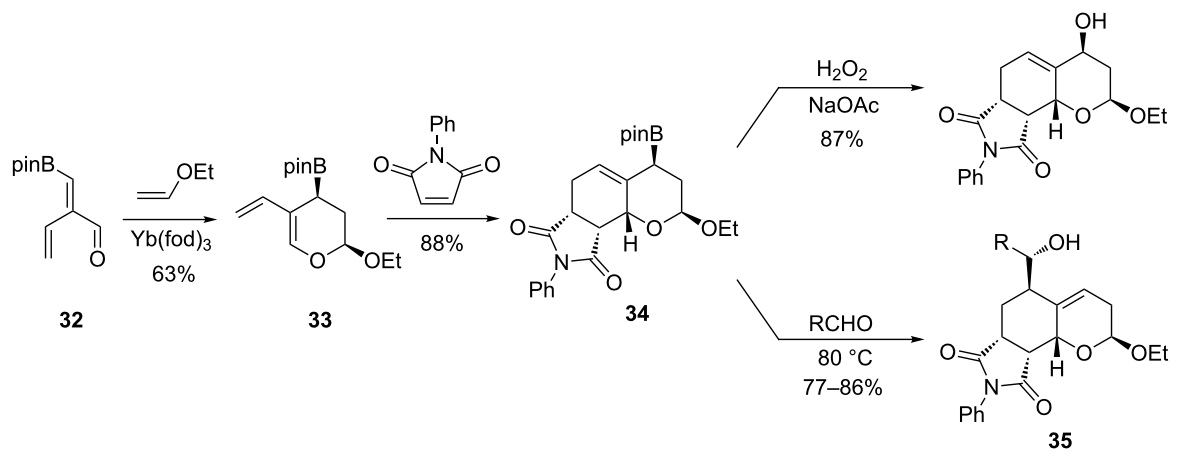
As 3-boronoacrolein esters which have been used in metal-catalyzed inverse electron demand [4 + 2]-cycloadditions, **32** reacted with ethyl vinyl ether in the presence of $Yb(fod)_3$ to afford 2-alkoxy-3,4-dihydro-5-vinyl-2*H*-pyran **33**. In the presence of electron-poor dienophiles, as *N*-phenylmaleimide, maleic anhydride, activated azo compounds or naphthoquinone, **33** underwent normal Diels–Alder reactions thus giving the corresponding cycloadducts **34** as single diastereomers (Scheme 25). No formation of products resulting from a first cycloaddition of the 1,3-butadienyl moiety was observed when these reactions were conducted in a tandem one-pot process. Various transformations were further carried out as oxidation with hydrogen peroxide or addition to aldehydes that gave access to the homoallylic alcohols **35** in 77–86% yields.



Scheme 23: Tandem aza-[4 + 2]-cycloaddition/allylboration/retrosulfinyl-ene sequence.



Scheme 24: Boronated heterodendralene **32** in [4 + 2]-cycloadditions.



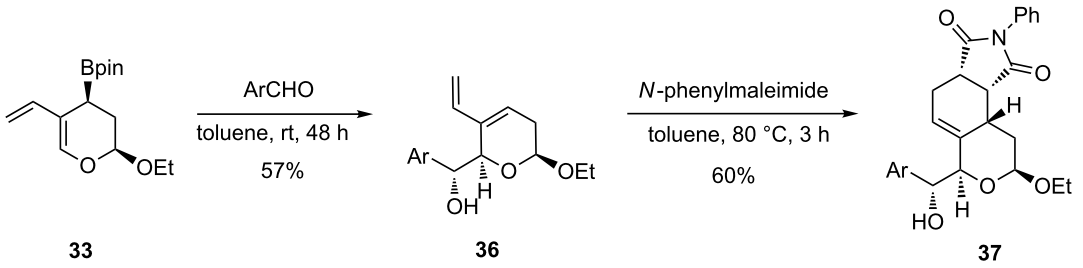
Scheme 25: Synthesis of tricyclic imides derivatives.

Alternatively, the presence of an allylic boronic ester group in the cycloadduct **33** was exploited in carrying out first the addition to 4-nitrobenzaldehyde to afford **36**. Further normal-electron demand [4 + 2]-cycloaddition step with *N*-phenylmaleimide furnished the single tricyclic compound **37** (Scheme 26).

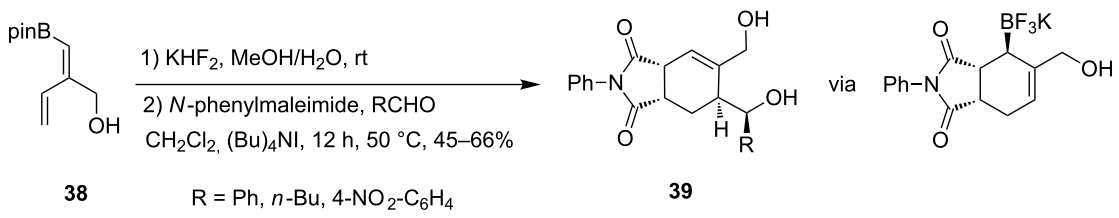
The initial boronic ester group of **38**, the direct precursor of **32**, can be also converted into a trifluoroborate substituent by treatment with KHF_2 in $MeOH/H_2O$ to increase the reactivity of the dienyl moiety towards electron-poor dienophiles. It was engaged in a one pot Diels–Alder cycloaddition with *N*-phenylmaleimide in the presence of various aldehydes to afford diols **39** as major diastereisomers (>95%) and in good overall yields (four steps) (Scheme 27).

Conclusion

Despite the synthetic potential of the boron-substituted 1,3-dienes and heterodienes presented herein in creating molecular complexity, the field of multicomponent reactions involving these versatile building blocks remains insufficiently explored. If Diels–Alder cycloadditions have been mainly employed as key steps in most of the reported processes, numerous other reactions can be envisaged. Further developments in this area



Scheme 26: Synthesis of **37** via a HDA/allylboration/DA sequence.



Scheme 27: Diels–Alder/allylboration sequence.

will certainly provide important improvements with regards to the scope of reagents, access to new structural scaffolds with control of the regio-, diastereo- and enantioselectivity and the efficiency of these multistep sequences.

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Secondary amine-initiated three-component synthesis of 3,4-dihydropyrimidinones and thiones involving alkynes, aldehydes and thiourea/urea

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Letter

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Abstract

The three-component reactions of aldehydes, electron deficient alkynes and ureas/thioureas have been smoothly performed to yield a class of unprecedented 3,4-dihydropyrimidinones and thiones (DHPMs). The reactions are initiated by the key transformation of an enamine-type activation involving the addition of a secondary amine to an alkyne, which enables the subsequent incorporation of aldehydes and ureas/thioureas. This protocol tolerates a broad range of aryl- or alkylaldehydes, *N*-substituted and unsubstituted ureas/thioureas and alkynes to yield the corresponding DHPMs with specific regioselectivity.

Introduction

DHPMs are well-known heterocyclic scaffolds with abundant biological relevance [1-3]. The DHPM backbone has been found in a class of marine natural products possessing anti-HIV activity [4]. What's more, diversified other biological activities have been discovered in many synthesized small DHPMs. For example, monastrol (**A**) [5], (R)-SQ 32926 (**B**) [6] and (+)-SNAP-7941(**C**) [7] are lead compounds possessing outstanding antitumor, antihypertensive and melanin-concentrating hormone receptor antagonism activities, respectively (Figure 1).

More recently, it was shown that DHPMs display many new bioactivities such as antioxidation [8], antibacterial [9], anti-malaria [10], antimicrobial [11] and sodium iodide symporter inhibition [12], suggesting the great potential of DHPMs in discovering new lead compounds and medicines. Besides their attractiveness in biological and medicinal researches, DHPMs have also been demonstrated as quite flexible precursors for the synthesis of many other derived heterocyclic scaffolds [13].

For a rather long period, the Biginelli reaction involving the condensation of aldehydes, β-ketoesters and ureas (thioureas) [14] has been dominantly employed for DHPMs synthesis in both racemic [15-18] and asymmetric versions [19-23]. Despite of many recognized advantages of the Biginelli reaction, the

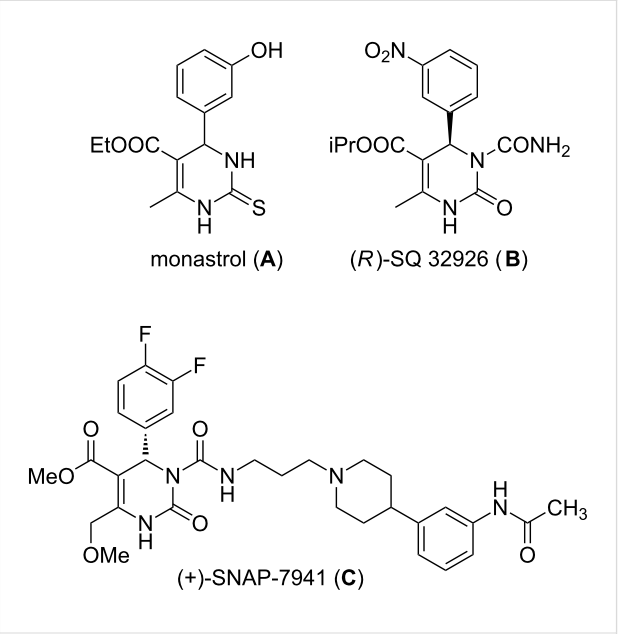
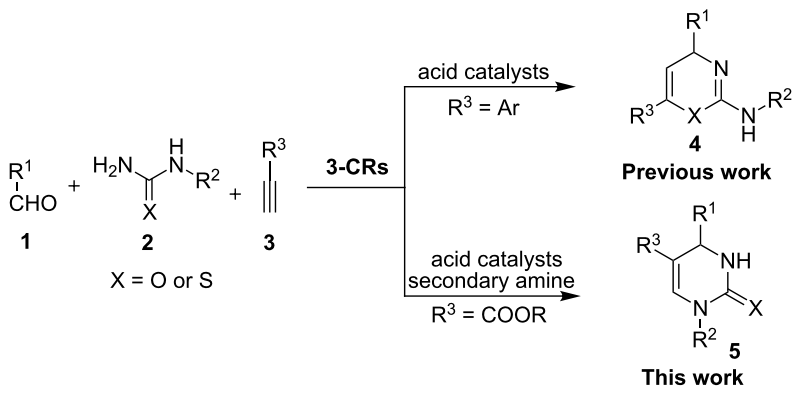


Figure 1: Some DHPMs-based lead compounds.

product diversity suffered from limitations because β-ketoesters or 1,3-diketones are intrinsically required as donors of the C5–C6 fragment in this reaction, which predetermined the presence of a C6 substitution in the produced DHPMs. On the other hand, DHPMs without a substituent at the C6 site were hardly accessible by the classical Biginelli reaction, probably because of either the rare availability of the corresponding β-formylketone/ester substrates or the intolerance of β-formylketones/esters in the Biginelli reaction. In regard to the daily increasing requirements on molecular diversity, developing powerful methods for the rapid synthesis of DHPMs with diverse and unprecedented substitution patterns has become an issue of central importance. During the last decade, tremendous endeavours have been made to devise efficient synthetic routes to access structurally diverse DHPMs by employing multicomponent reactions (MCRs) [24-26]. Interestingly, in the process of designing new MCRs yielding DHPMs, the utilization of new C5–C6 fragment donors constituted the major strategy. Representative new C5–C6 building blocks used in the multicomponent synthesis of DHPMs are 2-oxosuccinic acid [27], acetylaldehydes [28], cyclic and acyclic ketones [29-31], β-oxo dithioesters [32], diketenes [33] and enaminones [34]. On the other hand, as frequently utilized building blocks in organic synthesis, alkynes have been known to possess versatile reactivity in the synthesis of small molecules. For example, a previous protocol employing aryl alkynes, aldehydes and urea/thiourea has been found to selectively provide various 1,3-thiazine derivatives **4** [35]. Amazingly, a generally applicable alkyne-based method regioselectively yielding DHPMs has not yet been achieved [36]. Herein, we report the regioselective three-component synthesis of DHPMs employing alkynes, aldehydes and ureas/thioureas by making use of the activation effect of a secondary amine to alkynes (Scheme 1) [37].

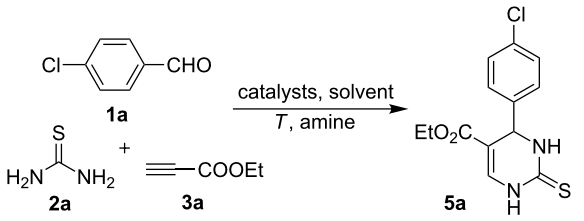
Results and Discussion

The work began from the three-component model reaction of *p*-chlorobenzaldehyde (**1a**), thiourea (**2a**) and ethyl propiolate (**3a**). The optimization results are outlined in Table 1. Firstly, parallel studies respectively employing TMSCl, morpholine and mixed TMSCl/morpholine as catalysts have been conducted. It was found that the target product could be formed only when both morpholine and TMSCl were present (Table 1, entries 1–3). Extended experiments using different amounts and types of amine catalysts demonstrated that 0.5 equiv of piperazine was favorable (Table 1, entries 4–6). Reducing the amount of TMSCl led to a decrease in product yield (Table 1, entry 7). Other Lewis acid or Brønsted acids such as $FeCl_3$ and *p*-TSA gave no better result for the same reaction (Table 1, entries 8 and 9). In addition, the non-polar solvent toluene was not able



Scheme 1: Regioselective 1,3-thiazines and DHPMs via aldehydes, ureas/thioureas and alkynes.

Table 1: Optimization of reaction conditions[a].



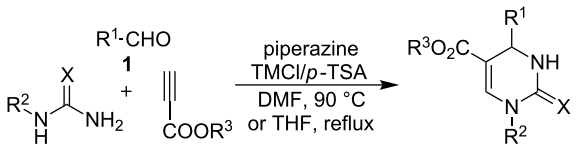
Entry	Catalysts	Solvent	*T* (°C)	Yield (%)[b]
1	morpholine/TMSCl	DMF	90	45
2[c]	TMSCl	DMF	90	nr
3[c]	morpholine	DMF	90	nr
4[d]	morpholine/TMSCl	DMF	90	25
5	pyrrolidine/TMSCl	DMF	90	13
6	piperazine/TMSCl	DMF	90	59
7[e]	piperazine/TMSCl	DMF	90	40
8	piperazine/$FeCl_3$	DMF	90	nr
9	piperazine/*p*-TSA	DMF	90	15
10	piperazine/TMSCl	CH_3CN	90	39
11	piperazine/TMSCl	toluene	90	nr
12	piperazine/TMSCl	DMF	80	27
13	piperazine/TMSCl	DMF	100	39
14[f]	piperazine/TMSCl	DMF	90	81

[a]General conditions: **1a** (0.3 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), secondary amine (0.15 mmol) and acid (0.6 mmol) in 4 mL solvent, stirred for 12 h. [b]Yields of isolated product. [c]No reaction. [d]0.09 mmol (30 mol %) morpholine was used. [e]0.45 mmol TMSCl was used. [f]Additional 0.5 equiv of *p*-TSA was used.

to mediate the reaction, while a lower yield of product was observed when MeCN was used as solvent (Table 1, entries 10 and 11). Altering the reaction temperature also failed to enhance the yield (Table 1, entries 12 and 13). Finally, employing additional 0.5 equiv of *p*-TSA has been found to significantly improve the yield (Table 1, entry 14). This result may be attributed to the double activation effect involving both Lewis and Brønsted acid (see Scheme 3).

With the optimal conditions in hand, we conducted the investigation on examining the application scope. Various aldehydes of different properties have been subjected to react with thioureas/*N*-substituted thioureas/urea as well as different propiolates. Typical results were listed in Table 2. It can be seen from these reactions that aldehydes containing various functional groups tolerate the protocol of the corresponding DHPMs synthesis. For reactions involving aromatic aldehydes, the electronic properties of the substituent exhibited evident impact on the product yield. Aldehydes containing an electron withdrawing group (EWG) facilitated the reactions to give related DHPMs with evidently higher yields than those containing an

Table 2: Multicomponent synthesis of different DHPMs.[a]



R^1	R^2	R^3	X	Product	Yield (%)[b]
4-ClC_6H_4	H	Et	S	**5a**	81
4-BrC_6H_4	H	Et	S	**5b**	70
4-$CF_3C_6H_4$	H	Et	S	**5c**	72
4-$NO_2C_6H_4$	H	Et	S	**5d**	85
4-MeC_6H_4	H	Et	S	**5e**	58
4-ClC_6H_4	Me	Et	S	**5f**	78
4-BrC_6H_4	Me	Et	S	**5g**	63
4-$CF_3C_6H_4$	Me	Et	S	**5h**	83
4-ClC_6H_4	H	Me	S	**5i**	72
4-$CF_3C_6H_4$	H	Me	S	**5j**	81
4-MeC_6H_4	H	Me	S	**5k**	66
3-$OHCC_6H_4$	H	Et	S	**5l**	68
3-$MeOC_6H_4$	H	Et	S	**5m**	61
2,4-$Cl_2C_6H_3$	H	Et	S	**5n**	64
2-ClC_6H_4	Me	Et	S	**5o**	75
2-ClC_6H_4	H	Me	S	**5p**	60
4-ClC_6H_4	H	Et	O	**5q**[c]	43
4-BrC_6H_4	H	Et	O	**5r**[c]	55
4-$NO_2C_6H_4$	H	Et	O	**5s**[c]	47
Et	H	Et	S	**5t**	82
Pr	H	Et	S	**5u**	68
$PhCH_2$	H	Et	S	**5v**	81

[a]General conditions: **1** (0.3 mmol), **2** (0.4 mmol), **3** (0.3 mmol), piperazine (0.15 mmol), TMSCl (0.6 mmol), *p*-TSA (0.15 mmol) in 4 mL DMF, stirred at 90 °C for 12 h. [b]Yield of isolated product. [c]Reactions in refluxing THF, piperazine (0.15 mmol), TMSCl (0.9 mmol) and *p*-TSA (0.3 mmol).

electron donating group (EDG) (Table 2, products **5a**–**5e**, **5i**–**5k**). A similar tendency occurred in the experiments using *N*-methyl thiourea (Table 2, products **5f**–**5h**). Attempts on employing EDG-substituted aldehydes such as *p*-tolylaldehyde to react with *N*-substituted thiourea and alkyne were not successful. On the other hand, benzaldehydes with *ortho*- and *meta*-substitution could also react with thioureas and propiolates to give the corresponding DHPMs **5l**–**5p**. However, compared with thiourea, urea has been found to undergo a similar transformation more toughly, and DHPMs **5q**–**5s** from urea reactions have been obtained with only moderate yields under the conditions of refluxing THF (Table 2, products **5q**–**5s**). Notably, this synthetic methodology displayed also good tolerance to aliphatic aldehydes to provide 4-alkyl DHPMs **5t**–**5v** with good to excellent yield (Table 2).

Following these obtained results, especially the key function of the secondary amine to activate electron deficient alkynes [34] we conducted the control experiments on both the synthesis of the possible enamino ester and its transformation to the corresponding DHPM product. The results proved that enamino ester **6a** could be easily generated and efficiently transformed to target product **5a** under standard conditions (without using secondary amine, Scheme 2).

Based on the results from the control experiments, we postulate the reaction mechanism: At first, the addition of the secondary amine to the propiolate gives enamino ester intermediate **6**. On the other hand, ureas/thioureas were known to be readily activated by TMSCl to give intermediate **10** [38,39]. Intermediate **10** consequently condenses with the aldehyde which was activated by *p*-TSA to generate imine **7**. The combination of **6** and **7** allows the production of iminium ion **8**. Finally, an intramolecular cyclization of **8** leads to the formation of **9** which subsequently undergoes deaminative elimination to result product **5** by releasing the amine catalyst for further recycling (Scheme 3).

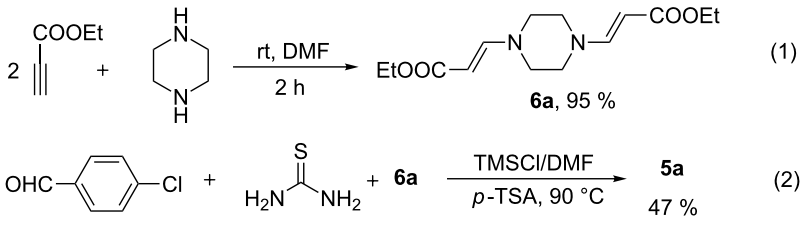
Conclusion

In conclusion, we have established an unprecedented amine-initiated three-component protocol for the synthesis of new DHPMs wherein readily available alkynes served as C5–C6 building blocks. This methodology displayed general applicability for aryl- and alkylaldehydes, urea, thiourea, *N*-substituted thiourea and different alkyl propiolates. The method is useful for the synthesis of diverse new DHPMs which were hardly accessible through known methods such as the Biginelli reaction.

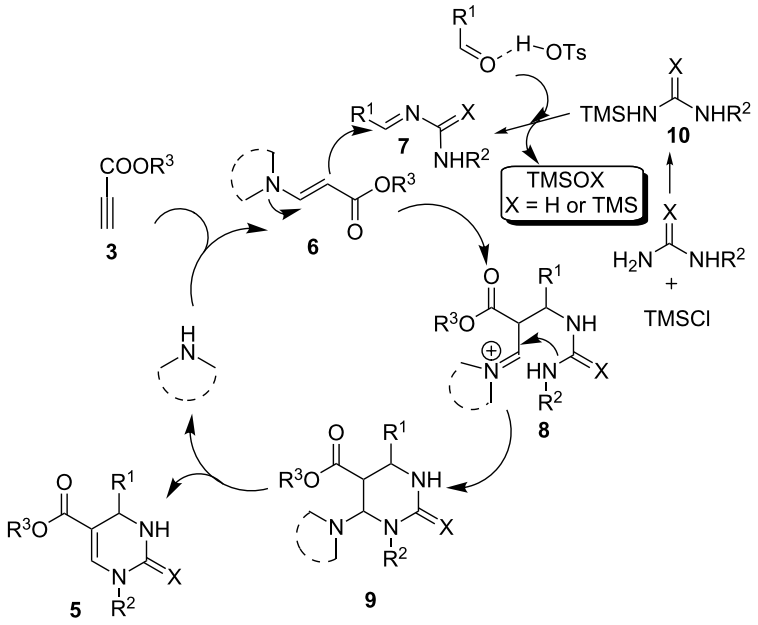
Experimental

General information

All reagents were obtained from commercial sources and used directly without further purification, solvents have been treated following standard processes prior to use. ^{1}H and ^{13}C NMR



Scheme 2: Synthesis of enamino ester intermediate and its transformation to DHPM.



Scheme 3: Proposed reaction mechanism.

spectra were recorded on a 400 MHz or 600 MHz apparatus. The frequencies for ^{1}H NMR and ^{13}C NMR experiments are 400 MHz/600 MHz and 100 MHz/150 MHz, respectively. The chemical shifts were reported in ppm employing TMS as internal standard. Melting points were measured with an X-4A instrument without correcting the temperature, IR spectra were measured in KBr on a Spectrum One apparatus and the HRMS were obtained under ESI mode in a Bruker 7-tesla FT-ICR MS instrument.

General procedure for the three-component synthesis of DHPMs **5**

Aldehyde **1** (0.3 mmol), urea/thiourea **2** (0.4 mmol) and alkyl propionate **3** (0.3 mmol) piperazine (0.15 mmol), and *p*-tolylsulfonic acid (0.15 mmol, 0.3 mmol for the reaction of urea) were charged in a 25 mL round bottom flask equipped with a stirring bar. DMF (THF for the reaction of urea) (4 mL) and TMSCl (0.6 mmol, 0.9 mmol for the reaction of urea) were added and the mixture was stirred at 90 °C for 12 h (TLC). After cooling down to room temperature, 5 mL water was added, and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The organic layers were combined and dried overnight with anhydrous $MgSO_4$. After filtration and removing of the solvent under reduced pressure, the residue was subjected to flash column chromatography to provide pure products.

Synthesis of intermediate 6a. Into a 25 mL round bottom flask was added ethyl propiolate (0.6 mmol) and piperazine (0.3 mmol). 1.5 mL DMF was added and the mixture was stirred at rt for 8 h (TLC). Upon completion, 10 mL water was added and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4. After removing of the solid by filtration and evaporation of the solvent the product **6a** was isolated as white solid.

Supporting Information

Supporting Information File 1

Experimental details on the synthesis of all DHPMs **5** and intermediate **6a**, full characterization data as well as ^{1}H and ^{13}C NMR spectra of all products **5** and **6a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-25-S1.pdf]

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The Flögel-three-component reaction with dicarboxylic acids – an approach to bis(β-alkoxy-β-ketoenamides) for the synthesis of complex pyridine and pyrimidine derivatives

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Full Research Paper

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Abstract

An extension of the substrate scope of the Flögel-three-component reaction of lithiated alkoxyallenes, nitriles and carboxylic acids is presented. The use of dicarboxylic acids allowed the preparation of symmetrical bis(β-ketoenamides) from simple starting materials in moderate yields. Cyclocondensations of these enamides to 4-hydroxypyridine derivatives or to functionalized pyrimidines efficiently provided symmetrically and unsymmetrically substituted fairly complex (hetero)aromatic compounds containing up to six conjugated aryl and hetaryl groups. In addition, subsequent functionalizations of the obtained heterocycles by palladium-catalyzed couplings or by oxidations are reported. We also describe the simple synthesis of a structurally interesting macrocyclic bispyrimidine derivative incorporating a 17-membered ring, whose configuration was elucidated by DFT calculations and by subsequent reactions.

Introduction

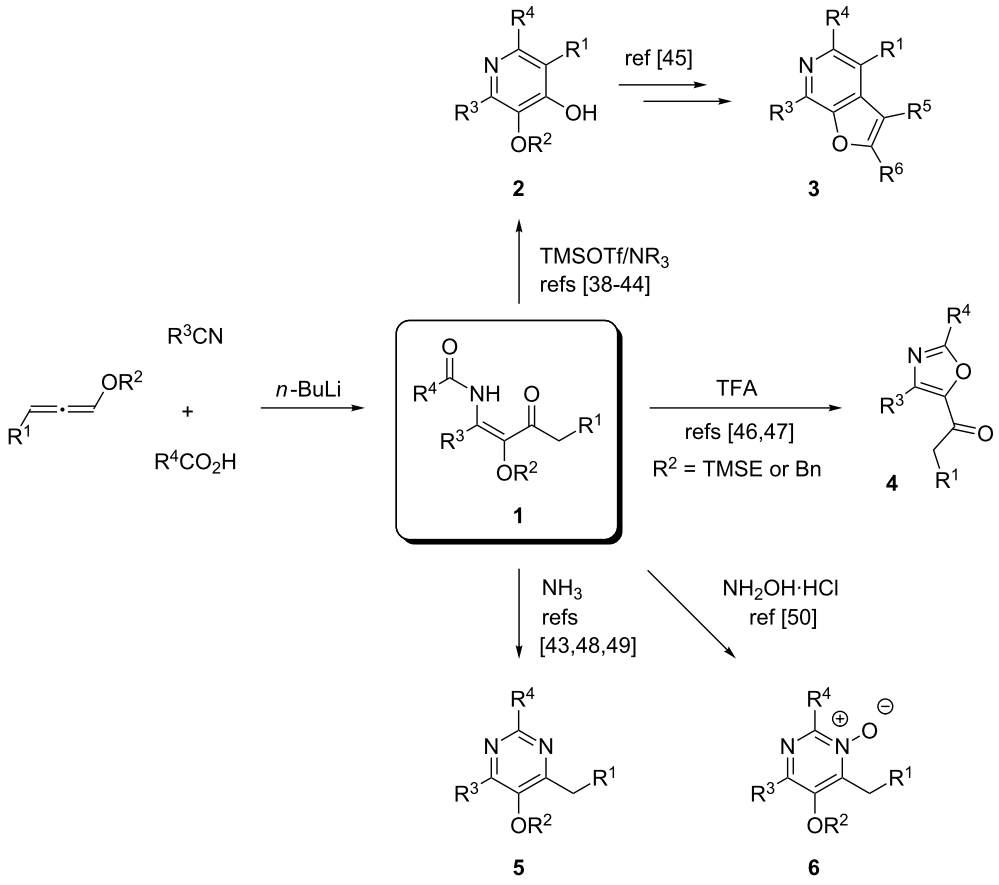
Multicomponent reactions (MCRs) generally allow a diversity-oriented fast and efficient access to complex synthetic intermediates and are thus powerful tools for the assembly of small-molecule libraries [1,2]. MCRs leading to functionalized *N*-heterocycles [3-7] have long been known before the general concept of MCRs was introduced, e.g. the Hantzsch dihydropyridine synthesis [8] or the Biginelli reaction [9] leading to dihydropyrimidinones or the corresponding dihydropyrimidinethiones. Due to their general importance (e.g. as biologically active compounds) the development of efficient protocols for the preparation of functionalized pyridine [10-20] and pyrimidine derivatives [21-33], in particular by MCRs, is of

permanent high interest. In the course of exploring the reactivity of alkoxyallenes and their utilization as C-3 building blocks [34-37] our group developed a highly flexible method to synthesize β-alkoxy-β-ketoenamides of type **1** that are remarkably versatile cyclization precursors for the synthesis of functionalized heterocycles such as 4-hydroxypyridines [38-44], furopyridines [45], 5-acetyloxazoles [46,47], pyrimidines [43,48,49] and their corresponding *N*-oxides [50] (Scheme 1). This approach – discovered and mechanistically elucidated by Oliver Flögel – features a three-component reaction that employs alkoxyallenes, nitriles and carboxylic acids: upon treatment with *n*-butyllithium the allene is lithiated in α-position to the alkoxy moiety; the addition of a nitrile as electrophile to this highly reactive nucleophile results in the formation of an iminoallene adduct [38] that is protonated and subsequently acylated by the addition of a carboxylic acid furnishing a β-alkoxy-β-ketoenamide **1**. A detailed mechanistic proposal for this reaction has been disclosed in previous reports [38,39].

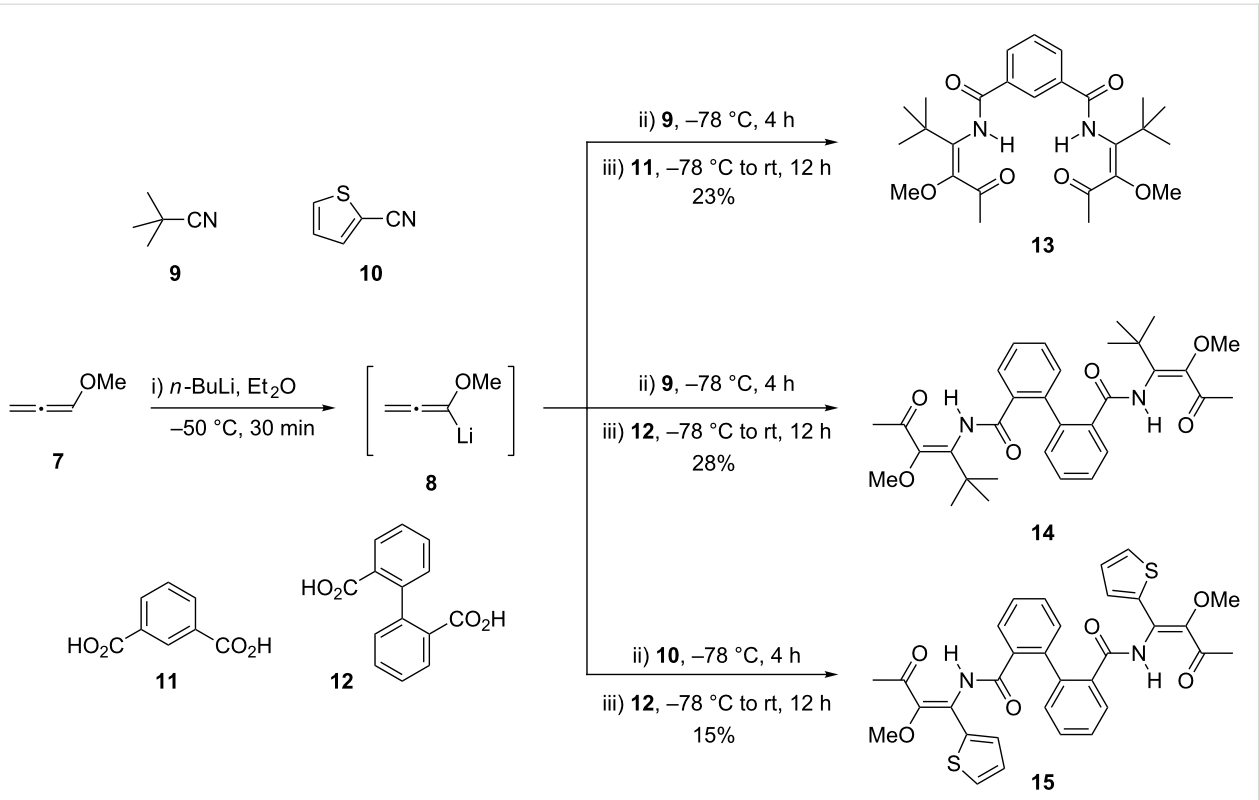
Our earlier investigations revealed that this method tolerates a broad variety of differently substituted starting materials – inter alia (het-)aromatic and (branched) aliphatic nitriles and carboxylic acids. It is also noteworthy to mention that the configurational integrity of enantiopure α-chiral carboxylic acids and/or nitriles is retained during this reaction [40]. In the present report we describe our efforts to further broaden the substrate scope of this multicomponent reaction and the subsequent cyclizations by employing aromatic dicarboxylic acids. This extension should allow a rapid access to fairly complex heteroaromatic systems containing up to six conjugated aryl and hetaryl groups. Complementary examples employing aromatic dinitriles in this Flögel-three-component reaction have previously been presented [39].

Results and Discussion

As typical model substrates we chose to employ isophthalic acid (**11**) and diphenic acid (**12**) in combination with methoxyallene (**7**), pivalonitrile (**9**) and thiophene-2-carbonitrile (**10**) in the three-component reaction (Scheme 2). Gratifyingly we were able to isolate the expected bis(β-ketoenamides) **13**–**15** in reasonable yields of 15–28%. Taking the number of individual steps into account (six new bonds are formed for



Scheme 1: Flögel-three-component reaction of lithiated alkoxyallenes, nitriles and carboxylic acids providing β-alkoxy-β-ketoenamides **1** – versatile precursors for the synthesis of functionalized *N*-heteroaromatics **2**–**6**.

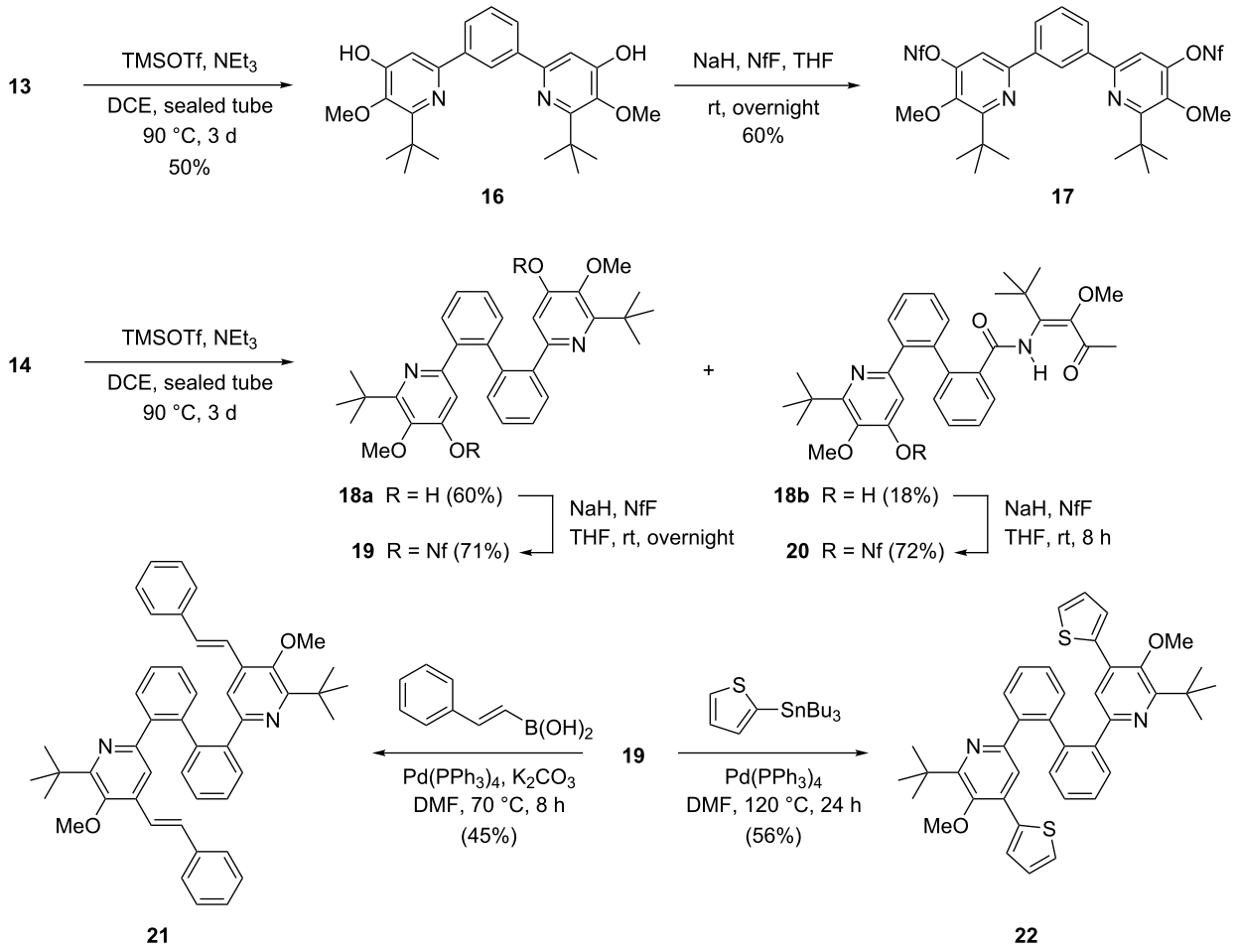


Scheme 2: Synthesis of bis(β-ketoenamides) **13**–**15** by three-component reactions of lithiated methoxyallene **8** with nitriles **9** or **10** and isophthalic acid (**11**) or diphenic acid (**12**).

each product) and considering possible (unknown) side reactions these yields are quite satisfactory. In analogy to our previously published results [38,51,52] the double bond geometry of the enamide moiety is likely to be *E*-configured as shown in Scheme 2, allowing an intramolecular hydrogen bridge between the amide NH and the β-carbonyl group. However, we did not further investigate the nature of the double bond geometry, since it was irrelevant for the planed subsequent cyclization reactions where the (Lewis-)acidic conditions allow a facile isomerization of *E*- and *Z*-configured enamide moieties [51,52], finally leading to identical products.

After these successful multicomponent reactions we investigated the intramolecular condensations of the bis(β-ketoenamides) **13**–**15** to pyridine and pyrimidine derivatives. Enamides **13** and **14** were treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine to provide the bis(4-hydoxypyridines) **16** in 50% yield and **18a** in 60% yield, respectively (Scheme 3). A mechanistic proposal for this aldol type condensation has been presented in a previous report [53]. For precursor **14** partial monocyclization was observed under the applied conditions, affording in 18% yield 4-hydroxypyridine **18b** with a retained β-ketoenamide moiety. Treatment of compounds **16**, **18a** and **18b** with sodium hydride followed by nonafluorobutanesulfonyl fluoride (NfF) provided the corresponding sulfonates **17**, **19** and **20** in yields in the range of 60–72%. Pyrid-4-yl nonaflates are excellent precursors for transition metal-catalyzed cross-coupling reactions [42,54-58], which was demonstrated here by the successful Suzuki coupling of bisnonaflate **19** with (*E*)-styrylboronic acid and the Stille coupling of **19** with 2-(tributylstannyl)thiophene. Albeit the expected twofold coupling products **21** and **22** were obtained in only moderate yields, the presented approach nevertheless features a quite rapid access to these fairly complex heteroaromatic systems containing six conjugated aryl and hetaryl groups. Upon excitation with UV light (253 nm) compound **22** shows fluorescence with a maximum intensity at 378 nm (see Supporting Information File 1 for details). The photophysical properties of structurally related pyridine–thiophene conjugates were recently investigated in detail [55,57,58].

Next, we investigated the cyclocondensation of bis(β-ketoenamides) **13**–**15** to pyrimidines (Scheme 4) using ammonium acetate as ammonia source. Initially we subjected enamide **13** to conditions that had been optimized for mono-β-ketoenamides [48,49], in this case resulting in incomplete conversion: after heating **13** with 8 equiv of ammonium acetate in a sealed tube we obtained a 1:1 mixture of bis(pyrimidine) derivative **23a** and

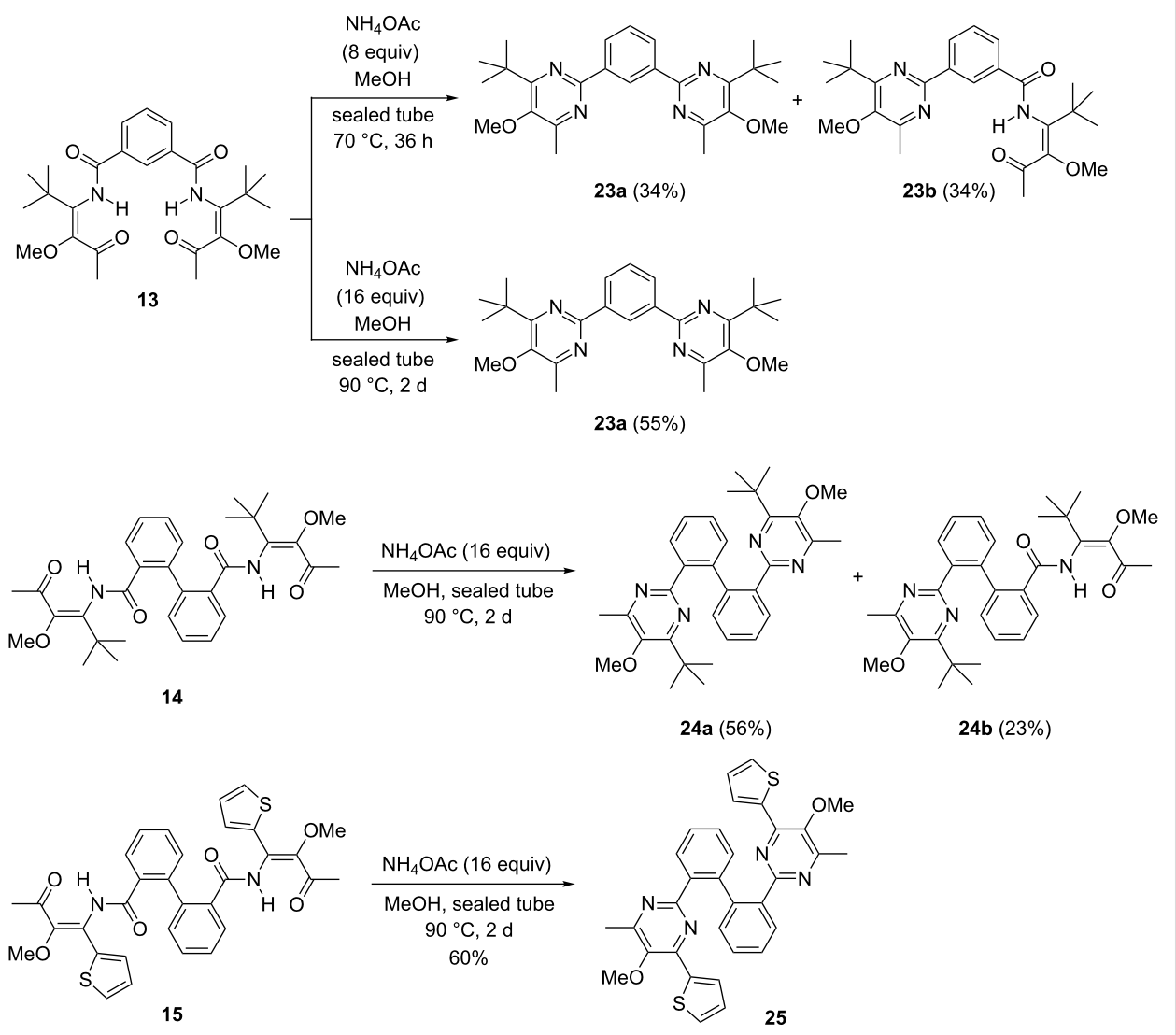


Scheme 3: Cyclocondensations of β-ketoenamides **13** and **14** to 4-hydroxypyridines **16**, **18a** and **18b**, their subsequent nonaflations and palladium-catalyzed coupling reactions of **19** leading to compounds **21** and **22**. NfF = $C_4F_9SO_2F$

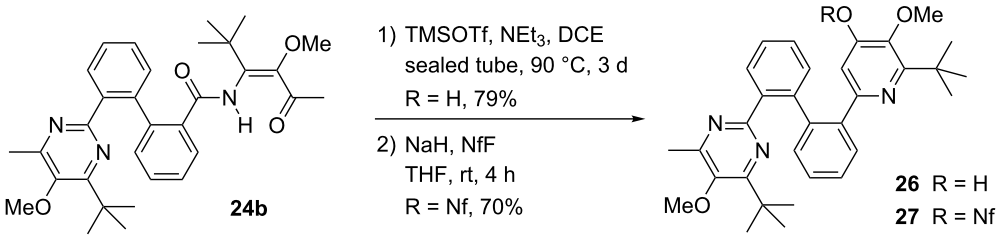
pyrimidine **23b** still containing one β-ketoenamide unit with an overall yield of 68%. However, full conversion of **13** into **23a** was achieved by increasing the amount of ammonium acetate to 16 equiv and using a higher reaction temperature, raising the yield of **23a** from 34% to 55% yield. When enamide **14** was cyclized under these optimized conditions the conversion was nevertheless incomplete giving the desired bis(pyrimidine) derivative **24a** in 56% yield and the corresponding mono-pyrimidine **24b** in 23% yield. For enamide **15** however, the cyclization was complete under these conditions furnishing bis(pyrimidine) derivative **25** as a single product in 60% yield.

Although initially not desired the incomplete conversions of the bis(β-ketoenamides) leading to mono-pyridine derivatives such as **18b** or to mono-pyrimidine derivatives like **23b** and **24b** provided new synthetic options to construct unsymmetrically substituted mixed heteroaromatic systems. As an example we used mono-pyrimidine derivative **24b** and cyclized its β-ketoenamide moiety by treatment with TMSOTf and triethylamine. Pyrimidine/pyridinol derivative **26** was isolated in 79% yield (Scheme 5) and subsequently converted into the corresponding nonaflate **27** in 70% yield.

As recently described, β-alkoxy-β-ketoenamides may also be directly cyclized to pyrimidine-*N*-oxides under mild conditions if hydroxylamine hydrochloride is used as reagent [50]. Accordingly, the reactions of β-ketoenamides **14** and **20** with hydroxylamine hydrochloride provided the symmetric bis(pyrimidine-*N*-oxide) **28** in 39% yield or the mono-pyrimidine-*N*-oxide **30** in 54% yield (Scheme 6). The acetoxylation of 2- and 4-alkyl substituted pyridine-*N*-oxides by treatment with acetic anhydride is known as the Boekelheide rearrangement [59,60]. For pyrimidine-*N*-oxides however, only few examples of this type of transformation have been reported [50,61-65]. Therefore we were pleased to find that upon treatment with acetic anhydride the obtained pyrimidine-*N*-oxides **28** and **30** smoothly under-

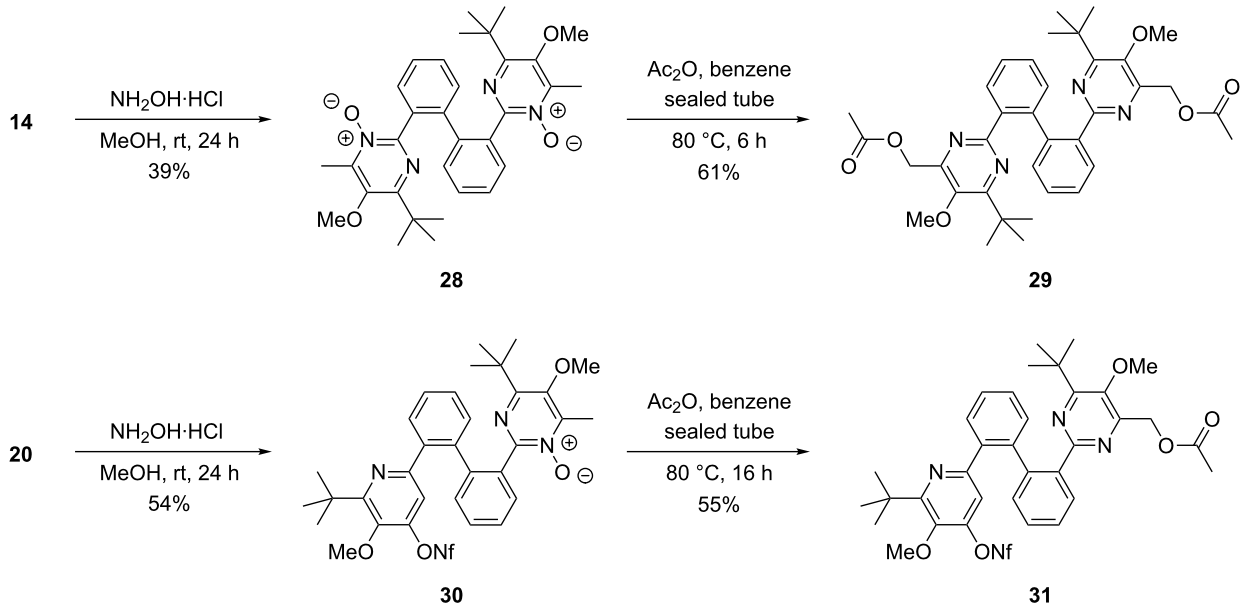


Scheme 4: Cyclocondensations of β-ketoenamides **13–15** with ammonium acetate to bis(pyrimidine) derivatives **23a**, **24a** and **25** and mono-pyrimidines **23b** and **24b**.



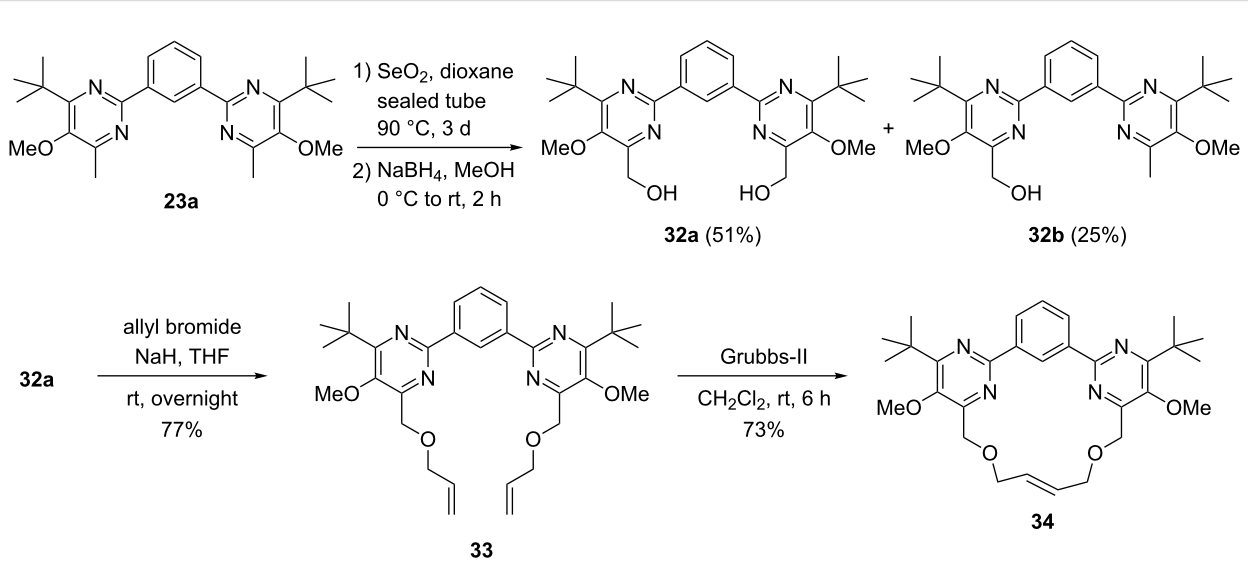
Scheme 5: Conversion of mono-pyrimidine derivative **24b** into unsymmetrically substituted biphenylen-bridged pyrimidine/nonafloxypyridine conjugate **27**. NfF = $C_4F_9SO_2F$

went the expected rearrangement to give the acetoxymethyl-substituted pyrimidine derivatives **29** and **31** in 61% and 55% yield, respectively. This approach thus allows the simple functionalization of the 4-methyl group of the pyrimidine derivatives and is a very useful tool for the preparation of other compounds.



Scheme 6: Condensation of β-ketoenamides **14** and **20** with hydroxylamine hydrochloride to pyridine-*N*-oxides **28** and **30** and their subsequent Boekelheide rearrangements furnishing functionalized bis(pyrimidine) derivative **29** and pyrimidine/pyridine conjugate **31**.

An alternative option for the side chain functionalization of 4- or 6-methyl substituted pyrimidines involves an oxidation with selenium dioxide (Riley oxidation [66-68]). To explore the synthetic potential of the newly prepared compounds we exemplarily oxidized bis(pyrimidine) **23a** by this method in order to finally prepare a macrocyclic compound such as **34** (Scheme 7). Treatment of **23a** with an excess of selenium dioxide at 90 °C resulted in the formation of an inseparable mixture of two different aldehydes (probably the dialdehyde and the monoaldehyde). After reduction of the mixture with sodium borohydride the obtained products could be separated by column chromatography providing the dialcohol **32a** in 51% yield over two steps and the monoalcohol **32b** in 25% yield, respectively. The subsequent O-allylation of **32a** furnished bisallyl ether **33** with 77% yield that was subjected to a ring closing metathesis (RCM) [69] with Grubbs-II-catalyst smoothly leading to the struc-



Scheme 7: Riley oxidation of bis(pyrimidine) derivative **23a** and conversion of diol **32a** into macrocycle **34**.

turally interesting macrocyclic compound **34** in 73% yield. Compounds of this type – incorporating a 17-membered ring – have the potential to serve as structurally quite unique ligands for a variety of applications, e.g. in catalysis.

With ruthenium-based catalysts bearing *N*-heterocyclic carbene (NHC) ligands, RCM usually delivers macrocyclic olefins as mixtures of *E*- and *Z*-isomers, in most cases in favor of the *E*-isomer [70-73]. The *E*/*Z*-ratio is often under thermodynamic control, reflecting the energy difference between the two isomers. According to TLC and NMR spectroscopy, macrocycle **34** was isolated as a single compound. Due to the symmetry of **34** no couplings of the olefinic protons in its ^{1}H NMR spectrum can be observed. Thus at this stage, we were unable to assign the configuration of the double bond. In lack of suitable crystals for an X-ray analysis, we calculated the energy for the two possible isomers of **34**, suggesting that the *E*-isomer should be considerably more stable than the corresponding *Z*-isomer (Table 1). Using the semi-empirical AM1 method an energy difference of $\Delta E_{Z\text{-}E}$ of 28.7 kJ/mol was determined. DFT calculations using the B3LYP method with the basis sets 6-31(d) or 6-31G(d,p) both gave a $\Delta E_{Z\text{-}E}$ value of 16.4 kJ/mol. This energy difference may be attributed to the strain of the macrocycle and higher torsion angles between the central benzene unit and the pyrimidine rings for the *Z*-isomer of **34**, resulting in less efficient conjugation of the aromatic π-systems.

The optimized molecular geometries of *E*-**34** and *Z*-**34** as well as the calculated torsion angles are depicted in Figure 1.

Table 1: Calculated relative energy differences of the *Z*- and *E*-configured isomers of macrocycle **34**.

Entry	Method	$\Delta E_{Z\text{-}E}$ (kJ/mol)
1	AM1	28.7
2	B3LYP/6-31(d)	16.4
3	B3LYP/6-31G(d,p)	16.4

In order to unambiguously identify the double bond configuration of **34**, we oxidized this compound with potassium osmate/NMO to obtain the vicinal diol **35** in 76% yield (Scheme 8). In the case of a *Z*-configured olefin **34** this dihydroxylation should give a *cis*-configured diol (meso compound), whereas an *E*-configured olefin **34** would lead to a racemic mixture of the corresponding *trans*-configured diol. However, due to the symmetry of both vicinal diols a distinction between *cis*- and *trans*-**35** (σ_v- or C_2-symmetry respectively) by NMR is still not possible. The resulting diol **35** was therefore treated with an excess of (*S*)-Mosher's acid chloride to obtain the bis-(*R*)-Mosher ester **36** [74]. TLC analysis and NMR-spectroscopy revealed, that compound **36** was obtained as a pair of C_2-symmetric diastereomers and that the obtained diol **35** was

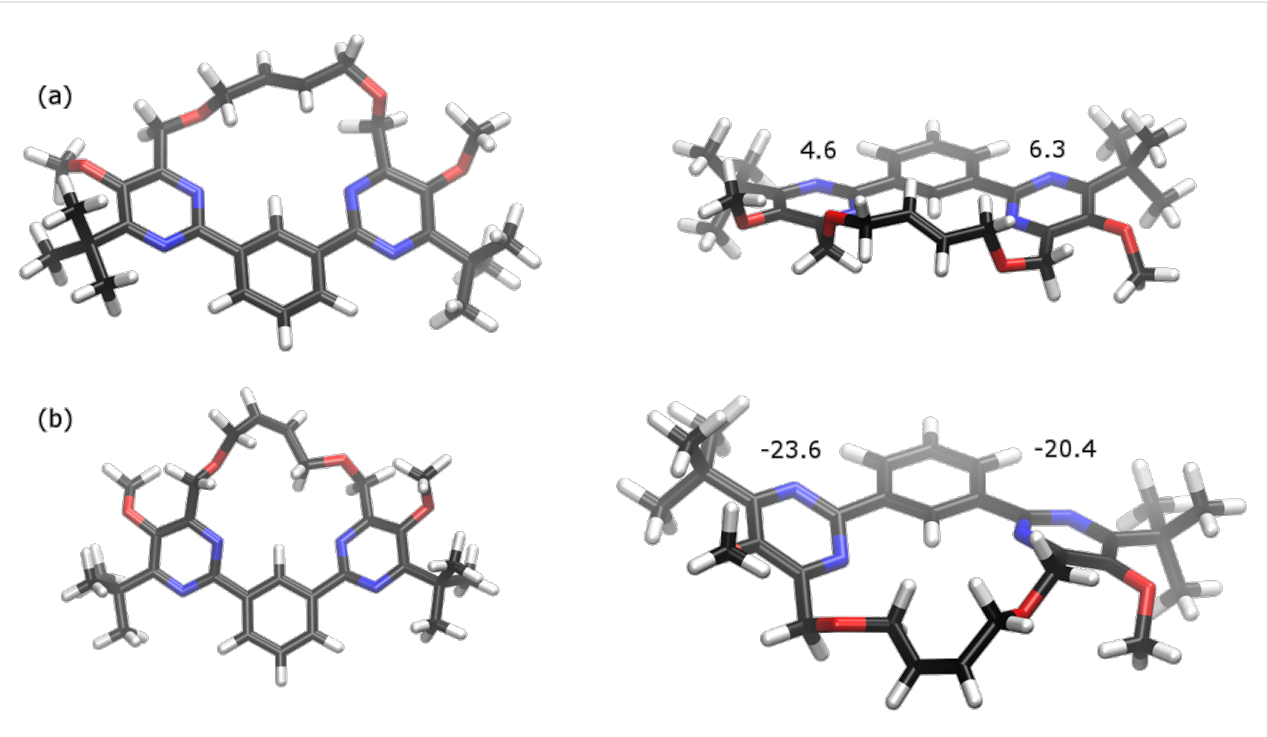
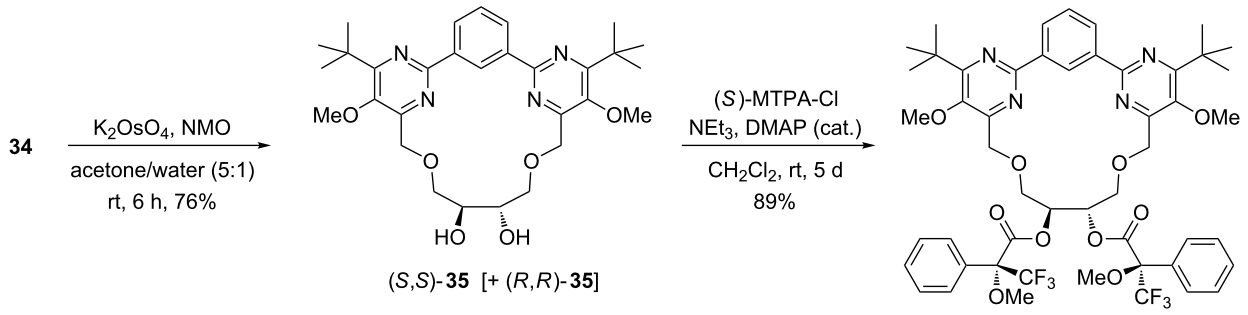


Figure 1: Optimized geometries of (a) *E*-configured and (b) *Z*-configured macrocycle **34** at B3LYP/6-31G(d,p) level. The numbers represent the calculated torsion angles between the aromatic rings.



Scheme 8: Dihydroxylation of the macrocyclic olefin **34** to diol **35** and subsequent esterification to the bis-(*R*)-Mosher ester **36**; (*S*)-MTPA-Cl = (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride.

in fact a racemic mixture. This observation allowed the conclusion that the RCM reaction of **33** produced the expected thermodynamically more stable *E*-configured macrocyclic olefin **34**. Hence this experimental result is in perfect agreement with the DFT calculations.

Conclusion

We were able to extend the substrate scope of the Flögel-three-component reaction of alkoxyallenes, nitriles and carboxylic acids by successfully utilizing aromatic dicarboxylic acids to prepare three new bis(β-methoxy-β-ketoenamides). With these products of a multicomponent reaction we performed cyclizations to rapidly construct symmetrically and unsymmetrically substituted pyridine and pyrimidine derivatives. Hence a very short approach to fairly complex functionalized oligoaromatic systems was established. In addition we exemplarily investigated subsequent transformations of these compounds either by palladium-catalyzed cross-couplings or by oxidations of the 4-methyl groups of the pyrimidine subunits. Although the yields for the crucial initial multicomponent reactions leading to the bis(β-methoxy-β-ketoenamides) are only moderate when dicarboxylic acids are used the simplicity of the processes and the diversity of the products accessible is impressive. The described methods allow the preparation of oligo(hetero)aromatic compounds not available by alternative procedures.

Experimental

General methods

Reactions were performed under an atmosphere of argon in flame-dried flasks. Solvents and liquid reagents were added by syringe. Et_2O, CH_2Cl_2 and THF were transferred from a MB SPS-800-dry solvent system into the reaction vessels. Dry DMF was purchased from Acros Organics and stored in the presence of molecular sieve under an atmosphere of argon. NEt_3 was distilled from CaH_2 and stored over KOH under argon. Methoxyallene was prepared from propargylic alcohol in two steps according to literature procedures [34,75]. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. Thin-layer chromatography (TLC) analyses were performed on TLC plates purchased from Merck (silica gel 60, fluorescence indicator F254, 0.25 mm layer thickness). Products were purified by flash column chromatography on silica gel 60 (230–400 mesh, Macherey-Nagel). NMR spectra were recorded with Bruker (AC 500, AVIII 700) and JEOL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to solvent residual peaks or TMS. Integrals are in accordance with assignments, and coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. ^{13}C NMR signals of Nf-groups [$CF_3(CF_2)_3$] are not given since unambiguous assignment is not possible due to strong splitting by coupling with the ^{19}F nuclei. IR spectra were measured with a Jasco FT/IR-4100 spectrometer. HRMS analyses were performed with a Varian Ionspec QFT-7 (ESI–FT ICRMS) or an Agilent 6210 (ESI–TOF) instrument. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

Three-component-reaction of methoxyallene, nitriles and dicarboxylic acids (typical procedure 1)

To a solution of methoxyallene (**7**, 2.07 g, 29.6 mmol) in dry Et_2O (25 mL) was added *n*-BuLi (10.8 mL, 27.0 mmol, 2.5 M in hexanes) at −50 °C. After 30 min stirring at −50 °C, the reaction mixture was cooled to −78 °C and pivalonitrile (**9**, 0.752 g, 9.06 mmol) in dry Et_2O (10 mL) was added to the mixture. After stirring for 4 h a suspension of diphenic acid (**12**, 6.54 g, 27.0 mmol) in dry Et_2O (50 mL) was added. The temperature was allowed to rise to rt and the mixture was stirred overnight. The reaction was quenched with sat. aq $NaHCO_3$ solution (25 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with brine (25 mL), dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure and

the obtained crude product was purified by column chromatography (silica gel, hexanes/EtOAc = 1:2) to provide bis(β-ketoenamide) **14** (1.39 g, 28%) as a pale yellow solid.

***N*^{2},*N*$^{2'}$-Bis(4-methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl)biphenyl-2,2'-dicarboxamide** (**14**): mp 140–143 °C; IR (ATR) ν: 3145 (NH), 3040–2835 (=C-H, C-H), 1695 (C=O), 1525–1390 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (s, 18H, *t*-Bu), 2.09 (s, 6H, Me), 3.42 (s, 6H, OMe), 7.07–7.09, 7.31–7.37, 7.49–7.51 (3 m, 2H, 4H, 2H, Ar), 8.13 (br s, 2H, NH) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 27.6 (q, Me), 28.4, 36.5 (q, s, *t*-Bu), 58.8 (q, OMe), 127.0, 127.9, 129.6, 130.4 (4 d, Ar), 131.9, 136.4, 138.4, 151.0 (4 s, C=C, Ar), 169.5 (s, CONH), 200.1 (s, C=O) ppm; ESI–TOF (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{40}N_2NaO_6$, 571.2779; found, 571.2783.

Cyclization of β-ketoenamides to 4-hydroxypyridines (typical procedure 2)

Bis(β-ketoenamide) **14** (0.310 g, 0.57 mmol) was placed in an ACE-sealed tube and dissolved in DCE (10 mL). NEt_3 (0.40 mL, 2.89 mmol) and TMSOTf (0.50 mL, 2.76 mmol) were added and the resulting mixture was stirred at 90 °C for 3 d. After cooling to rt the reaction was quenched with sat. aq NH_4Cl solution (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the obtained crude product was purified by column chromatography (silica gel, EtOAc) to provide bis(4-hydroxypyridine) **18a** (0.174 g, 60%) as a brown liquid and **18b** (54 mg, 18%) as pale yellow oil. The products were directly converted into the corresponding nonaflates **19** and **20**.

Nonaflation of 4-hydroxypyridines (typical procedure 3)

Bis(4-hydroxypyridine) **18a** (0.805 g, 1.57 mmol) was dissolved in THF (25 mL) and NaH (0.313 g, 7.86 mmol, 60% in mineral oil) was added under argon atmosphere. Nonafluorobutanesulfonyl fluoride (2.35 g, 7.79 mmol) was added dropwise and the mixture was stirred at rt for 12 h. After dilution with Et_2O (25 mL), the reaction was slowly quenched with ice and water (25 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 9:1 to 4:1) to provide pyridyl nonaflate **19** (1.20 g, 71%) as a pale yellow oil.

6,6'-(Biphenyl-2,2'-diyl)bis(2-*tert*-butyl-3-methoxypyridine-6,4-diyl) bisnonaflate (**19**): IR (ATR) ν: 3065–2870 (=C-H, C-H), 1555–1410 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.19 (s, 18H, *t*-Bu), 3.89 (s, 6H, OMe), 6.92 (s, 2H, Py), 7.10 (dd, *J* = 7.5, 1.2 Hz, 2H, Ar), 7.30 (td, *J* = 7.5, 1.4 Hz, 2H, Ar), 7.36 (dd, *J* = 7.5, 1.4 Hz, 2H, Ar), 7.59 (dd, *J* = 7.5, 1.2 Hz, 2H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 29.1, 38.7 (q, s, *t*-Bu), 61.7 (q, OMe), 115.2 (d, Py), 127.4, 128.6, 130.1, 131.6 (4 d, Ar), 138.2, 140.6 (2 s, Ar), 145.3, 149.3, 153.2, 163.7 (4 s, Py) ppm; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −80.6 (t, *J* = 9.6 Hz, 6F, CF_3), −109.5 (t, *J* = 13.7 Hz, 4F, CF_2), −120.7, −125.8 (2 m_c, 4F each, CF_2) ppm; ESI–TOF (*m*/*z*): $[M + Na]^+$ calcd for $C_{40}H_{34}F_{18}N_2NaO_8S_2$, 1099.1361; found, 1099.1394.

Cyclization of β-ketoenamides to pyrimidines (typical procedure 4)

Bis(β-ketoenamide) **14** (0.162 g, 0.296 mmol) and NH_4OAc (0.365 g, 4.73 mmol) were placed in an ACE-sealed tube. The mixture was dissolved in MeOH (5 mL) and stirred for 2 d at 90 °C. After addition of H_2O (10 mL) and Et_2O (20 mL) the layers were separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 5:1) to provide pyrimidines **24a** (88 mg, 56%) and **24b** (35 mg, 23%), both as colorless oils.

2,2'-Bis(4-*tert*-butyl-5-methoxy-6-methylpyrimidin-2-yl)biphenyl (**24a**): IR (ATR) ν: 3070–2855 (=C-H, C-H), 1550–1440 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (s, 18H, *t*-Bu), 2.28 (s, 6H, Me), 3.70 (s, 6H, OMe), 7.30 (dt, *J* = 7.7, 1.9 Hz, 2H, Ar), 7.34–7.39 (m, 4H, Ar), 7.70 (dd, *J* = 7.7, 1.0 Hz, 2H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 19.7 (q, Me), 28.7, 37.6 (q, s, *t*-Bu), 60.9 (q, OMe), 126.4, 128.7, 130.2, 131.4 (4 d, Ar), 138.4, 142.6 (2 s, Ar), 149.8, 159.3, 159.4, 166.9 (4 s, Py) ppm; ESI–TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{32}H_{39}N_4O_2$, 511.3068; found, 511.3085.

2'-(4-*tert*-Butyl-5-methoxy-6-methylpyrimidin-2-yl)-*N*-(4-methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl)biphenyl-2-carboxamide (**24b**): IR (ATR) ν: 3325 (N-H), 3065–2865 (=C-H, C-H), 1700, 1665 (C=O), 1550–1445 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (s, 9H, *t*-Bu), 1.26 (s, 9H, *t*-Bu), 2.31, 2.33 (2 s, 3H each, Me), 3.45, 3.70 (2 s, 3H each, OMe), 6.64 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar), 7.07, 7.25 (2 dt, *J* = 7.5, 1.2 Hz, 1H each, Ar), 7.32 (dd, *J* = 7.5, 1.2 Hz, 1H, Ar), 7.39 (dt, *J* = 7.5, 1.8 Hz, 1H, Ar), 7.43 (dt, *J* = 7.5, 1.0 Hz, 1H, Ar), 7.50 (dd, *J* = 7.8, 1.2 Hz, 1H, Ar), 7.91 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar), 8.40 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 19.2 (q, Me), 27.2 (q, Me), 28.1, 29.2, 35.9, 37.9 (2 q, 2 s, *t*-Bu), 58.9, 61.0 (2 q, OMe), 126.8, 127.9, 128.0, 128.5, 129.0, 129.4, 130.3, 130.7, 131.0 (8 d, s, Ar, =C), 137.5, 138.4,

138.9, 140.5, 150.1 (5 s, Ar, =C), 150.4, 159.6, 160.0, 168.4 (4 s, Py), 169.3 (s, CONH), 199.8 (s, C=O) ppm; ESI–TOF (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{34}N_3NaO_4$, 552.2833; found, 552.2844.

Supporting Information

Supporting Information File 1

Additional experimental procedures and analytical data, as well as copies of NMR spectra of representative examples.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-37-S1.pdf]

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A new manganese-mediated, cobalt-catalyzed three-component synthesis of (diarylmethyl)sulfonamides

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Letter

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Abstract

The synthesis of (diarylmethyl)sulfonamides and related compounds by a new manganese-mediated, cobalt-catalyzed three-component reaction between sulfonamides, carbonyl compounds and organic bromides is described. This organometallic Mannich-like process allows the formation of the coupling products within minutes at room temperature. A possible mechanism, emphasizing the crucial role of manganese is proposed.

Introduction

(Diarylmethyl)amines constitute an important class of pharmacologically active compounds, displaying e.g. antihistaminic, antiarrhythmic, diuretic, antidepressive, laxative, anesthetic and anticholinergic activities [1-5]. These attractive properties have made them prominent synthetic targets for the organic chemist and various strategies, including for instance arylation of iminium salts [6], displacement of polymer-supported benzotriazole [7] with arylmagnesium reagents, addition of phenyllithium to selenoamides [8], addition of organometallic species [9-21] or arylboronic acids [22-27] to imines, reaction of organolithium and Grignard reagents with thioformamides [28], multistep reactions involving carbonyl compounds [29,30], intramolecular electrophilic arylation of lithiated ureas [31], and Petasis-type multicomponent reaction [32-34] have been reported for their preparation. Although these methods propose complementary approaches to the synthesis of (diarylmethyl)amines, their scope might be hampered by functional group incompatibilities or the number of steps. In addition, no straightforward and tunable method currently exists for the one-step preparation of (diarylmethyl)amines in N-protected form. Consequently, we felt that a multicomponent procedure intended to the synthesis of N-protected (diarymethyl)amines and related compounds would be highly desirable.

In preceding works, we described the Mannich-like multicomponent synthesis of α-branched amines from organic halides, aldehydes and amines, using a zinc-mediated process [35-38]. Although the scope of the reaction was demonstrated to be quite

broad, some limitations were noticed, especially in reactions involving aryl halides. For instance, primary amines and enolizable aldehydes were unusable in this process. As a part of our ongoing efforts to improve reliability and versatility of multicomponent procedures, we describe herein a new manganese-mediated, cobalt-catalyzed three-component reaction, which circumvents the above-mentioned limitations by allowing the synthesis of an extended range of (diarylmethyl)sulfonamides (and related compounds) within minutes at room temperature. To the best of our knowledge, this constitutes the first manganese-mediated multicomponent reaction involving aryl halides as the source for nucleophilic species.

Results and Discussion

We previously reported that primary amines are not active in a Mannich-like multicomponent reaction with aldehydes and arylzinc compounds [37]. It was assumed that the imine, which is initially formed by a condensation of the aldehyde and the amine, is not sufficiently electrophilic to undergo a coupling with the arylzinc compound. Considering the increased electrophilicity of sulfonylimines, we aimed to use sulfonamides as potential synthetic equivalents of ammonia in a procedure that additionally avoids the preformation of an imine and/or an organometallic compound. Thus, we turned our attention to a multicomponent reaction between aldehydes, aryl halides and sulfonamides, which involves an in situ activation (Barbier conditions) of the aryl halide by cobalt salts in the presence of a reducing metal. Initial experiments employed zinc as the reducing agent and were carried out under standard conditions. However, only trace amounts of the coupling product were detected in the reaction mixture. A screening of the reducing metal was then performed and revealed that only manganese is active in the process. Other reaction conditions such as the amount of reagents and catalyst, the solvent, the reaction time, the temperature and the nature of the halogen atom were also examined. The results are reported in Table 1.

As mentioned above, metals other than manganese did not work in the reaction (Table 1, entries 1–7). In accordance with previously reported works, a minimum of two equiv of the halide were required for the reaction to take place. However, yields were noticeably improved by using 3 equiv of the halide (Table 1, entry 8) or 2.5 equiv (Table 1, entry 9) instead of 2 equiv (Table 1, entry 10). The amount of manganese was also of crucial importance. Indeed, whereas an increase to 15 equiv (Table 1, entry 11) led to a slightly improved yield, a decrease to 7.5 (Table 1, entry 12) or even 5 equiv (Table 1, entry 13) resulted in a dramatic decrease of the yield, which dropped to 32% in the latter case. However, the usage of an increased amount of manganese led to a more challenging work-up and the generation of more metallic waste. Consequently, for practical and environmental reasons, we chose to keep 10 equiv of manganese for the rest of the study. In general, the reaction proceeded very quickly and came to completion within 10 min at room temperature. An extended reaction time (20 min) did not result in a notably improved reaction yield (Table 1, entry 14).

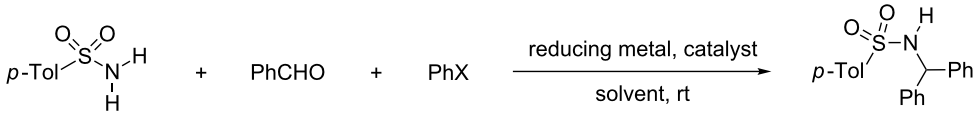
Bromides proved to be the most efficient halides. Indeed, while the reaction also worked with iodides (Table 1, entry 15), albeit in lower yield, it did not work with chlorides (Table 1, entry 16). A decrease of the amount of cobalt salts to 10 mol % (Table 1, entry 17) or 1.5 mol % (Table 1, entry 18) resulted in a significant decrease of the reaction efficiency, thus indicating the prevalent role of the catalyst. This was confirmed by the absence of the coupling product when the reaction was conducted in the absence of cobalt bromide (Table 1, entry 19). Another nickel-based catalyst, e.g., $NiBr_2$bpy, was not active under standard conditions (Table 1, entry 20), and solvents other than acetonitrile did not allow the reaction to proceed (Table 1, entries 21 to 24).

The scope of the reaction was then investigated by using various sulfonamides **1**, aldehydes **2** and organic bromides **3**, and the results are presented in Table 2.

Results indicated a rather broad functional tolerance of the reaction, although some yields are limited and might be likely improved under more specific conditions. In all cases, the organic bromide was completely consumed and the main side-products were the imine and the biaryl. The imine results from the reaction of the tosylamide with the aldehyde, and the biaryl was formed by reductive coupling of the starting halide. A preformed imine can be used in the process (Table 2, entry 3, result in brackets), indicating that this species might be the reactive electrophilic intermediate of the reaction. Aryl halide is generally prone to dimerization under such reductive conditions. Thus, we assume that if the imine is formed slowly or is less reactive, the more rapid consumption of the halide results in the lack of a nucleophilic partner in the reaction medium. In this case, the imine remains partly unconsumed at the end of the process. Nevertheless, we were pleased to observe that the reaction works with enolizable aldehydes (Table 2, entries 4 and 5), a notable result considering the acidity of the protons α to the carbonyl. Logically, Ms-containing sulfonamides (Table 2, entries 12–15) worked in the same fashion as their Ts-containing counterparts.

Considering the crucial importance of the reducing metal in the synthetic process and the probable involvement of an imine as the electrophilic intermediate, we were able to propose a possible reaction mechanism (Scheme 1).

Table 1: Optimization of the reaction conditions[a].

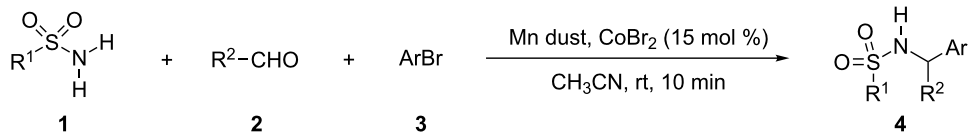


1a **2a** **3** **4a**

Entry	PhX (equiv)[b]	X	Reducing metal	Amount (equiv)[c]	Cat. (mol %)[d]	Solvent	Time (min)	Yield (%)[e]
1	3	Br	Mg	10	–	THF	60	–
2	3	Br	Al	10	$CoBr_2$ (15)	CH_3CN	60	–
3	3	Br	Ti	10	$CoBr_2$ (15)	CH_3CN	60	–
4	3	Br	Cr	10	$CoBr_2$ (15)	CH_3CN	60	–
5	3	Br	Fe	10	$CoBr_2$ (15)	CH_3CN	60	–
6	3	Br	Sn	10	$CoBr_2$ (15)	CH_3CN	60	–
7	3	Br	Zn	10	$CoBr_2$ (15)	CH_3CN	60	–
8	**3**	**Br**	**Mn**	**10**	**$CoBr_2$ (15)**	**CH_3CN**	**5**	**68**
9	2.5	Br	Mn	10	$CoBr_2$ (15)	CH_3CN	5	52
10	2	Br	Mn	10	$CoBr_2$ (15)	CH_3CN	5	44
11	3	Br	Mn	15	$CoBr_2$ (15)	CH_3CN	5	76
12	3	Br	Mn	7.5	$CoBr_2$ (15)	CH_3CN	5	50
13	3	Br	Mn	5	$CoBr_2$ (15)	CH_3CN	5	32
14	3	Br	Mn	10	$CoBr_2$ (15)	CH_3CN	20	70
15	3	I	Mn	10	$CoBr_2$ (15)	CH_3CN	5	40
16	3	Cl	Mn	10	$CoBr_2$ (15)	CH_3CN	5	-
17	3	Br	Mn	10	$CoBr_2$ (10)	CH_3CN	5	52
18	3	Br	Mn	10	$CoBr_2$ (1.5)	CH_3CN	20	21
19	3	Br	Mn	10	–	CH_3CN	60	–[f]
20	3	Br	Mn	10	$NiBr_2$bpy (15)	CH_3CN	60	–
21	3	Br	Mn	10	$CoBr_2$ (15)	THF	60	–
22	3	Br	Mn	10	$CoBr_2$ (15)	DMF	60	–
23	3	Br	Mn	10	$CoBr_2$ (15)	Dioxane	60	–
24	3	Br	Mn	10	$CoBr_2$ (15)	Toluene	60	–

[a]Reactions were conducted at room temperature with 5 mL of solvent, 0.43 g (2.5 mmol) of *p*-toluenesulfonamide (**1a**), 0.25 mL (2.5 mmol) of benzaldehyde (**2a**), 7.5 mmol of phenyl halide **3**, 1.125 mmol of the catalyst, and 25 mmol of the reducing metal, preactivated by using 0.1 mL $BrCH_2Ch_2Br$ and 0.1 mL TFA. [b]Calculated relative to the sulfonamide. [c]Calculated relative to the sulfonamide. [d]Calculated relative to the halide. [e]GC yield. [f]1 h at room temperature, then heating 5 h under reflux.

Table 2: Scope of the reaction[a].



1 **2** **3** **4**

Entry	R^1	R^2	Ar	Product	Yield (%)[b]
1	*p*-Tol	Ph	Ph	**4a**	68

Table 2: Scope of the reaction[a]. (continued)

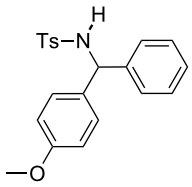
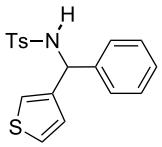
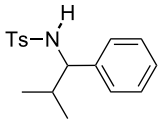
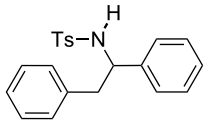
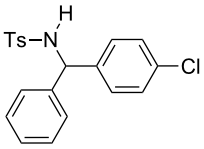
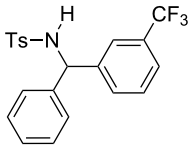
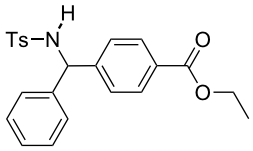
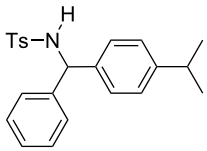
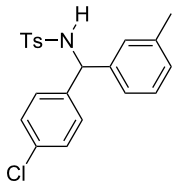
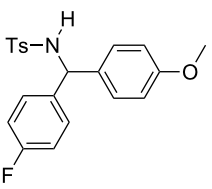
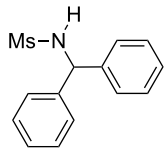
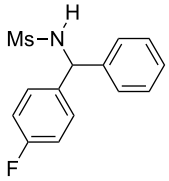
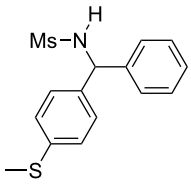
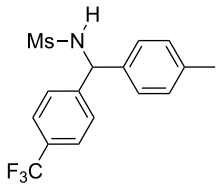
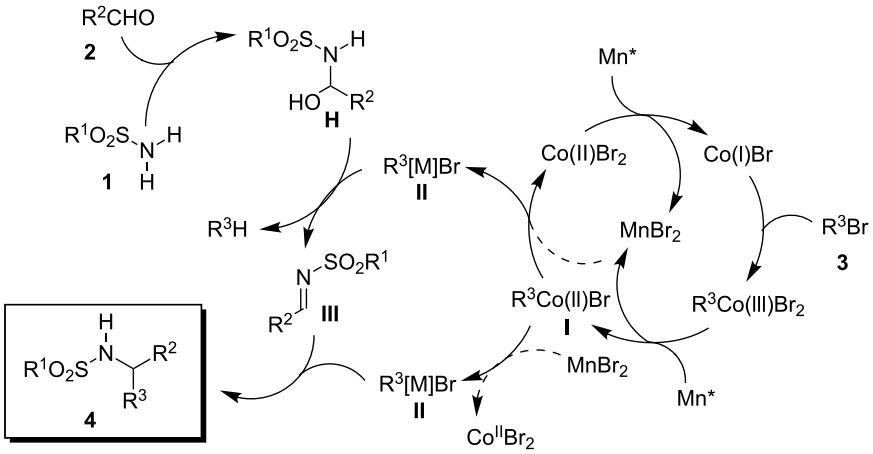
2	*p*-Tol	4-MeO-C_6H_4	Ph		**4b**	60
3	*p*-Tol	3-thienyl	Ph		**4c**	15 (35[c])
4	*p*-Tol	iPr	Ph		**4d**	45
5	*p*-Tol	Bn	Ph		**4e**	32
6	*p*-Tol	Ph	4-Cl-C_6H_4		**4f**	39
7	*p*-Tol	Ph	3-CF_3-C_6H_4		**4g**	32
8	*p*-Tol	Ph	4-EtO_2C-C_6H_4		**4h**	46
9	*p*-Tol	Ph	4-iPr-C_6H_4		**4i**	20
10	*p*-Tol	4-Cl	3-Me-C_6H_4		**4j**	25
11	*p*-Tol	4-F-C_6H_4	4-MeO-C_6H_4		**4k**	34

Table 2: Scope of the reaction[a]. (continued)

12	Me	Ph	Ph		**4l**	65
13	Me	4-F-C_6H_4	Ph		**4m**	27
14	Me	4-MeS-C_6H_4	Ph		**4n**	36
15	Me	4-CF_3-C_6H_4	4-Me-C_6H_4		**4o**	39

[a]Reactions were conducted with 5 mL of acetonitrile, 2.5 mmol of sulfonamide **1**, 2.5 mmol of aldehyde **2**, 7.5 mmol of aryl bromide **3**, 0.25 g (1.125 mmol) of cobalt bromide, and 1.4 g (25 mmol) of manganese dust (preactivated by using 0.1 mL $BrCH_2Ch_2Br$ and 0.1 mL TFA), for 10 min at room temperature. [b]Isolated yield. [c]Reaction conducted with the preformed sulfonyl imine.



Scheme 1: Possible reaction mechanism.

It was previously established that zinc is able to reduce cobalt(II) in the presence of an aryl halide to promote the formation of a transient arylcobalt(II) species, which undergoes a fast transmetallation with zinc to furnish an organozinc species [39]. It can thus be assumed that a reductive metal other than zinc, e.g., manganese, can also promote a similar process. The first reaction step is the manganese-mediated formation of the organocobalt intermediate **I**. Depending on the kinetics of the

transmetallation of **I** by manganese salts, two different scenarios may be envisaged featuring either an organocobalt or an organomanganese species as the key organometallic **II**.

In the first scenario, manganese undergoes a slow transmetallation with the organocobalt species **I**. It has been shown earlier that zinc salts undergo rapid transmetallations with organocobalt(II) species to furnish organozinc compounds. However, as mentioned above, the usage of zinc does not allow the reaction to proceed, so that we assume that the active organometallic species **II** could not be an organozinc compound. Provided manganese salts cannot undergo the transmetallation step at a comparable rate, but react significantly slower, it could be envisaged that the organometallic species **II** is in fact the organocobalt **I**. Thus, by transforming **I** into an inactive organozinc species, zinc salts would hamper the reaction.

In the other scenario, in which the transmetallation of **I** with manganese is very rapid, manganese plays a dual role by acting both as a reducing agent of cobalt (to form **I**) and as the active salt of a transmetallation step by forming an organomanganese reagent **II** (or a mixed manganese–cobalt-containing bimetallic compound). The intermediate **II** then acts both as a water scavenger at the stage of a formal hemiaminal intermediate **H** [40] to form the imine **III** and as a nucleophile furnishing **4** by trapping **III**.

Conclusion

In conclusion, the results presented in this study indicate that the manganese(0)/cobalt(II) system is a suitable combination for the multicomponent synthesis of (diarylmethyl)sulfonamides and related compounds. Although this multicomponent reaction system has not been completely optimized yet, it is the first to allow the one-step preparation of (diarylmethyl)amines under a protected form. Current works include the examination of the effect of a manganese surface and granulometry on the reaction efficiency.

Experimental

General procedure: A dried 50 mL round bottomed flask equipped with a reflux condenser was flushed with argon and charged with acetonitrile (5 mL). Manganese dust (1.4 g, 25 mmol), trifluoroacetic acid (0.1 mL, 1.3 mmol) and 1,2-dibromoethane (0.1 mL, 1.15 mmol) were added under vigorous (~500 rpm) stirring, and the mixture was heated to 60 °C. After cooling to room temperature, the organic bromide **3** (7.5 mmol), the aldehyde **2** (2.5 mmol), the sulfonamide **1** (2.5 mmol), and cobalt bromide (0.25 g, 1.125 mmol) were added successively, and the resulting mixture was stirred for 10 minutes at room temperature. The reaction mixture was poured into a sat. NH_4Cl solution (75 mL) and extracted with diethyl ether (2 × 50 mL). The organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel chromatography by using a solvent gradient (pentane/diethyl ether 90:10 to pentane/diethyl ether 70:30) to yield the three-component coupling product **4** as a generally white solid.

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A catalyst-free multicomponent domino sequence for the diastereoselective synthesis of (*E*)-3-[2-arylcarbonyl-3-(arylamino)allyl]chromen-4-ones

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Full Research Paper

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Abstract

The three-component domino reactions of (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones, 3-formylchromone and anilines under catalyst-free conditions afforded a library of novel (*E*)-3-(2-arylcarbonyl-3-(arylamino)allyl)-4*H*-chromen-4-ones in good to excellent yields and in a diastereoselective transformation. This transformation generates one C–C and one C–N bond and presumably proceeds via a reaction sequence comprising a Michael-type addition–elimination reaction, a nucleophilic attack of an enamine to a carbonyl reminiscent of one of the steps of the Bayllis–Hilman condensation, and a final deoxygenation. The deoxygenation is assumed to be induced by carbon monoxide resulting from the thermal decomposition of the dimethylformamide solvent.

Introduction

Chromones are widely present in nature, especially in the plant kingdom, and a wide variety of useful biological properties are associated with them [1,2]. Chromone derivatives act as effective tyrosine and protein kinase C inhibitors [3] and display antifungal [4,5], antimycobacterial [6], antiviral [7], antihypertensive [8], anti-oxidant [9-12], HIV-inhibitory [13], anti-inflammatory [14,15], immunomodulatory [16], antithrombotic [17], and anticancer [18-20] activities. Furthermore, some chromone derivatives have been identified as suitable fluorophores for live cell imaging [21]. In view of its importance chromone has emerged as a pharmacophore in drug discovery programmes, leading to several drugs in the market (e.g. cromolyn and nedocromil) and thereby continuing to draw the attention of synthetic organic and medicinal chemists [22-

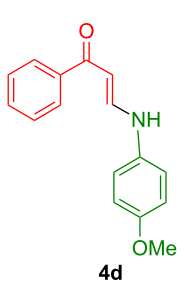
24]. However, there are relatively few methods, which allow the preparation of hybrid structures containing chromone derivatives attached to other heterocyclic systems due to the lack of suitable building blocks. In order to come up with such building blocks, we planned the preparation of chromones containing a β-enaminone structural fragment, since enaminones are versatile starting materials in organic synthesis and are notably important for the synthesis of nitrogen heterocycles [25-27]. In particular, β-enaminoketones are endowed with electrophilic and nucleophilic reaction centers and have a versatile reactivity that allows their application in the synthesis of important heterocycles such as indole [28], dihydropyridine [29], quinoline [30], pyrrole [31] and pyridinone [32]. Furthermore, they can take part in one-pot multicomponent reactions with both nucleophilic and electrophilic reactants, leading to a fast access to structurally diverse carbocycles and heterocycles, an area in which we have recently become interested [33-42]. Thus, the present study ia a continuation of our research program on the construction of novel heterocycles employing one-pot green domino-multicomponent transformations [43-54].

In order to achieve our goal, we embarked on the study of the three-component reactions between 3-formylchromone (**1**), (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones **2** and anilines **3**, which we expected to furnish novel (*E*)-3-[2-arylcarbonyl-3-(arylamino)allyl]-4*H*-chromen-4-ones **5** comprising the desired chromonone and β-enaminoketone moieties via intermediate species **4**. The overall synthetic strategy is summarized in Scheme 1.

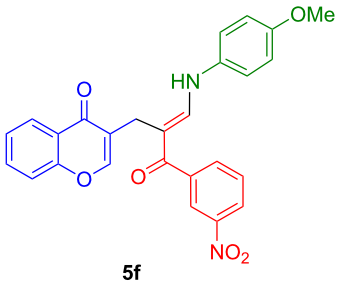
Results and Discussion

We started our study with the optimization of a model reaction between 3-formylchromone (**1**, 1 mmol), (*E*)-3-(dimethylamino)-1-(3-nitrophenyl)prop-2-en-1-one (1 mmol) and 4-methoxyaniline (1 mmol). This three-component reaction was initially examined in solvents such as acetonitrile, dioxane, dimethyl sulfoxide, toluene and ethanol under heating. However, the only isolable product was compound **4d**, which originated from a reaction between the last two components without participation of the chromone substrate (Table 1, entries 1–5). The use of dimethylformamide as a solvent, on the other hand, allowed the isolation of the target (*E*)-3-[3-(4-methoxyphenylamino]-2-(3-nitrobenzoyl)allyl)-4*H*-chromen-4-one (**5f**). After temperature fine-tuning (Table 1, entries 6–11), we identified heating in DMF at 130 °C for 6 h as the optimal conditions, which afforded **5f** in 94% yield (Table 1, entry 11).

Table 1: Solvent screen and temperature optimization for the synthesis of compound **5f**.



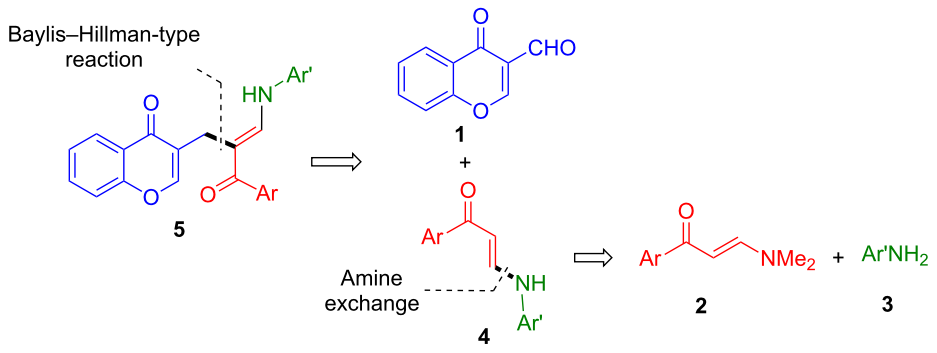
4d



5f

Entry	Solvent	Time (h)	Temp. (°C)	Yield (%)[a]
1	CH_3CN	12	80	–[b]
2	dioxane	10	102	–[b]
3	DMSO	10	140	–[b]
4	toluene	10	110	–[b]
5	EtOH	10	78	–[b]
6	DMF	6	60	27
7	DMF	6	80	34
8	DMF	6	100	43
9	DMF	6	110	61
10	DMF	6	120	74
11	DMF	6	130	94

[a]Isolated yield after purification by column chromatography.
[b]Compound **4d** was obtained predominantly.



Scheme 1: Summary of the transformations involved in the synthesis of compounds **5**, containing chromone and β-enaminoketone moieties.

All the subsequent reactions of 3-formylchromone (**1**), (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones **2** and substituted anilines **3** were performed under the optimal conditions (equimolecular amounts, DMF at 130 °C) and were completed in 6–7 h. After completion of the reaction, removal of the solvent and purification of the residue by column chromatography, (*E*)-3-[2-arylcarbonyl-3-(arylamino)allyl]-4*H*-chromen-4-ones **5** were obtained in pure form in 78–94% yields (Scheme 2 and Table 2). It is noteworthy, that a similar reaction, in which the less hindered, more reactive formaldehyde was employed as the aldehyde component, took a completely divergent course and afforded 5-arylcarbonyl-1,3-diarylhexahydropyrimidines arising from pseudo five-component reactions of (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones, two molecules of formaldehyde and two molecules of aniline [55].

The structure of compounds **5** was deduced from one and two-dimensional NMR spectroscopic data, as detailed in Supporting Information File 1 for **5h** as a representative example. The structure of **5h** deduced from the NMR spectroscopic studies was subsequently confirmed by single-crystal X-ray crystallographic data, as shown in Figure 1 [56].

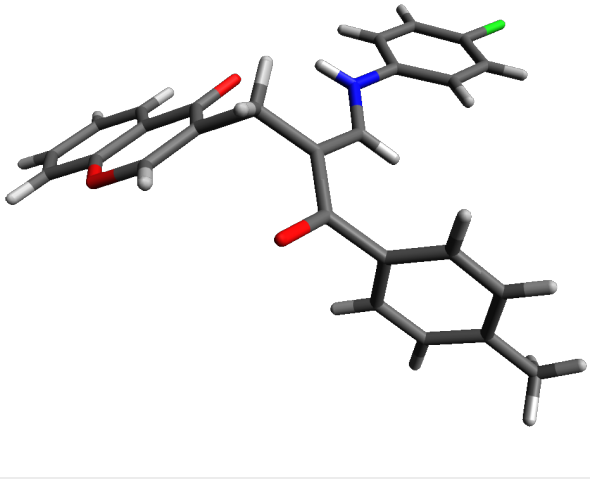
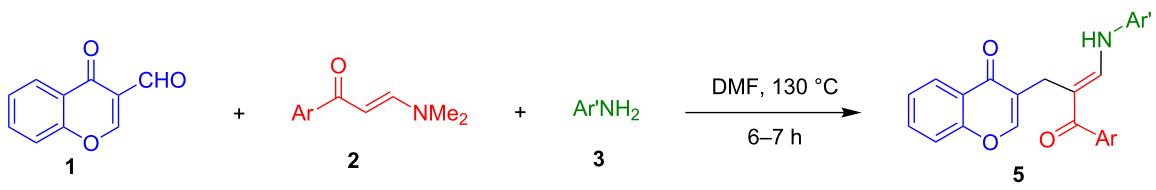


Figure 1: X-ray structure of compound **5h**.



Scheme 2: Synthesis of compounds **5**.

Table 2: Scope and yields of the synthesis of compounds **5**.

Entry	Comp.	Ar	Ar'	Time (h)	Yield (%)[a]
1	**5a**	C_6H_5	4-MeC_6H_4	6	85
2	**5b**	4-ClC_6H_4	4-MeC_6H_4	6	87
3	**5c**	3-$NO_2C_6H_4$	4-MeC_6H_4	6	90
4	**5d**	C_6H_5	4-$MeOC_6H_4$	6	89
5	**5e**	4-ClC_6H_4	4-$MeOC_6H_4$	6	91
6	**5f**	3-$NO_2C_6H_4$	4-$MeOC_6H_4$	6	94
7	**5g**	4-ClC_6H_4	4-ClC_6H_4	6	86
8	**5h**	4-MeC_6H_4	4-ClC_6H_4	7	84
9	**5i**	4-$MeOC_6H_4$	4-ClC_6H_4	7	82
10	**5j**	3-$NO_2C_6H_4$	4-ClC_6H_4	6	87
11	**5k**	C_6H_5	4-BrC_6H_4	6	80
12	**5l**	4-MeC_6H_4	4-BrC_6H_4	6	81
13	**5m**	4-MeC_6H_4	4-FC_6H_4	7	83
14	**5n**	4-MeC_6H_4	3-$NO_2C_6H_4$	7	78
15	**5o**	4-ClC_6H_4	C_6H_5	6	86
16	**5p**	3-$NO_2C_6H_4$	C_6H_5	6	88

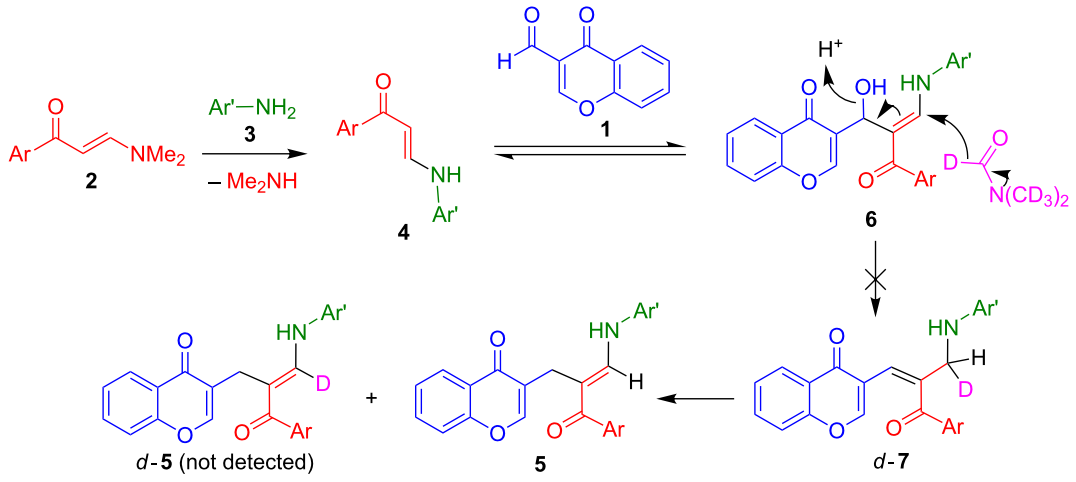
[a]Isolated yield after purification by column chromatography.

Our initial mechanistic hypothesis accounting for the formation of compounds **5** is depicted in Scheme 3. An initial Michael addition–elimination reaction, leading to the exchange between the starting arylamine **3** and dimethylamine, explains the formation of intermediates **4**, which were the final reaction products in most investigated solvents. However, in DMF, the enamine moiety of **4** attacks the aldehyde group in **1** giving rise to **6**. This reaction resembles one of the steps of the Baylis–Hilman condensation and is presumably promoted by the presence of traces of formic acid as a contaminant of the solvent [57].

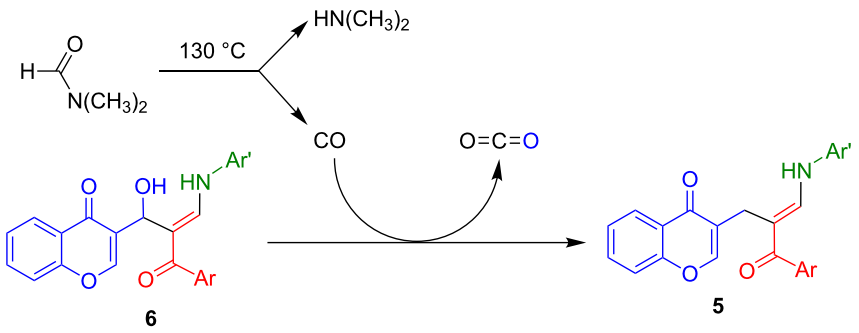
We established the feasibility of the first step by showing that the reaction between two of our starting enaminones, namely **2a** (Ar = Ph) and **2c** (Ar = 3-$NO_2C_6H_4$) with aniline under our standard reaction conditions (DMF, 130 °C) affords the corresponding compounds **4** after 3 h in 94% and 90% yields, respectively. As previously mentioned (Table 1), the nature of the solvent was found to be of critical importance, and the transformation of intermediate **4** into the final products **5** was found to work only in DMF, among many investigated solvents. Since the reaction between **4** and **1** is proposed to be catalyzed by acid, we carried out the multicomponent reaction in a selection of solvents (dioxane, acetonitrile, dimethyl sulfoxide, ethanol, ethylene glycol) in the presence of one equivalent of HCl, but all these attempts failed, while the same conditions were successful in DMF. These results can be explained by assuming that the initial aldol-type reaction between **1** and **4** to give **6** is reversible and is driven to completion by the reduction step, which takes place in DMF only. Thus, interestingly, the reaction does not stop at compound **6**, but instead undergoes a reductive termination step, which leads to the final products **5**.

This reduction step is intriguing, and a first mechanistic possibility could be a hydride transfer from formate anion. While this mechanism might partly account for the observed reduction, we acknowledge that it is problematic to rely on solvent impurities to account for a stoichiometric reduction. Alternatively, dimethylformamide itself might have been the reducing agent. There are a few scattered literature reports on the use of DMF as a reducing agent, the first of which seems to be the reduction of diazonium tetrafluoroborate salts to arenes [58]. DMF has also been described as a reducing agent acting by hydride transfer in Pd-catalyzed processes, where the metal plays a critical role in the reduction by decomposing it and facilitating hydride transfer from a Pd intermediate [59-61]. However, it is not clear whether the same type of reaction may take place under our conditions. In order to test this ideas experimentally, we carried out the reaction between 3-formylchromone (**1**), (*E*)-3-(dimethylamino)-1-(4-chlorophenyl)prop-2-en-1-one and *p*-toluidine in DMF-d_7. If the mechanistic hypothesis was correct, this reaction should lead to a *d*-**7** intermediate and hence to a mixture of **5** and *d*-**5**, with the latter being major due to isotope effects in the tautomeric equilibrium. However, this reaction failed to show any incorporation of deuterium into **5**, and therefore we had to abandon the hydride-transfer hypothesis.

We came up with an alternative explanation based on the well-known fact that DMF decomposes into dimethylamine and carbon monoxide at its boiling point. Carbon monoxide can act as a deoxygenating agent [62] and thus explain the transformation of **6** into **5** as shown in Scheme 4. Because of the synthetic interest of allylic and benzylic deoxygenations, further research into this reaction is under way in our laboratories.



Scheme 3: Initial mechanistic proposal to explain the formation of compounds **5** that was ruled out by deuteration experiments.



Scheme 4: Alternative mechanistic proposal based on a carbon monoxide-induced deoxygenation.

Conclusion

We have developed a facile three-component diastereoselective synthesis of novel (*E*)-3-[2-arylcarbonyl-3-(arylamino)allyl]-4*H*-chromen-4-ones containing chromone and β-enaminoketone structural fragments from simple, readily available starting materials in a one-pot operation and in good to excellent yields. This transformation occurs via a domino sequence of reactions, which generates one C–C and one C–N bond. Presumably, this transformation proceeds via a reaction sequence comprising a Michael-type addition–elimination reaction, a nucleophilic attack of an enamine to a carbonyl, and a final deoxygenation step. We propose that the deoxygenation step is induced by carbon monoxide resulting from thermal decomposition of the dimethylformamide solvent.

Experimental

General methods. Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument by using TMS as an internal standard and $CDCl_3$ as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale), and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as an eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

General procedure for the synthesis of (*E*)-3-(2-arylcarbonyl-3-(arylamino)allyl)-4*H*-chromen-4-one derivatives 5a–5p. In a similar manner as described in [55], a mixture of 3-formylchromone (**1**, 1 mmol), enaminone **2** (1 mmol) and aniline **3** (1 mmol) in DMF (5 mL) was heated at 130 °C for 6–7 h. The reaction progress was monitored by TLC. After completion of the reaction, the solvent was removed and the product was purified by column chromatography with a petroleum ether–ethyl acetate mixture (4:1 v/v) as an eluent to afford compounds **5**. Characterization data for representative compounds are given below. The characterization data for the full library can be found in Supporting Information File 1.

***(E)-3-(2-Benzoyl-3-(p-tolylamino)allyl)-4H-chromen-4-one* (5a):** Isolated yield 0.336 g (85%); colorless solid; mp 215–216 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 2.28 (s, 3H), 3.71 (s, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.37–7.45 (m, 4H), 7.47–7.56 (m, 4H), 7.66–7.71 (m, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.52 (s, 1H), 9.93 (d, J = 12.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 20.1, 20.6, 113.3, 115.8, 118.3, 123.7, 123.9, 125.0, 125.9, 128.0, 128.5, 129.8, 130.1, 132.3, 133.7, 138.9, 140.9, 146.6, 156.2, 156.7, 179.8, 195.0; HRMS–ESI (m/z): $[M - H]^-$ calcd for $C_{26}H_{20}NO_3$, 394.14432; found, 394.144817; Anal. calcd for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.54; found: C, 79.02; H, 5.29; N, 3.62.

***(E)-3-(2-(3-Nitrobenzoyl)-3-(p-tolylamino)allyl)-4H-chromen-4-one* (5c):** Isolated yield 0.396 g (90%); yellow solid; mp 206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 2.32 (s, 3H), 3.72 (s, 2H), 6.93 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 7.40–753 (m, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.68–7.74 (m, 1H), 7.81 (d, J = 7.5 Hz, 1H), 8.28–8.35 (m, 3H), 8.51 (s, 1H), 10.2 (d, J = 12.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 20.1, 20.7, 113.0, 116.2, 118.4, 123.3, 123.6, 123.7, 124.4, 125.2, 125.9, 129.2, 130.2, 133.1, 133.9, 134.1, 138.4, 142.5, 147.3, 148.0, 156.1, 156.7, 179.9, 191.8; HRMS–ESI (m/z): $[M - H]^-$ calcd for $C_{26}H_{19}N_2O_5$, 439.12940; found, 439.12995; Anal. calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36; found: C, 70.84; H, 4.62; N, 6.29.

***(E)-3-(3-(4-Chlorophenylamino)-2-(4-methylbenzoyl)allyl)-4H-chromen-4-one* (5h):** Isolated yield 0.361 g (84%); colorless solid; mp 219–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 2.40 (s, 3H), 3.70 (s, 2H), 6.95 (d, J = 8.7 Hz, 2H), 7.19–7.26 (m, 4H), 7.40–7.46 (m, 3H), 7.48–7.52 (m, 2H), 7.69 (t, J = 7.1 Hz, 1H), 8.30 (d, J = 7.2 Hz, 1H), 8.51 (s, 1H), 10.04 (d, J = 12.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 20.4, 21.4, 114.4, 116.8, 118.4, 123.7, 125.1, 125.8, 127.4, 128.6,

128.8, 129.5, 133.8, 137.7, 140.1, 140.4, 145.3, 156.3, 156.7, 179.9, 195.2; HRMS–ESI (*m*/*z*): [M − H]$^-$ calcd for $C_{26}H_{19}ClNO_3$, 428.10535; found, 428.10589; Anal. calcd for $C_{26}H_{20}ClNO_3$: C, 72.64; H, 4.69; N, 3.26; found: C, 72.57; H, 4.75; N, 3.31.

***(E)-3-(3-(4-Bromophenylamino)-2-(4-methylbenzoyl)allyl)-4H-chromen-4-one* (5l):** Isolated yield 0.384 g (81%); colorless solid; mp 223–224 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 2.40 (s, 3H), 3.70 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.36–7.41 (m, 3H), 7.43–7.52 (m, 4H), 7.69 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.30 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 8.51 (s, 1H), 10.04 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 20.4, 21.4, 114.5, 114.7, 117.2, 118.4, 123.6, 125.1, 125.8, 128.6, 128.8, 132.5, 133.8, 137.7, 140.4, 140.6, 145.1, 156.4, 156.7, 179.9, 195.2; HRMS–ESI (*m*/*z*): [M − H]$^-$ calcd for $C_{26}H_{19}BrNO_3$, 472.05483; found, 472.05538; Anal. calcd for $C_{26}H_{20}BrNO_3$: C, 65.83; H, 4.25; N, 2.95; found: C, 65.70; H, 4.34; N, 2.91.

***(E)-3-(2-(4-Chlorobenzoyl)-3-(phenylamino)allyl)-4H-chromen-4-one* (5o):** Isolated yield 0.357 g (86%); colorless solid; mp 245–246 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 3.71 (s, 2H), 7.00–7.05 (m, 3H), 7.26–7.33 (m, 2H), 7.37–7.40 (m, 2H), 7.44–7.55 (m, 5H), 7.67–7.72 (m, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 8.50 (s, 1H), 10.08 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 20.2, 113.7, 115.9, 118.4, 122.9, 123.7, 125.1, 125.9, 128.4, 129.7, 129.9, 133.8, 136.1, 139.2, 141.1, 146.2, 156.2, 156.7, 179.8, 193.8; HRMS–ESI (*m*/*z*): [M − H]$^-$ calcd for $C_{25}H_{17}ClNO_3$, 414.08970; found, 414.09024; Anal. calcd for $C_{25}H_{18}ClNO_3$: C, 72.20; H, 4.36; N, 3.37; found: C, 72.09; H, 4.24; N, 3.41.

General procedure for the isolation of intermediates 4. A mixture of the suitable enaminone **2** (1 mmol) and aniline **3** (1 mmol) in DMF (5 mL) was heated at 130 °C for 3 h. The reaction progress was monitored by TLC. After completion of the reaction, the solvent was removed and the product was purified by column chromatography with a petroleum ether–ethyl acetate mixture (4:1 v/v) as an eluent. Characterization data for compounds **4** can be found in Supporting Information File 1.

Supporting Information

Supporting Information File 1

Experimental details, full characterization data, detailed structural characterization of compound **5h** and copies of the spectra of all compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-43-S1.pdf]

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Silver and gold-catalyzed multicomponent reactions

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Review

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Abstract

Silver and gold salts and complexes mainly act as soft and carbophilic Lewis acids even if their use as σ-activators has been rarely reported. Recently, transformations involving Au(I)/Au(III)-redox catalytic systems have been reported in the literature. In this review we highlight all these aspects of silver and gold-mediated processes and their application in multicomponent reactions.

Introduction

Coinage metals (copper, silver and gold) are extensively used in the homogenous catalysis of organic reactions. Similarities and differences in the catalytic activity of these elements have been recently reviewed in an excellent book chapter by Hashmi [1]. Hashmi emphasized the difference between the "oldest" member of the family (copper), silver and the "youngest" one (gold) in terms of the literature references available for each of these three elements. Thus, the catalysis-related literature is more comprehensive for copper than for silver and gold. However, silver and gold experienced a continuous growth in interest by the scientific community. This also holds true in the field of multicomponent reactions (MCRs). A rough investigation of the literature dealing with Ag or Au-mediated MCRs published since 2000 reveals an exponential growth in the number of published papers. A deeper analysis allows discriminating between a specific class of multicomponent reactions, the A^3-coupling reactions, which are subjected to systematic investigations, and a plethora of miscellaneous reactions. Thus, this review pursues two objectives. Firstly, we want to provide a brief overview of the most recent advances of silver and gold-mediated A^3-coupling reactions. Seecondly, we aim for classifying the remaining classes of MCRs mediated by silver and gold species covering the literature from 2000 to early 2013. Advancements of the A^3-coupling reactions have been recently highlighted in exhaustive and outstanding reviews by Li [2] and Van der Eycken [3], both of which cover the literature until 2010. Thus, our contribution will cover the past three years with a particular emphasis on the incorporation of the A^3-coupling products into tandem reactions. The second goal could be achieved by classifying reactions on the basis of the involved reactants, the reaction type or the role of the catalyst.

Review

A^3-coupling-type reactions

Silver catalysis

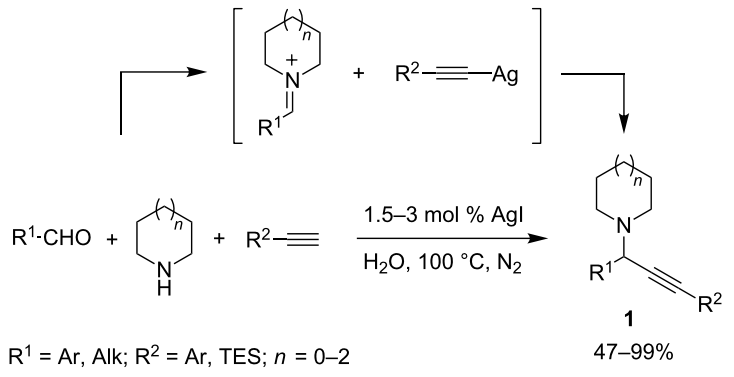
The catalytic direct 1,2-addition of alkynes to imines and iminium ions, generated from the condensation of amines and aldehydes, represents the most convenient method to access propargylamines [4]. Although numerous examples of the A^3-coupling reaction have been reported, there are still many challenges and opportunities for this multicomponent coupling reaction. The expansion of its scope to include difficult substrates such as aliphatic primary amines and ammonia, the development of highly enantioselective A^3-coupling reactions with broad substrate specificity, and the incorporation of the A^3-coupling reaction into tandem processes are all challenges that are expected to be overcome in the near future.

The first example of Ag(I)-catalyzed A^3-coupling was reported by Li and co-workers in 2003 [5]. In this pioneering work, a simple silver(I) salt demonstrated to be able to catalyze the coupling between aliphatic/aromatic aldehydes, cyclic secondary amines and arylacetylenes in water at 100 °C under a nitrogen atmosphere. Among the different silver salts tested, AgI gave the best results. Alkyl aldehydes displayed a higher reactivity with respect to aryl aldehydes, whereas acyclic secondary amines were not well tolerated. Most importantly, the AgI-catalyzed A^3-coupling avoided the annoying aldehyde trimerization usually observed when reacting aliphatic aldehydes under the more investigated Cu(I) and Au(I) catalysis (see below). The proposed mechanism involved the formation of a silver acetylide, which is able to react with the iminium ion generated in situ from aldehydes and amines to give the corresponding propargylamines **1** (Scheme 1).

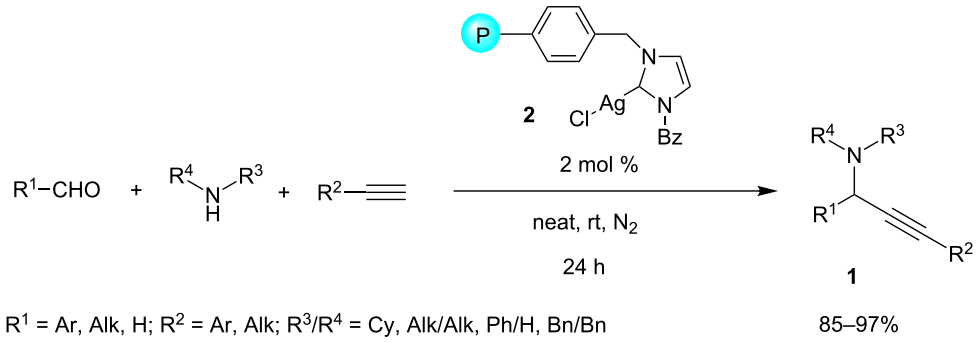
As Li and Van der Eycken reported in their valuable reviews, some other silver salts (e.g., $Ag_3PW_{12}O_{40}$ [6], AgX [7]), complexes [8], zeolites [9] and nanoparticles [10,11] have been explored to catalyze the A^3-coupling, but only recently, silver–NHC complexes were found to be valuable catalysts for this MCR. Their first application was reported by Wang and co-workers in 2008 [12], who developed a polystyrene-supported NHC–Ag(I) complex as an efficient catalyst for the A^3-coupling under solvent-free conditions, at room temperature, and under a nitrogen atmosphere. The in situ generated polymer-supported complexes **2** were claimed to be more active than the parent NHC–silver halides. The reactions afforded the corresponding propargylamines **1** in excellent yields starting from aromatic and aliphatic aldehydes, a wide range of secondary amines, as well as aryl and alkyl-substituted alkynes (Scheme 2). It is noteworthy that the approach tolerated challenging substrates such as formaldehyde, *o*-substituted benzaldehydes, and secondary aromatic amines. Moreover, the PS–NHC–Ag(I) catalyst was proven to be reusable at least 12 times without a significant loss of its catalytic activity. Similar PS–NHC–silver complexes were recently prepared via click-chemistry, and their aptitude to catalyze A^3-coupling was verified [13].

The suitability of NHC–Ag(I) complexes as catalysts for A^3-coupling MCR was confirmed, and independently developed some years later by the research groups of Zou [14], Navarro [15] and Tang [16] (Figure 1).

Zou and co-workers reported structurally well-defined *N*-heterocyclic carbene silver halides of 1-cyclohexyl-3-arylmethylimidazolylidene to be effective catalysts in a model reaction among 3-phenylpropionaldehyde, phenylacetylene and piperidine in dioxane at 100 °C in open air [14]. Although the scope was not investigated, the authors observed that the activity of the catalyst was notably affected by the nature of the anion in the order Cl > Br >> I. They argued that the true catalytic species would be a structurally stable and coordinatively unsaturated *N*-heterocyclic carbene silver halide NHC–AgX rather



Scheme 1: General reaction mechanism for Ag(I)-catalyzed A^3-coupling reactions.



Scheme 2: A^3-coupling reaction catalyzed by polystyrene-supported NHC–silver halides.

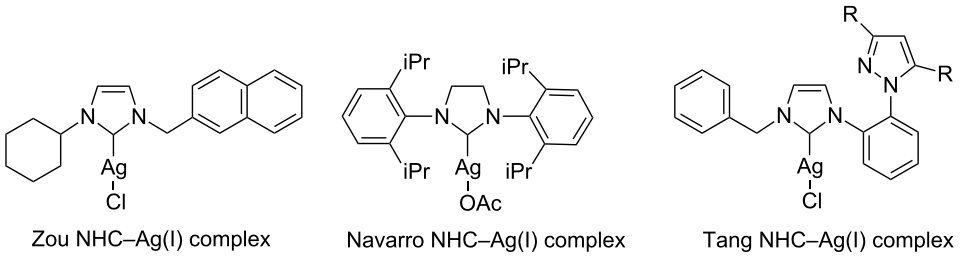
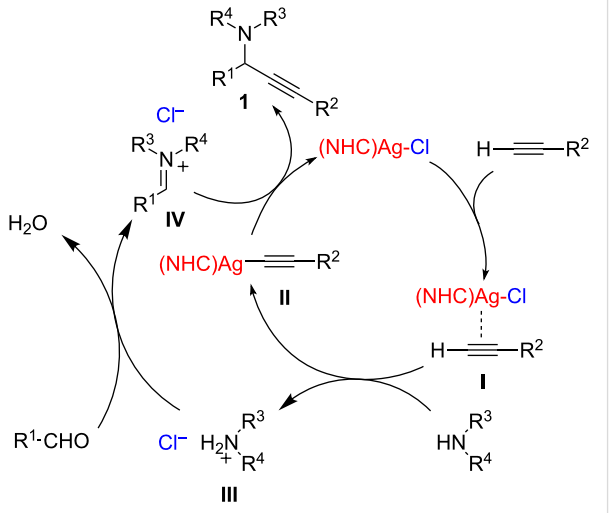


Figure 1: Various NHC–Ag(I) complexes used as catalysts for A^3-coupling.

than a silver cation. Thus, a more detailed mechanism was proposed, in which the π-complex of the catalyst with the alkyne **I** reacts with an amine to form the silver acetylide **II** and the amine hydrohalide **III**. The latter then condenses with the aldehyde to generate the iminium halide **IV**, which reacts with the previously generated silver acetylide **II** to afford the desired product **1** and regenerate the catalyst (Scheme 3).



Scheme 3: Proposed reaction mechanism for NHC–AgCl catalyzed A^3-coupling reactions.

Bearing in mind the importance of the counter ion of the Ag complex, Navarro and co-workers developed a new saturated 1,3-bis(2,6-diisopropylphenyl)imidazolium (SIPr) silver complex, characterized by the presence of a less bulky acetoxy anion [15]. The new NHC–Ag(I) complex displayed a broad scope in A^3-coupling reactions, tolerating alkyl and arylaldehydes (also unactivated ones), cyclic and linear secondary aliphatic amines, and terminal alkyl/aryl alkynes. It is noteworthy that the reactions occurred under mild conditions with a low catalyst loading. The solvent of choice was methanol (technical grade), but the reaction ran also well in other alcohols and acetonitrile, whereas yields were rather low in toluene.

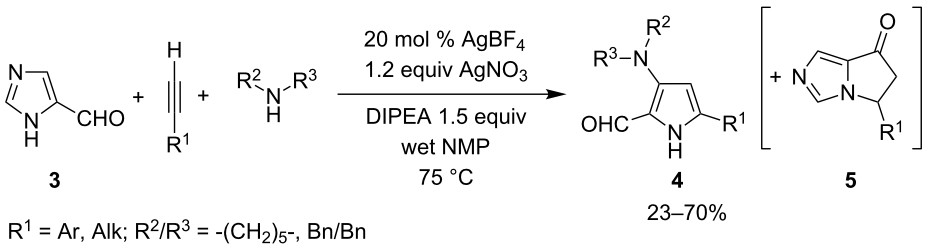
In this context, Tang and co-workers very recently presented some original mono- and dinuclear silver–NHC complexes derived from 1-[2-(pyrazol-1-yl)phenyl]imidazole, which displayed good catalytic activity on a model A^3-coupling reaction under Zou conditions at a slightly lower temperature (80 °C), but under an argon atmosphere [16].

An interesting Ag-promoted cascade synthesis of pyrrole-2-carboxyaldehydes involving an A^3-coupling followed by an unusual imidazole ring opening, was reported by Liu in 2011 [17]. The authors found that propargylamines derived from the $AgBF_4$-catalyzed coupling of imidazole-4-carboxyaldehydes **3**, differently substituted alkynes and secondary amines were

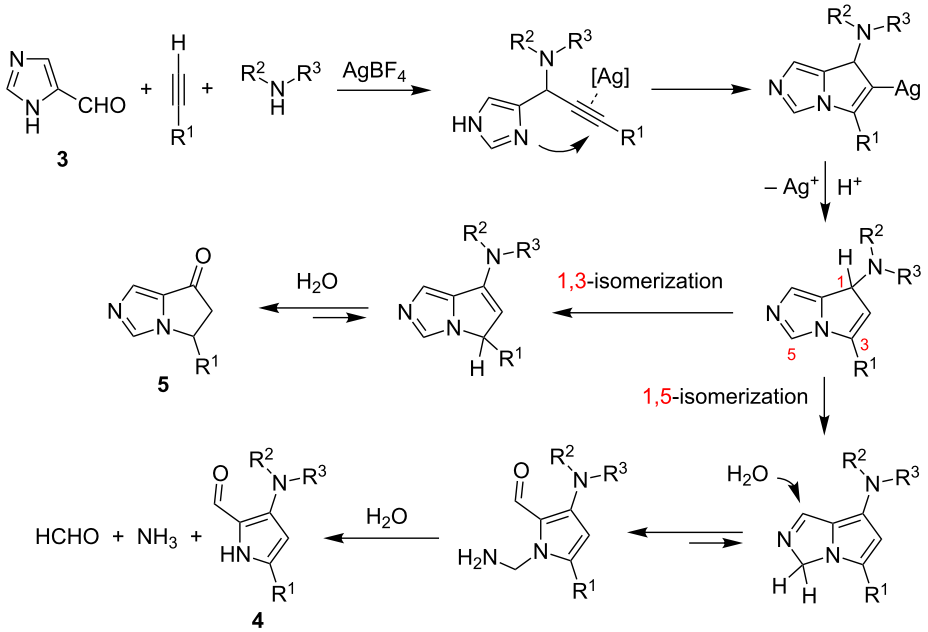
susceptible to a subsequent in situ transformation to give 3,5-disubstituted pyrrole-2-carboxaldehydes **4** in moderate to good yields in addition to variable amounts of 5-substituted-5*H*-pyrrolo[1,2-*c*]imidazol-7(6*H*)-one **5** (Scheme 4). To obtain the best results and to reduce the formation of the pyrroloimidazolone **5**, the reactions were performed in the presence of 20 mol % of $AgBF_4$, 1.2 equiv of $AgNO_3$ and 1.5 equiv of DIPEA in wet NMP.

Yields dramatically fall away when alkylalkynes were employed. Water was proven to be necessary in the reaction system. A series of experiments with 1-, 2- or 5-formylimidazoles and selected control reactions with the isolated propargylamine intermediate, partly in the presence of D_2O or $H_2{}^{18}O$, were helpful to clarify the mechanism of the formation of pyrrole-2-carboxaldehydes and its byproduct. Key steps of the process are the silver-catalyzed intramolecular cyclization of propargylamine followed by a competitive 1,3- or 1,5-isomerization and a subsequent hydrolysis, yielding the pyrroloimidazolone **5** or the pyrrole **4**, respectively (Scheme 5). The 1,5-isomerization path leads to formaldehyde and ammonia, so that in the presence of silver salt the well-known silver mirror reaction could take place, thus justifying the need of at least one equiv of $AgNO_3$.

A silver supramolecular complex was proposed by Sun and co-workers as an efficient catalyst for A^3-coupling reactions between aldehydes, phenylacetylene and classical secondary amines under mild conditions (i.e., room temperature, open air, chloroform) [18]. The complex was prepared by the reaction of $AgNO_3$ with 1,4-bis(4,5-dihydro-2-oxazolyl)benzene to give a tridimensional supramolecular structure characterized by three-coordinated -[Ag(NO_2)]-L- chains, linked together by hydrogen bonds. The complex demonstrated to be more suited to aliphatic than aromatic aldehydes, whereas the presence of an EWG on the aldehyde resulted in low reaction yields.



Scheme 4: Liu's synthesis of pyrrole-2-carboxaldehydes **4**.



Scheme 5: Proposed reaction mechanism for Liu's synthesis of pyrrole-2-carboxaldehydes **4**.

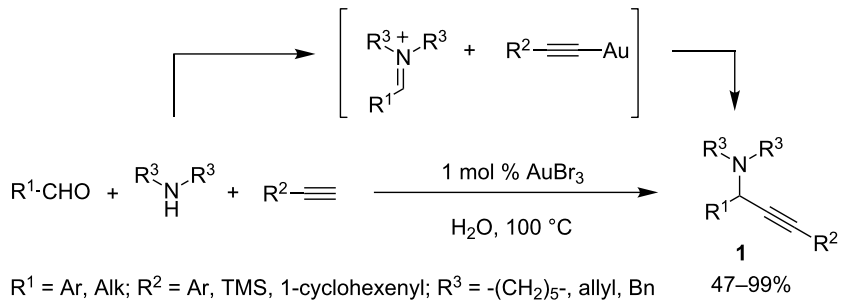
Gold catalysis

The first example of a gold-catalyzed synthesis of tertiary propargylamines from aldehydes, secondary amines and alkynes was reported by Li and co-workers [19], a bare three months before the work on silver cited above [5]. Both Au(I) and Au(III) salts demonstrated to be effective with low catalyst loading (1 mol %). Surprisingly, water was the solvent of choice, while the employment of common organic solvents gave worse results. The approach tolerated both aromatic and aliphatic alkynes and aldehydes, delivering the corresponding propargylamines **1** with fair to excellent yields. In contrast to the observations in their work on silver-catalyzed A^3-coupling, aromatic aldehydes gave better results than aliphatic ones, and the authors ascribed this to the competitive trimerization of aliphatic aldehydes. Moreover, the approach tolerates both cyclic and acyclic aliphatic secondary amines (Scheme 6). The proposed mechanism is similar to the one suggested for the silver-catalyzed approach, involving the activation of the C–H bond of alkyne by an Au(I) species. For the $AuBr_3$-catalyzed reaction, the authors argued that Au(I) could be generated in situ by a reduction of Au(III) from the alkyne.

Starting from this seminal work, many other gold catalysts, including [Au(III)salen] [20] and [Au(III)(2-phenylpyridine)Cl_2] [21] complexes, immobilized heterogeneous catalysts [22], and gold nanoparticles (Au NP) [23-26] have been reported until 2010, as well as recognized in two recent exhaustive reviews by Li [2] and Van der Eycken [3]. In the past three years the development of new and effective nanostructured catalytic systems dominated the gold-catalyzed approach to A^3-coupling. For example, ultrasmall gold(0) nanoparticles embedded in a mesoporous carbon nitride stabilizer [27] proved to be a highly active, selective and recyclable heterogeneous catalysts for coupling arylaldehydes, piperidine and phenylacetylene in toluene at 100 °C. One year later, the same research group obtained comparable results under identical reaction conditions by using gold(0) nanoparticles stabilized by nanocristalline magnesium oxide [28]. In this work, the scope was thoroughly investigated, and a wide range of aldehydes were tested affording the corresponding propargylamines in good to excellent yield. The method demonstrated to be suitable for challenging substrates, such as highly-activated aldehydes (i.e., nitrobenzaldehydes), whereas sterically demanding ones (i.e., *o*-substituted benzaldehydes) gave worse results. Other strengths of the approach are the ultralow catalyst loading (0.236 mol % gold) and the great TON (>400).

Periodic mesoporous organosilicas (PMOs), properly functionalized with HS/SO_3H [29] or alkylimidazolium [30], were recently used as support for Au NP, and these heterogeneous systems were tested as recyclable catalysts in an A^3-coupling. The former was effective in three simple model reactions as a bifunctional catalyst (Au/acid) in aqueous medium at 70 °C. The latter works well in chloroform at 60 °C and tolerates a number of substituted aryl and alkylaldehydes, cyclic secondary amines, and electron-rich arylacetylenes, affording the corresponding tertiary propargylamines in very good yields. On the basis of experiments with a reduced catalytic system and X-ray photoelectron spectroscopy (XPS) the authors suggested that Au(III) is the active component of the catalyst.

A two-step flow process catalyzed by Montmorillonite K-10 (MM K-10) and gold nanoparticles on alumina was proposed by Groß and co-workers [31] to improve the efficiency of traditional A^3-MCRs. The flow system allows a fine-tuning of each step, i.e., ethanol as a solvent, 25 °C for aldimine formation (first step) in the MM K-10 containing packed-bed capillary reactor (PBCR), and 80 °C for the reaction with phenylacetylene (second step) in Au NP@Al_2O_3 containing PBCR. The system, tested with some different aryl/heteroaryl/alkylaldehydes and cyclic/acyclic secondary amines in the presence of phenylacetylene, gave the corresponding coupling products in very good to excellent yields, apart from the reactions with furfural, which obtained low yields.



Scheme 6: Gold-catalyzed synthesis of propargylamines **1**.

An intriguing catalytic system composed of zinc oxide supported Au NP, activated by LED irradiation (plasmon mediated catalysis), was recently suggested by the group of Scaiano and González-Béjar [32] as a mild and green system to perform A^3-MCRs. The scope was concisely explored crossing three different aldehydes (i.e., benzaldehyde, formaldehyde and 3-methylbutanal) with phenylacetylene, and three cyclic secondary amines. The coupling products were quickly obtained (2 h) at rt with yields ranging from 50 to 95%.

In the field of heterogenized gold complexes, the group of Sánchez and Iglesias [33] prepared a series of Au(I/III) complexes with some known (NHC)dioxolane and pincer-type (NHC)NN ligands, and heterogenized them on a mesoporous support, i.e., MCM-41. The authors tested them in A^3-couplings and found that, although under homogeneous conditions the conversion to the respective propargylamine was higher than under heterogeneous ones, the heterogenized complexes were stable, recyclable for at least six cycles, active in a small amount, and under open-air conditions.

Besides the notable growing of heterogeneous catalytic systems, new gold complexes were recently developed as suitable catalysts for A^3-MCRs under homogeneous conditions. López-Ortiz and co-workers [34] synthesized an original phosphinamidic Au(III) metallacycle **6** (via tin(IV) precursors) active at low catalyst loadings (1–3%) in acetonitrile at 60 °C under a nitrogen atmosphere. The catalyst was effective with aromatic and aliphatic aldehydes, cyclic secondary amines, and phenyl- or TMS-acetylene providing the corresponding propargylamines **1** in excellent yields (Scheme 7). When enantiomerically pure prolinol was used as amine the process took place with excellent diastereoselectivity (dr 99:1, determined by ^{1}H NMR).

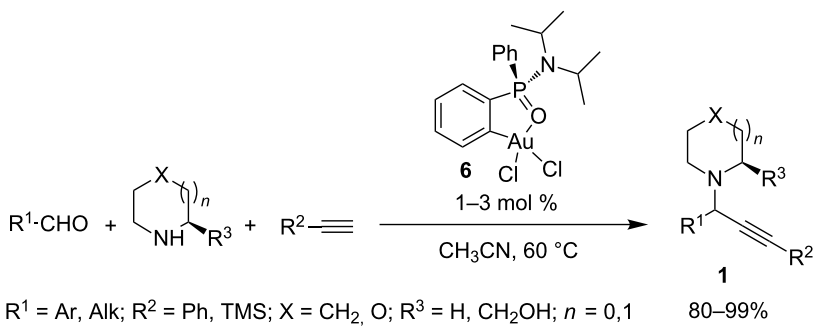
A series of new imidazole-based phosphane ligands were prepared by the research group of Kunz [35]. The corresponding Au(I) NP complexes displayed a potent catalytic activity in a model A^3-coupling reaction. The best result was obtained with 0.5 mol % catalyst at 40 °C without a solvent. The scope and limitations were not investigated.

Bowden and co-workers did not propose a new catalytic system but developed a smart method to extend the lifetimes of gold(III) chloride catalysts in A^3-MCRs by the addition of inexpensive and commercially available reagents such as $CuCl_2$ and TEMPO [36]. The proposed rationale seems simple and elegant: the reduction of gold(I) (real active species) to colloidal Au(0) was responsible for the deactivation of the catalyst. $CuCl_2$ was able to reoxidize Au(0) to Au(I) which increased the number of turnovers (up to 33 cycles). The Cu(I) was oxidized back to Cu(II) by TEMPO. Also O_2 had a role in this cycle, probably as a reoxidizing agent for TEMPO.

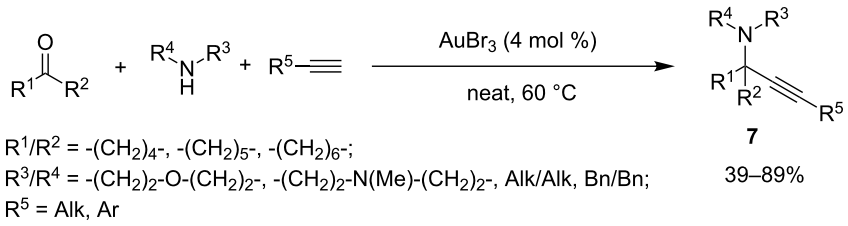
Another challenge in an A^3-coupling strategy is its transformation in an effective KA^2-MCR, that is, the substitution of aldehyde partners with less reactive ketones. This issue was partially solved by Ji and co-workers, who found with $AuBr_3$ (4 mol %), no-solvent and 60 °C the best conditions to react alkyl ketones, secondary amines and aryl/alkylacetylenes to give the corresponding propargylamines **7** containing a quaternary carbon center [37] (Scheme 8). Aliphatic alkynes and acyclic amines gave the corresponding products in low yields, whereas the methodology was ineffective for aromatic ketones.

Gold-catalyzed A^3-MCRs were also applied with the aim to functionalize particular molecules or were employed as a key step for the synthesis of more complex structures in domino approaches.

For example, Che, Wong and co-workers successfully applied A^3-coupling to aldehyde-containing oligosaccharides **8** [38]. The best catalyst for this reaction was 10 mol % of the $[Au(C^N)Cl_2]$ complex (HC^N = 2-benzylpyridine) in water at 40 °C. The reaction yields ranged from good to excellent, and the method allowed the introduction of alkynes and amines



Scheme 7: A^3-coupling catalyzed by phosphinamidic Au(III) metallacycle **6**.

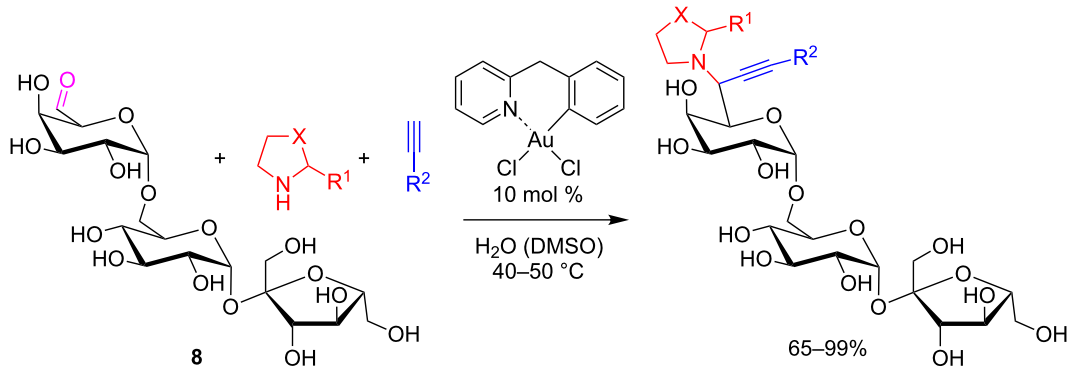


Scheme 8: Gold-catalyzed KA^2-coupling.

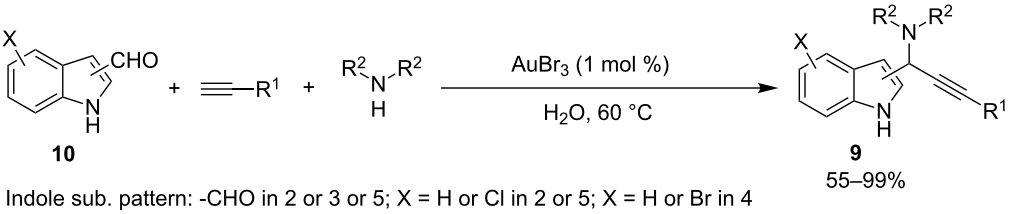
properly functionalized with particular groups,(i.e., dansyl and biotin), or *m*/*p*-ethynylbenzenes, suitable for further orthogonal transformation, i.e., [3 + 2] cycloaddition (Scheme 9).

Another application of an A^3-MCR for the improvement of molecular complexity was published by Kokezu and Srinivas [39]. The authors suggested a straightforward $AuBr_3$-catalyzed route to 2-, 3-, or 5-propargylamine substituted indoles **9**. The reactions were performed in water at 60 °C starting from indolecarboxaldehydes **10**, phenyl- and trimethylsilylacetylenes and cyclic/acyclic secondary amines, with the reaction yields ranging from fair to excellent (Scheme 10).

Two elegant examples of cascade reactions involving an A^3-MCR for the synthesis of valuable heterocyclic scaffolds were recently reported by the research groups of Liu and Fujii/Ohno. The Liu group developed a smart approach to furans starting from arylglyoxals **11**, secondary amines and arylacetylenes in methanol under a nitrogen atmosphere [40]. In this reaction, the best catalyst was $AuBr_3$ (5 mol %) and the optimal temperature was 60 °C. The aryl moieties on alkynes and glyoxals tolerated the presence of ED and EW groups. The proposed mechanism implied the coupling among reaction partners to give an α-amino-β,γ-ynone intermediate **I** capable to undergo a 5-*endo*-*dig* cyclization by an intramolecular attack of



Scheme 9: A^3-coupling applied to aldehyde-containing oligosaccharides **8**.

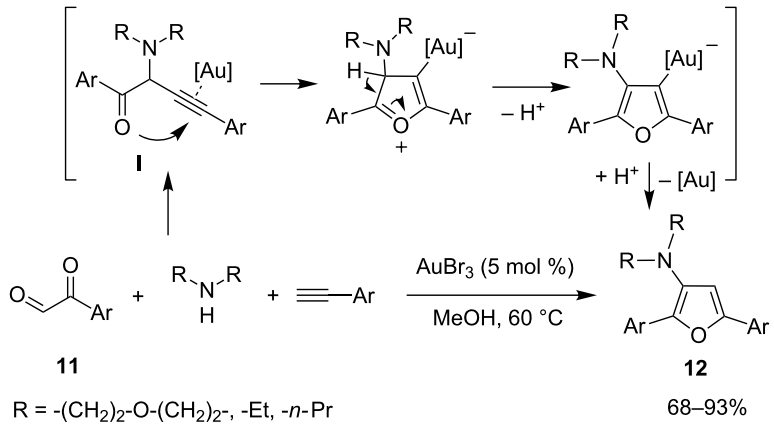


Scheme 10: A^3-MCR for the preparation of propargylamine-substituted indoles **9**.

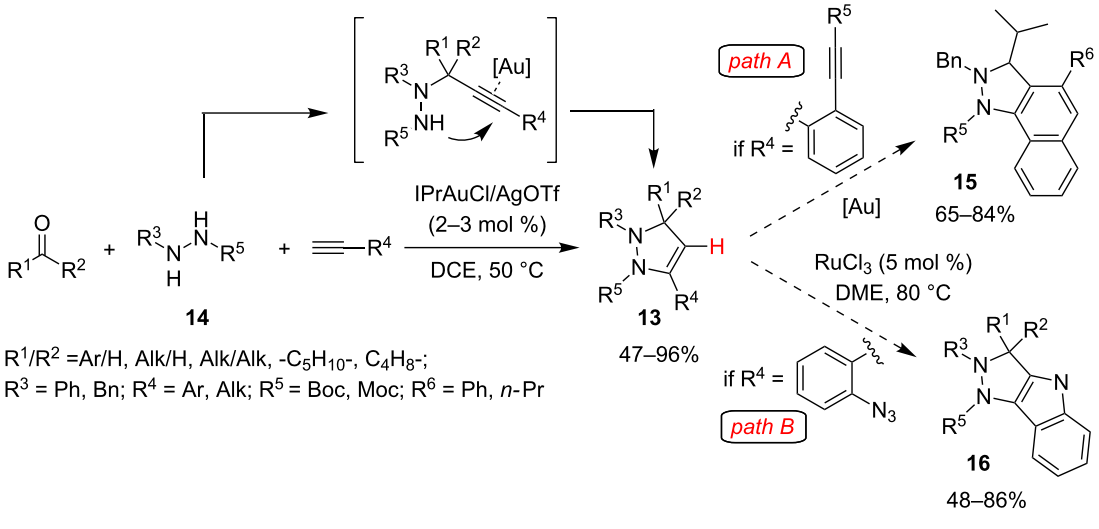
the oxygen nucleophile to the Au-activated triple bond. Aromatization and protodeauration closed the catalytic cycle to give furans **12** and to regenerate the catalyst (Scheme 11).

A conceptually similar approach – and a comparable mechanism – was proposed by Ohno and Fujii for the synthesis of functionalized dihydropyrazoles **13** starting from aryl/alkylacetylenes, aldehydes – and also more challenging ketones – and *N*-Boc-*N'*-substituted hydrazines **14** [41] (Scheme 12). Among several gold complexes tested, best results were obtained with IPrAuCl/AgOTf (2–5 mol %) in DCE (AcOH for aromatic aldehydes) at 50 °C, but also the cheaper Ph_3PAuCl/AgOTf gave respectable results. Surprisingly, $AuBr_3$ was not able to promote this cascade reaction. A special feature of this approach is that when R^4 is a *o*-alkynylbenzene a further Au-catalyzed cascade process involving C–H activation can occur to give the corresponding tricyclic naphthalene fused pyrazoles **15** (Scheme 12, path A). Moreover, in a subsequent work, the authors applied the same strategy to obtain pyrazolo[4,3-*b*]indoles **16**, a new class of CK2 inhibitors [42]. These products were obtained starting from properly substituted dihydropyrazoles **13** in which R^4 was an *o*-azidobenzene group by a $RuCl_3$ catalyzed C–H amination (Scheme 12, path B).

As explained above, A^3-MCR is a reaction in which the formation of a metal acetylide and its reaction with an in situ formed iminium cation are the key steps of the process. In the recent literature, there are related cascade multicomponent processes of interest, which involve gold acetylides and imines. Among them, a new Au(I)-catalyzed entry to cyclic carbamimidates **17**



Scheme 11: A^3-coupling interceded synthesis of furans **12**.



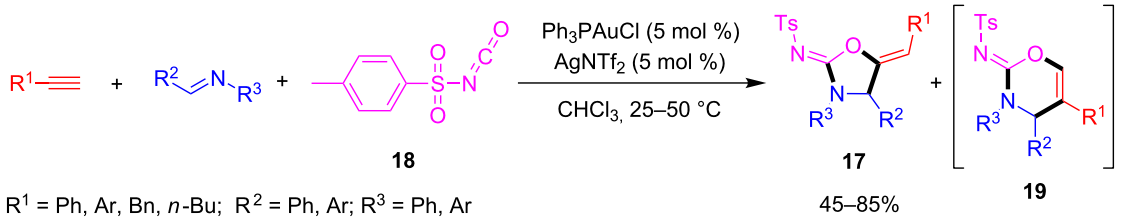
Scheme 12: A^3/KA^2-coupling mediated synthesis of functionalized dihydropyrazoles **13** and polycyclic dihydropyrazoles **15** and **16**.

starting from acetylenes, imines and *p*-toluenesulfonylisocyanate (**18**) was reported by Toste and Campbell [43]. The reaction gave mainly the 5-membered carbamimidates **17** besides a variable amount of the 6-membered analog **19** (Scheme 13). The reaction partners, the more suitable catalytic system, the ratio among reagents and other reaction conditions were carefully chosen by a series of extensive experiments. In particular, the highly electrophilic *p*-toluenesulfonylisocyanate (**18**) is essential for the formation of the key intermediate. Moreover, the formation of the five-membered product **17** is thermodynamically favored by the use of small ligands in the Au complex. Only aryl substituents were well tolerated on imine and alkyne reaction partners, but imines bearing hindered *ortho* substituents or too electron-rich imines were not allowed. The reaction with alkylacetylenes(i.e., 1-hexyne), resulted in low yields and selectivity (Scheme 13).

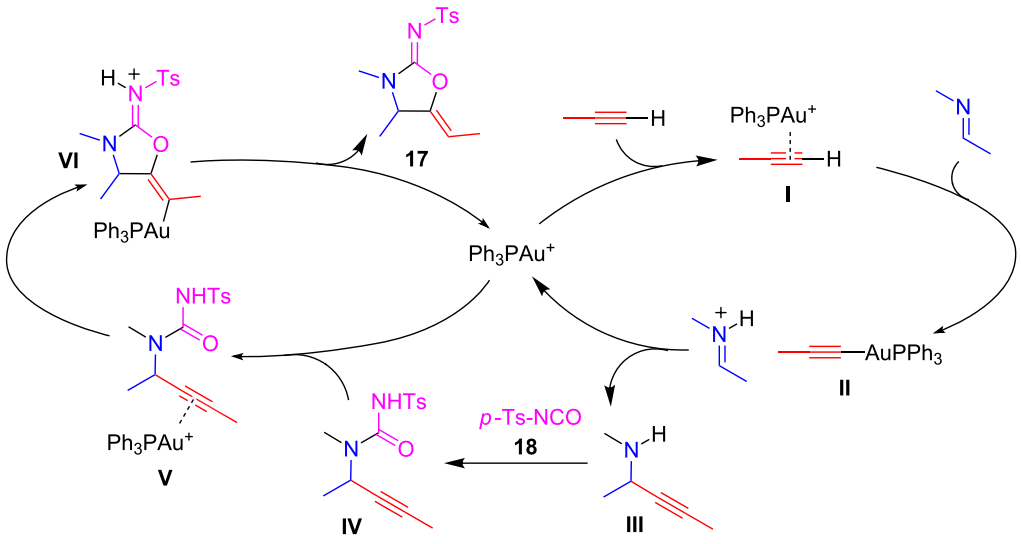
The proposed mechanism is shown in Scheme 14. The coordination of acetylene to gold produces the alkyne π-complex **I** with the acidification of the acetylenic hydrogen atom. Deprotonation by the imine produces the electrophilic iminium ion with simultaneous production of the Au(I)-acetylide **II**. An addition reaction produces propargylamine **III** and regenerates the gold cation. Amine **III** is trapped with *p*-TsNCO **18** to generate the acyclic urea **IV**, and the alkyne moiety of **IV** coordinates to gold to form a new alkyne π-complex **V**. A 5-*exo*-*dig* cyclization by nucleophilic attack of the urea oxygen forms the vinylgold carbamimidinium ion **VI** (the minor 6-*endo*-*dig* **19** product is not shown), which undergoes proton transfer to release the product **17** and regenerates the Au(I) catalyst.

The authors also developed an enantioselective version of the approach. After an in-depth preliminary screening, the catalyst and the optimal reaction conditions were found to be the original arylsulfonylurea-containing *trans*-1-diphenylphosphino-2-aminocyclohexane–Au(I) complex **20** (Figure 2), $AgNTf_2$ as an additive, toluene as a solvent, rt, and a concentration of imine above 0.2 M. The obtained ee ranged from 41 to 95%.

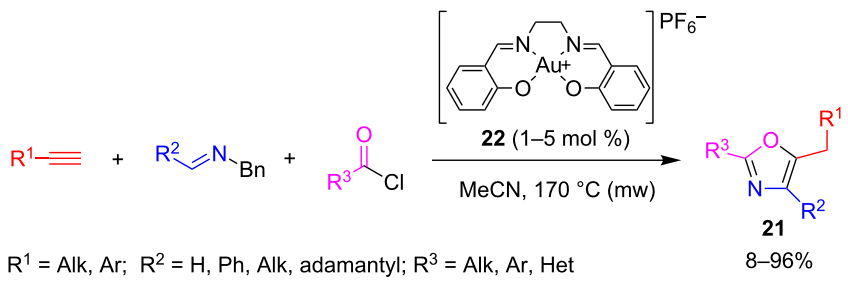
In a similar approach, Strand and co-workers [44] worked out a new entry to oxazoles **21** starting from terminal alkynes, *N*-benzylimines and acid chlorides. The reaction was catalyzed by a Au(III)–salen complex **22** and occurred in acetonitrile at 170 °C under dielectric heating (Scheme 15).



Scheme 13: Au(I)-catalyzed entry to cyclic carbamimidates **17** via an A^3-coupling-type approach.



Scheme 14: Proposed reaction mechanism for the Au(I)-catalyzed synthesis of cyclic carbamimidates **17**.



Scheme 15: A^3-coupling-type synthesis of oxazoles **21** catalyzed by Au(III)–salen complex.

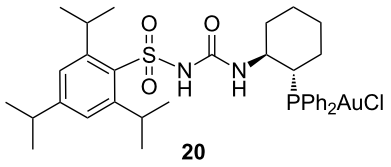
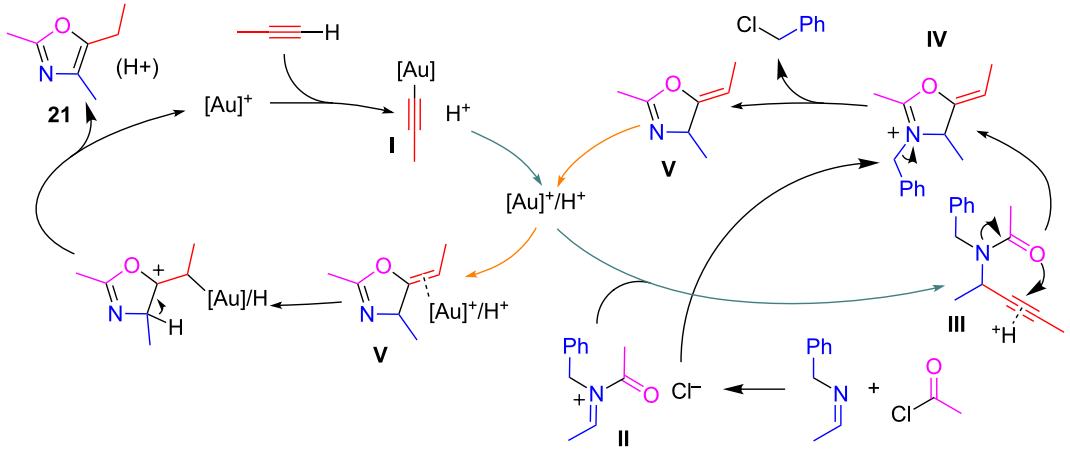


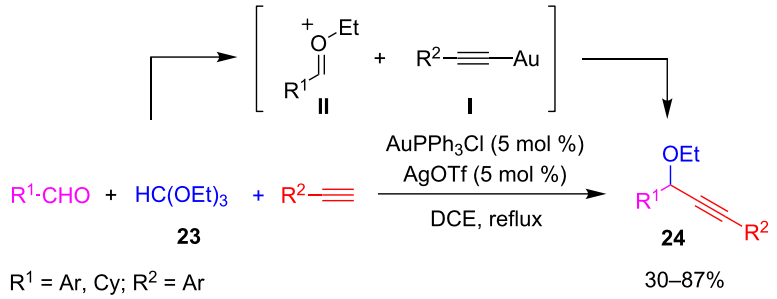
Figure 2: Chiral *trans*-1-diphenylphosphino-2-aminocyclohexane–Au(I) complex **20**.

On the basis of the results of some smart kinetic experiments on ad-hoc synthetized plausible intermediates (**III** and **V**) in the presence of different amounts of catalyst (from 0 to 10 mol %) and/or 2,6-lutidine hydrochloride as a suitable proton source, the authors proposed the mechanism depicted in Scheme 16. The process involves the addition of gold-acetylide **I** to the activated *N*-acyliminium salt **II** resulting from the reaction between acyl chloride and imine, to give the propargylamide **III**. The proton released during the formation of the acetylide **I** activates the triple bond of propargylamide **III** which undergoes the attack from the amide oxygen atom. The benzyl group of the resultant iminium ion **IV** is lost as benzyl chloride by reaction with the chloride ion released during the initial imine acylation. Finally, a combination between Brønsted acid and metal catalysis, promote the isomerization of **V** to oxazole **21**. It is noteworthy, that the gold catalyst seemed to be essential only for the formation of the gold-acetylide intermediate **I**.

In a different approach strictly related to Au-catalyzed A^3-coupling, Wang and co-workers substituted the classical amine partner with triethyl orthoformate (**23**) to give the corresponding propargyl ethyl ethers **24** [45] (Scheme 17). After a brief screening for the best reaction conditions (i.e., $AuPPh_3Cl$/AgOTf (5 mol %), DCE heated under reflux), the scope was investigated and best results were obtained when the reaction partners were substituted with aryl groups. In particular, the reaction of cyclohexanecarbaldehyde resulted in fair yield whereas *p*-nitrobenzaldehyde and pyridinecarbaldehyde did not react at all. During their investigations, the authors observed that $AuPPh_3$/AgOTf was able to catalyze the reaction of benzaldehyde with triethyl orthoformate (**23**) to give the corresponding aldehyde diethylacetal. Consequently, the proposed mechanism involves the addition of the gold acetylide **I** to the C=O bond of an oxocarbenium intermediate **II**, formed by a Au-catalyzed reaction between aldehydes and orthoformate **23**.



Scheme 16: Proposed reaction mechanism for the synthesis of oxazoles **21**.



Scheme 17: Synthesis of propargyl ethyl ethers **24** by an A^3-coupling-type reaction.

Other multicomponent processes

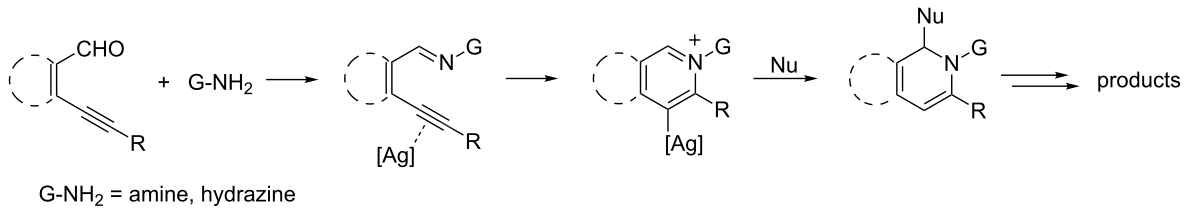
Silver assisted multicomponent reactions

Newly reported and notable synthetic strategies based on silver-mediated processes are discussed in this chapter. Silver-mediated MCRs mainly take advantage by the well-known π- and σ-philic properties of Ag(I) salts and complexes [46-48]. Thus, coordination and activation of both carbon–carbon multiple bonds or heteroatoms fulfill a MC process involving more than one chemical transformation or reaction mechanism. This part of the review is divided in sections related to the nature of the activated functionalities.

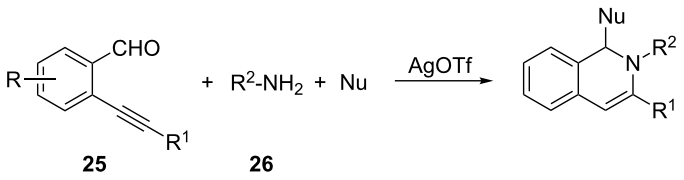
Reaction involving activation of carbon–carbon multiple bonds. This section primarily discusses cycloisomerization reactions involving the addition of imines to silver-activated carbon–carbon triple bonds [49]. Imine-based MCRs have received considerable attention in recent years [50]. The increasing interest in imine-based MCRs can be attributed to the easy preparation (even in situ) of many differently substituted derivatives from commercially available aldehydes and amines. This leads to great chemical diversity of the products of MCRs. Moreover, imines can participate in MCRs as electrophilic or nucleophilic partners, azadienes, dienophiles and 1,3-dipoles. All these reactions may benefit from the presence of a Lewis acid, a Brønsted acid or a transition metal catalyst. Silver-catalyzed MCRs involving imines in cycloisomerization reactions follow the main reaction pathway shown in Scheme 18.

Starting from a γ-ketoalkyne [51] encompassed in a (hetero)aromatic framework, a condensation step with a suitable G–NH_2 group (amine or hydrazine) provides the imine intermediate, which undergoes a silver-catalyzed 6-*endo*-*dig* cyclization, thus giving rise to a key iminium intermediate suitable to react with a third nucleophilic component (Nu in Scheme 18). In these reactions the imine acts as a nucleophile and the silver serves as a π-philic catalyst enhancing the reactivity of the triple bond toward the nucleophile. A role of the silver salt as Lewis acid in the condensation step between amine and carbonyl group has never been claimed even though it could be plausible [52]. This chemistry has been exhaustively evaluated by Wu's group, whose main interest was the development of new MCRs as a powerful tool for the synthesis of medium-sized libraries of bioactive compounds. Thus, straightforward syntheses of 1,3-disubstituted-1,2-dihydroisoquinolines have been achieved by three-component reactions between alkynylbenzaldehydes **25** (γ-carbonylalkyne), primary amines **26** (mainly anilines) and a third nucleophilic reagent (Nu) in the presence of a silver triflate catalyst (Scheme 19).

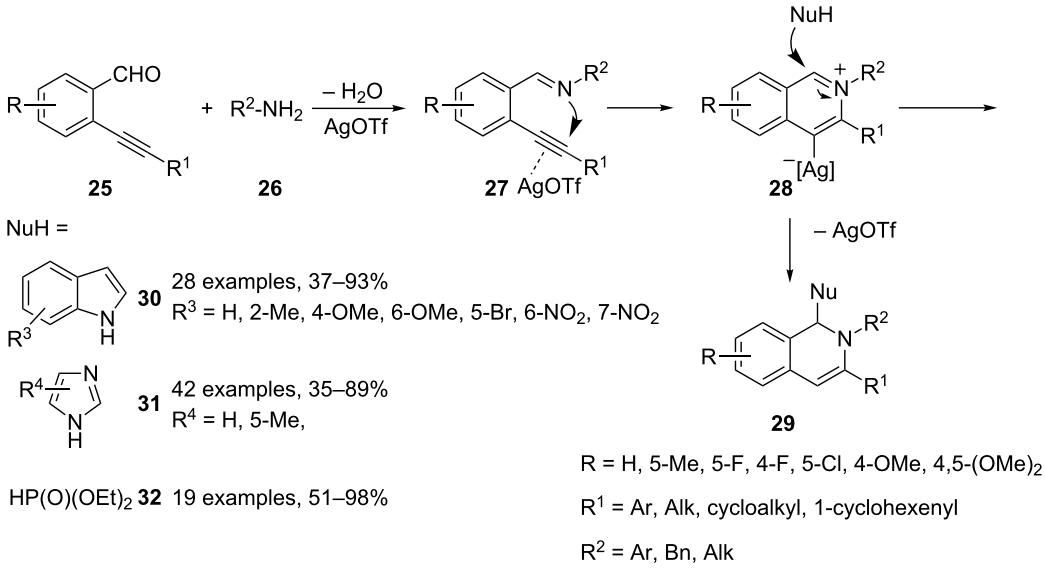
All reported reactions share the same key iminium intermediate **28** generated in situ from imine **27** via a silver triflate catalyzed 6-*endo* cyclization, but differ in the third reaction partner (Scheme 20 and Scheme 21). This can be a simple nucleophile (indole **30**, imidazole **31**, diethyl phosphite (**32**), Scheme 20) [53-55] or can be generated in situ (enolate **33**, enamine **34**,



Scheme 18: General mechanism of Ag(I)-catalyzed MCRs of 2-alkynylbenzaldehydes, amines and nucleophiles.



Scheme 19: General synthetic pathway to 1,3-disubstituted-1,2-dihydroisoquinolines.



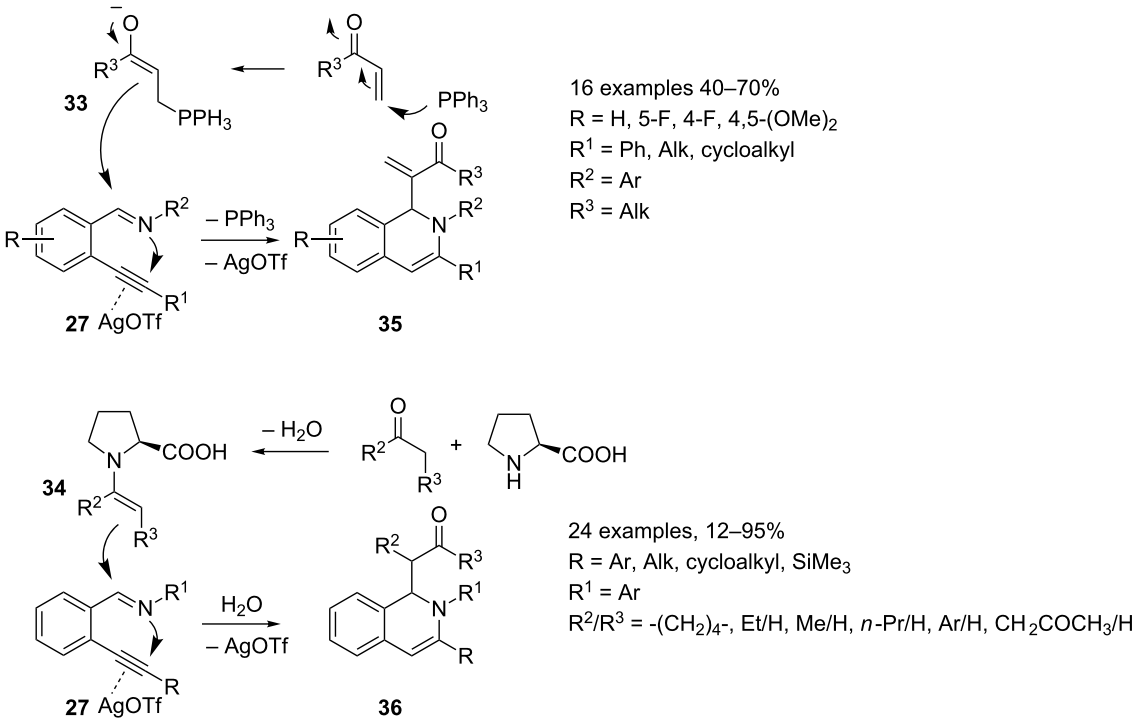
Scheme 20: Synthesis of 1,3-disubstituted-1,2-dihydroisoquinolines **29**.

Scheme 21) [56,57] from a suitable precursor and a second catalyst (dual activation strategy) affording 1,3-disubstituted-1,2-dihydroisoquinolines **29**, **35** and **36**, respectively. The author suggested a mechanism that, starting from iminium intermediate **28**, involves the nucleophilic addition on the electrophilic carbon atom of **28** and a protodemetalation yielding the desired 1,2-dihydroquinolines **29**, **35** and **36**. The annulation step giving rise to **28**, and the nucleophilic attack on the imine C=N bond could also be synchronized. The two proposed mechanisms are described in Scheme 20 and Scheme 21, respectively.

The scope of these reactions has been examined with a wide range of substrates. Therefore, 2-alkynylbenzaldehydes can be functionalized on the aryl ring with EWG or EDG, the former better performing than the latter. However, a serious limitation on the substituents on the triple bond has been reported. Thus, phenyl and more generally aryl substituents on the triple bond are well tolerated whereas alkyl groups gave poor results. Both electron-rich and electron-poor anilines are suitable partners for these reactions, whereas alkylamines and benzylamine gave worse results. Moreover, the third partner (Nu in Scheme 19) is limited to one substrate as in the reaction employing diethyl phosphite (**32**). Indoles **30** and imidazoles **31** can bear several substituents and enolates **33** can be generated from methyl- or ethyl vinyl ketone, the corresponding α,β-unsaturated esters being unreactive. Enamines **34** arise from cyclic or linear C3–C5 ketones, acetophenones and β-diketones. It is noteworthy, that the reactions are highly regiospecific for nonsymmetric ketones. Moreover, an optical active compound could be generated during the reaction process since a chiral catalyst (proline) is used in the reactions. However, enantioselectivity was not observed by chiral HPLC analysis, and 3-pentanone gives rise to a mixture of diastereoisomers.

Following this synthetic strategy, a solution-phase parallel synthesis of 1,2-dihydroisoquinolines has been developed by Larock, providing a 105-membered library for biological assays [58]. Moreover, an extension to γ-ketoalkyne encompassed in diverse heterocyclic frameworks (quinoline, pyridine or benzo[*b*]thiophene) has been reported [59].

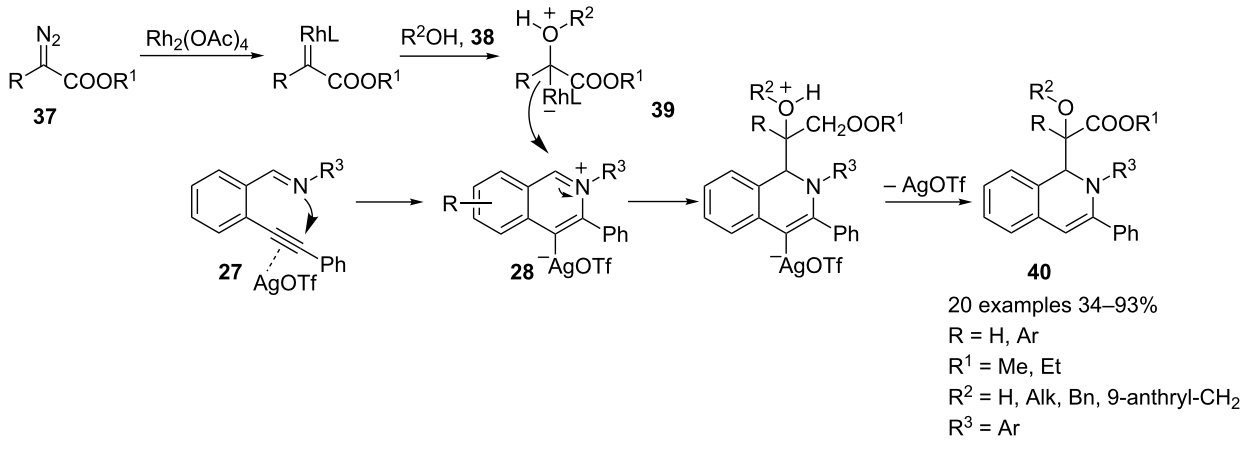
Preformed 2-(1-alkynyl)arylaldimines **27** have been used in a MCR involving tandem cyclization/three-component reactions



Scheme 21: Synthesis of 1,3-disubstituted-1,2-dihydroisoquinolines **35** and **36**.

with diazo compounds **37** and water or alcohols **38** in the presence of dirhodium acetate and silver triflate cooperative catalysis resulting in excellent yields of diastereoisomeric 1,2-dihydroisoquinolines **40** (Scheme 22) [60].

Iminium intermediate **28**, generated in situ from the aldimine **27** under silver triflate catalysis is the usual electrophilic intermediate, whereas the nucleophile, in this case, is the oxonium ylide **39**. The reaction resulted in the synthesis of highly substituted 1,2-dihydroisoquinolines **40** characterized by the presence of an α-hydroxy/alkoxy-α-carboxylate carbon pendant. The oxonium ylide **39** was prepared by a well-known procedure involving a rhodium carbenoid intermediate, generated in situ from the corresponding diazoacetate **37** under $Rh_2(OAc)_4$ catalysis, and water or alcohols **38**. The scope of the reaction was thoroughly investigated. Thus, methyl aryl diazoacetates and *N*-aryl aldimines, with electronically diverse *metha* or *para*-substituents on the aryl moieties, as well as ethyl 2-diazobu-



Scheme 22: Rh(II)/Ag(I) co-catalyzed synthesis of 1,3-disubstituted-1,2-dihydroisoquinolines **40**.

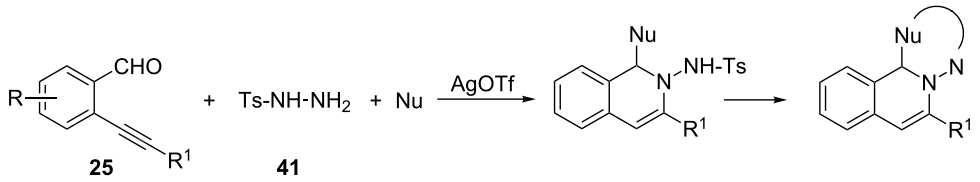
tanoate gave good results, only nitro and *ortho*-substituted aryl derivatives were unreactive. Interestingly, two stereocenters are generated during the reactions. However, the observed diastereoselectivities were poor, ranging from 50:50 to 76:24.

MCRs yielding isoquinoline cores are well documented in the literature and several examples involving alkynylbenzaldehydes and G–NH_2 groups under palladium/copper [61,62], copper [63,64], copper/magnesium [65], or base [66] catalysis have been reported.

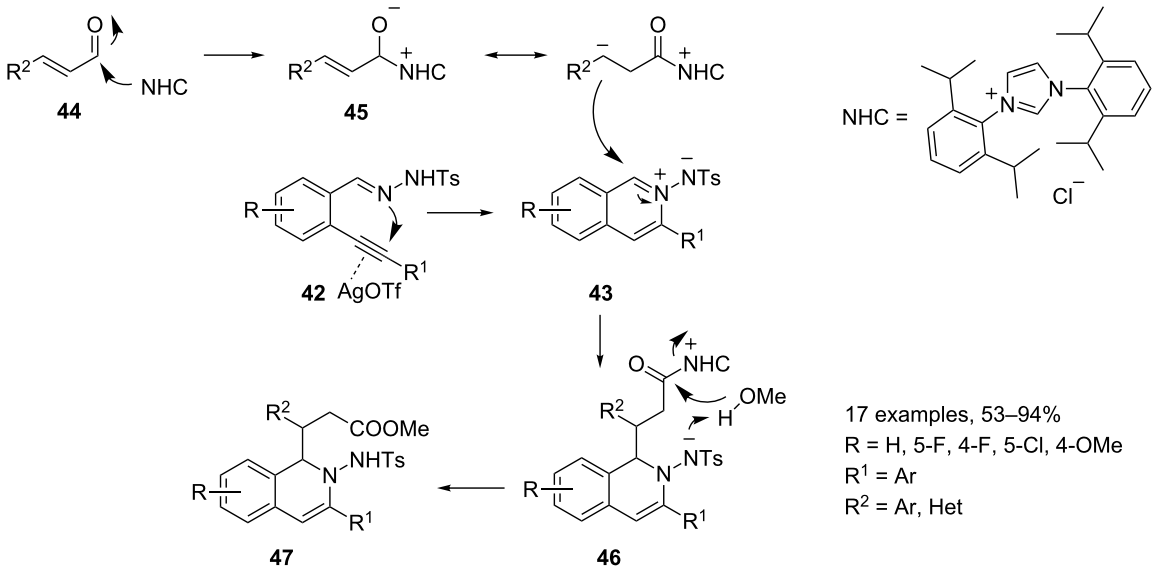
When tosylhydrazide (**41**) is used as G–NH_2 component, the silver promoted MCR can afford 2-amino-1,3-disubstituted-1,2-dihydroquinolines and, when the third component (Nu) bears the appropriate substituents, to polycyclic derivatives (Scheme 23).

The reactions between 2-alkynylbenzaldehydes **25** and tosylhydrazide (**41**) afford the corresponding hydrazono derivatives **42**, which, in turn, yield the isoquinolinium-2-ylamides **43** under silver triflate catalysis (Scheme 24). These new key intermediates encompass the structural motif $C=N^+–N^–$, a very useful framework for further functionalizations. Wu and co-workers widely used preformed *N*'-(2-alkynylbenzylidene)hydrazides **42** in two component reactions involving **43** as an intermediate for the construction of N-heterocycles. Moreover, in the field of MCRs, in 2010 the same authors assembled a small library of 2-amino-1,2-dihydroisoquinolines **47** starting from *N*'-(2-alkynylbenzylidene)hydrazides **42**, methanol and α,β-unsaturated aldehydes **44**. The three-component process is co-catalyzed by silver triflate and an *N*-heterocyclic carbene. (Scheme 24) [67].

As mentioned above, *N*'-(2-alkynylbenzylidene)hydrazide **42** could easily be transformed to isoquinolinium-2-ylamide **43** by a 6-*endo*-cyclization in the presence of silver triflate catalyst. Meanwhile, the in situ formed homoenolate **45** (derived from α,β-unsaturated aldehydes **44** in the presence of NHC catalyst, IPr) would attack the isoquinolinium-2-ylamide **43** to generate the new intermediate **46**. Subsequently, methanol would be involved in the reaction via deprotonation and the nucleophilic addition to the carbonyl group to produce the desired 2-amino-1,2-dihydroisoquinoline **47**. Concurrently, the released *N*-hete-



Scheme 23: General synthetic pathway to 2-amino-1,2-dihydroquinolines.



Scheme 24: Synthesis of 2-amino-1,2-dihydroquinolines **47**.

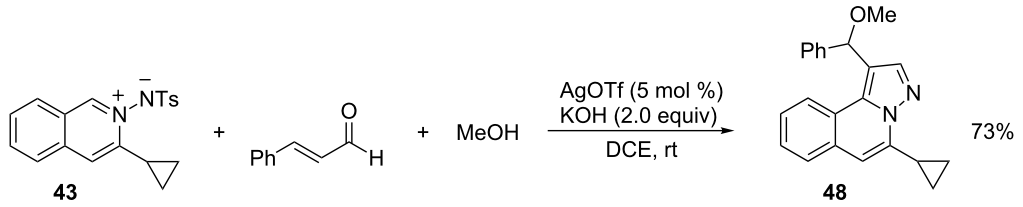
rocyclic carbene would re-enter the catalytic cycle. Nevertheless, the reaction suffers from severe limitation on the nature of the R^1 group attached to the triple bond of *N*′-(2-alkynylbenzylidene)hydrazides **42** and only aryl groups proofed to be effective. Broadening the scope of this transformation, the same authors reinvestigated the reaction on the preformed isoquinolinium-2-ylamide **43** (R = H, R^1 = cyclopropyl) with cinnamaldehyde and methanol under silver triflate catalysis [68]. The avoidance of the use of IPr and the usage of 2 equiv of potassium hydroxide leads to a different reaction mechanism and allows for the synthesis of tricyclic *H*-pyrazolo[5,1-*a*]isoquinoline **48** (Scheme 25).

With these results in hand, a MCR involving 2-alkynylbenzaldehydes **25**, tosylhydrazide (**41**), methanol and α,β-unsaturated aldehydes or ketones **49** was set up to synthesize a library of 24 *H*-pyrazolo[5,1-*a*]isoquinolines **48** under silver triflate catalysis (Scheme 26).

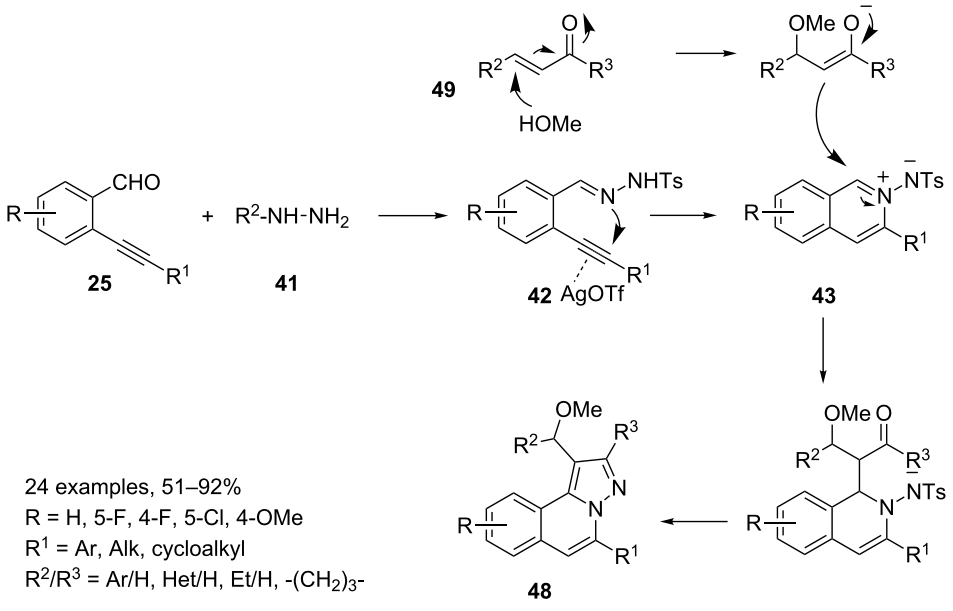
The synthesis of both 1,2-dihydroquinolines **47** and **48** takes advantage from the easy formation of the isoquinolinium-2-ylamide **43** under silver triflate catalysis. This intermediate can be trapped by other nucleophilic reagents (enamines and carbanions) or be involved in cycloaddition reactions affording tricyclic compounds by cascade processes.

An unprecedented, co-catalyzed reaction involving enamines **51** as nucleophilic partners, also yields the *H*-pyrazolo[5,1-*a*]isoquinoline nucleus **48**, in the presence of silver triflate and copper(II) chloride under air (Scheme 27) [69]. However, with respect to the reaction reported in Scheme 26, also affording isoquinolines of general formula **48**, a diverse arrangement of substituents can be achieved.

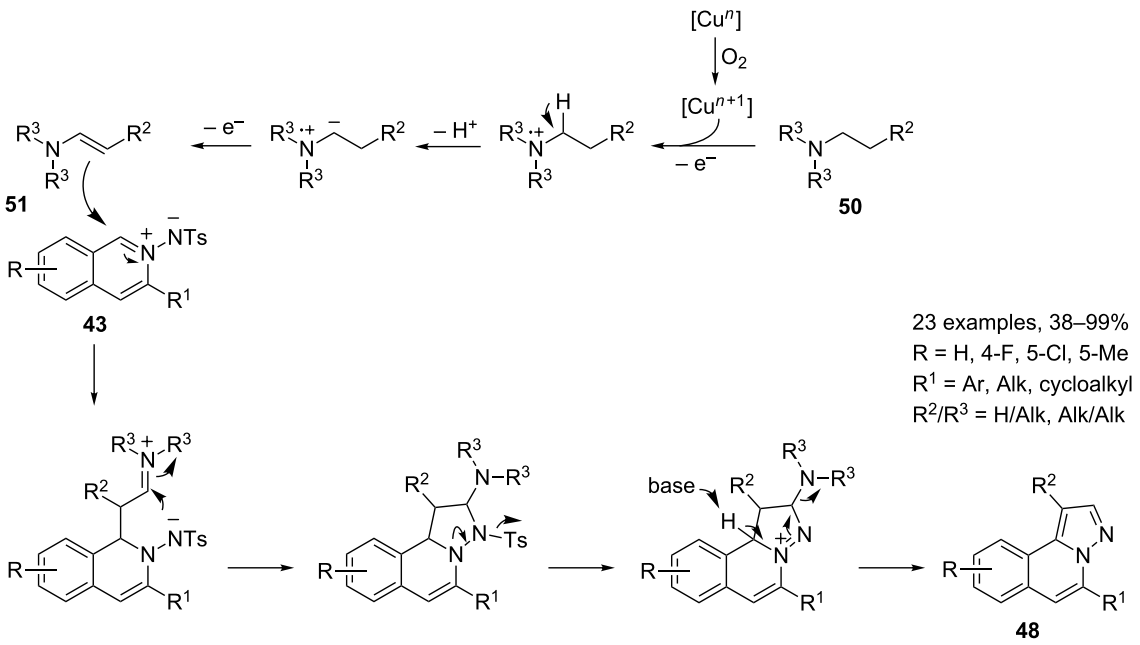
The proposed reaction mechanism takes into account the recent applications of an oxygen-copper catalytic system for the oxidation of aliphatic C–H bonds [70]. Thus, oxidation of the ali-



Scheme 25: Synthesis of tricyclic *H*-pyrazolo[5,1-*a*]isoquinoline **48**.



Scheme 26: Synthesis of tricyclic *H*-pyrazolo[5,1-*a*]isoquinolines **48**.

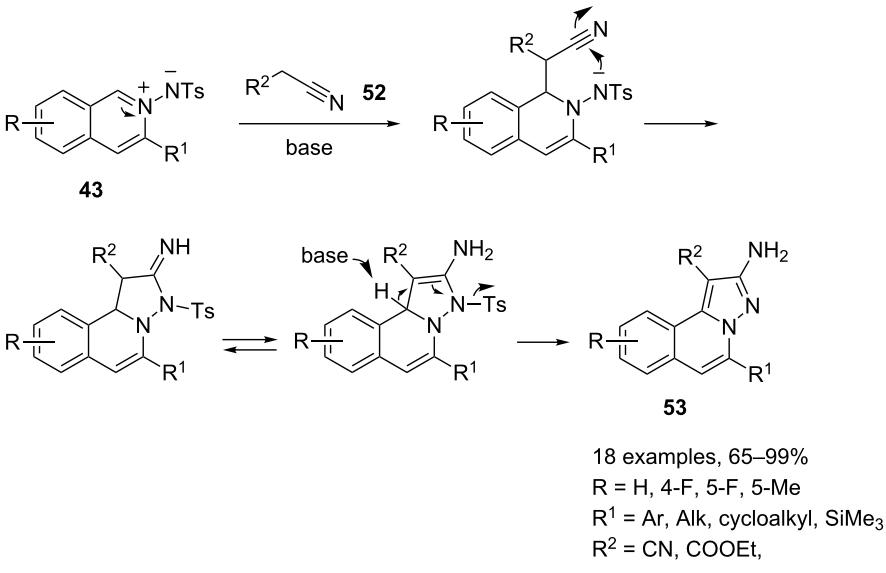


Scheme 27: Cu(II)/Ag(I) catalyzed synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines **48**.

phatic C–H bond, alpha to the reacting amine **50**, resulted in the formation of nucleophilic enamine **51**, which is able to react with the isoquinolinium-2-ylamide **43**, thereby affording a tricyclic intermediate, which by loss of the tosyl group and base-catalyzed aromatization yields the *H*-pyrazolo[5,1-*a*]isoquinoline **48**.

Finally, a new series of fully aromatic pyrazolo[5,1-*a*]isoquinolines **53**, bearing an amino group in position 2 can be synthesized under silver triflate catalysis by the usual three-component reaction involving nitriles **52** as pro-nucleophiles (Scheme 28) [71].

Wu and co-workers successfully employed the isoquinolinium-2-ylamides **43** as an ylidic species in two-component tandem [3 + 2]-cycloaddition reactions with a series of substrates including dimethyl acetylenedicarboxylate [72], phenylacetylene [73,74], and methyl acrylate [75]. Starting from these



Scheme 28: Synthesis of 2-aminopyrazolo[5,1-*a*]isoquinolines **53**.

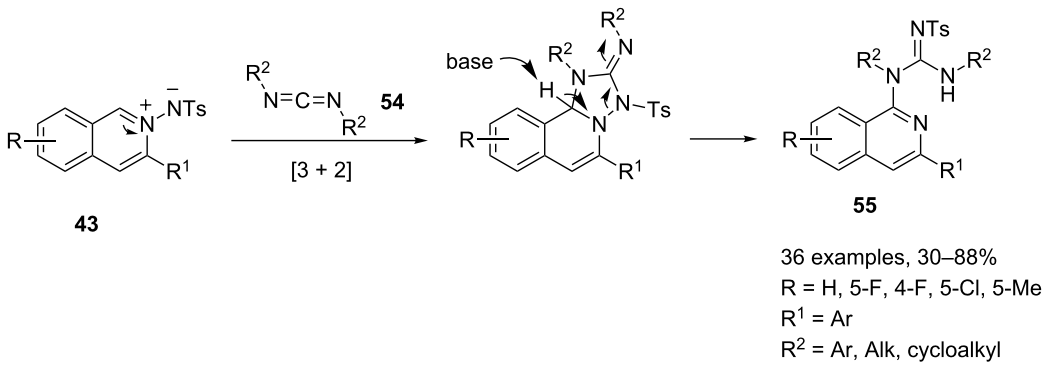
results, a MC approach to 1-(isoquinolin-1-yl)guanidines **55** was efficiently developed by a silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehydes **25**, tosylhydrazide (**41**) and carbodiimides **54** (Scheme 29) [76].

The isoquinolinium-2-ylamide **43** undergoes a [3 + 2]-cycloaddition reaction with carbodiimide **54**. Further intramolecular rearrangement yields the desired 1-(isoquinolin-1-yl)guanidine **55**.

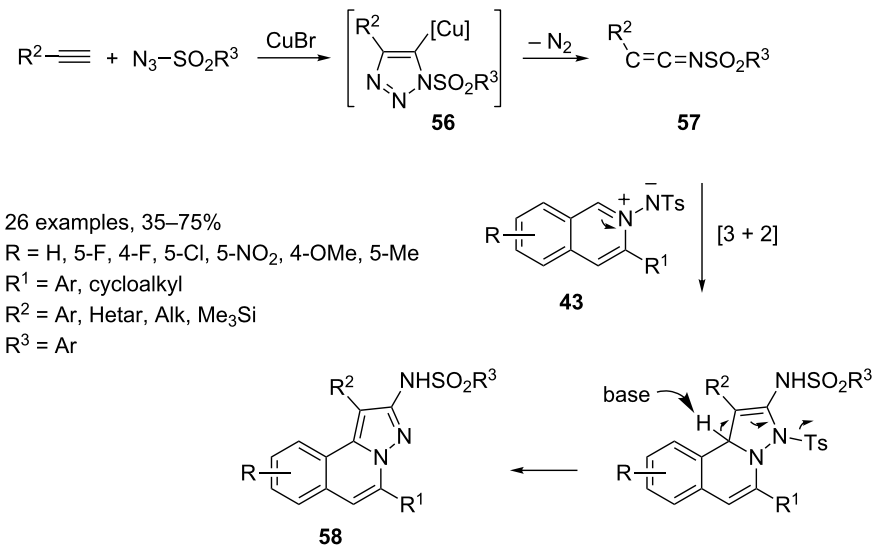
Moreover, isoquinolinium-2-ylamides **43** can participate as 1,3-dipoles in [3 + 2]-cycloaddition reactions with in situ generated keteneimines **57** [77] or in [3 + 3] processes with dimethyl cyclopropane-1,1-dicarboxylates **59** [78]. Both these reactions are co-catalyzed, the former by silver triflate and copper bromide and the latter by silver triflate and nickel(II) perchlorate (Scheme 30 and Scheme 31).

In [3 + 2]-cycloaddition reactions between isoquinolinium-2-ylamide **43** and keteneimine **57** [79], silver salt plays the usual role of a π-philic catalyst, whereas ketene imine **57** is generated by a well-known procedure involving a copper(I)-catalyzed azide–alkyne [3 + 2] cycloaddition (CuAAC) giving rise to 5-cuprated triazole intermediate **56** which, by subsequent ring opening and loss of nitrogen gas, smoothly resulted in keteneimine **57** [80]. The overall process proceeds efficiently to generate the 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines **58** in moderate to excellent yields under mild conditions and with good substrate tolerance.

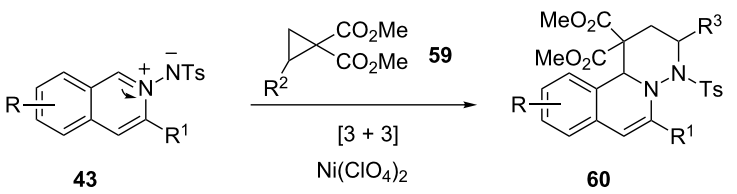
The co-catalyzed process described in Scheme 31 takes advantage of the usual formation of **43** which undergoes a [3 + 3]-cycloaddition reaction with cyclopropanes **59** under nickel perchlorate catalysis. Cycloaddition reactions of activated cyclopropanes with nitrones under Lewis acid catalysis



Scheme 29: Synthesis of 1-(isoquinolin-1-yl)guanidines **55**.



Scheme 30: Ag(I)/Cu(I) catalyzed synthesis of 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines **58**.

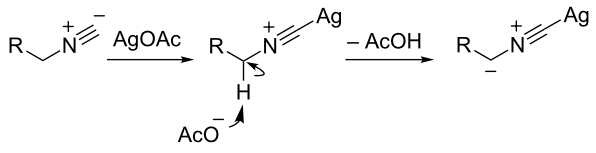


Scheme 31: Ag(I)/Ni(II) co-catalyzed synthesis of 3,4-dihydro-1*H*-pyridazino[6,1-*a*]isoquinoline-1,1-dicarboxylate **60**.

have been previously described by Kerr and may proceed on the activated cyclopropane by a stepwise or concerted mechanism [81]. Similar mechanisms could be also operative in the reaction of ylidic species **43** for the synthesis of **60**. Good substrate tolerance and moderate to excellent yields are reported.

Reactions involving σ-activation of carbon and heteroatoms. This section gives an overview of the multifaceted field of silver-catalyzed processes involving a σ-activation of carbon or heteroatoms. We focus on Mannich-type reactions characterized by the addition of a nucleophile to an imine. In several MCRs with this type of reactivity, silver(I) salts and complexes have been used to activate either the nucleophile or the imine.

Isocyanides have been found to be versatile reagents in heterocyclic synthesis [82,83]. In particular, the α-metallation of isocyanides was accomplished by Schöllkopf [84] and Van Leusen [85] for the synthesis of the imidazole core structure via a Mannich-type condensation of imines. An alternative method to activate the α-carbon atom of an isocyanide group as a nucleophile is the coordination of a metal at the terminal carbon in the isocyanide group resulting in an increase in the acidity of the α-protons and thus allowing for an easy α-deprotonation with weak bases (Scheme 32) [86,87].

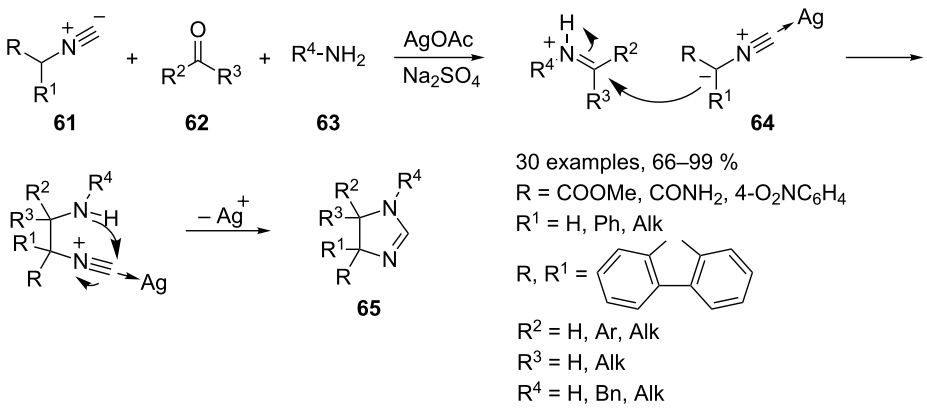


Scheme 32: Ag(I) promoted activation of the α-carbon atom of the isocyanide group.

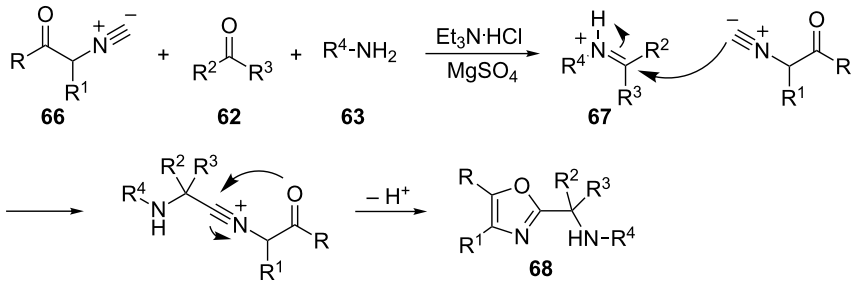
Recently, Orru's group successfully translated the stepwise Schöllkopf–Van Leusen synthesis of dihydroimidazoles **65** in a MCR involving isocyanides **61**, aldehydes **62** and primary amines **63** [88]. Initial results, obtained in the presence of a simple dehydrating agent, were limited to the use of simple aldehydes, amines and α-acidic α,α-disubstituted isocyanides such as methyl isocyano(phenyl)acetate and 9-isocyano-9*H*-fluorene [89]. The scope of these reactions could be extended to isocyanides with other substituents by using methanol as a solvent. Further improvements can be achieved in the presence of a catalytic amount of AgOAc acting as a Lewis acid to improve the α-acidity of the isocyanide component. However, the presence of an electron withdrawing group in α-position of **61** is essential in any case (Scheme 33) [90,91].

The reaction occurs via a Mannich-type addition of the deprotonated isocyanide intermediate **64** to an in situ generated iminium salt, a subsequent intramolecular cyclization and proton shift results in dihydroimidazole **65** showing predominantly *cis*-arrangment around the C4–C5 bond. However, an alternative reaction pathway, involving a concerted [3 + 2] cycloaddition of **64** to the imine, cannot be ruled out. Additionally, the use of sterically demanding amines results in lower yields. It is noteworthy, that the same reactions performed in the presence of a weak Brønsted acid instead of Ag(I) leads to oxazoles **68** when isocyano amides or isocyano esters **66** were used as substrates. The reaction proceeds through the formation of iminium ion **67** [92]. The isocyanide carbon atom is sufficiently nucleophilic to attack iminium ion **67**. Subsequent deprotonation and cyclization yields oxazoles **68** (Scheme 34).

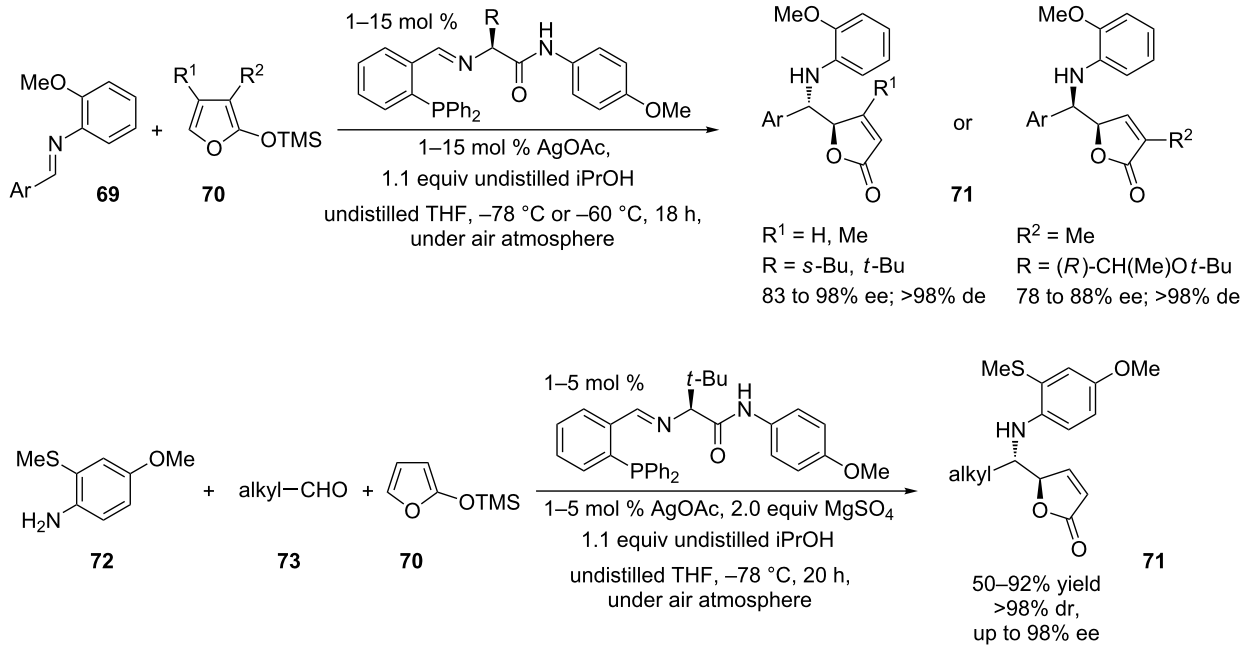
Another cluster of silver-mediated Mannich-type reactions involves the enantioselective addition of siloxyfurans **70** to imines **69** (vinylogous Mannich reaction, VM) affording chiral butenolide derivatives **71** (Scheme 35). The reaction proceeds in the presence of amino acid-based chiral phosphine ligands and AgOAc via bidentate chelation of a properly substituted aldimine. Chiral phosphine–silver(I) complexes are emerging as a valuable tool for carbon–carbon bond forming reactions.



Scheme 33: Synthesis of dihydroimidazoles **65**.



Scheme 34: Synthesis of oxazoles **68**.



Scheme 35: Stereoselective synthesis of chiral butenolides **71**.

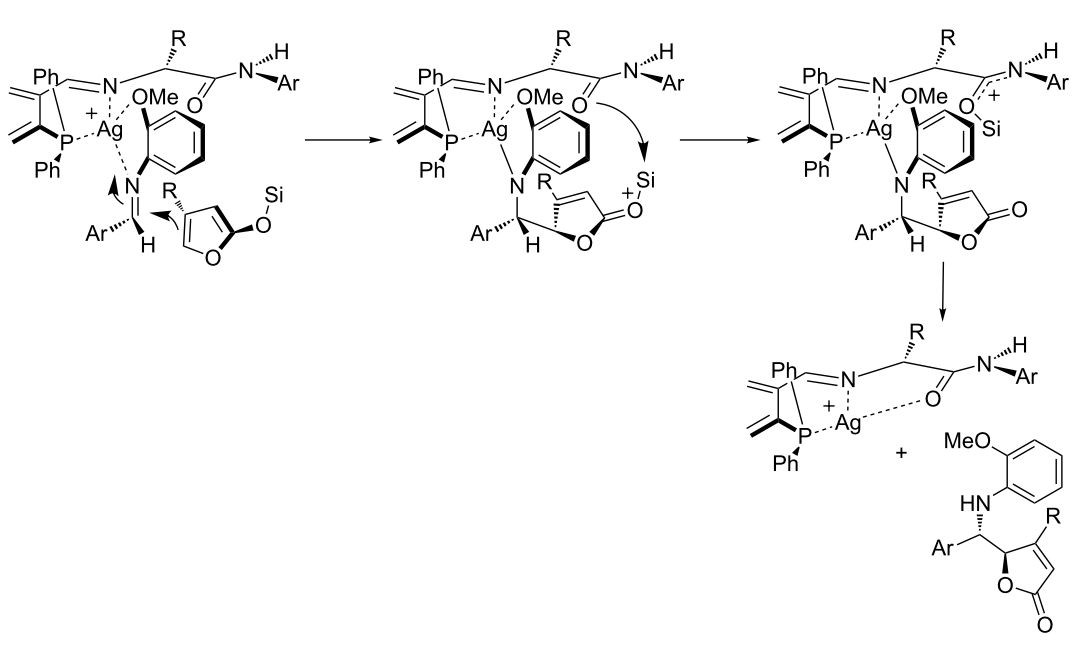
These catalysts are effective in promoting enantioselective allylations, aldol reactions, Mannich-type reactions, hetero Diels–Alder reactions, 1,3-dipolar cycloadditions and nitroso aldol reactions [93]. The process was firstly accomplished with preformed aryl-substituted aldimines [94] and then developed as a MCR for less stable alkyl-substituted aldimines, which were prepared in situ from arylamines **72** and alkylaldehydes **73** to avoid decomposition [95]. Scheme 35 shows the general reaction outcome for both processes.

The two main features of the reported three-component Ag-catalyzed process are (i) the mild reaction conditions and (ii) the high degree of diastereo- and enantioselectivity. The VM process can be performed with linear, cyclic, α-branched, β-branched and *tert*-butylaldehydes as well as with heteroatom-containing aldehydes. Hence, COOMe, OBn and NHBoc substituents are well tolerated and afford the corresponding butenolide derivatives in moderate yields (44–56%). Moreover, the *N*-aryl group can be easily removed from the final compounds under oxidative conditions yielding the corresponding amino compounds.

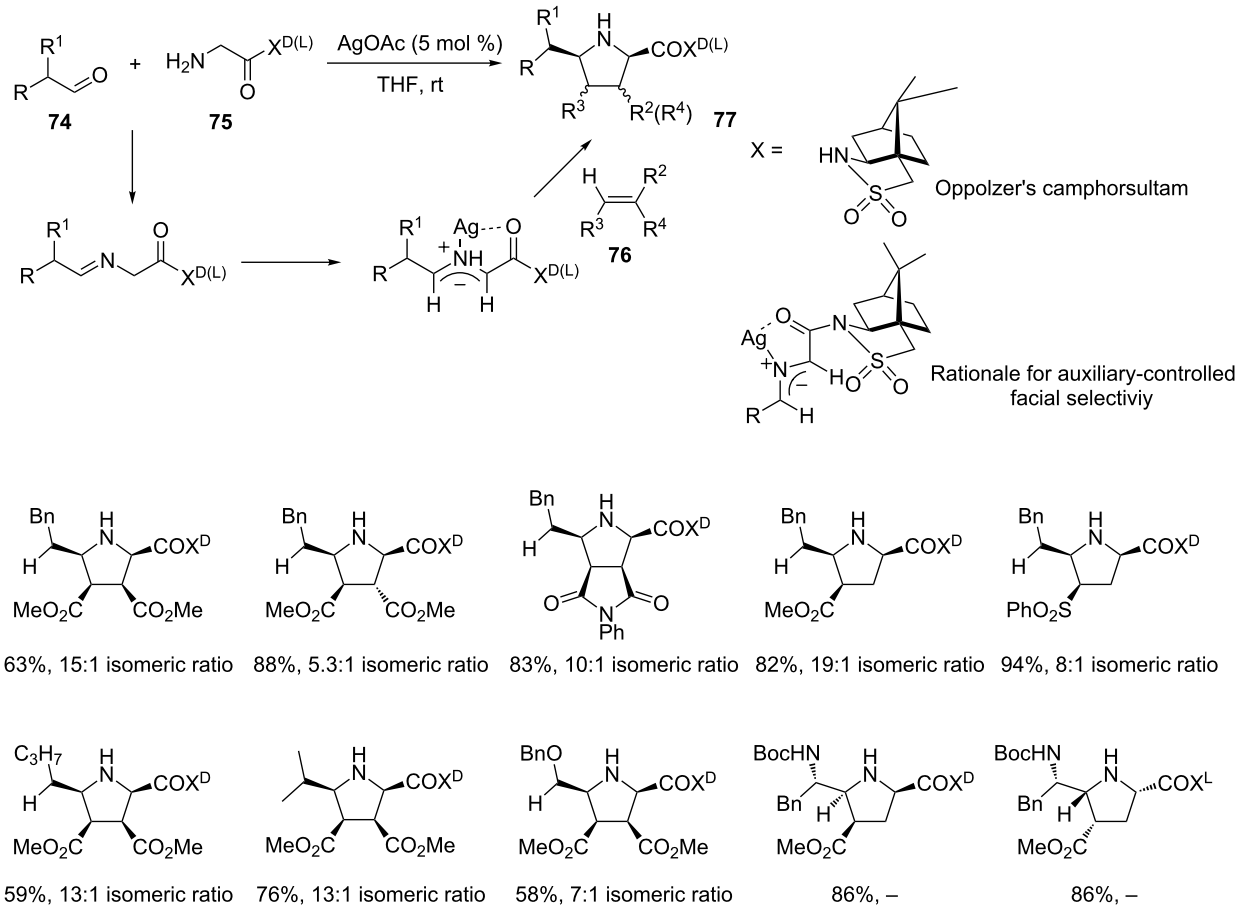
An OMe substituent is essential as a directing group for aryl-substituted aldimines. Thus, the Lewis acidic chiral complex may associate with the aldimine substrate through bidentate chelation (Scheme 36). The substrate is bound *anti* to the bulky amino acid substituent (R) and reacts with the siloxyfuran via *endo*-type addition. Intramolecular silyl transfer, iPrOH mediated desilylation of the amide terminus, and protonation of the N–Ag bond delivers the final product and the catalyst. Such a pathway is not allowed for the siloxyfuran bearing a methyl group in position 3, which reacts by an *exo* addition. Alkyl-substituted aldimines can also participate in these reactions. However, they must be generated in situ (MCR). In the latter reactions, best results were obtained when arylamines **72** bear an *o*-thiomethyl and a *p*-methoxy substituent instead of a single *o*-methoxy substituent. The corresponding electron-rich aldimines are less electrophilic and subsequently more stable under the reported reaction conditions. Moreover, the authors report on a more effective association of the "softer" chelating heteroatom (sulfur) with the late transition metal, which in turn resulted in improved enantiodifferentiation via a more organized transition state.

Two more examples of enantioselective reactions involving silver catalysts have been recently reported. Both reactions involve amines, aldehydes and alkenes in a three-component reaction based on the cascade imine formation, azomethine ylide generation and [3 + 2] cycloaddition reaction for the synthesis of pyrrolidines. However, the adopted method to induce chirality in the final products is rather dissimilar. Thus, in 2006 Garner's group reported the synthesis of highly functionalized pyrrolidines **77** in a MCR involving classical aliphatic aldehydes **74**, chiral glycyl sultam **75** and activated alkenes **76** (Scheme 37) [96].

The Oppolzer's camphorsultam, incorporated in the amine **75** by means of an amide linkage, plays two different roles. On the



Scheme 36: Proposed reaction mechanism for the synthesis of butenolides **71**.



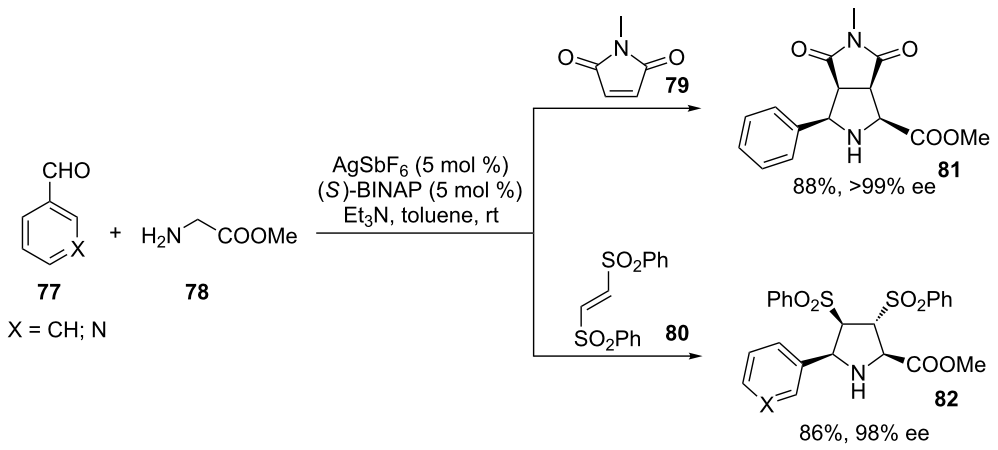
Scheme 37: Stereoselective three-component approach to pirrolidines **77** by means of a chiral auxiliary.

one hand, as an electron withdrawing group, it decreases the nucleophilicity of the amine, thus avoiding the formation of detrimental Michael-type adducts with the alkene. On the other hand, it increases the α-acidity of the imine intermediate, thus favoring the azomethine ylide formation. Moreover, as a chiral auxiliary it promotes the cycloaddition governing the stereochemistry of the process. The chiral auxiliary can be removed at the end of the reaction. Another interesting peculiarity concerns the exceptionally mild reaction conditions preventing unwanted aldehyde/enol or imine/enamine tautomerization.

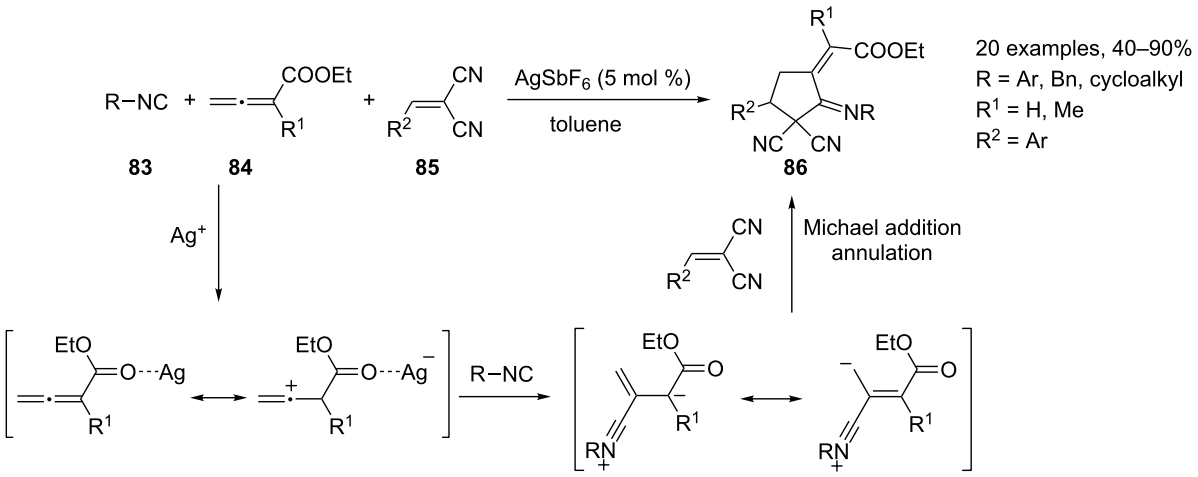
Instead, an Ag(I) complex based on BINAP and $AgSbF_6$ was employed as a catalyst for the enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides and alkenes for the synthesis of pyrrolidines **81** and **82** (Scheme 38) [97]. The reaction was developed mainly as a two-component reaction and only two examples of MC approaches have been included in the manuscript. The reported examples involve (hetero)aryl aldehydes **77**, methyl glycinate (**78**) and maleimide **79** or (*E*)-1,2-bis(phenylsulfonyl)ethylene (**80**) as electrophilic alkenes.

The reported work is an extension of a previous paper dealing with the use of BINAP–$AgClO_4$ as a chiral catalyst in the same two-component reaction [98]. Higher enantioselectivities were rarely observed with SbF_6^- being the weaker coordinating counter ion.

An interesting application of silver catalysis in the allene chemistry field has been recently proposed by Jia and co-workers [99]. The authors got inspired by the recent development of the phosphine-catalyzed [3 + 2] cycloaddition of allenoates with electron-deficient species such as olefins and imines, which involves the in situ formation of a zwitterionic intermediate from the nucleophilic addition between allenoate and phosphine. Thus, they believed that new cycloaddition reactions could be accessed if isocyanide was employed as a nucleophile instead of phosphine. The developed reaction allows the synthesis of five-membered carbocycles **86** by the silver hexafluoroantimonate-catalyzed three-component [2 + 2 + 1] cycloaddition of allenoates **84**, dual activated olefins **85**, and isocyanides **83** (Scheme 39).



Scheme 38: Stereoselective three-component approach to pyrrolidines **81** and **82** by means of a chiral catalyst.



Scheme 39: Synthesis of substituted five-membered carbocyles **86**.

It is noteworthy, that only the external double bond of the allenic fragment is embedded in the final carbocyclic ring, whereas in the phosphine-catalyzed [3 + 2] cycloadditon process the allene moiety behaves as a traditional "three-carbon atom unit". This behavior originates from the involvement of the isocyanide in the cyclization step.

Reactions involving organosilver reagents. Information about organosilver compound chemistry with respect to the coordination chemistry of silver salts and complexes is scarce in the literature. This could be related to the lower stability of these compounds, increasing in the order C_{sp3}–Ag, C_{sp2}–Ag, C_{sp}–Ag, compared to other organometallic compounds. The majority of the screened literature discusses the use of organosilver compounds as reagents. A recent review on organosilver compounds by Pouwer and Williams exhaustively highlights all these aspects of silver chemistry [100].

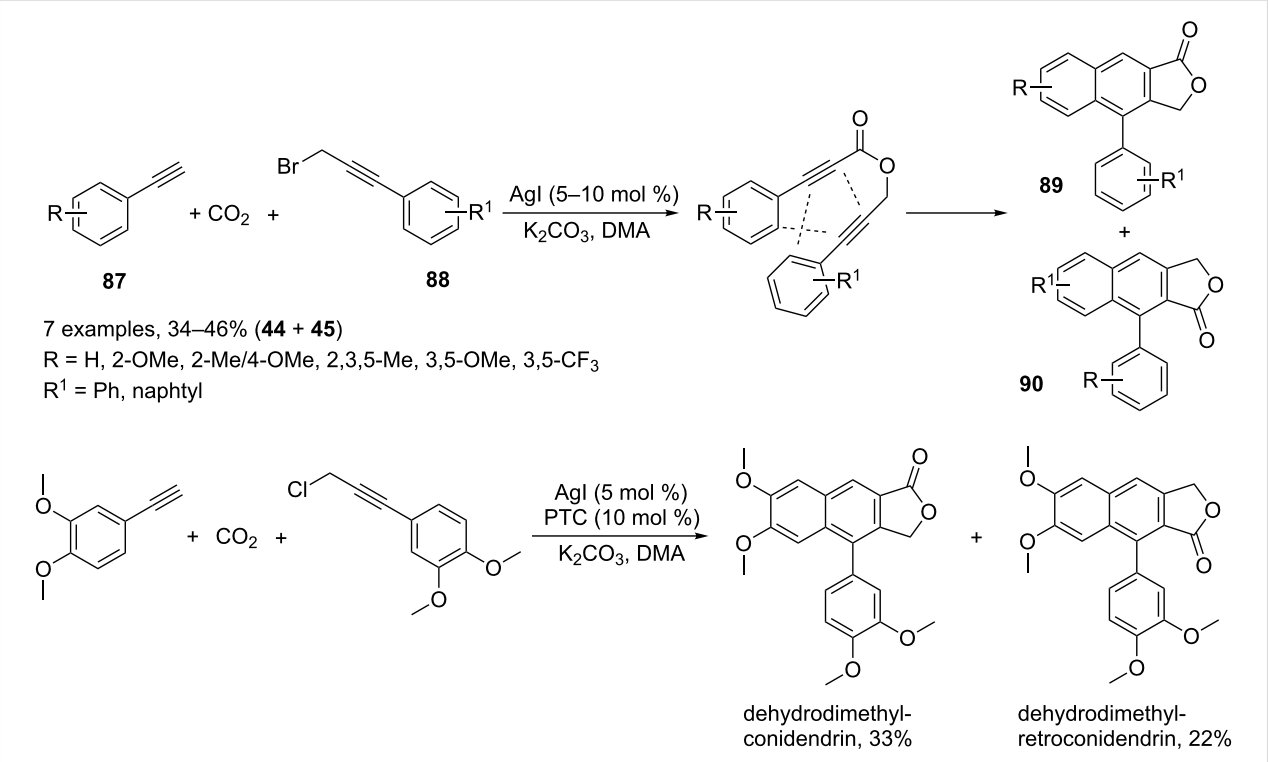
For example, functionalized propiolic acids can be selectively prepared by an AgI catalyzed carboxylation of terminal alkynes with CO_2 under ligand free conditions with the intermediacy of an organosilver compound, namely silver acetilide (C_{sp}–Ag) [101]. The direct carboxylation of active C–H bonds of (hetero)arenes [102] and terminal alkynes [103] with CO_2 in the presence of copper or gold-based catalysts has also been reported. However, these latter transformations require expensive ligands and often harsh bases, whereas the silver-mediated process depends on a simple but efficient catalyst such as AgI and Cs_2CO_3 as base. This feature has been clearly highlighted by Anastas who realized the multicomponent synthesis of

regioisomeric arylnaphthalene lactones **89** and **90** from arylacetylenes **87**, carbon dioxide and 3-bromo-1-aryl-1-propynes **88** (Scheme 40) [104]. In the reaction sequence a 1,6-diyne was generated in situ and cyclized to afford the two possible regioisomeric compounds. The level of regioselectivity can be enhanced by the tuning of electronic properties of the reactant species. AgI/K_2CO_3 and in a greener and more efficient protocol AgI/K_2CO_3/18-crown-6 with 3-chloro-1-phenyl-1-propyne have been employed (Scheme 40). The latter approach was successfully adopted for the preparation of dehydrodimethylconidendrin and dehydrodimethylretroconidendrin.

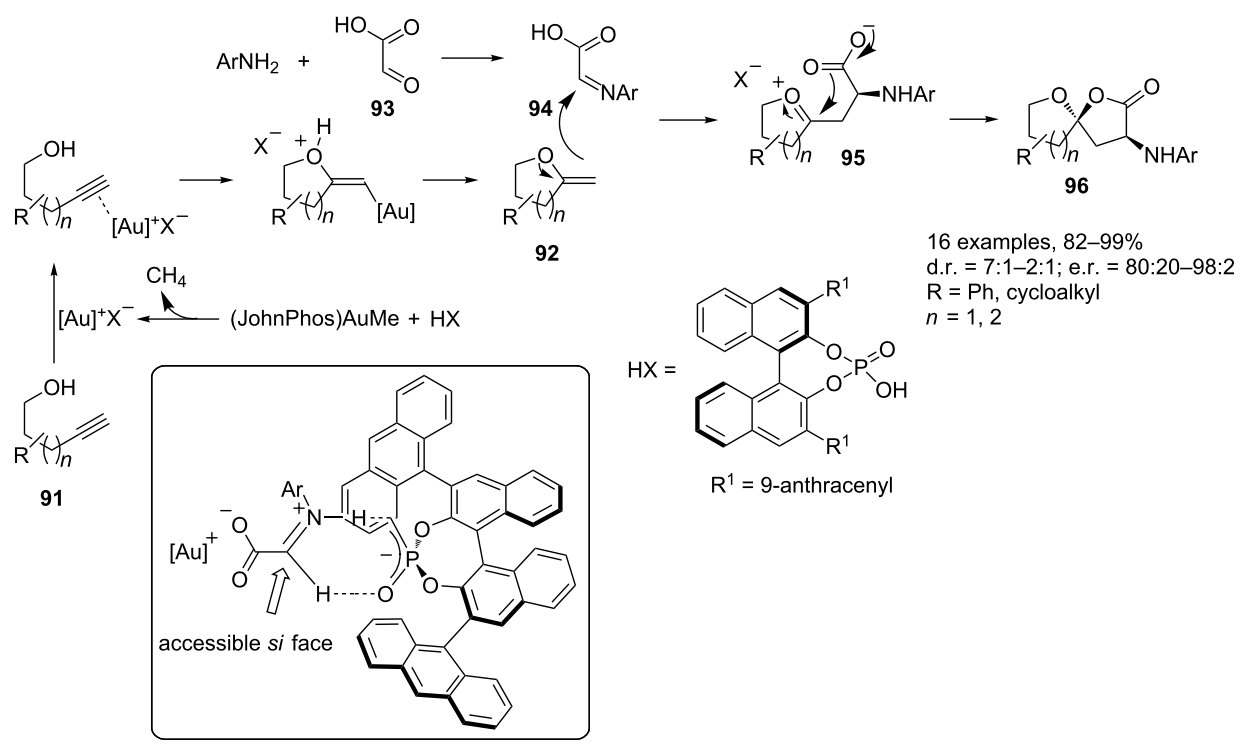
Gold-assisted multicomponent reactions

In gold(I) and gold(III)-catalyzed reactions the metal acts as a carbophilic Lewis acid, facilitating nucleophilic addition to unsaturated systems. Moreover, also the oxophilic character of gold species has been highlighted by several authors. More recently, gold-promoted transformations involving higher oxidation states from Au(I) precatalysts have been achieved by the addition of a stoichiometric oxidant enabling two-electron redox cycles typically exhibited by other late transition metals. With respect to Ag(I)-mediated MCRs, less information can be found in the literature about the corresponding gold-mediated processes. Thus, major research efforts have been directed to the development of tandem, sequential or cascade reactions and to the area of asymmetric transformations. As reported for silver, this part of the review is divided in sections relating to the nature of the activated functionalities.

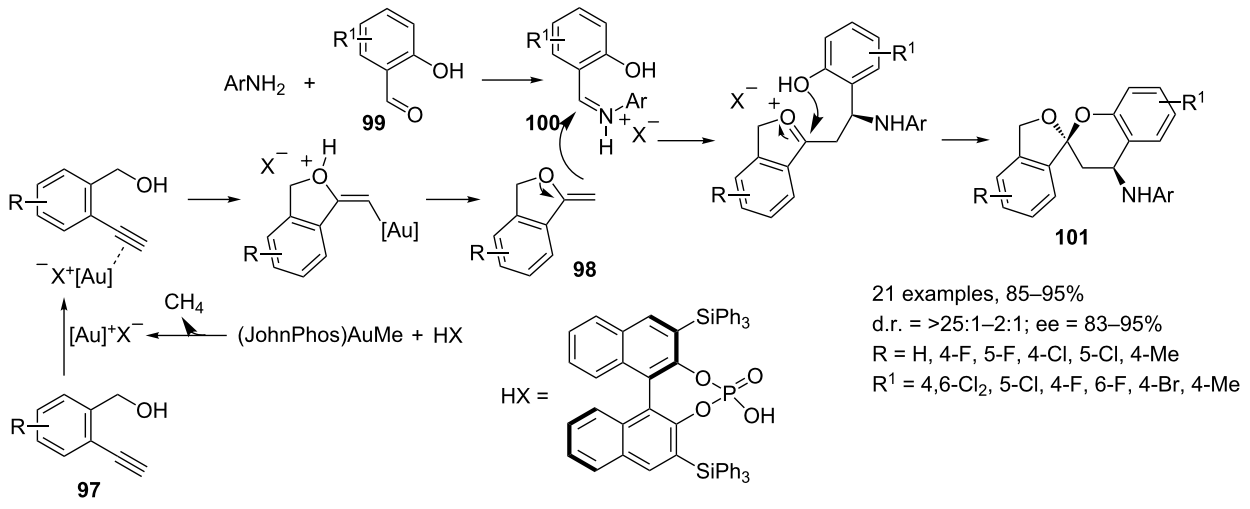
Reactions involving the activation of carbon–carbon multiple bonds. One of the most important reactions in gold-catalyzed synthesis is the addition of heteroatoms (O–H, N–H, C=O, C=N) to C–C triple bonds. The reactions take advantage from the high functional group tolerance and from the generally mild reaction conditions. MCRs involving this kind of reactions, however, are primarily limited to the nucleophilic addition of O–H and C=O functionalities to the Au-coordinated alkynes for the synthesis of spiroacetals, cyclic ketals and β-alkoxy ketones. The research group of Fañanás and Rodríguez [105] and the group of Gong [106] independently reported the enantioselective synthesis of spiroacetals **96** and **101** by a three-component reaction involving alkynols **91**, anilines and an α-hydroxy acid or β-hydroxyaldehydes (glyoxylic acid (**93**) or salicylaldehydes **99**), (Scheme 41 and Scheme 42, respectively). Both methodologies involve the in situ generation of a gold–phosphate complex by a reaction between (JohnPhos)AuMe and the Brønsted acid (XH) with release of a molecule of methane. These are the first examples of an intermolecular catalytic asymmetric synthesis of spiroacetals. Previously reported methodologies involved preformed substrates in intramolecular reactions [107-109].



Scheme 40: Synthesis of regioisomeric arylnaphthalene lactones.



Scheme 41: Enantioselective synthesis of spiroacetals **96** by Fañanás and Rodríguez [105].



Scheme 42: Enantioselective synthesis of spiroacetals **101** by Gong [106].

The synthetic approach proposed by Fañanás and Rodríguez involves the coordination of the gold cation to the carbon–carbon triple bond of alkynol **91** followed by an intramolecular *exo*-addition of the hydroxy group to the alkyne which delivers the exocyclic enol ether **92** regenerating the gold-derived catalyst. The condensation reaction between glyoxylic acid (**93**) and aniline gives rise to imine **94** which, by double interaction with the gold phosphate, leads to an activated species. Subsequent nucleophilic addition of **92** to **94** gives oxonium intermediate **95**, which provides the final product **96** upon cyclization regenerating the catalyst. Interestingly, in the first catalytic cycle the main role of the catalyst is played by its cationic part, the gold(I) ion, being responsible for the activation of the alkynol **91**. Meanwhile, in the second catalytic cycle, the main role is played by the anionic part of the catalyst, the phosphate, creating the appropriate chiral environment to

produce the final enantioenriched product. The model proposed for the chiral phosphoric acid catalyzed reactions between glyoxylates and enecarbamates is reported in Scheme 41 (see box). The key feature is the formation of a double hydrogen-bonded complex in which only the *si* face is fully accessible for the enol ether attack to afford the final cyclization product **96**.

As reported in Scheme 42 the method proposed by Gong and co-workers allows for the synthesis of aromatic spiroacetals **101**. The key step of the sequence is again the addition of an enol ether to an imine followed by an intramolecular cyclization reaction. The enol ether **98** is generated from *ortho*-alkynylbenzyl alcohol **97** under gold catalysis, and the imine **100** from salicylaldehyde **99** and aniline. Under the catalysis of a chiral Brønsted acid the reaction results in the synthesis of the corresponding chiral aromatic spiroacetals **101**.

The MC synthesis of bi- and tricyclic ketals **103** and **104** takes advantage from a mechanism involving the oxyauration of a carbon–carbon triple bond [110]. Thus, starting from 4-acyl-1,6-diynes **102**, H_2O and alkanols, under $AuCl_3$-catalysis, polyfunctionalized fused bicyclic ketals **103** and bridged tricyclic ketals **104** have been prepared with a high degree of regio- and diastereocontrol. (Scheme 43).

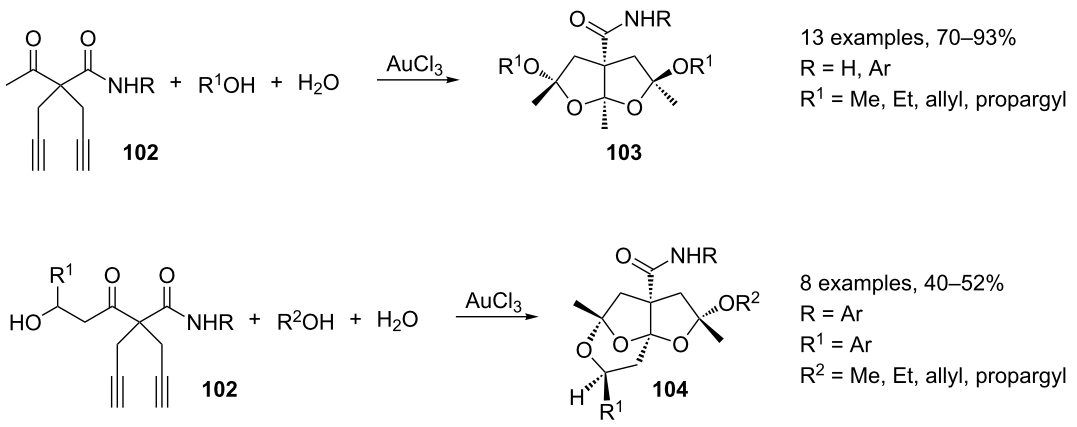
The reaction course can be directed toward the formation of **103** and **104** by a fine-tuning of the reaction conditions. The reactions were performed with $AuCl_3$ at a catalyst loading of 3 and 5 mol %, respectively, with 1 equivalent of **102** in alkanol/water (8 mL; 25:1) (Scheme 44).

Under the optimized reaction conditions mentioned above, a double oxyauration reaction leads to intermediate **I**. The addition of water then results in the formal hydration of **I** affording dicarbonyl compound **II**. The subsequent addition of alcohol and the hydrochloric acid release affords the intermediate auric complex **III**, from which cyclic ketals **103** and **104** are formed by the inter- or intramolecular addition of alcohol, respectively. The proposed reaction mechanism also accounts for the high degree of diastereoselectivity, which can be rationalized by a series of intramolecular chiral inductions.

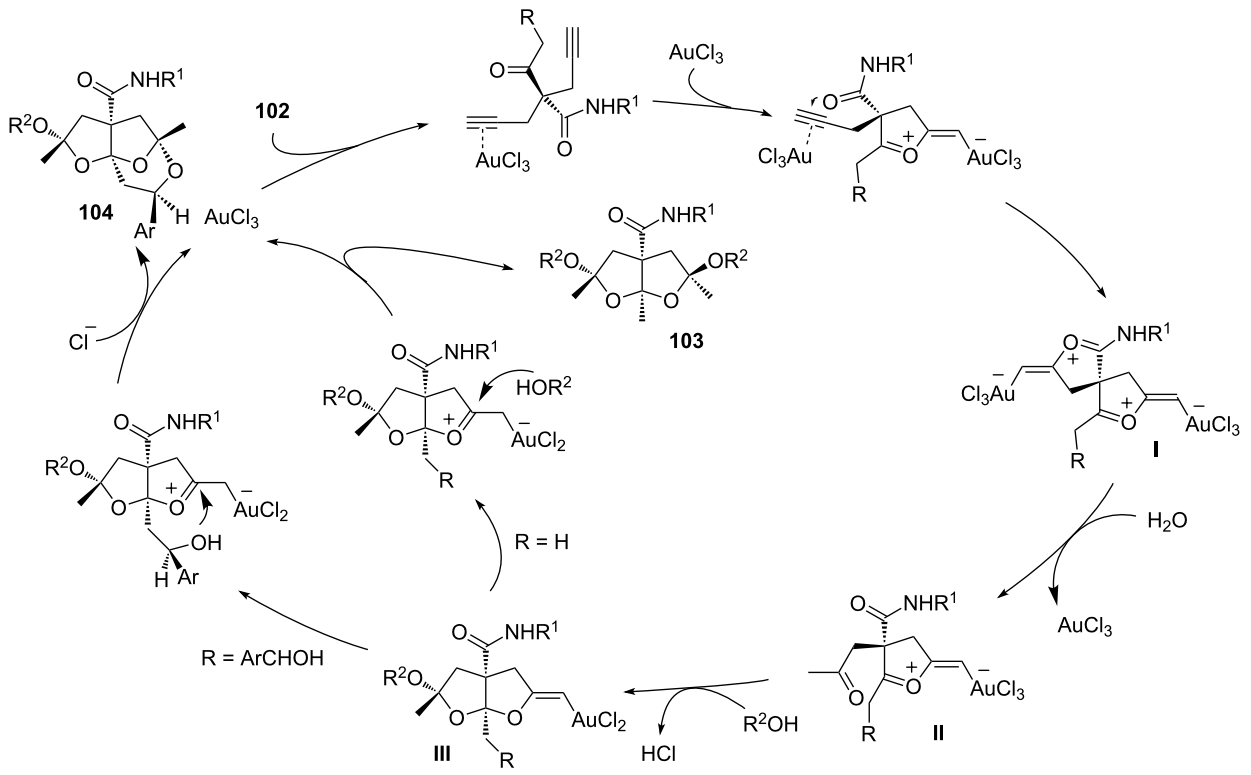
Finally, Wolfe and co-workers recently described a nice Au(I)-catalyzed MCR of readily available aldehydes, alcohols and alkynes for the synthesis of β-alkoxy ketones **108** [111]. The initial steps of the MCR encompass the Au(I)-catalyzed hydration of the alkyne to give the ketone **105** and the conversion of the aldehyde to the corresponding acetal **106**. The Au(I)-catalyzed ionization of the acetal then provides the oxocarbenium ion **107**, which is captured by the enol tautomer of ketone **105** (Scheme 45).

The authors reported a nice investigation of the involved reaction mechanism and carried out a catalytic screening devoted to the selection of the best catalytic system and optimal reaction conditions. The involvement of a protic acid ($HNTf_2$) or $AgNTf_2$ (used for catalyst preparation) was ruled out as control experiments performed under $HNTf_2$ catalysis did not afford the β-alkoxy ketones **108**.

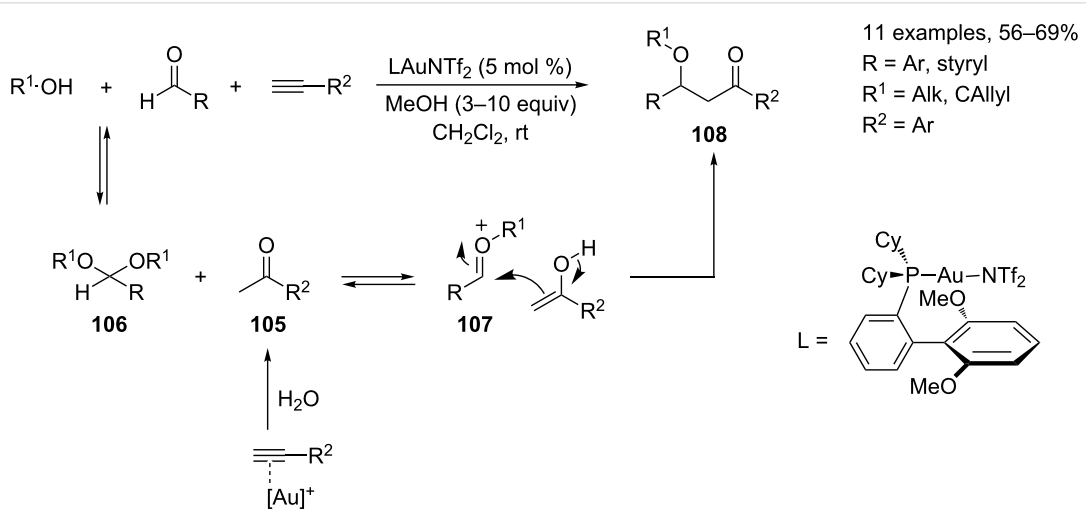
Newly reported examples of gold-catalyzed multicomponent reactions encompass the synthesis of nitrogen containing heterocycles, namely *N*-substituted 1,4-dihydropyridines [112] and tetrahydrocarbazoles [113]. The first example takes advantage of the ability of a cationic gold(I) catalyst to promote the formation of a new C–N bond through the hydroamination of a carbon–carbon triple bond. The three-component reaction includes methanamine (**109**), activated alkynes **110** and aldehydes **111** as reactants, a cationic gold(I) complex generated in situ from (triphenylphosphine)gold chloride and silver triflate as



Scheme 43: Synthesis of polyfunctionalized fused bicyclic ketals **103** and bridged tricyclic ketals **104**.



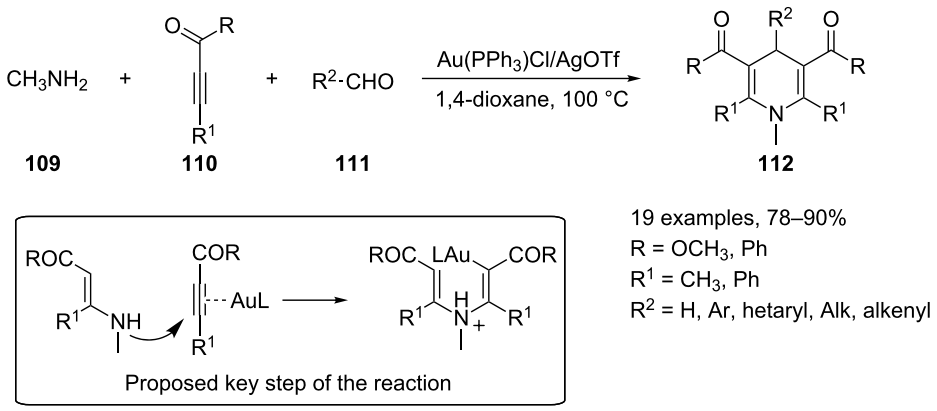
Scheme 44: Proposed reaction mechanism for the synthesis of ketals **103** and **104**.



Scheme 45: Synthesis of β-alkoxyketones **108**.

a catalyst, and $KHCO_3$ as base. The reaction was performed in 1,4-dioxane at 100 °C and smoothly produces polysubstituted *N*-methyl-1,4-dihydropyridines **112** in good yields (Scheme 46).

The scope of the reaction was limited to the use of methanamine as a nucleophilic partner, whereas a great variety of aldehydes can be employed, aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldheydes. Methyl but-2-ynoate and 1,3-diphenylprop-2-yn-1-one were tested as alkynylic counterparts. A tentative mechanistic explanation for the formation of compounds **112** was proposed by the authors. In an early stage, their theory involves a hydroamination reaction between the alkyne **110** and an enamine generated in situ by a Michael-type addition of the amine **109** on the activated carbon–carbon triple

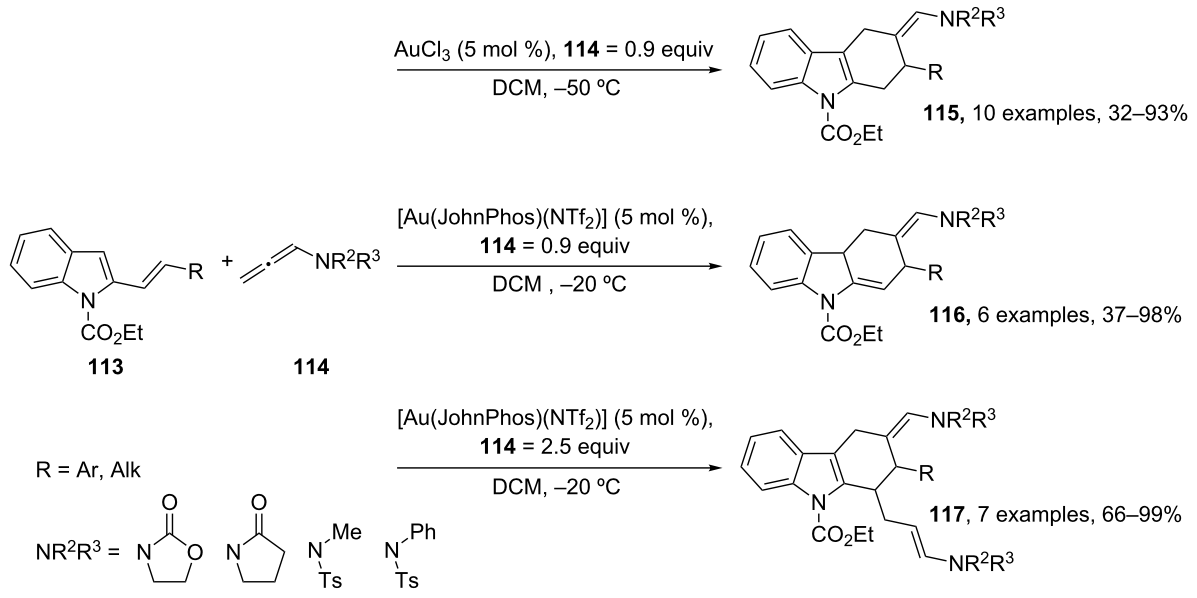


Scheme 46: Synthesis of *N*-methyl-1,4-dihydropyridines **112**.

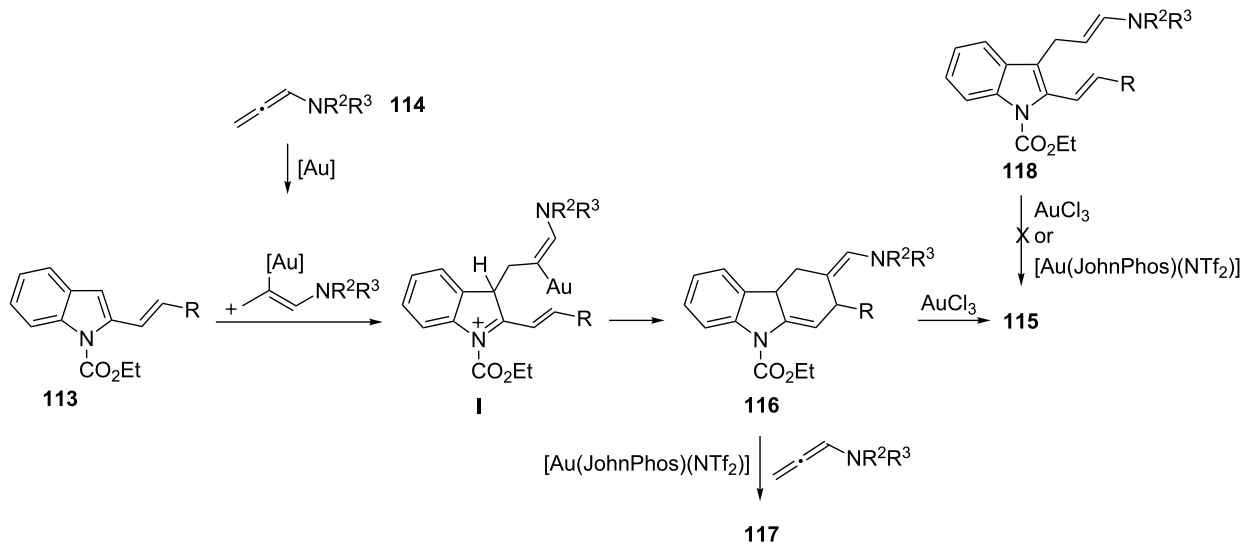
bond of a second molecule of **110** (see box in Scheme 46). The overall process closely reminds of a modified Hantzsch synthesis of dihydropyridines.

Furthermore, among unsaturated substrates involved in gold-catalyzed MCRs, allenes could offer an incomparable versatility since they participate in [2 + 2], [4 + 2] or [4 + 3] cyclizations [114,115]. However, they have been employed in a MC process only recently [113]. A gold-catalyzed formal [4 + 2] cycloaddition of vinylindoles **113** and *N*-allenamides **114** leading to tetrahydrocarbazoles has been described. An appropriate selection of the reaction conditions enabled the selective preparation of isomeric tetrahydrocarbazoles **115** and **116** or carbazole derivatives **117** arising from an unusual gold-catalyzed multicomponent cycloaddition cascade sequence with the participation of two allene molecules (Scheme 47).

Tetrahydrocarbazoles **115** were obtained as the only reaction products by using $AuCl_3$ at −50 °C in DCM. Interestingly, a change of the catalyst to [Au(JohnPhos)(NTf_2)] under similar reaction conditions afforded the isomeric tetrahydrocarbazoles **116** as the only diastereoisomer. As expected, the formation of multicomponent cycloadducts **117** was favored by using an excess of the allene (2.5 equiv). For this transformation, [Au(JohnPhos)(NTf_2)] provided **117** with complete selectivity. All obtained compounds arise from a common intermediate **I** (Scheme 48). Various experiments showed that both **115** and **117** arise from compound **116**. Thus, the treatment of **116** with



Scheme 47: Synthesis of tetrahydrocarbazoles **115–117**.



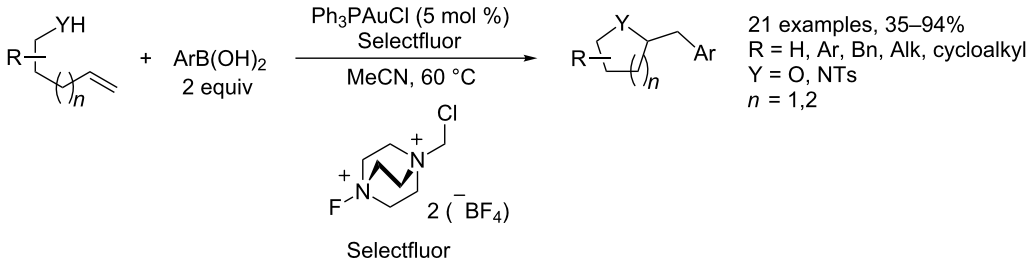
Scheme 48: Plausible reaction mechanism for the synthesis of tetrahydrocarbazoles **115–117**.

$AuCl_3$ or $[Au(PPh_3)(NTf_2)]$ led to the aromatized product **115** (>95%). In contrast, starting from **116** the use of $[Au(JohnPhos)(NTf_2)]$ as a catalyst in the presence of the allene (1.5 equiv) gave rise to **117** (90%), probably by a hydroarylation process. Interestingly, vinylindole **118**, independently prepared, could not be converted into **115–117** under optimized reaction conditions, pointing out that the cyclization occurred through the proposed intermediate **I**.

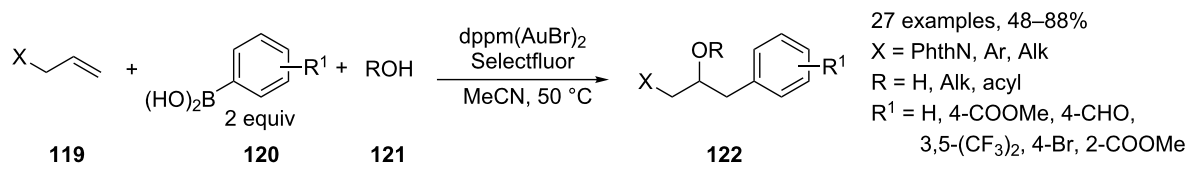
Reaction involving Au(I)/Au(III) redox cycles. As mentioned above, transformations involving Au(I)/Au(III) redox catalytic systems have been recently reported in the literature, further increasing the diversity of gold-mediated transformation. The Au(I)/Au(III) processes can be accessed through the use of an exogenous oxidant, such as *tert*-butylhydroperoxide, PhI(OAc), or Selectfluor [116]. Inter alias, two-component Au-catalyzed heteroarylation reactions, performed in the presence of Au(I)/Au(III) redox catalytic systems, have been reported by several authors. For example, the carboamination, carboalkoxylation and carbolactonization of terminal alkenes with arylboronic acids have been implemented under oxidative gold catalysis by Zhang and co-workers (Scheme 49) [117].

The same concept has been extended to the MC heteroarylation of alkenes. Toste reported the fully intermolecular alkene heteroarylation by a gold-catalyzed three-component coupling reaction of alkenes **119**, arylboronic acids **120**, and several types of oxygen nucleophiles **121**, including alcohols, carboxylic acids, and water [118]. The reaction employs a binuclear gold(I) bromide as a catalyst and the Selectfluor reagent as the stoichiometric oxidant. Alcohols, carboxylic acids, and water can be employed as oxygen nucleophiles, thus providing an efficient entry to compounds **122** (β-aryl ethers, esters, and alcohols) from alkenes (Scheme 50).

The reactions were performed with 2 equiv of boronic acid **120** and 2 equiv of Selectfluor in MeCN:ROH (9:1) at 50 °C and in the presence of 5 mol % of $dppm(AuBr)_2$ (dppm =



Scheme 49: Carboamination, carboalkoxylation and carbolactonization of terminal alkenes.

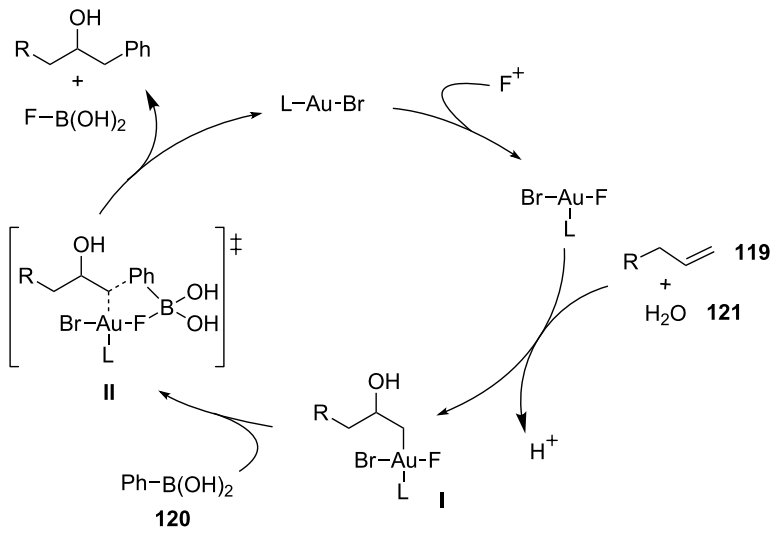


Scheme 50: Oxyarylation of alkenes with arylboronic acids and Selectfluor as reoxidant.

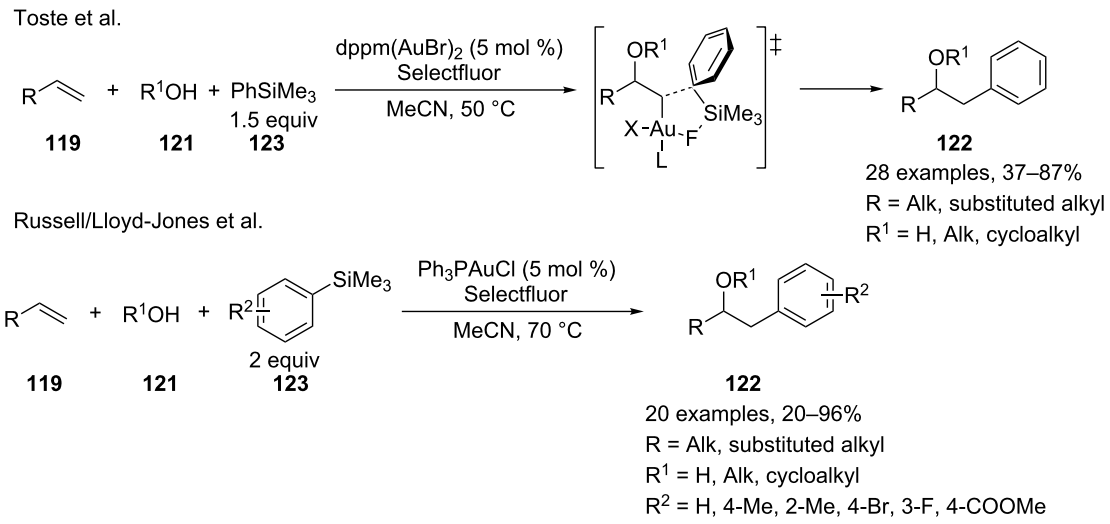
bis(diphenylphosphanyl)methane). Ligand and halide effects play a dramatic role in the development of a mild catalytic system for the addition to alkenes. The catalyst choice is a consequence of the screening, comparing the activity of simple Ph_3PAuX complexes and bimetallic gold complexes, accomplished by the same authors in a related two-component process [119]. The use of a bimetallic gold complexes as catalysts might minimize the formation of the unwanted bisphosphinogold(I) species $[(Ph_3P)_2Au]^+$ observed via NMR when Ph_3PAuCl or Ph_3PAuBr are mixed with Selectfluor and $PhB(OH)_2$. A careful investigation of the reaction mechanism resulted in the catalytic cycle reported in Scheme 51.

The first step of the catalytic cycle involves the oxidation of Au(I) into Au(III), which is the effective catalyst for the oxyauration step giving rise to the alkylgold(III) fluoride intermediate **I**. Then, the reaction of the boronic acid with intermediate **I** affords the desired final compounds with the release of fluoroboronate and the restoration of the catalyst by reductive elimination. The authors proposed a synchronized mechanism for this step, which involves the five-centered transition state **II**. Moreover, Toste and Russell/Lloyd-Jones independently demonstrated that the oxyarylation of alkenes can be achieved with arylsilanes as organometallic reagents, thus avoiding the use of less benign boronic acids [120,121]. Accordingly, Toste and co-workers established that the $dppm(AuBr)_2$/Selectfluor system can promote the reaction of phenyltrimethylsilane **123** with aliphatic alkenes and water or aliphatic alcohols giving rise to **122** in moderate to good yields. The Russell/Lloyd-Jones research group expanded the scope of these reactions to a series of differently substituted arylsilanes performing the reactions in the presence of commercially available Ph_3PAuCl and Selectfluor and obtaining the desired compounds **122** with comparable yields (Scheme 52). The proposed reaction mechanism resembles the one described in Scheme 51, and the fluoride anion is probably responsible for the activation of silane without the need of a stoichiometric base. Under the reported conditions the formation of homocoupling side products of boronic acids can be reduced.

More recently, Russell and Lloyd-Jones expanded the scope of these reactions to more challenging substrates such as styrenes



Scheme 51: Proposed reaction mechanism for oxyarylation of alkenes.



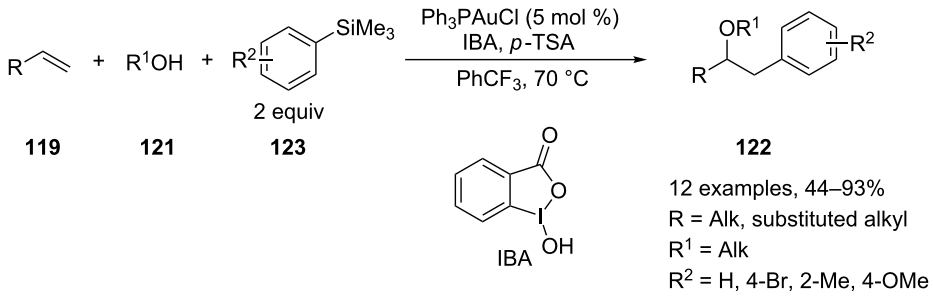
Scheme 52: Oxyarylation of alkenes with arylsilanes and Selectfluor as reoxidant.

and *gem*-disubstituted olefins, which are unreactive under the Selectfluor-based methodology reported above [122]. This goal has been achieved by introducing the 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (IBA, 2 equiv) as an oxidant in addition to *p*-toluenesulfonic acid (2 equiv) as an additive and the usual gold catalysts (Ph_3PAuCl) (Scheme 53).

The role of the acidic additive is unclear. However, the authors hinted at the in situ formation of a more electrophilic and soluble IBA-Ts oxidant. A solvent screening was carried out, and the scope of the reaction with monosubstituted, *gem*-disubstituted olefins and styrenes was carefully investigated.

Conclusion

The development of multicomponent processes is a continuously growing research area. In this context, gold(I/III) and silver(I) are able to promote a wide range of different MCRs as both simple salts and original complexes, with a particular emphasis on the reactions involving the σ- or π-activation. These coinage metals demonstrated to be "fraternal twins" with several features in common and many peculiar differences, for example, the capability of gold to participate in a redox cycle. However, the practical and industrial importance of A^3-coupling reactions fostered the efforts of many researchers. Other classes of silver and gold catalyzed MCRs are described and studied to a lesser extent and are often the transposition of domino reactions to multicomponent processes. Both metals ideally include all the essential features required for a catalyst devoted to control multifaceted transformations such as MCRs. Several hints could encourage the chemists' community to mix up MCRs and silver/gold catalysis. For example, the high affinity of silver and gold catalysts for unsaturated carbon systems (e.g., alkenes, alkynes and allenes) allows performing nucleophilic additions to these systems in a chemoselective manner under exceptionally mild conditions and at the same time avoids highly reactive carbocationic intermediates. Furthermore, Au and Ag carbene intermediates, able to undergo well-defined rearrangement and/or cycloaddition reactions, are emerging as a valuable tool for the construction of carbo- and heterocyclic compounds. Au and Ag catalyzed cycloadditions



Scheme 53: Oxyarylation of alkenes with arylsilanes and IBA as reoxidant.

itself are fields in continuous development, especially for those reactions that involve non-activated unsaturated systems. In this particular area the development of new chiral catalysts often allows to perform cycloaddition reactions in a stereocontrolled fashion. Finally, of utmost importance in the chemistry of silver and gold complexes is the possibility to control the reactivity and the properties of the metal by ligand or counterion variations. All these statements are supported by literature data and, in particular, by two topical and outstanding books, which deeply cover the chemistry of these metals [123,124].

We hope that both this review and those cited in the references could stimulate the chemists' community toward the rationale design of new silver and gold MCRs.

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Zirconoarylation of alkynes through *p*-chloranil-promoted reductive elimination of arylzirconates

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Full Research Paper

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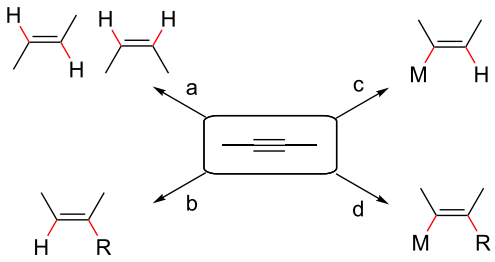
Abstract

A novel method for the zirconoarylation of alkynes was developed. TCQ-promoted reductive elimination of arylzirconate [$LiCp_2ZrAr(RC{\equiv}CR)$], which was prepared by the reaction of zirconocene–alkyne complexes with aryllithium compounds, afforded trisubstituted alkenylzirconocenes. This reaction can afford multi-substituted olefins with high stereoselectivity.

Introduction

The controlled synthesis of multi-substituted olefins is one of the most challenging tasks in organic synthesis [1,2]. A series of reactions have been developed for the construction of substituted olefins. Among them, an important route is the addition of various reagents to nonactivated alkynes to form substituted olefins. For example, semihydrogenation of internal alkynes can afford disubstituted olefins (Scheme 1, route a) [3-5]. Hydrocarbonation [6,7] and hydrometalation/functionalization [8-11] of internal alkynes can afford trisubstituted olefins (Scheme 1, routes b and c), respectively. The most exciting progress was the carbometalation of internal alkynes [12-23], which involves simultaneous addition of a metal atom and an organic residue to alkynes. The newly formed carbon–metal bond can be used for further synthetic transformation toward multi-substituted olefins [24-36] (Scheme 1, route d).

A large number of carbometalation reactions of alkynes have been reported. Most of the carbometal reagents, which were used, contained Li, Mg, Cu, Zn, B, or Al [12-16]. In the last several decades also zirconium-mediated or -catalyzed organic reactions have been extensively investigated [37-39]. In addition, a series of organic reactions using zirconocene species have been reported, in particular for the reductive coupling of alkenes or alkynes with other unsaturated compounds [40-43].



Scheme 1: Transformation of alkynes to olefins.

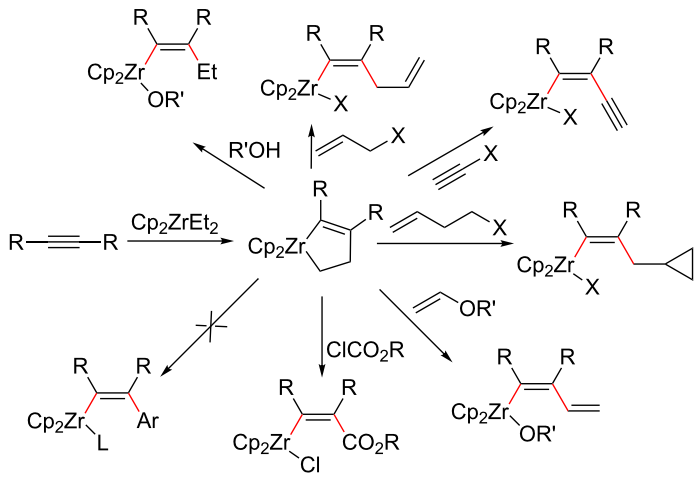
On the other hand, carbozirconation of alkynes via reaction of zirconacyclopentenes with alcohols, allyl ethers, homoallyl bromides, vinyl ethers, alkynyl halides, and chloroformates gave ethylzirconation [17], allylzirconation [18,19], cyclopropylmethylzirconation [20], vinylzirconation [21], alkynylzirconation [22], and zirconoestification [23] products of alkynes, respectively. However, to the best of our knowledge, this method failed to fulfill arylzirconation of alkynes (Scheme 2).

Recently, we have reported a *p*-chloranil (TCQ)-promoted reductive elimination reaction of the zirconate complex $Li[Cp_2Zr(C{\equiv}CR)_3]$ toward geminal enediynes [44]. As part of our ongoing project on organozirconate chemistry [45-48], we envisioned that the use of an aryl ligand instead of one of the alkynyl ligands would provide an arylzirconation product of the alkyne. Herein we describe the TCQ-promoted reductive elimination of arylzirconate to afford an arylzirconation product of the alkyne, which can be converted to multi-substituted olefins through coupling with electrophiles (Scheme 3).

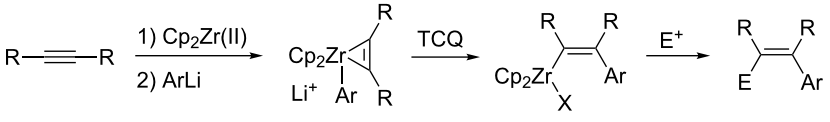
Results and Discussion

Initially, the reaction of $Cp_2Zr(PhC{\equiv}CPh)(DMAP)$ (**1a**), prepared by the reaction of Cp_2ZrBu_2 [48] with DMAP and diphenylacetylene according to reported literature [49], with phenyllithium produced arylzirconate **2a**. To this mixture, 2 equivalents of *p*-chloranil (TCQ) were added and the reaction mixture was stirred for 12 h at room temperature. After being quenched with HCl solution, the desired triphenylethylene (**3a**) was isolated in 62% yield. When the reaction mixture was quenched with DCl solution, the deuterated product **3a-D** was isolated in 60% yield with >95% of deuterium incorporation (Scheme 4). The deuterium experiment revealed the formation of triphenylvinylzirconocene **4a** as intermediate.

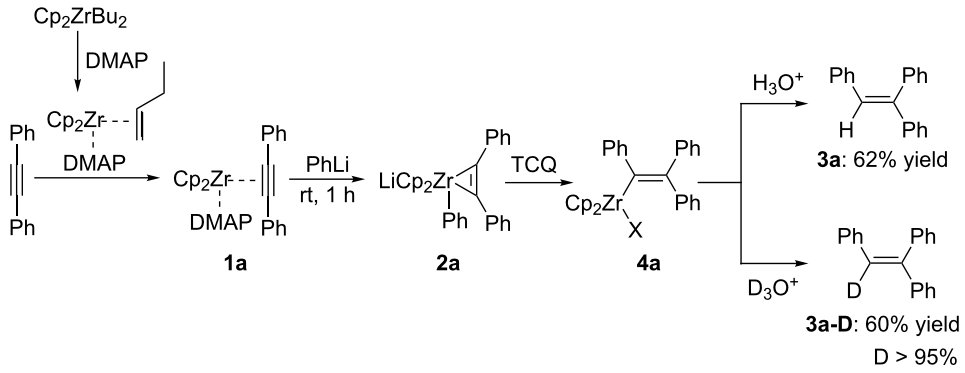
Under similar reaction conditions, a study on the substrate scope was carried out, and the results are summarized in Table 1. When diphenylacetylene was used as starting material, different aryllithium compounds were employed to afford triarylethylene in 38% to 62% isolated yields after being quenched with HCl (Table 1, entries 1–4). Bromination of the reaction mixture by NBS instead hydrolysis afforded bromo-



Scheme 2: Carbozirconation of alkynes via zirconacyclopentenes.



Scheme 3: TCQ-promoted reductive elimination of arylzirconate.



Scheme 4: TCQ-promoted arylzirconation of diphenylacetylene.

triphenylethylene in 37% isolated yield (Table 1, entry 5). When allyl bromide was employed as electrophile in the presence of CuCl, the allyltriarylethylenes were formed in 43% to 45% yields (Table 1, entries 6 and 7). Cross coupling with iodobenzene in the presence of CuCl/Pd(PPh_3)$_4$ afforded tetraarylethylene in 31% yield (Table 1, entry 8). When other diarylacetylene was employed in this reaction, the corresponding products were formed in 36% to 59% yields (Table 1, entries 9–12). No desired product was observed when alkylacetylenes were used.

Table 1: Formation of multi-substituted olefins via the reaction of alkynes with [Cp_2Zr(1-butene)(DMAP)] and aryllithium in the presence of TCQ[a].

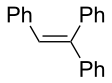
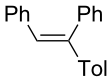
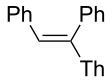
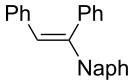
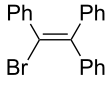
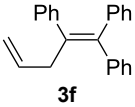
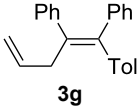
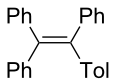
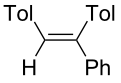
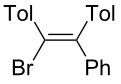
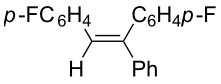
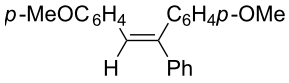
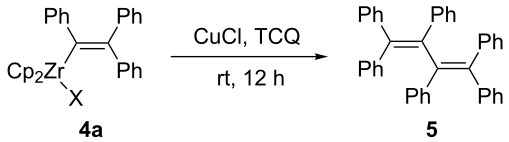
entry	alkynes	aryllithium	electrophiles	products	yield (%)[b]
1	Ph—≡—Ph	PhLi	HCl	 **3a**	62
2	Ph—≡—Ph	TolLi	HCl	 **3b**	58
3	Ph—≡—Ph	2-ThLi	HCl	 **3c**	47
4	Ph—≡—Ph	NaphLi	HCl	 **3d**	38
5	Ph—≡—Ph	PhLi	NBS	 **3e**	37
6	Ph—≡—Ph	PhLi	allyl-Br	 **3f**	45
7	Ph—≡—Ph	TolLi	allyl-Br	 **3g**	43

Table 1: Formation of multi-substituted olefins via the reaction of alkynes with [Cp_2Zr(1-butene)(DMAP)] and aryllithium in the presence of TCQ[a]. (continued)

8	Ph—≡—Ph	TolLi	PhI	 **3h**	31
9	Tol—≡—Tol	PhLi	HCl	 **3i**	57
10	Tol—≡—Tol	PhLi	NBS	 **3j**	36
11	*p*-FC$_6$H$_4$—≡—C$_6$H$_4$*p*-F	PhLi	HCl	 **3k**	59
12	*p*-MeOC$_6$H$_4$O—≡—C$_6$H$_4$*p*-OMe	PhLi	HCl	 **3l**	52

[a]Reaction conditions: Alkyne (1 mmol), [Cp_2Zr(1-butene)(DMAP)] (1 mmol), ArLi (2 mmol), TCQ (2 mmol), electrophile (2 mmol). Tol = *p*-tolyl, Th = 2-thienyl, Naph = 1-naphthyl. [b]Isolated yield.

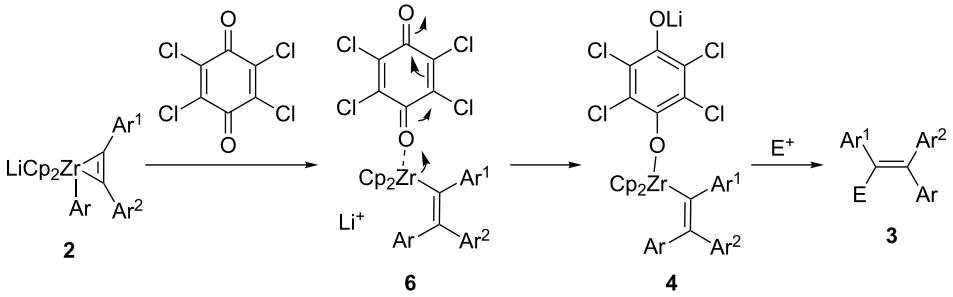
Recently, oxidative dimerization of alkenylcopper was reported to afford conjugated dienes and polyenes [44,50-57]. When triphenylvinylzirconocene **4a** was reacted in the presence of CuCl and TCQ, the 1,1,2,3,4,4-hexaphenyl-1,3-butadiene (**5**) was formed in 43% isolated yield (Scheme 5). It is noteworthy that in this reaction two molecular alkynes and two aryllithium compounds were coupled in one-pot in the presence of Cp_2Zr species to afford highly substituted 1,3-butadienes.



4a **5**

Scheme 5: Oxidative dimerization of **4a**.

The pathway of the oxidation of zirconate **2** to vinylzirconocene **4** is not yet clear. A possible mechanism is proposed in Scheme 6. Coordination of TCQ to zirconium results in reductive elimination to afford vinylzirconocene(II) **6**. Then intermediate **6** reacts with TCQ to form vinylzirconocene(IV) **4**. The intermediate **4** reacts with electrophiles to afford multi-substituted olefin **3**.



2 **6** **4** **3**

Scheme 6: Possible reaction mechanism.

Conclusion

We have developed a novel method for the zirconoarylation of alkynes through TCQ-promoted reductive elimination of arylzirconate. This reaction can afford multi-substituted olefins with stereoselectivity.

Experimental

General Comments. All manipulations were conducted in Schlenk tubes and under a nitrogen atmosphere with a slightly positive pressure. Unless otherwise noted, all starting materials were commercially available and were used without further purification. Tetrahydrofuran (THF) was refluxed and freshly distilled from dark purple solutions of sodium and benzophenone under nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz and 400 MHz NMR spectrometers with TMS as internal standard. GC–MS spectra were recorded on a Hewlett Packard GC–MS system.

Typical procedure for TCQ-promoted arylzirconation of alkynes

To a solution of Cp_2ZrCl_2 (1.2 mmol, 351 mg) in 5 mL THF, *n*-BuLi (2.4 mmol, 1.5 mL, 1.6 M in hexane) was added at −78 °C and the mixture was stirred for 1 h at the same temperature. To this solution, 4-dimethylaminopyridine (DMAP, 122 mg, 1.0 mmol) was added. The resulting mixture was warmed to room temperature and stirred for 1 h. Diphenylacetylene (1.0 mmol, 178 mg) was added and the mixture was stirred for 1 h at the same temperature. Subsequently, PhLi (2.0 mmol) was added and the solution was stirred for 12 h at room temperature. Then TCQ (2.0 mmol) was added and stirred for another 12 h to afford alkenylzirconocene **4a**. The mixture was quenched with HCl solution to afford product **3a** in 62% isolated yield.

1,1,2-Triphenylethene (**3a**) [58]: ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 6.93 (s, 1H), 6.99–7.30 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 126.6, 126.8, 127.5, 127.6, 127.7, 128.1, 128.3, 128.7, 129.7, 130.5, 137.5, 140.5, 142.7, 143.5; GC–MS *m*/*z*: 256.

2-Deuterium-1,1,2-triphenylethene (**3a-D**) [59]: The reaction mixture containing **4a** was quenched with DCl, and **3a-D** was isolated in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 7.00–7.51 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 127.0, 127.6, 127.7, 127.7 (t, J_{DC} = 7.2 Hz), 127.8, 128.2, 128.4, 128.8, 129.7, 130.6, 137.5, 140.5, 142.7, 143.6; GC–MS *m*/*z*: 257.

1,2-Diphenyl-1-(*p*-tolyl)ethene (**3b**) [58]: The reaction was using *p*-tolyllithium instead of phenyllithium, and **3b** was isolated in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.45 (s, 3H), 7.06 (s 1H), 7.20–7.42 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 21.4, 126.8, 127.6, 127.7, 128.2, 128.8, 129.1, 129.7, 130.6, 137.5, 137.7, 140.7, 140.9, 142.8; GC–MS *m*/*z*: 270.

(*E*)-1,2-Diphenyl-1-(2-thienyl)ethene (**3c**): The reaction was performed using 2-thienyllithium instead of phenyllithium, and **3c** was isolated in 47% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 6.69–6.71 (dd, J_{HH} = 3.8, 1.1 Hz, 1H), 6.87–6.90 (m, 1H), 6.93–6.96 (m, 2H), 7.04–7.09 (m, 4H), 7.13–7.15 (dd, J_{HH} = 4.8, 2.9 Hz, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 124.8, 126.2, 126.4, 126.9, 127.5, 127.9, 128.1, 128.9, 129.5, 130.0, 136.3, 136.7, 139.5, 148.0; GC–MS *m*/*z*: 262; HRMS: calcd for $C_{18}H_{14}S$, 262.0816; found, 262.0813.

(*E*)-1-(1-Naphthyl)-1,2-diphenylethene (**3d**) [59]: The reaction was performed using 1-naphthyllithium instead of phenyllithium, and **3d** was isolated in 38% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 6.85 (s, 1H), 7.23–8.17 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 125.4, 125.8, 126.1, 126.3, 127.1, 127.4, 127.5, 128.0, 128.2, 128.4, 128.5, 129.6, 129.9, 131.8, 132.0, 134.1, 137.5, 141.1, 141.4, 142.3; GC–MS *m*/*z*: 306.

1-Bromo-1,2,2-triphenylethene (**3e**) [60]: The reaction mixture containing **4a** was further treated with NBS (2 mmol) for 4 h at room temperature and **3e** was isolated in 37% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 6.93–6.97 (m, 3H), 7.02–7.05 (m, 3H), 7.11–7.17 (m, 3H), 7.27–7.33 (m, 3H), 7.35–7.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 122.3, 127.1, 127.7, 128.0, 128.1, 128.2, 128.4, 129.7, 130.4, 130.4, 141.1, 141.2, 143.7, 143.9; GC–MS *m*/*z*: 334, 336.

1,1,2-Triphenylpenta-1,4-diene (**3f**) [27]: To the reaction mixture containing **4a**, CuCl (1 mmol) and allyl bromide (2 mmol) were added. The reaction mixture was stirred for 12 h at room temperature and **3f** was isolated in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 3.28–3.30 (d, J_{HH} = 6.1 Hz, 2H), 4.97–5.05 (m, 2H), 5.73–5.79 (m, 1H), 6.91–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 40.6, 116.1, 126.2, 126.5, 127.1, 127.6, 127.7, 128.0, 128.3, 129.8, 130.0, 131.0, 136.5, 138.0, 140.9, 142.4, 143.1, 143.4; GC–MS *m*/*z*: 296.

(*E*)-1,2-Diphenyl-1-(*p*-tolyl)penta-1,4-diene (**3g**): The reaction was performed using *p*-tolyllithium instead of phenyllithium. After treatment with TCQ for 12 h, CuCl (1 mmol) and allyl bromide (2 mmol) was added. The reaction mixture was stirred for 12 h at room temperature and **3g** was isolated in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.44 (s, 3H), 3.36–3.38 (d, J_{HH} = 6.1 Hz, 2H), 5.80–5.89 (m, 2H), 7.01–7.25 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 21.4, 40.6, 116.0, 126.1,

126.3, 127.6, 128.0, 128.9, 129.7, 130.0, 131.0, 136.6, 136.6, 137.7, 140.5, 140.8, 142.5, 143.3; GC–MS *m*/*z*: 310; HRMS: calcd for $C_{24}H_{22}$, 310.1722; found, 310.1724.

1,2,2-Triphenyl-1-(*p*-tolyl)ethene (**3h**) [61]: The reaction was performed using *p*-tolyllithium instead of phenyllithium. To the reaction mixture, CuCl (1 mmol), $Pd(PPh_3)_4$ (0.05 mmol), and iodobenzene (2 mmol) were added. The reaction mixture was stirred for 12 h at room temperature and **3h** was isolated in 31% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.28 (s, 3H), 3.94–7.12 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 21.3, 126.4, 126.4, 127.7, 127.8, 128.5, 131.3, 131.4, 131.5, 136.1 ,140.6, 140.9 ,141.0, 144.1; GC–MS *m*/*z*: 346.

(*Z*)-1-Phenyl-1,2-di(*p*-tolyl)ethene (**3i**) [58]: The reaction was performed using ditolylacetylene instead of diphenylacetylene, and **3i** was isolated in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.31 (s, 3H), 2.43 (s, 3H), 6.96 (s, 1H), 7.00–7.36 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 21.3, 21.5, 127.4, 127.7, 128.0, 128.3, 128.8, 129.5, 129.6, 130.4, 134.8, 136.6, 137.1, 137.7, 141.8, 144.0; GC–MS *m*/*z*: 284.

(*E*)-1-Bromo-2-phenyl-1,2-di(*p*-tolyl)ethene (**3j**): The reaction was performed using ditolylacetylene instead of diphenylacetylene. After bromination by NBS (2 mmol), **3j** was isolated in 36% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.18 (s, 3H), 2.25 (s, 3H), 6.80–7.38 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 21.3, 21.4, 122.1, 127.5, 128.2, 128.7, 128.8, 129.6, 130.3, 130.3, 136.7, 137.8, 138.4, 138.5, 143.0, 144.3; GC-MS: 362, 364; HRMS: calcd for $C_{22}H_{19}Br$, 362.0670; found, 362.0674.

(*Z*)-1-Phenyl-1,2-di(*p*-fluorophenyl)ethene (**3k**) [59]: The reaction was performed using 4,4′-difluorodiphenylacetylene instead of diphenylacetylene, and **3k** was formed in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 6.87–6.78 (m, 2H), 6.90 (s, 1H), 7.05–6.95 (m, 4H), 7.18–7.10 (m, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δ115.2 (d, J = 21.4 Hz), 115.9 (d, J = 21.5 Hz), 127.4, 127.7, 127.9, 128.4, 131.2 (d, J = 7.8 Hz), 132.2 (d, J = 7.8 Hz), 133.4, 136.1, 141.5, 143.2, 161.6 (d, J = 247.4 Hz), 162.3 (d, J = 246.7.8 Hz); GC–MS *m*/*z*: 292.

(*Z*)-1-Phenyl-1,2-di(*p*-methoxylphenyl)ethene (**3l**) [59]: The reaction was performed using 4,4'-dimethoxyldiphenylacetylene instead of diphenylacetylene, and **3l** was formed in 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 3.76 (s, 3H), 3.85 (s, 3H), 6.71 (d, J = 8.8 Hz, 2H), 6.88 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.37–7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δ 55.2, 55.3, 113.5, 114.2, 127.3, 127.5, 127.6, 128.2, 130.4, 130.9, 131.7, 132.9, 140.4, 144.1, 158.4, 158.9.

1,1,2,3,4,4-Hexaphenyl-1,3-butadiene (**5**) [62]: To the reaction mixture containing **4a**, CuCl (1 mmol) and TCQ (2 mmol) were added. The reaction mixture was stirred for 12 h at room temperature and compound **5** was isolated in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 6.96–7.40 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 127.1, 127.6, 128.0, 128.0, 128.1, 128.2, 139.5, 140.4, 141.1, 142.0.

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Isocyanide-based multicomponent reactions towards cyclic constrained peptidomimetics

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Review

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Abstract

In the recent past, the design and synthesis of peptide mimics (peptidomimetics) has received much attention. This because they have shown in many cases enhanced pharmacological properties over their natural peptide analogues. In particular, the incorporation of cyclic constructs into peptides is of high interest as they reduce the flexibility of the peptide enhancing often affinity for a certain receptor. Moreover, these cyclic mimics force the molecule into a well-defined secondary structure. Constraint structural and conformational features are often found in biological active peptides. For the synthesis of cyclic constrained peptidomimetics usually a sequence of multiple reactions has been applied, which makes it difficult to easily introduce structural diversity necessary for fine tuning the biological activity. A promising approach to tackle this problem is the use of multicomponent reactions (MCRs), because they can introduce both structural diversity and molecular complexity in only one step. Among the MCRs, the isocyanide-based multicomponent reactions (IMCRs) are most relevant for the synthesis of peptidomimetics because they provide peptide-like products. However, these IMCRs usually give linear products and in order to obtain cyclic constrained peptidomimetics, the acyclic products have to be cyclized via additional cyclization strategies. This is possible via incorporation of bifunctional substrates into the initial IMCR. Examples of such bifunctional groups are *N*-protected amino acids, convertible isocyanides or MCR-components that bear an additional alkene, alkyne or azide moiety and can be cyclized via either a deprotection–cyclization strategy, a ring-closing metathesis, a 1,3-dipolar cycloaddition or even via a sequence of multiple multicomponent reactions. The sequential IMCR-cyclization reactions can afford small cyclic peptide mimics (ranging from four- to seven-membered rings), medium-sized cyclic constructs or peptidic macrocycles (>12 membered rings). This review describes the developments since 2002 of IMCRs-cyclization strategies towards a wide variety of small cyclic mimics, medium sized cyclic constructs and macrocyclic peptidomimetics.

Introduction

Peptides and proteins fulfill a key role in many biological and physiological functions of living organisms. Therefore, they are interesting starting points for the development of novel drugs [1,2]. Peptides may act as neurotransmitters, hormones or antibodies and are involved in the progress of several diseases. However, natural peptides and proteins possess several properties which make them less suitable as a drug candidate. First, the amide bond is easily cleaved by proteases and their hydrophilic character results in a low permeability, rapid metabolic processing and excretion. Also, natural peptides often occur in an ensemble of conformations thereby reducing their specificity for biological targets resulting in unwanted side effects [3,4]. Consequently, chemists started to develop so-called peptidomimetics; *compounds that mimic the action or active conformation of a peptide by incorporating non-peptidic structural and functional features that imitate those of the parent peptide but with improved biological properties*. During the last decades, several classes of peptidomimetics have been described such as peptide bond isosteres or conformational constraint mimics [5,6]. Insertion of conformational restrictions is of high interest since they reduce the number of conformations, which may result in higher affinity for the target/receptor and improved protease stability, bioavailability and specificity [6-8]. Conformational bias can be achieved via *N*-alkylation, α-alkylation or the introduction of alkene amide bond isosteres, but also via local or global cyclization. A prominent advantage of cyclized constraints is that they force the molecule into a well-defined secondary structure. Such structural features are often found in biologically active peptides and proteins [8]. Mimicking the secondary structure is of high interest since these motifs are regularly located at the surface of peptide–peptide interactions [9]. Another important reason for the design and synthesis of these cyclic mimics is that they can give in-depth insight in the biologically active conformation of a peptide or protein [10].

In the context of design and synthesis of peptidomimetics, several approaches have been applied and most of them include a sequence of multiple reactions along with a variety of protection and deprotection steps. However, via these rather long sequential procedures it is often not straightforward to introduce structural diversity in a set of targeted peptide mimics, which is essential for effective fine tuning of biological activity [11-13]. Therefore, the use of more straightforward and robust reactions that can introduce complexity and structural diversity in only a few steps is highly desirable. A promising approach that combines those features is the use of multicomponent reactions (MCRs). Multicomponent reactions are convergent one-pot transformations involving three or more substrates that give a single product with high atom-economy. The reagents herein react in a sequential manner and all intermediate-steps are in equilibrium except often the last irreversible step, which provides the product. Besides saving time and reagents, another major advantage of these reactions is the ability to combine commercially available or readily accessible starting materials with a variety of functionalities in one-step. Further, MCR-based strategies can cover a broader range of chemical space because a large set of structurally different starting materials is tolerated and structural diversity is relatively easily achieved. Finally, the highly convergent nature of MCRs results in the generation of highly complex structures in only one step. In addition, because of their practical simplicity they are also ideally suited for automated synthesis [14-18]. Among the MCRs, the isocyanide-based multicomponent reactions (IMCRs), such as the Ugi and the Passerini reaction, are the most relevant reactions for constructing peptidomimetics since they give access to (depsi)peptide-like structures. However, these IMCRs provide linear products, whereas their cyclic analogues are highly desirable as discussed above for potentially improved structural and biological properties. Fortunately, these linear products can be cyclized via post-condensation transformations since a wide range of unreactive functional groups are tolerated in the IMCRs [19].

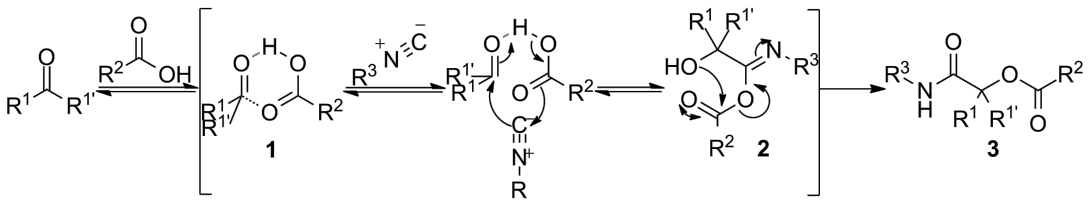
In this overview we focus on all recent developments in the last decade in the field of cyclic peptidomimetics obtained from IMCRs and their subsequent cyclization reactions. The cyclic mimics herein range from small rings (four to seven membered), medium sized rings (9–12 membered) to macrocycles.

Isocyanide-based multicomponent reactions for cyclic peptidomimetics

Multicomponent reactions that include isocyanide or isocyanide derivatives (e.g. isocyanoacetates) have been widely applied for the synthesis of peptidomimetics. The main advantage of these isocyanide-based reactions is that the isocyanide functionality can act both as nucleophile and electrophile at the C1-carbon, which makes the construction of linear peptide-like structures possible [20]. Cyclic peptidomimetics can be obtained via subsequent transformations that in turn are possible via e.g. the incorporation of bifunctional substrates or by activation of functionalized substrates in the initial MCR [19].

The Passerini reaction

The first isocyanide-based MCR was described by Mario Passerini in 1921 and named after him. The Passerini reaction is a three-component reaction (3-CR) and provides α-acyloxy carboxamides by reacting carbonyl compounds, carboxylic acids and isocyanides. The reaction is usually performed with



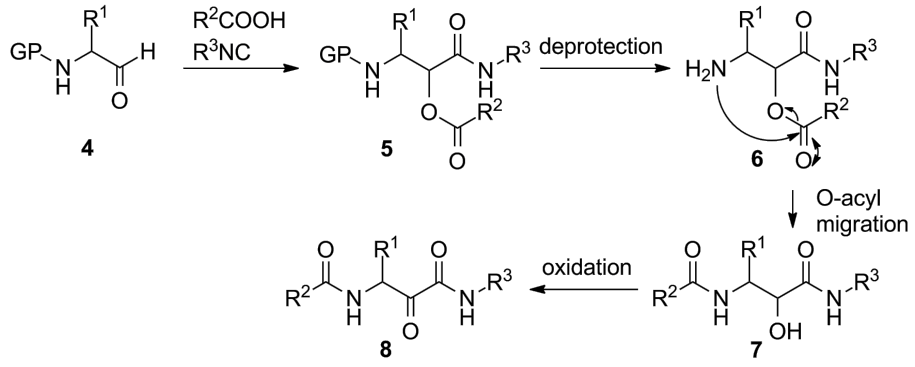
Scheme 1: The proposed mechanism of the Passerini reaction.

high concentrations of starting materials using aprotic solvents. A wide range of all three components is tolerated in the Passerini 3-CR, which makes this reaction ideally suited for addressing scaffold diversity. The higher rates observed in aprotic solvents suggest that the Passerini 3-CR proceeds via a non-ionic pathway. A generally accepted mechanism starts with the generation of the loosely hydrogen-bonded adduct **1** from the oxo-component and the carboxylic acid (Scheme 1). The next step involves the α-addition of both the electrophilic carbonyl-carbon of the oxo-component and the nucleophilic oxygen of the acid component to the isocyanide, to afford the α-adduct **2**. A subsequent rearrangement then provides the α-acyloxy amide **3** [20-22].

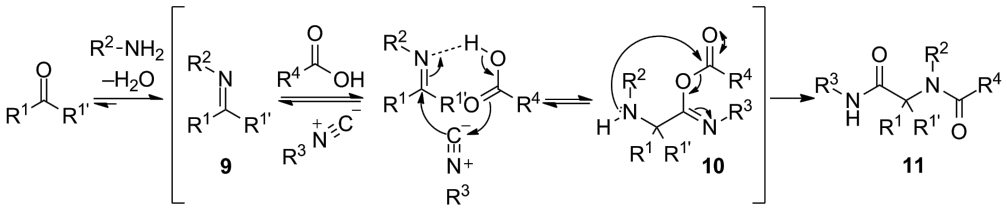
With regard to peptidomimetic design, the incorporation of *N*-protected aldehydes **4** (Scheme 2) is of great importance since deprotection of the α-adduct **5** allows acyl-migration and give access to α-hydroxy-β-amino amide derivatives **7** that possess important biological properties. This Passerini–amine deprotection–acyl migration (PADAM) strategy was reported for the first time by Banfi and co-workers in 2003 [23]. In addition, subsequent oxidation of **7** gives access to α-keto amides **8** that show important protease inhibitory activities.

The Ugi reaction

One of the most important MCRs that generates peptide-like structures was reported for the first time by Ivar Ugi in 1959. This Ugi four-component reaction (U-4CR) furnishes α-acylamino amides **11** by combining oxo-substrates, carboxylic acids, amines and isocyanides in one-pot and like the Passerini reaction a wide variety of substrates is tolerated. In contrast to the Passerini 3-CR, the Ugi 4-CR is favoured in polar protic solvents like low-molecular weight alcohols such as methanol, ethanol or trifluoroethanol. However, many examples in polar aprotic solvents are also reported. The generally accepted mechanism for the Ugi reaction proceeds via in situ imine formation of **9**, followed by the generation of α-adduct **10** formed via an attack of the isocyanide to the imine and a subsequent attack of the carboxylate to the resulting nitrilium ion (Scheme 3). The final dipeptide-like product is formed via a subsequent Mumm rearrangement of the α-adduct **10**. In addition, pre-formation of the imine or the use of bifunctional inputs (e.g. amino acids) can reduce this Ugi-4CR to an Ugi-3CR. In particular, the Ugi reaction with bifunctional inputs is called an Ugi-four-center-three-component reaction (U-4C-3CR) and has been extensively applied in peptidomimetic synthesis [21,22,24,25].



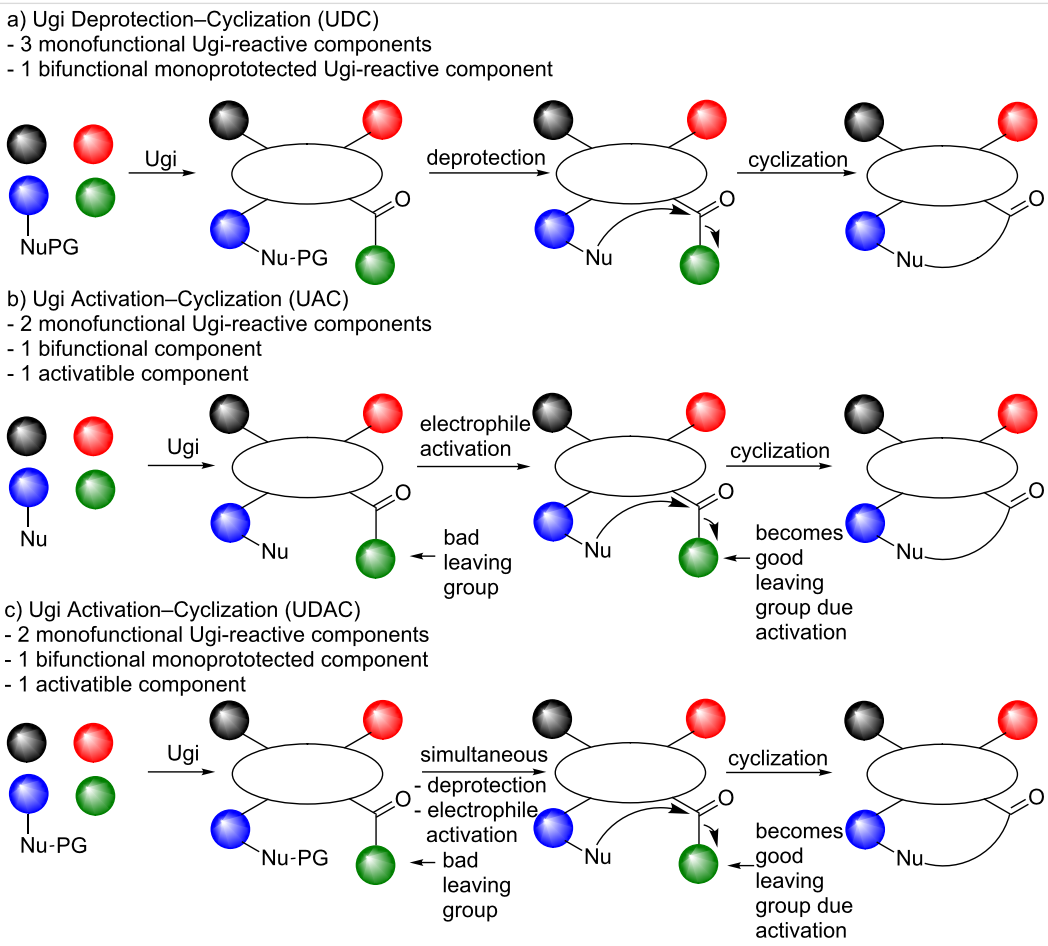
Scheme 2: The PADAM-strategy to α-hydroxy-β-amino amide derivatives **7**. An additional oxidation provides α-keto amides **8**.



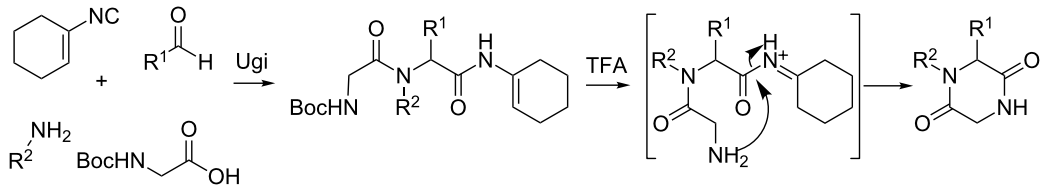
Scheme 3: The general accepted Ugi-mechanism.

Post-condensation strategies

In the last decade, several peptidomimetics containing four to seven membered rings (including bicyclic systems), medium sized rings and macrocyclic systems have been reported via IMCRs. However, as both the Ugi and Passerini reactions provide linear products, several cyclization strategies have been utilized in order to obtain cyclic constructs. For example, the incorporation of cyclic imines immediately gives cyclic MCR-products, whereas other strategies make use of unreactive, convertible or protected functional Ugi-substrates that can be cyclized via subsequent transformations [19,22,26]. Examples of IMCR orthogonal species or functionalities are alkenes, alkynes and azides which may give the cyclic analogues via subsequent ring closing metathesis (RCM) or 1,3-dipolar cycloadditions. In contrast, protected functional groups first require a deprotection before a follow-up cyclization event can take place. An example of this is the use of *N*-Boc protected amino acids in the Ugi reaction. Subsequent deprotection of the linear Ugi-product allows cyclization and reactions of this type are classified as Ugi Deprotection–Cyclizations (UDC, Scheme 4). Moreover, cyclizations can also be initiated by activation of the Ugi-product via an Ugi Activation–Cyclization



Scheme 4: Three commonly applied Ugi/cyclization approaches. a) UDC-process, b) UAC-sequence, c) UDAC-combination.



Scheme 5: Ugi reaction that involves the condensation of Armstrong's convertible isocyanide.

procedure and involves the use of convertible isocyanides as Ugi-substrates. An example of a convertible isonitrile is Armstrong's isocyanide which can be cleaved after acidic treatment (Scheme 5). A combination of deprotection and activation is also possible and is found in the literature as an Ugi Deprotection/Activation–Cyclisation (UDAC). In addition, other MCR-post-condensation reactions, especially for macrocycles, include intramolecular aryl couplings, amidations, S_nAr reactions, nucleophilic substitutions, and macrolactonizations. Even more interestingly, it is possible to perform the cyclization step via a second multicomponent reaction [22] or the MiB (*m*ultiple multicomponent macrocyclizations *i*ncluding *b*ifunctional building blocks) protocol developed by Wessjohann et al. (vide infra) [26].

Review

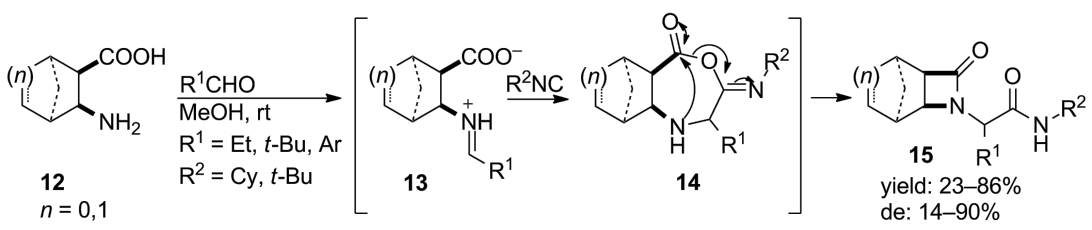
Small ring constraints

In the first part of this review four- to seven-membered cyclic peptidomimetics will be discussed. These small rings, particularly heterocycles, have received much attention as dipeptide mimics due to their capable interaction with defined protein motifs and due to their ease of preparation via IMCRs [27-29]. First, the β-lactams will be described followed by five-membered rings varying from pyrrolidines to tetrazoles based amide bond isosteres. Examples of the six-membered rings showing peptide like-properties are the piperazines, homoprolines, dihydropyrimidones and triazines, whereas azepines form an important class of seven-membered cyclic peptidomimetics.

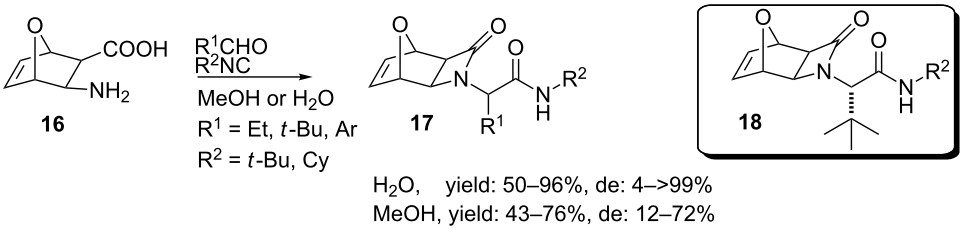
Four membered ring constraints β-Lactams

The smallest class of cyclic peptidomimetics is that of the β-lactams. β-lactams are effective antibiotics [30] but also show inhibitory activities against serine- [31], elastase- [32-35], and HIV-1 protease [36] and papain [37]. For the design of β-lactams, the Staudinger reaction involving a [2 + 2] cycloaddition of ketenes and imines is the most common method used [38]. However, Ugi reactions starting form β-amino acids are also described. In 2002, the group of Fülöp reported an efficient synthesis of bicyclic β-lactams from monocyclic β-amino acids via an Ugi four-center three-component reaction (U-4C-3R) [39]. Herein, the monocyclic β-amino acid acts as bifunctional moiety containing both an amino and carboxylic acid group. A variety of cyclic β-amino acids, in which the ring was varied, were combined with a variety of aldehydes and isocyanides in methanol to obtain the desired β-lactams. In Scheme 6, a plausible mechanism of this reaction is shown.

The β-lactam ring herein is formed via a ring contraction of the seven-membered oxazepanone intermediate **14**, which in turn is formed from α-addition of the isocyanide to the bifunctional imine. Fülöp considered both racemic *cis*- and *trans*-β-amino acids, in which only the *cis*-racemates resulted in cyclized product **15**. The *cis*-products were obtained in moderate to good yields (23–86%) with diastereoselectivities varying from 14 to 90% (de). In 2007, they extended their protocol by performing the MCR in water, which is considered as environmentally benign, cheap and allowing simple isolation as the products



Scheme 6: Mechanism of the U-4C-3CR towards bicyclic β-lactams.



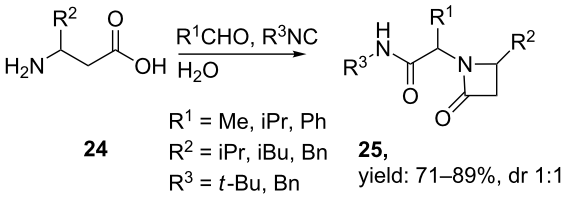
Scheme 7: The Ugi 4C-3CR towards oxabicyclo β-lactams.

precipitate [40]. Although, no improvements in yield or diastereoselectivity were observed, the reaction time was remarkably reduced in water (24 h vs. 72 h). One explanation for this acceleration could be the enhanced hydrogen bonding effect in the transition state [41]. Unfortunately, the construction of a large library was hampered, due to the poor solubility of several aldehydes in the aqueous media.

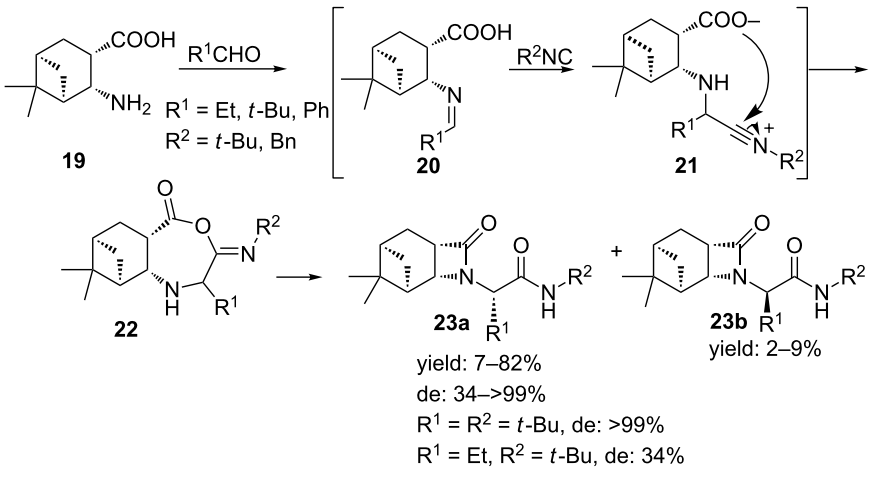
In a variation, the same group constructed a 10-membered library of oxabicyclo β-lactam derivatives (**17,** Scheme 7) from the bifunctional heteronorborene **16** in either water or methanol [42]. It was shown that both solvents gave similar results with regard to the yield (43–76% vs. 50–96%), whereas the diastereoselectivity was somewhat improved in water (12–72% vs. 4– >99%), in which the use of aliphatic aldehydes showed improved diastereoselectivity in this reaction. The highest diastereoselectivity was obtained with pivaldehyde **18** (100:0).

In 2010, Szakonyi et al. further extended their Ugi 4C-3CR-approach with enantiopure monoterpene-based β-amino acids [43] (**19**, Scheme 8), giving **22** as major isomer [44]. The stereoselectivity for **22** was explained by the steric effects of the dimethyl bridge that might prefer a *Re*-attack of the isocyanide. Compared to methanol, again the reaction in water proved to be faster. However, a solvent-free approach also resulted in the desired β-lactams with similar results in yield, diastereoselectivity and time.

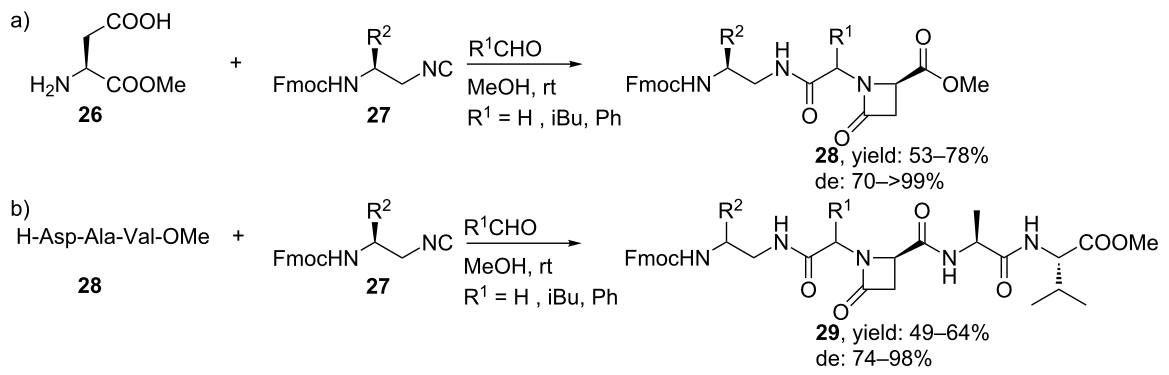
Besides bicyclic systems, Ugi 4C-3CRs towards monocyclic β-lactams are also described in both organic and aqueous media. Pirrung et al. published a library of 32 different β-lactams from four β-amino acids **24**, four different aldehydes and two isonitriles (Scheme 9) [41,45]. The reaction was performed in water at ambient temperature and yielded the desired products in good yields (71–89%), however, without diastereoselectivity (dr 1:1).



Scheme 9: General MCR for β-lactams in water.



Scheme 8: Ugi MCR between an enantiopure monoterpene based β-amino acid, aldehyde and isocyanide resulting in bicyclic β-lactams.



Scheme 10: a) Ugi reaction for β-lactam-linked peptidomimetics. b) Varying the β-amino acid resulted in β-lactam-linked peptidomimetic structures.

To improve the diastereoselectivity, the group of Sureshbabu utilized chiral N^{β}-Fmoc-amino alkyl isocyanides (obtained from N^{β}-Fmoc-amino acids) and *L*-aspartic acid α-methyl esters as Ugi-substrates (Scheme 10) [46]. The resulting β-lactam-linked peptidomimetics were obtained in good yields (53–78%) with high diastereoselectivities (70–99%). In a variation, they also performed the reaction with *L*-aspartic acid α-peptide esters yielding *endo*-β-lactam mimics **29** in good yields (49–64%, de 74–98%).

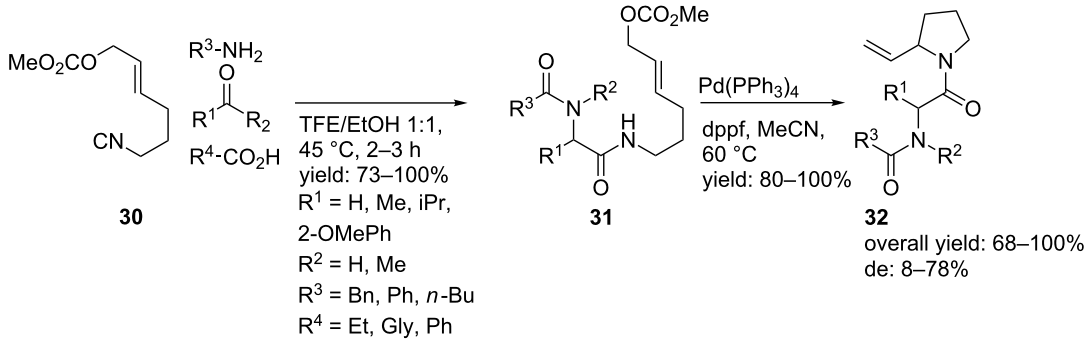
Five-membered ring constraints

In natural peptides, the cyclic proteinogenic amino acid proline has stabilizing and turn-inducing properties determining the secondary and teriary structure and conformation of peptides [7,47,48]. Moreover, their influence on an altered *cis*/*trans* ratio of the amide bond has provided in-depth insights in conformation and receptor binding [49]. Thus, the specific properties of proline play a crucial role to determine the biological activity of peptides and peptidomimetics,[50] and research towards such peptidic structures containing proline-analogues has received much attention [48]. In this part, multicomponent reactions to access pyrrolidines and other five-membered derivatives such as γ-lactams, oxazoles, thiazoles and triazoles incorporated into peptide structures will be described.

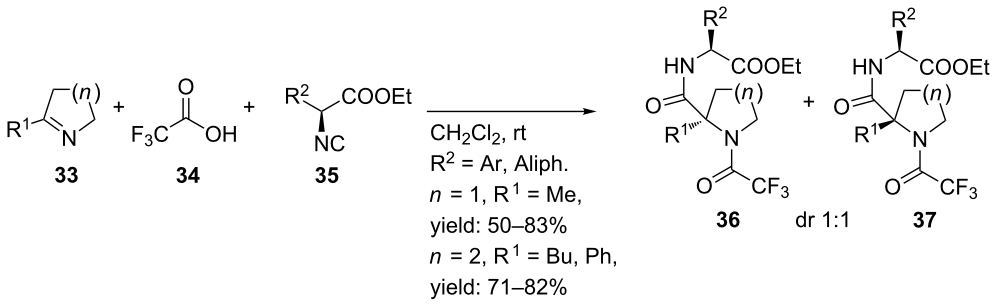
Pyrrolidines

2-substituted pyrrolidine-based dipeptide mimics were obtained from an Ugi-4CR followed by a Pd-catalyzed S_n2 cyclization as described by Banfi et al. [51] . Herein, the Ugi reaction provided a small library of acyclic products (Scheme 11), in which the isocyanide input **30** was derived from the corresponding amine via an *N*-formylation/dehydration sequence [52]. An additional palladium-catalyzed cyclization gave the pyrrolidine mimics **32** in excellent yields and modest to good selectivities (de 8–78%). In addition, the mild conditions tolerate a wide range of Ugi-substrates, resulting in a broad range of different pyrrolidine mimics **32**.

A more straightforward method [53] includes a single Joullié-Ugi 3CR using previously described alkyl substituted cyclic imines [54] giving the cyclic constraint peptides **36** and **37** (Scheme 12). In this work, no limitations regarding the type of isocyanide inputs were observed. Several alkyl-, aryl- and ester-substituted isocyanides gave the desired products. On the other



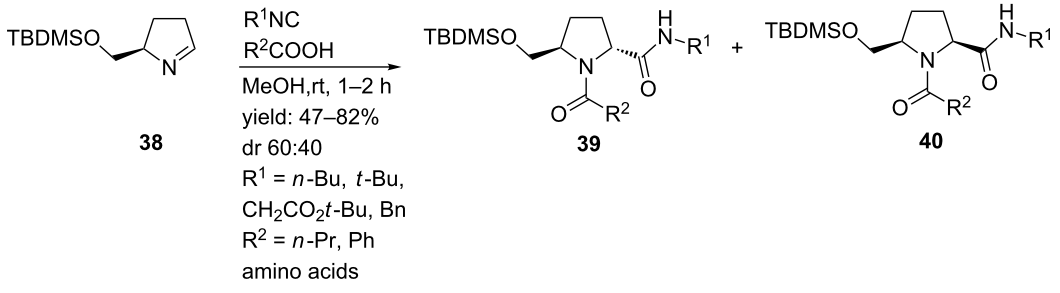
Scheme 11: Ugi-4CR followed by a Pd-catalyzed S_n2 cyclization.



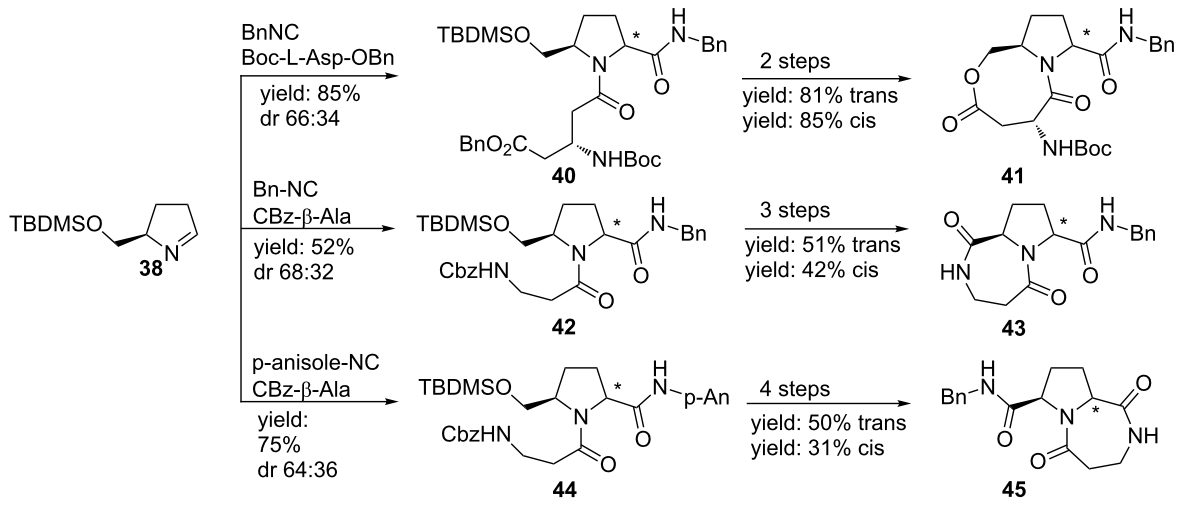
Scheme 12: Ugi-3CR of dipeptide mimics from 2-substituted pyrrolines.

hand, aryl-substituted pyrrolines as the imine input proved less efficient. The authors argued that the lower electrophilicity of arylimines and the possible enamide conjugation could account for this. Furthermore, it was shown that the pKa of the carboxylic acid significantly influenced the reaction rates, in which TFA gave the best results (2 days vs. 5 days for benzoic acid). No diastereoselectivity was observed in this reaction (dr 1:1) and the use of racemic isocyanides gave all four possible diastereomers.

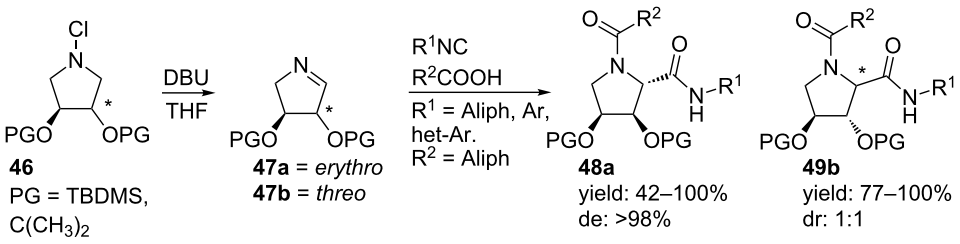
As an alternative, Banfi and co-workers focused on a library of 2,5-disubstitued pyrrolidines with potential external turn-motifs [55]. They described a Joullié–Ugi reaction from the highly reactive chiral pyrroline **38** and several carboxylic acids and isocyanides (Scheme 13). The disubstituted pyrrolidines were obtained in moderate to high yields, with a small preference for the *trans*-diastereomer **39** [56,57]. The judicious choice of carboxylic acid substituents allows a subsequent cyclization towards bicyclic systems (Scheme 14) such as pyrrolo-



Scheme 13: Joullié–Ugi reaction towards 2,5-disubstituted pyrrolidines.



Scheme 14: Further elaboration of the Ugi-scaffold towards bicyclic systems.



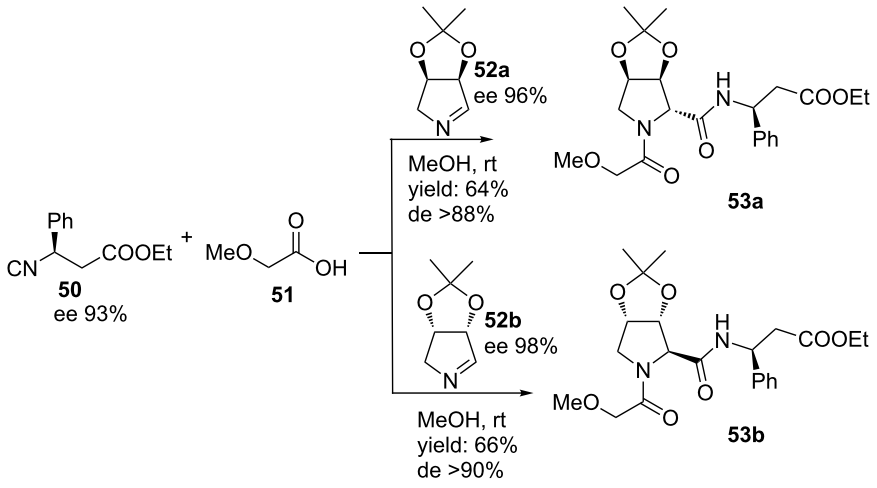
Scheme 15: Dihydroxyproline derivatives from an Ugi reaction.

oxazepinediones **41** and pyrrolodiazepinediones **43**. The latter could be used as inhibitor for aminopeptidase P. In addition, incorporation of convertible isocyanides gave access to bicyclic compound **45** [13].

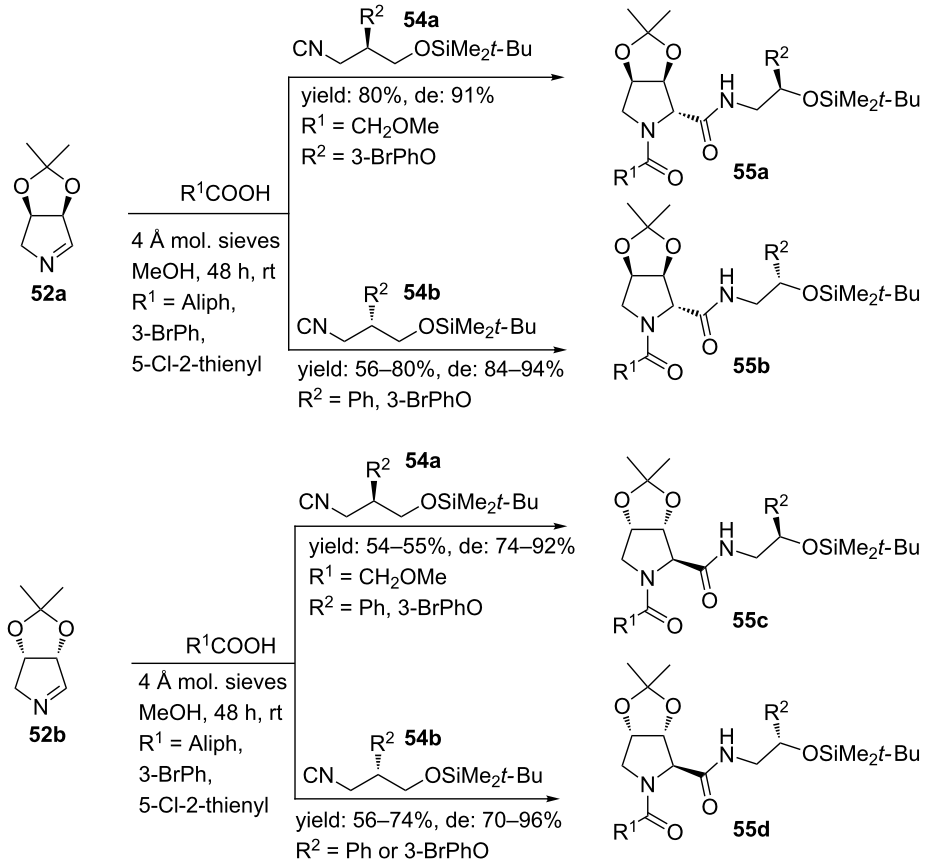
A one pot synthesis towards hydroxylated pyrrolidines was published by the group of Chapman (Scheme 15) [58]. Hydroxyproline derivatives have been reported as proline peptidase inhibitors [47]. The authors performed a Joullié–Ugi reaction with either the erythritol or the threitol imine **47a,b** and afforded both isomers **48a** and **49b**, respectively, in moderate to excellent yields. The reaction with the *erythro* isomer resulted in a single diastereomer **48a** whereas no selectivity was observed for the *threo* isomer.

Based on this diastereoselective MCR, the group of Banfi developed an Ugi-Joullié 3-CR with carboxylic acids, chiral bicyclic imines and chiral isocyanides (Scheme 16) [59]. The chiral isocyanides were prepared following an organocatalytic phase-transfer Mannich-type reaction [59], whereas the chiral imines **52a**,**b** were obtained from a bio-catalytic protocol [60]. In particular, the rigid bicyclic imines are powerful starting points and they provide the Ugi-products **53a**,**b** in high yields and mainly as *trans*-isomers (de >88%), without racemization. As an extension, two other enantiopure isocyanides were combined with a variety of carboxylic acids furnishing a small library of bicyclic dipeptide mimics (**55a**–**d,** Scheme 17) in good yields and in high diastereomeric excess (de 70–96%) [60]. It is worth noting that deprotection of the acetal-group allows modulation of rigidity and polarity of the final molecules.

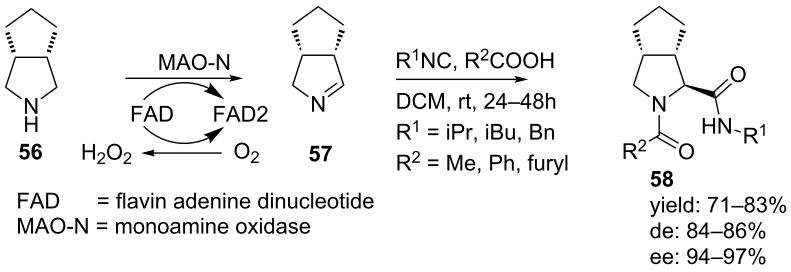
Our group reported a highly diastereoselective Ugi-MCR towards 3,4-alkyl-substituted prolyl mimics by reacting several isocyanides and carboxylic acids with optically pure 3,4-*cis*-substituted imines **57** (ee 94–97%, Scheme 18) [61]. The chiral imines were derived from a biocatalytic oxidation of *meso*-pyrrolidines **56** using monoamine oxidase N (MAO-N) [62]. The Ugi-products were exclusively obtained as single *trans*-isomers in high yields (71–83%, de 84–86 % and ee 94–97%).



Scheme 16: Diastereoselective Ugi reaction described by Banfi and co-workers.

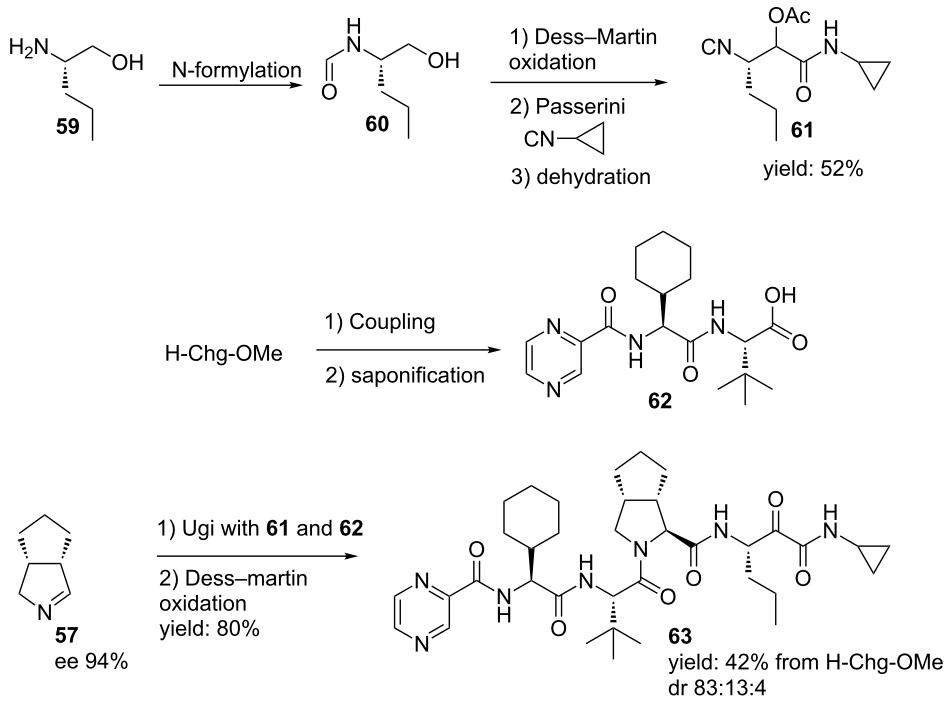


Scheme 17: Similar Ugi reaction as in Scheme 16 but with different acids and two chiral isocyanides.



Scheme 18: Highly diastereoselective synthesis of pyrrolidine-dipeptoids via a MAO-N/MCR-procedure.

It is noteworthy that these enantiopure imines can be used in a MCR-based approach to access telaprevir, a known protease inhibitor of hepatitis C (Scheme 19) [63]. The key steps in this route are a Passerini 3-CR to afford the isocyanide substrate **61** and a subsequent Ugi 3-CR/oxidation protocoll to provide the final compound in a much shorter and more straightforward route compared to earlier described syntheses (11 vs. 24 steps). The bicyclic imine **57** was obtained via the MAO-N desymmetrizaton described above, whereas a peptide-coupling between L-cyclohexylglycine methyl ester pyrazinecarboxylic acid followed by a saponification afforded the carboxylic acid **62**. Moreover, for the isocyanide component, the Dess–Martin oxidation of **60** and the subsequent Passerini reaction could be performed in one-pot, since the former reaction produces acetic acid as byproduct. Addition of cyclopropyl isocyanide followed by dehydration of the Passerini-product furnished the



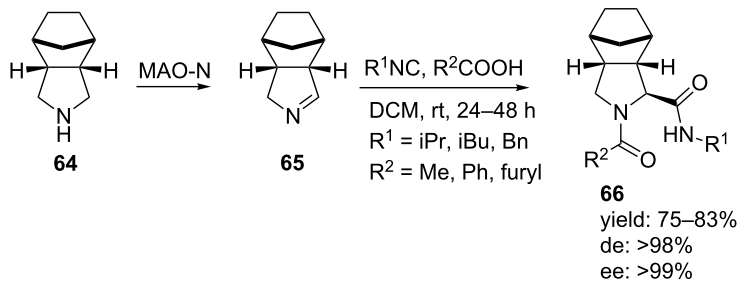
Scheme 19: MAO-N/MCR-approach towards the hepatitis C drug telaprevir.

third Ugi-component **61**. The subsequent Ugi 3-CR of **61**, **62** and **57** followed by a final oxidation resulted in **63** (42% from H-Chg-OMe, dr 84:13:4).

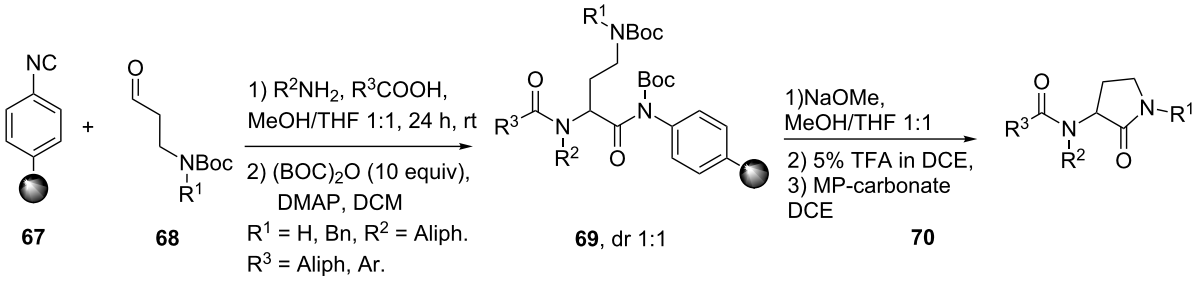
Even better selectivities were observed using the more sterically hindred **64** (Scheme 20) [61] in a similar MAO-N/MCR combination. In this way, dipeptide mimics **66** were obtained in good yields (75–83%), however, now with very high diastereomeric (>98%) and enantiomeric excesses (>99%).

γ-lactams

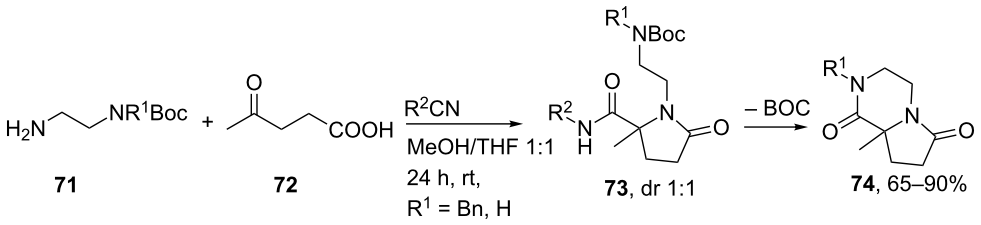
The γ-lactam unit is an important dipeptide pharmacophore since it can induce β-turns. A well-known example was described by Freidinger in 1980, who successfully developed a γ-lactam β-turn mimic of the luteinizing hormone-releasing hormone (LHRH) almost nine times more potent than the original hormone [64]. Since then, these "Freidinger lactams" have been used in numerous pharmaceutical and biological active compounds. For example, they are found in compounds used for the treatment of epilepsy [65,66], HIV [67,68], and depression [69]. Multicomponent reactions towards γ-lactam peptidomimetics were earlier described by Ugi [70], Mjalli [71] and Harriman [72]. However, in the last decade two other groups, independently, published Ugi-MCRs towards these cyclic dipeptide isosteres. Hulme et al. reported an Ugi-Deprotection–Cyclization strategy using resin-bound convertible isonitrile **67** to provide primary and secondary γ-lactams **70** in high purities over five steps (Scheme 21) [73]. As an extension,



Scheme 20: Enantioselective MAO-U-3CR procedure starting from chiral pyrroline **64**.



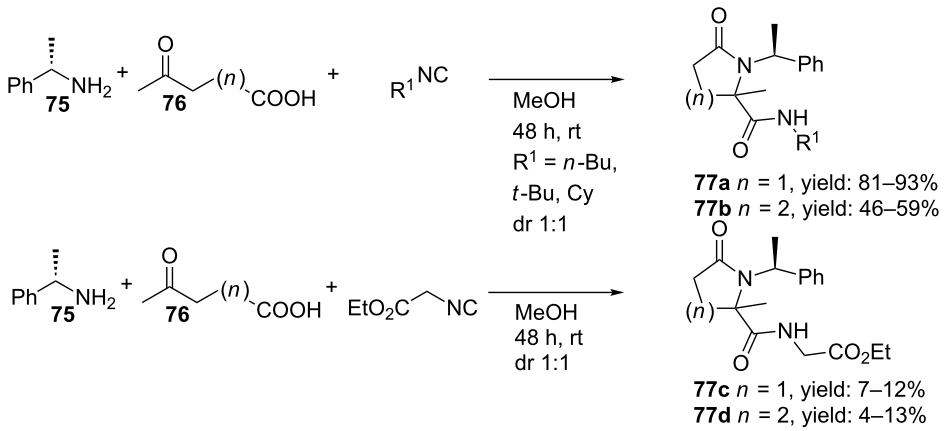
Scheme 21: Synthesis of γ-lactams via an UDC-sequence.



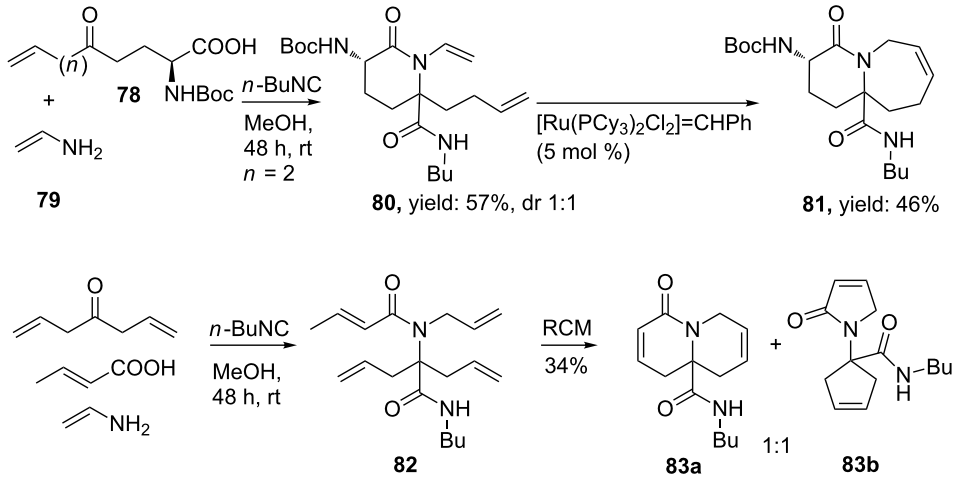
Scheme 22: Utilizing bifunctional groups to provide bicyclic γ-lactam-ketopiperazines.

they also performed the reaction sequence with bifunctional building blocks **71** and **72**, in which subsequent *N*-Boc-deprotection of **72** provided bicyclic γ-lactam-ketopiperazines **74** (Scheme 22).

Krelaus et al. described the one-pot synthesis of both γ- and δ-lactams from an Ugi 4C-3CR (Scheme 23) [74]. Screening a variety of isocyanides resulted in a small library of γ-lactams **77a** and δ-lactams **77b**, in which the former were obtained in higher yields probably due to a more favourable six-membered transition state in the Mumm-rearrangement. Moreover, the nucleophilicity of the isocyanide used also seems important. Thus, isocyano butane provided the γ-lactams in high yields (81–93%), whereas more acidic ethyl 2-isocyano acetate showed less efficient conversion (7–13%). The stereoselectivity of the process was also studied, however, even with two chiral inputs no stereoinduction was observed for the newly formed stereocenter (dr 1:1). As an extension, the authors performed the Ugi reaction with allyl amine **79** and olefinic amino acids **78** (derived from pyroglutamic acid), that, after a following ring-closure-metathesis (RCM) with Grubb's catalyst, resulted in bicyclic lactams (**81**, 46% over the two steps, Scheme 24). In addition, an even shorter route by utilizing three olefinic Ugi-substrates was also reported. Herein,



Scheme 23: The Ugi reaction provided both γ- as δ-lactams depending on which inputs were used.



Scheme 24: The sequential Ugi/RCM with olefinic substrates provided bicyclic lactams.

the ring closing step included a double RCM and resulted in an equal amount of both products **83a** and **83b** (ratio 1:1) [75,76].

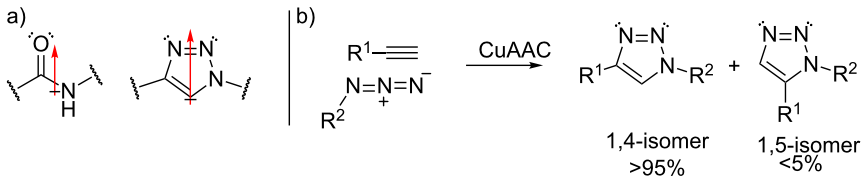
Triazoles

The replacement of amide bonds by 1,2,3-triazoles, especially the 1,4-disubstituted isomer, provided a wide variety of biological active peptidomimetics. Peptidomimetics containing these triazole cores can serve as blood components [77], anticancer medications [78], inhibitors of cysteine [79] and HIV-1 proteases [80-82]. The relative planarity of 1,2,3-triazoles, the strong dipole moment (~5 D) and the ability to both donate and accept hydrogen bonds indicate the physicochemical similarities with amide bonds (Scheme 25), however, they are inert towards oxidation, hydrolysis and enzymatic degradation [88]. Several studies have revealed the bio-similarity of triazoles with amide bonds. For example, X-ray studies towards triazole based-mimics of the HIV-1 protease inhibitor amprenavir showed an equivalent binding mode with the protease active site as compared to the amide-bond inhibitor [81,83,84].

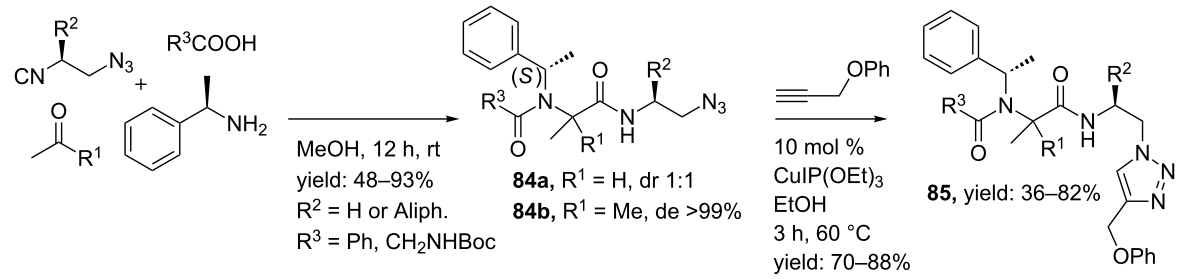
Multicomponent reactions towards amide isosteres often involve an Ugi reaction followed by a Click reaction, in which two of the Ugi-inputs either contain an alkyne or an azide moiety. A well-known example of the latter reaction is the Copper(I) catalyzed azide–alkyne cycloaddition (CuAAC) between acetylenes and azides (Scheme 25) [85]. Advantages of this reaction are the kinetic stability of both functional groups under a range of different conditions. Also, the triazole products can be formed in both organic and aqueous solvents and by using the Cu(I)-catalyst which induces regioselective formation of the 1,4-isomer over the 1,5-isomer [85].

In 2010, Nenajdenko et al. described an Ugi/Click-approach using chiral isocyanoazides, which in turn were derived from L-amino alcohols [85]. The Ugi-products were obtained in good yields, with high diastereoselectivity (de >99%). A follow-up Click reaction using 10 mol % $CuIP(OEt)_3$ and phenyl propargyl ether as the alkyne provided triazole-peptidomimetics **85** in 70–80% yield (Scheme 26).

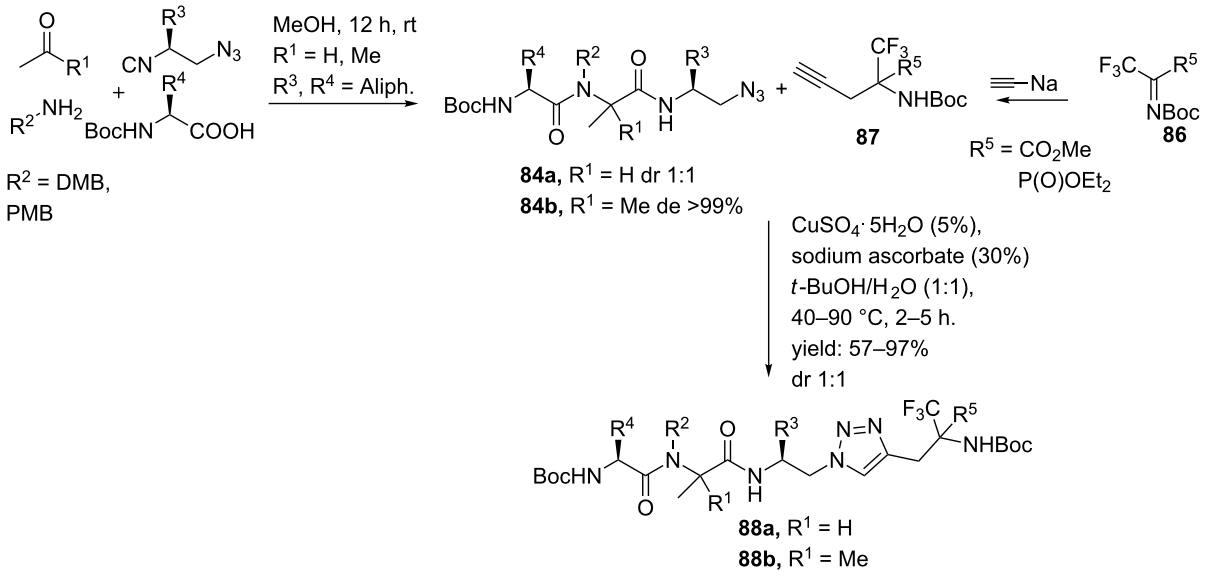
In a follow-up publication the same authors reported the development of tetrapeptides bearing α-CF_3-α-amino and α-CF_3-α-amino phosphonate cores (Scheme 27) [86]. Fluorinated compounds may enhance the biological properties of target molecules and especially CF_3-containing amino acids have demonstrated to be hydrolytically more stable as compared to the native amino acids [87]. In addition, the insertion of α-amino phosphonates to peptides has shown enhanced antibacterial, antivirus and anticancer activities [88]. The Ugi reaction



Scheme 25: a) The structural and dipole similarities of the triazole unit with the amide bond. b) The copper-catalyzed Click reaction.



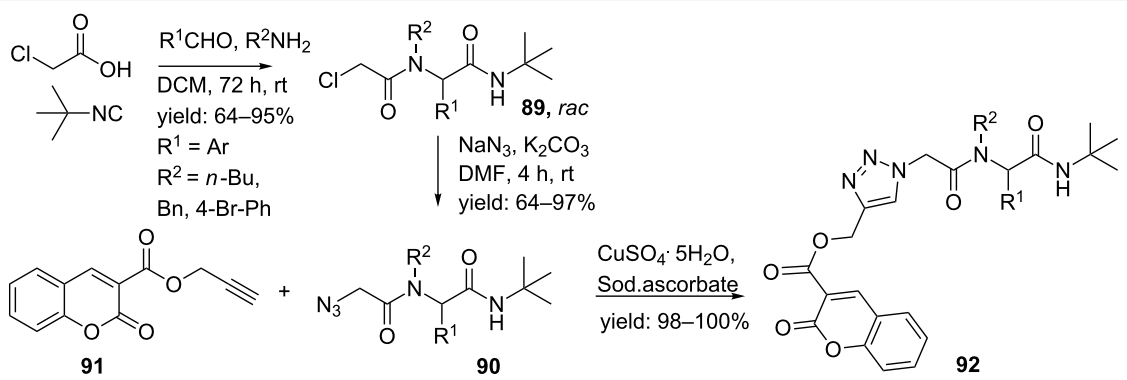
Scheme 26: The Ugi/Click sequence provided triazole based peptidomimetics.



Scheme 27: The Ugi/Click reaction as described by Nanajdenko.

provided the azide moieties **84a** or **84b**, whereas a reaction between sodium acetylide and imines of general structure **86** afforded the alkyne derivatives [89,90]. A subsequent Click reaction gave the final triazole-mimics (**88a** or **88b**) in good to excellent yields (57–97%).

A less common approach was reported by Pramitha and Bahulayan [91]. Herein, the Ugi reaction was performed with chloroacetic acid, *tert*-butyl isocyanide and different aldehydes and amines yielding chloro-Ugi products **89** (Scheme 28). A subsequent substitution with sodium azide followed by the



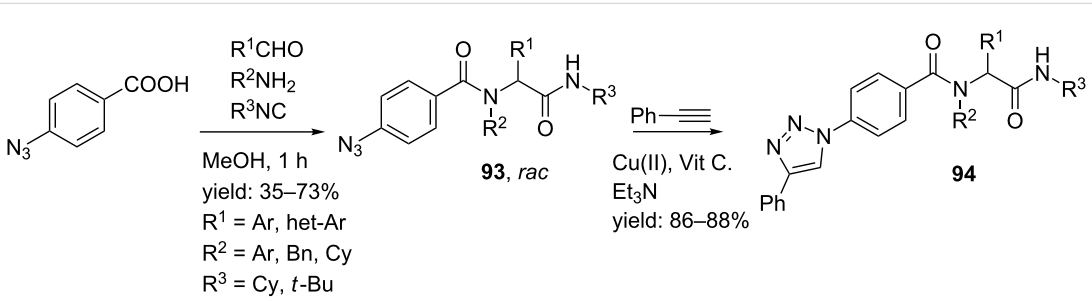
Scheme 28: The Ugi/Click-approach by Pramitha and Bahulayan.

Click reaction resulted in the triazole-linked peptidomimetics **92**.

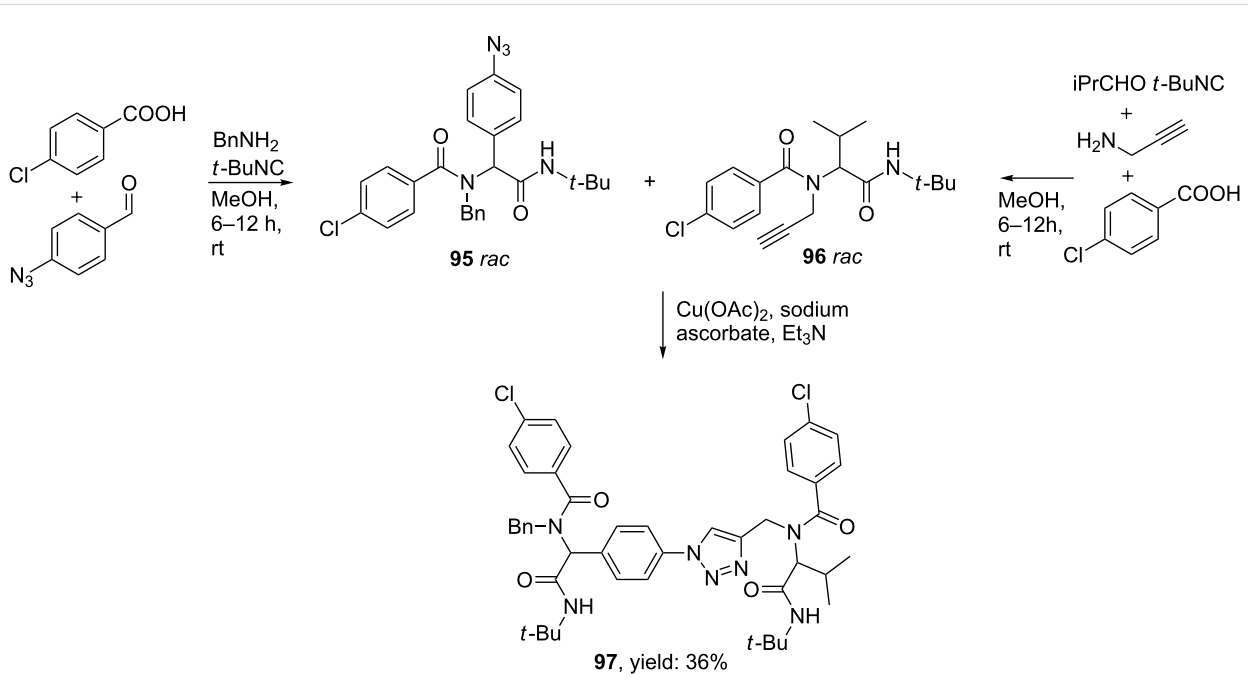
Recently, Niu et al. reported an Ugi/Click method to obtain peptidomimetics that have triazole units at the terminal, center and/or at the side chain position [92]. Terminal triazoles were obtained via an Ugi reaction of 4-azidobenzoic acid and different isocyanides, aldehydes and amines (Scheme 29). No limitations for the amine substrate were observed, whereas electron-withdrawing groups in the aldehyde decrease the yield compared to electron donating groups. For practical reasons, the authors used $Cu(OAc)_2$/vitamin C/Et_3N as Cu^{II}-complex, in which vitamin C functioned as reducing agent.

Side-chain triazoles were obtained from 4-azidobenzaldehyde in 48–62% yield, whereas incorporation of both 4-azidobenzaldehyde and 4-azidobenzoic acid provided mimics containing both a triazole unit in the side chain as in the terminal part (43%). More interestingly, the authors also described an Ugi/Click-combination in which both Click-substrates were obtained from an Ugi reaction. The subsequent Click cycloaddition provided the triazole linker **97** in 36% overall yield (Scheme 30). The authors also considered the possibility to perform these three steps simultaneously in one-pot, however, as isocyanides are also good ligands to transition metals, the Ugi products were only obtained in low yield (19%) without observing any triazole product.

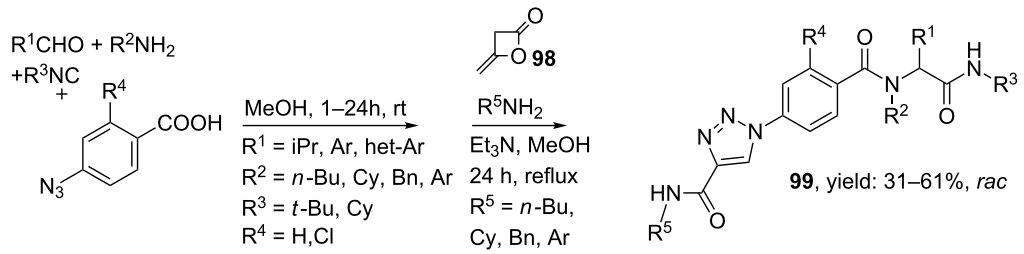
Even more interestingly was the copper-free procedure published by the group of Cai, especially since copper was found in some cases to be toxic to bacterial and mammalian cells [93]. Through a sequential Ugi 4-CR and a three-compo-



Scheme 29: The Ugi/Click-combination by Niu et al.



Scheme 30: Triazole linked peptidomimetics obtained from two separate MCRs and a sequential Click reaction.

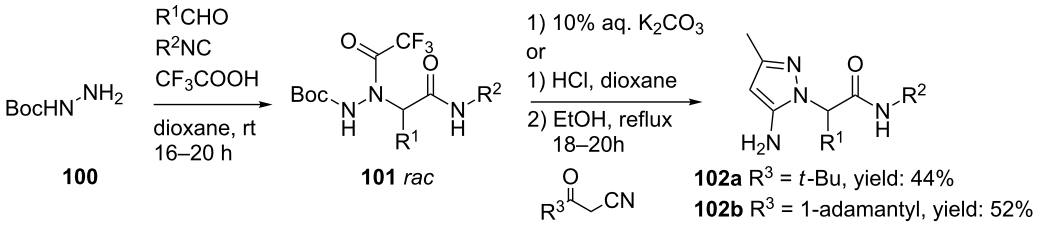


Scheme 31: Copper-free synthesis of triazoles via two MCRs in one-pot.

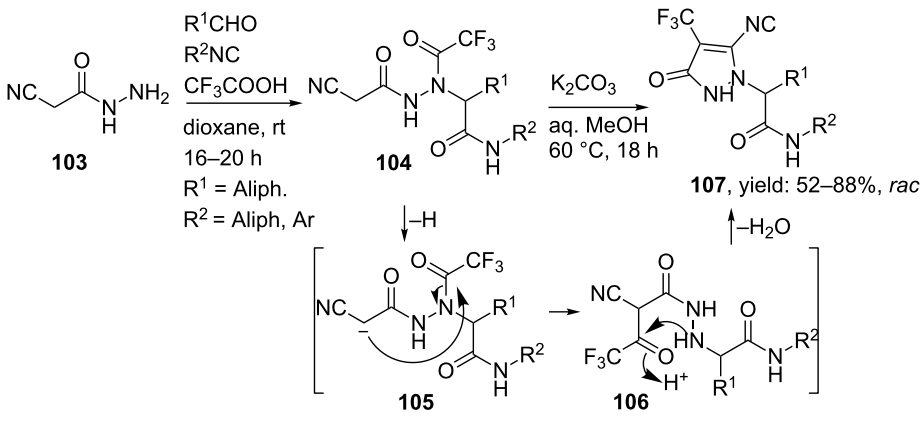
nent cycloaddition they exclusively prepared 1,4-disubstituted triazoles (**99**, Scheme 31). Thus, the Ugi 4-CR produced the azide precursor that further reacted in the subsequent 3-CR with diketene **98** and a wide variety of primary amines to afford the triazole linker. The scope of the Ugi reaction was investigated with several aliphatic and aromatic aldehydes and amines and gave the Ugi-products in good yields (34-61%). Moreover, the scope of sequential cycloaddition was also explored with several aliphatic and aromatic amines, in which the more electron-rich inputs gave the higher yields. In a variation, first the triazole-unit was formed followed by the Ugi MCR. However this resulted in lower yields compared to the initial sequence (33–39% vs. 31–61%).

Pyrazoles and pyrazolones

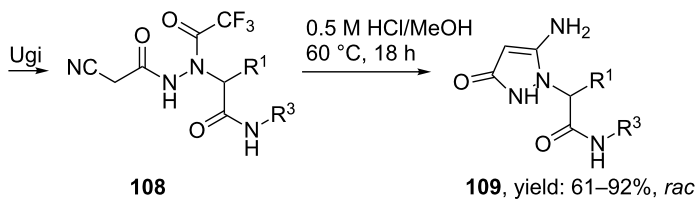
The group of Krasavin prepared both pyrazole- as well as pyrazolone-containing peptidomimetics via a sequential hydrazino-Ugi/Paal–Knorr condensation [94]. In their first approach, pyrazoles were obtained in good yields, however, with a limited scope of the condensation substrates (Scheme 32). Therefore, an intramolecular Paal–Knorr condensation of **104,** derived from an Ugi reaction of bifunctional hydrazine **103** (Scheme 33), under basic conditions was considered. Surprisingly, use of a base did not cleave the trifluoroacetyl group but instead deprotonation of the methylene group was found, yielding pyrrazol-3-ones **107**. The authors assumed that the cyclization proceeds via an N–C acyl migration of the trifluoroacetyl group, based on the



Scheme 32: The sequential Ugi/Paal–Knorr reaction to afford pyrazoles.



Scheme 33: An intramolecular Paal–Knorr condensation provided under basic conditions pyrazolones.



Scheme 34: Similar cyclization performed under acidic conditions provided pyrazolones without the trifluoroacetyl group.

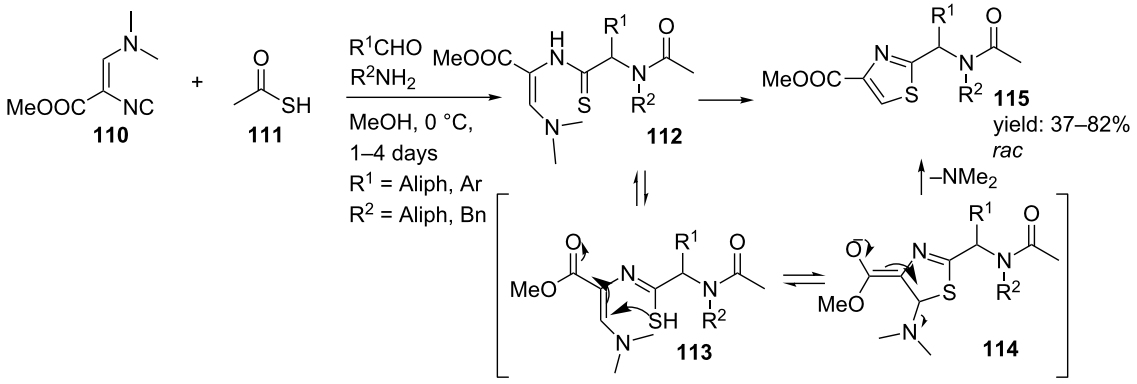
labile character of the latter moiety (Scheme 33). In contrast, acid-promoted cyclization cleaved the trifluoroacetyl group and revealed the initially expected compound **109** (Scheme 34).

Thiazoles

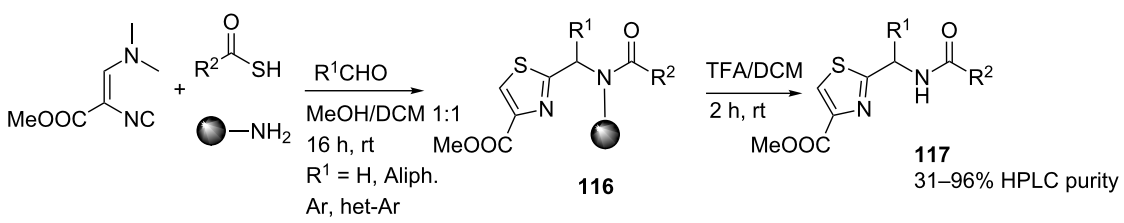
In several natural products, the thiazole ring can be found as a backbone linker, probably resulting from easy cyclization/oxidation of cysteine residues. These compounds show interesting antifungal and antibiotic [95,96], algicidal [97], and antitumor [98,99] biological activities. In addition, thiazole-based pharmaceuticals are also used as anti-prion agents (neurodegenerative disorders) [100]. Dömling and co-workers were the first that reported an Ugi-based synthesis of 2,4-disubstituted thiazoles (Scheme 35) [101,102]. The procedure involved a condensation of isocyanoacrylate **110** (derived from a known protocol by Schöllkopf) [103], thiocarboxylic acid, a variety of aliphatic amines and several aliphatic and aromatic oxo-components, furnishing the thiazoles **115** as racemic mixtures in moderate to excellent yields (37–82%). Based on the fact that the Ugi-product tautomerizes, the authors proposed a plausible mechanism, in which tautomer **113** undergoes cyclization via an intramolecular Michael reaction to give intermediate **114**. The next step involves cleavage of the dimethylamine group to afford the thiazole structures **115**.

In 2003, the same group also described a solid-phase approach with either thioacetic acid or thiobenzoic acid to obtain the 2-acylaminomethylthiazoles [104]. Deprotection of the resin onto the amide, resulted in compound **117** (Scheme 36).

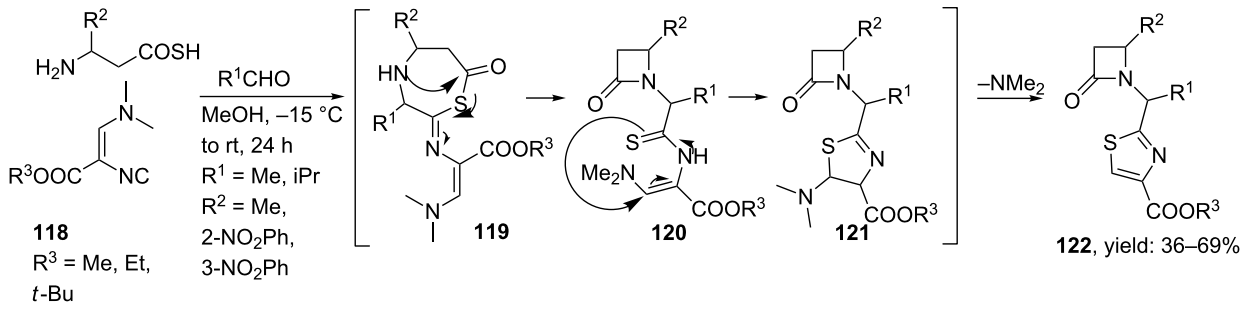
As an extension, Dömling and co-workers designed thiazole-based dipeptide mimics with an additional β-lactam moiety at-



Scheme 35: The Ugi-4CR towards 2,4-disubstituted thiazoles.



Scheme 36: Solid phase approach towards thiazoles.



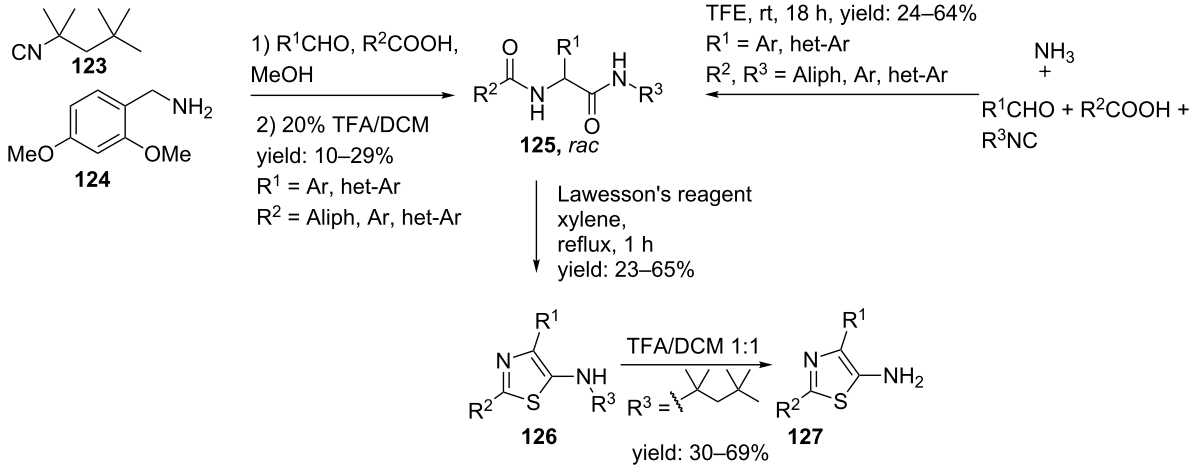
Scheme 37: Reaction mechanism of formation of thiazole peptidomimetics containing an additional β-lactam moiety.

tached to the scaffold. These compounds could find application as potent antibiotics, protease inhibitors or as cholesterol absorption modifiers (Scheme 37) [18]. In this particular reaction, the scaffolds were obtained by reacting the complex isocyanide **118** with different aldehydes and β-amino thiocarboxylic acids, in which the latter component was obtained from Z-protected β-amino acids via a cyclic anhydride in two steps [105]. Most likely this reaction proceeds via a 7-membered Ugi-intermediate that after an intramolecular acylation results in β-lactam intermediate **120**. A subsequent Michael-type addition followed by dimethylamine absorption then affords the observed thiazoles (((1-thiazole-2-yl)methyl)azetidin-2-ones) in moderate to good yields (36–69%).

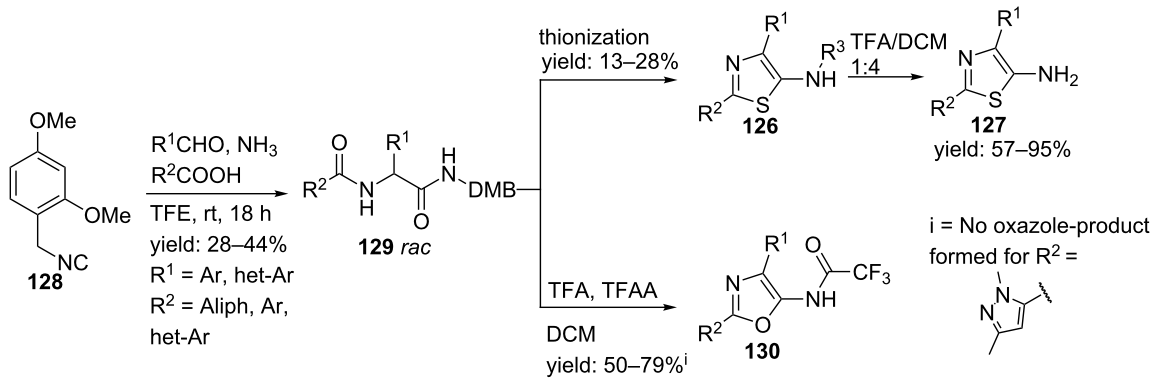
In contrast, Thompson et al. described the synthesis of 2,4-disubstituted 5-aminothiazoles via a sequential Ugi/deprotection/thionation/cyclization strategy, in which both R^1 and R^2-positions could be easily varied (Scheme 38) [106,107]. They derived the linear dipeptide from an Ugi 4-CR involving the Walborsky reagent **123** (1,1,3,3-tetramethylbutyl isocyanide) as a cleavable isocyanide input, 2,4-dimethoxybenzylamine **124** (DMB–NH_2), different aldehydes and carboxylic acids [106]. Subsequent TFA-treatment provided the precursor **125** that via a follow-up reaction with Lawesson's reagent and an intramolecular cyclization gave access to the thiazole derivative **126**. A second TFA-cleavage of the *N*-(1,1,3,3-tetramethylbutyl) group resulted in the 5-aminothiazole peptidomimetics **127** in sufficient overall yields (5–13%).

In a variation, the authors designed an ammonia-based Ugi reaction that avoids the use of protected amines (Scheme 38) [107]. It was shown that this protecting-group-free protocol tolerates a great variety of different isocyanides and also allows acid sensitive substrates. In particular, the use of isocyanide **128** gave access to 5-aminothiazoles **127** after deprotection of the DMB-group (Scheme 39).

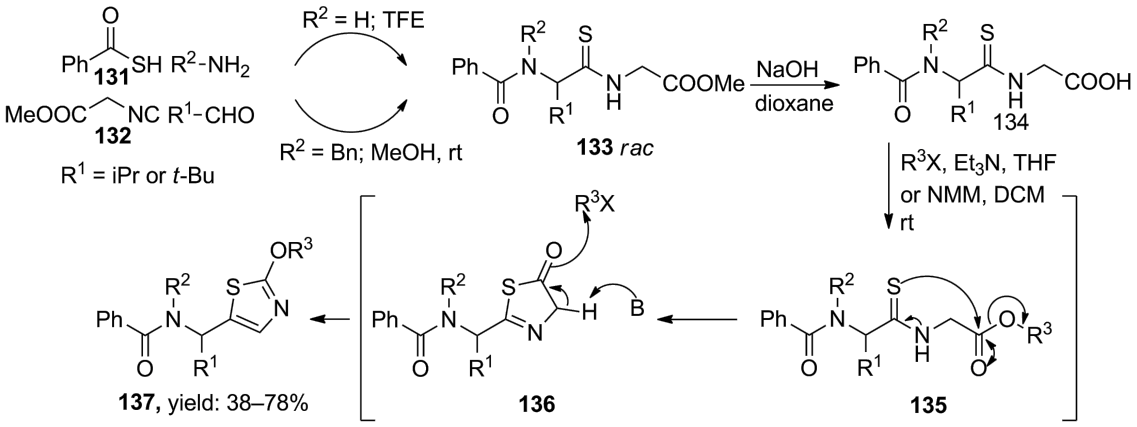
Kazmaier and Persch studied a versatile thio-Ugi MCR towards 2,5-disubstituted thiazoles (Scheme 40). The authors first obtained the Ugi-products by reacting thiobenzoic acid,



Scheme 38: The synthesis of the trisubstituted thiazoles could be either performed via an Ugi reaction with protected amines or with ammonia.



Scheme 39: Performing the Ugi reaction with DMB-protected isocyanide gave access to either oxazoles or thiazoles.



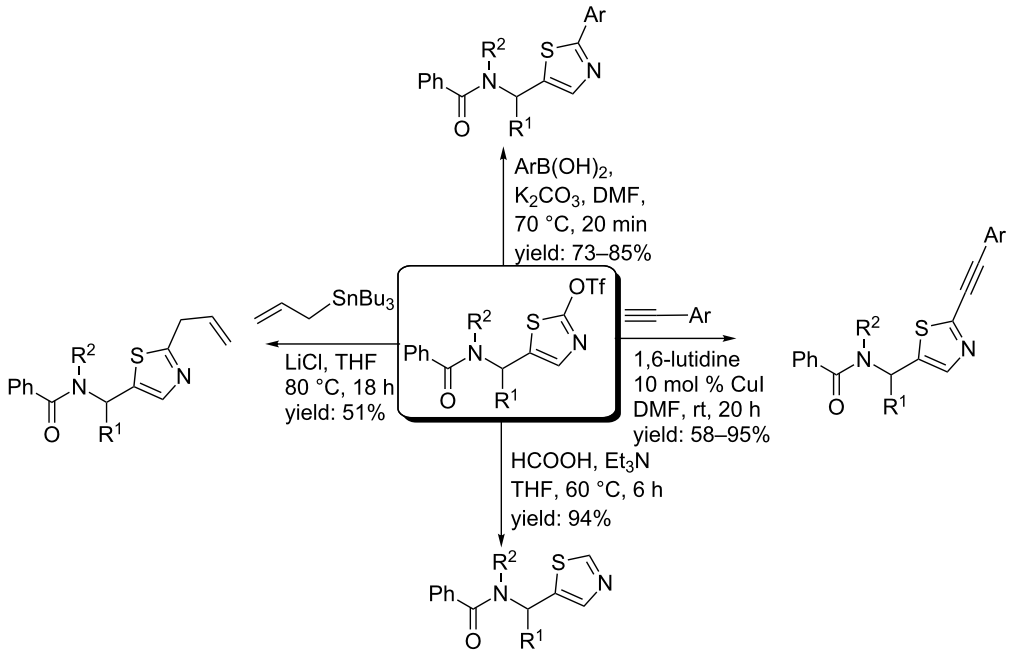
Scheme 40: Ugi/cyclization-approach towards 2,5-disubstituted thiazoles. The Ugi reaction was performed with different benzylamines or ammonia.

isocyanoacetate, two aliphatic aldehydes (iPr, *t*-Bu) and benzylamines/ammonia in either methanol (for benzylamines) or trifluoroethanol (for ammonia) [108]. Then, subsequent hydrolysis of the methylester followed by activation via acid chlorides or triflates gave the 5-substituted thiazoles (38–78%), probably via a thiazolone intermediate. It is noteworthy that the triflate-thiazoles can be further elongated via cross coupling reactions, resulting in even higher functionalized 5-substituted or non-functionalized thiazoles in good to excellent yields (51–95%, Scheme 41) [108].

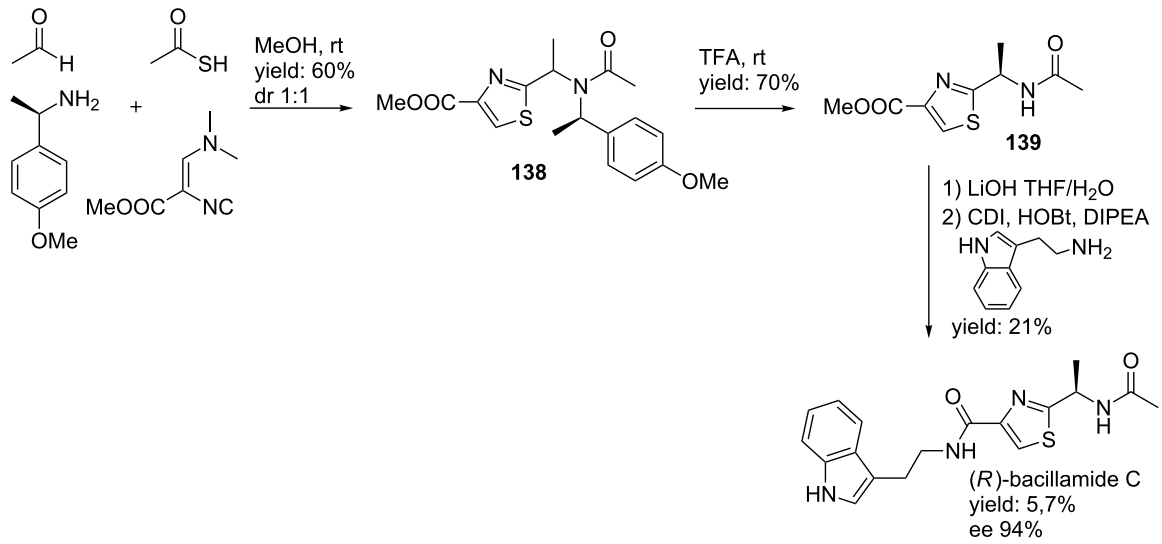
In 2009, the group of Dömling reported an Ugi-approach towards the synthesis of Bacillamide C (Scheme 42) [109]. (*R*)-Bacillamide C is a natural product with algicidal and antibacterial properties [97]. It was shown that a stereoselective reaction between Schöllkopf's isocyanide, acetaldehyde, thioacetic acid and 4-methoxy-phenylethylamine (also as chiral auxiliary) provided the corresponding Ugi product **138** in 60% yield (dr 1:1). Chiral separation and deprotection in TFA resulted in compound **139** in 70% yield, after which saponification followed by an amide coupling with tryptamine and CDI afforded the final (*R*)-bacillamide C in 6% yield over three steps (ee 94%).

Oxazoles

The oxazole unit has been applied in different bioactive marine natural products [110]. The group of Zhu reported a Ugi 3-CR to a small library of 2,4,5-trisubstituted oxazole-containing peptide-like structures from bifunctional α-isocyanoacetamides (Scheme 43) [111,112]. A plausible mechanism for this reaction involves the formation of **141**, that after tautomerization, cyclizes to the oxazole product **143**. It is noteworthy, that this reaction proceeds without the addition of a carboxylic acid because amino-oxazoles are unstable under acidic conditions. In total, six different aldehydes, twelve amines and three isocyanides yielded the corresponding desired oxazole mimics **143** in good yields (60–96%), however, the products were obtained as racemates even when the reaction was performed



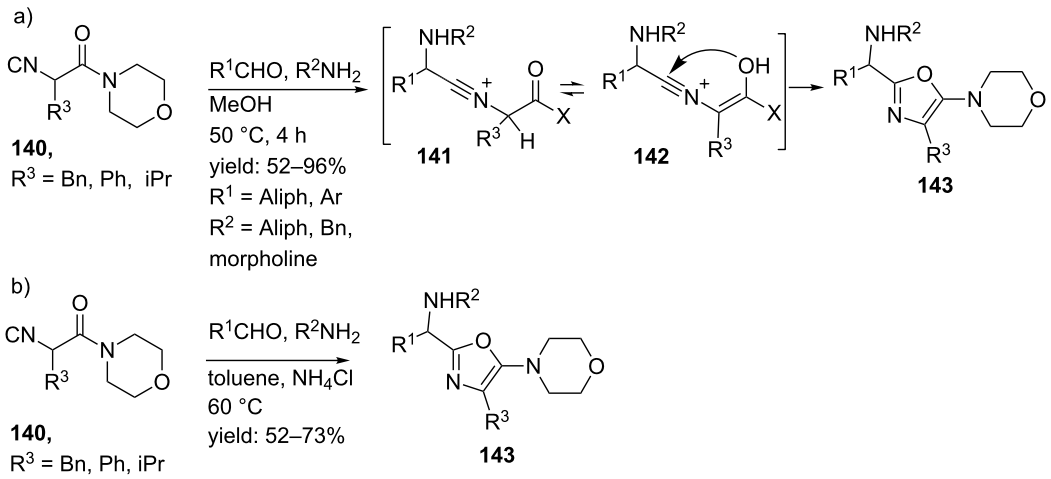
Scheme 41: Further derivatization of the thiazole scaffold.



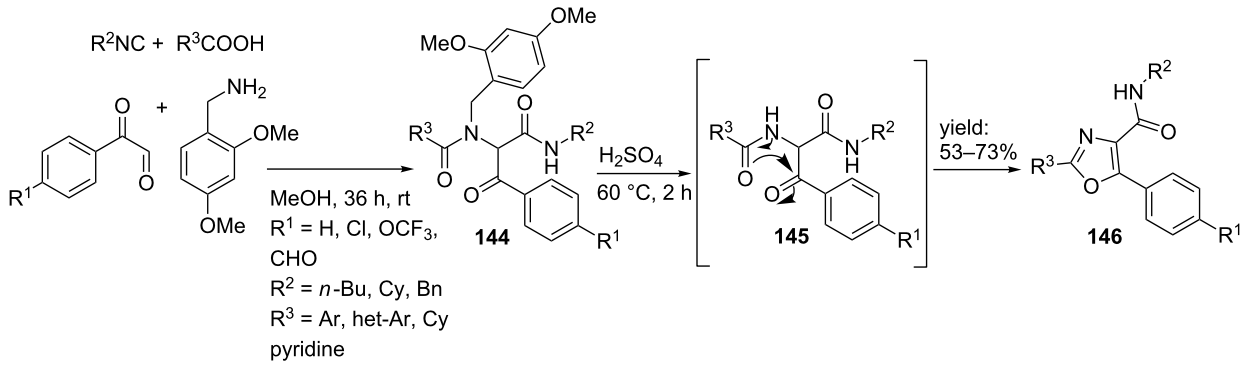
Scheme 42: Three-step procedure towards the natural product bacillamide C.

with chiral isocyanides. Some diastereoselectivity was only observed when the methyl ester of (*S*)-proline was used as an amine input (de 42%, Scheme 43). As an extension, the authors also performed the Ugi reaction in (the non-polar solvent) toluene and ammonium chloride as proton source (for the imine) at evaluated temperatures to provide the oxazoles in 52–73% yield (Scheme 43). It is noteworthy that during this latter approach no Passerini products or side-products with NH_3 (from ammonium chloride) were observed.

In contrast, Shaw et al. [113] reported another convenient approach in which a sequential Ugi 4-CR followed by a Robinson–Gabriel reaction resulted in the desired oxazoles (Scheme 44). Herein, dimethoxybenzylamine, several



Scheme 43: Ugi-4CR to oxazoles reported by Zhu and co-workers.



Scheme 44: Ugi-based synthesis of oxazole-containing peptidomimetics.

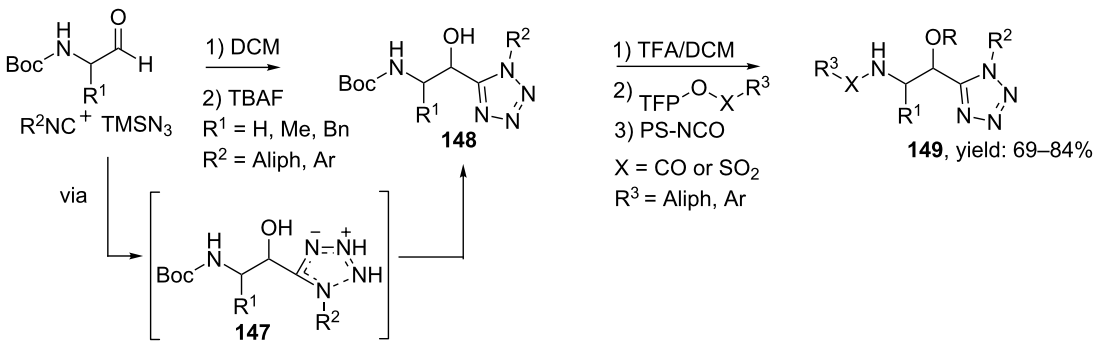
isocyanides, aryl-glyoxals and (hetero)-aryl carboxylic acids afforded the desired corresponding Ugi-products **144** in reasonable to good yields (42–65%). Subsequent exposure to concentrated sulfuric acid at 60 °C deprotected and cyclized the linear products towards the oxazole derivatives **146** in yields up to 73%.

Tetrazoles

In medicinal chemistry, tetrazoles are often used as carboxylic acid bio-isosteres due to their comparable acidity [114]. However, studies towards 1,5-disubstituted tetrazoles have shown that these heterocycles also show geometrical properties similar to *cis*-amide bonds [115]. Therefore, they have been incorporated as constrained *cis*-amide bond isosteres in several bio-active compounds such as inhibitors of cyclooxygenase-2 (COX-2) [116], hepatitis C NS3 proteases [117], HIV-1 proteases [111,112,117], the CB1 receptor of cannabinoid and fatty acid amide hydrolase [114,118-121].

In this context, Hulme and co-workers described a Passerini multicomponent approach towards *cis*-constrained norstatine mimics, a class of HIV-1 protease inhibitors with a tetrazole core (Scheme 45) [122]. They showed that a $TMSN_3$-modified Passerini 3-CR gave easy access to tetrazole building blocks that, after *N*-Boc-deprotection, could be coupled with polymer-bound tetrafluorophenol-esters. Subsequent heating provided the desired *N*-coupled Norstatine peptidomimetics **149** (HPLC purities: 30–74%), in which additional scavenging of the unreacted amines with polystyrene-based isocyanate (PS-NCO) improved the purities of the final products (69–84%). It is noteworthy that the use of $TMSN_3$ has several advantages, as it is less toxic and explosive than commercial derivatives and the byproduct (methoxytrimethylsilane) is easily evaporated.

Based on this Passerini reaction, the group of Zhu developed an enantioselective approach using hydrazoic acid as the azide source and [(salen)Al^{III}Me] as the catalyst [123]. A variety of



Scheme 45: $TMNS_3$ based Ugi reaction for peptidomimics containing a tetrazole.

aliphatic aldehydes and both aliphatic and aromatic isocyanides were tolerated in their approach and resulted in a library of tetrazoles **150** with excellent yields and high enantiomeric excesses (51–97%). For this enantioselectivity, the authors proposed a mechanism as shown in Scheme 46. In addition, from their study it became clear that the azide moiety is directly transferred from HN_3 and not from the Al-bound azide, since no product was formed in the absence of HN_3.

5-substituted tetrazoles could also be obtained from an Ugi 4-CR between aldehydes, amines and $TMSN_3$ and cleavable isocyanides as was described by Mayer et al. [124] Cleavable isocyanides consist of acidic protons at the β-position and can be obtained for example from β-amino acids. During the Ugi reaction, the tetrazole moiety is obtained from a sigmatropic rearrangement (Scheme 47). Subsequent base-treatment enables β-elimination, which is driven by mesomeric stabilization of the triazole ring, resulting in the desired 5-substituted tetrazoles **154** in moderate to good yields with three points of diversity.

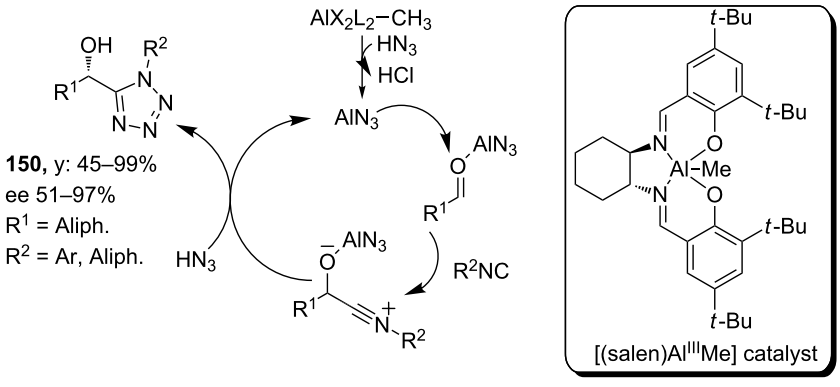
Alternatively, 5-substituted tetrazoles can be obtained via an Ugi–reaction between a (Rink) resin bound isocyanide, $TMSN_3$, several aldehydes and amines [125]. The final tetrazoles **156** were obtained from TFA cleavage (Scheme 48).

In a combined approach, Gunawan et al. also described such an Ugi-azide reaction to develop γ/δ/ε-lactam tetrazoles [126,127]. Depending on the keto-ester or acid used, an Ugi reaction with different primary amines, isocyanides and $TMSN_3$ followed by subsequent cyclization gave either γ-, δ- or ε-lactam tetrazoles (Scheme 49). Herein, cyclization for the γ-lactam derivatives was performed under acidic conditions, while CDI was used as cyclization agent in the δ-lactam formation and $SOCl_2$ was required for the ε-lactam tetrazoles. All multicomponent reactions were performed in MeOH at room temperature and the final tetrazoles **158a–c** were obtained in moderate to good yields.

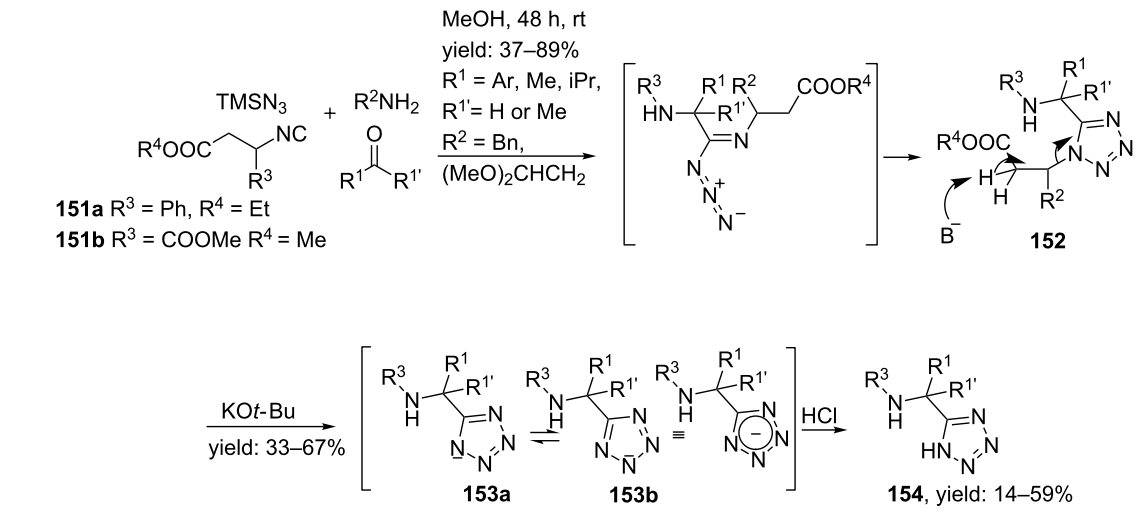
Six-membered ring constraints

Pipecolic acid

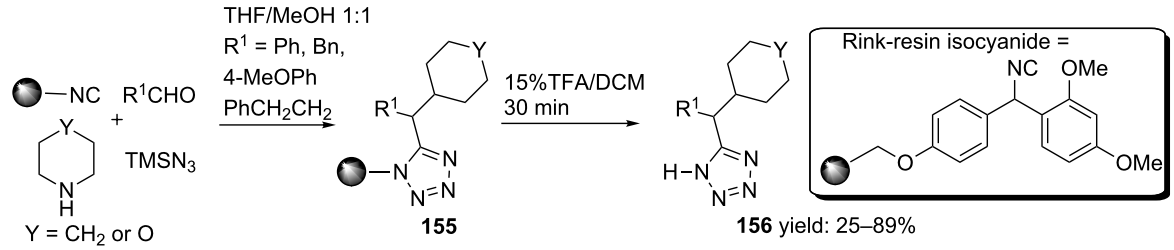
In the previous section we discussed some important conformational properties of proline derivatives playing an important role in controlling peptide and protein secondary structures.



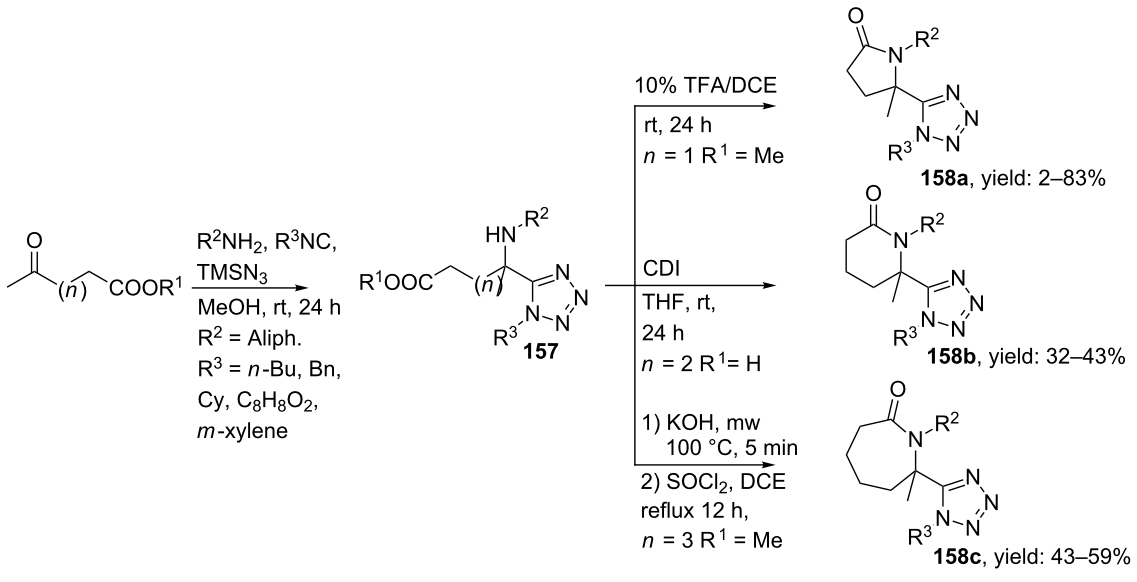
Scheme 46: Catalytic cycle of the enantioselective Passerini reaction towards tetrazole-based peptidomimetics.



Scheme 47: Tetrazole-based peptidomimetics via an Ugi reaction and a subsequent sigmatropic rearrangement.



Scheme 48: Resin-bound Ugi-approach towards tetrazole-based peptidomimetics.



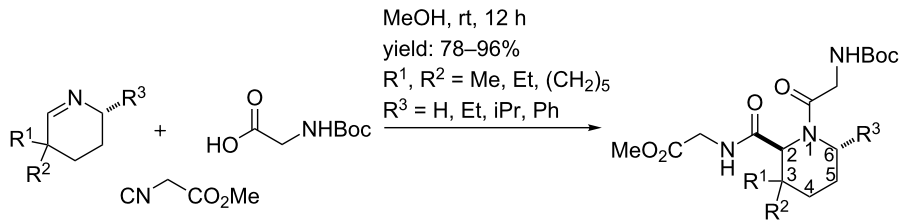
Scheme 49: Ugi/cyclization approach towards γ/δ/ε-lactam tetrazoles.

Replacement of the proline residue by its six-membered analogue, pipecolic acid, has provided valuable insights in peptide folding and bioactive conformations [128,129]. In particular, pipecolic acid derivatives often find their application as β-turn mimetics [130], and are therefore included in several pharmaceutical compounds such as antipsychotics, anticonvulsants, local anaesthetics or analgesics [131]. An interesting diastereoselective multicomponent approach towards such six-membered pipecolic acid-based analogues was described by Maison et al. [128] Although this work is closely related to earlier work of Dömling and Ugi [129], it is an interesting extension of the original protocol. Maison investigated 3- and 6-substituted pipecolic acid analogues **159a–b** via a reaction with achiral and chiral imines, methyl-2-isocyanoacetate and *N*-Boc-protected glycine (Scheme 50). It was shown that the products were obtained in excellent yields and in high diastereoselectivity when chiral imines were employed (**159b**, de >95%).

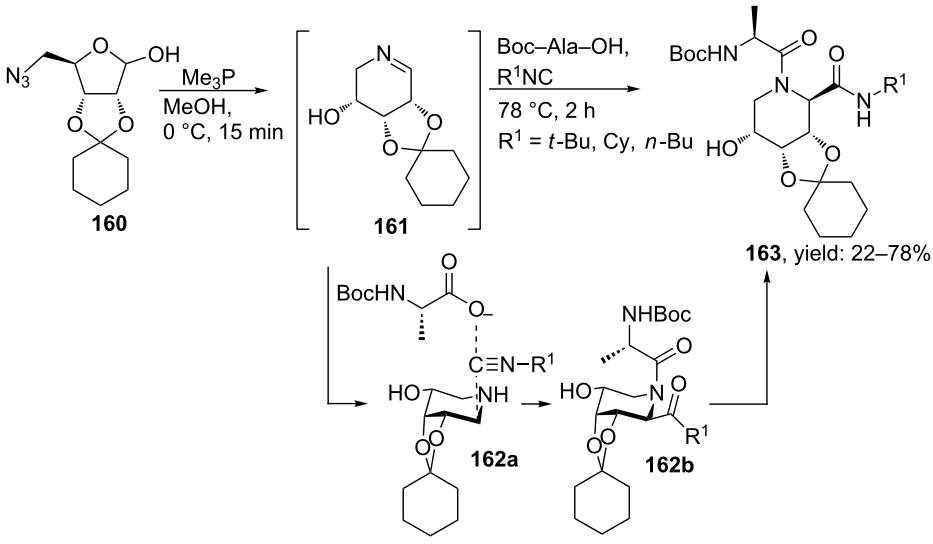
The group of van Boom and Overkleeft reported pipecolic amides via a Staudinger–Aza-Wittig/Ugi sequence (SAWU 3CR, Scheme 51) [132]. First the Staudinger reaction between an orthogonally protected carbohydrate-derived azido-acetal and trimethylphosphine yielded the necessary cyclic imine, which then was exposed to benzoic acid and different isocyanides. The resulting Ugi-bisamides **163** were obtained in moderate to good yields (22–78%), in which the more sterically demanding isocyanides gave the best results. In addition, the Ugi-products were obtained as single diastereomers with a *trans*-configuration. They argue that the isocyanide and acid substrates react at the least hindered side of the imine.

2,5-Diketopiperazines

Diketopiperazines (DKPs) are the smallest class of naturally occurring cyclic peptides containing a six-membered core ringsystem. Such DKPs were shown to possess several interesting medicinally relevant properties such as antifungal



Scheme 50: Ugi-3CR to pipecolic acid-based peptidomimetics.



Scheme 51: Staudinger–Aza-Wittig/Ugi-approach towards pipecolic acid peptidomimetics.

[133,134], antibacterial [135], and antitumor activity [136,137] but are also used to introduce for example a bitter taste in e.g. beer, cacao and coffee [138-140]. The DKPs occur in three different isomers, in which the position of one oxo-group is different at the piperazine-ring [26]. The 2,5-diketopiperazines are most relevant due to the structural similarity with peptides (Figure 1).

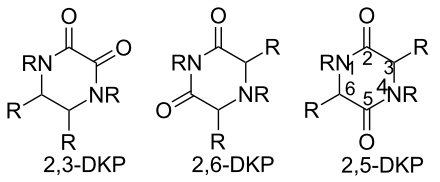


Figure 1: The three structural isomers of diketopiperazines. The 2,5-DKP isomer is most common.

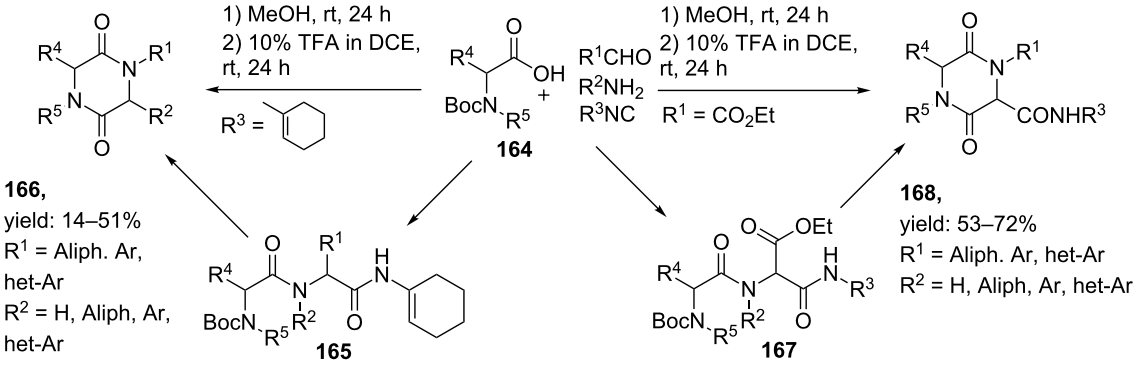
The DKP core shows properties for enhanced interaction with biological targets such as metabolic stability, conformational rigidity and the scaffold can both donate and accept hydrogen bonds. Furthermore, diversity can be introduced at four positions (N1, N4, C3 and C6). An important feature of DKPs is that they are able to induce secondary structures such as β-turns, β-hairpins in β-sheets and α-helices [141]. Therefore, DKPs are often used as peptidomimetic building blocks. A more detailed review of diketopiperazines is published by Borthwick and Piarulli [141,142].

Standard multicomponent reactions towards DKPs have the disadvantage that cyclization of the linear dipeptide unit is difficult. Instead of relatively easy ester cyclizations, the Ugi-product contains a C-terminal amide that is more difficult to cyclize. Therefore, Ugi MCRs towards diketopiperazines require subsequent post-condensation modifications such as Ugi-deprotection-cyclizations (UDC), Ugi-activation-cyclizations (UAC) or the combination of both (UDAC). Hulme et al. [143,144] was the first who reported a library of DKPs via a solution phase UDC approach as shown in Scheme 52. An Ugi reaction of Armstrong's convertible isocyanide, a variety of aldehydes and amines and bifunctional amino acid **164** in methanol afforded the corresponding linear Ugi-products **165** in good yields (72–92%). Subsequent *N*-Boc deprotection and activation of the isocyanide amide in acidic environment allowed cyclization to the diketopiperazines scaffolds **166** (overall 14–51%). As alternative, the authors reported an Ugi reaction with ethylglyoxalate as bifunctional component since in certain cases the convertible isocyanide performed sub-optimal in the cyclization [145]. Via this procedure dipeptide **167** was obtained, that after TFA- treatment in dichloroethane (DCE) resulted in the desired DKPs products **168** in good to excellent yields (53–72%).

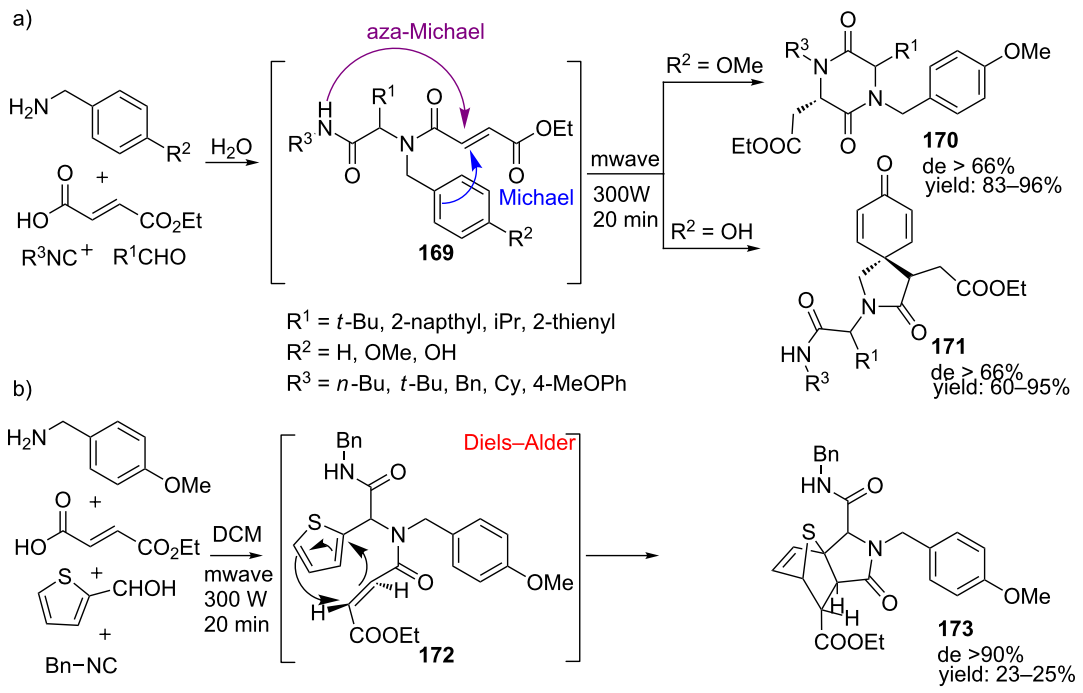
Solvent effects of the Ugi reaction under microwave irradiation were considered by Santra and Andreana (Scheme 53) [146]. Protic solvents such as water gave rise to either 2.5-diketopiperazines **170** via an aza-Micheal reaction or 2-azaspiro-[4,5]deca-6,9-diene-3,8-diones (**171**) via a 5-*exo*-Michael addition, whereas DCM as solvent induced an intramolecular thiophene Diels–Alder reaction yielding tricyclic lactam **173**.

In an alternative approach an Ugi-protocol employing a resin-bound carbonate-based convertible isocyanide **174** (CCI) was reported [147]. A wide variety of aldehydes, primary amines and carboxylic acids were tolerated resulting in a library of 80 different linear dipeptides. Cleavage from the carbonate resin with KO*t*-Bu afforded compound **176** which was converted to the methyl ester **177** using NaOMe (Scheme 54). Subsequent TFA-treatment resulted in the desired diketopiperazines **178**.

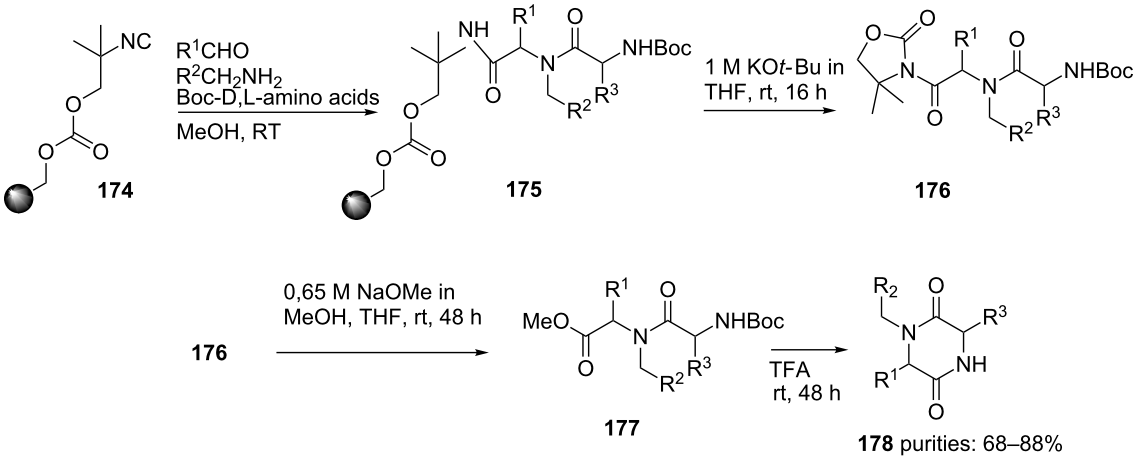
The group of Wessjohann reported a small library of DKPs using the acidic-labile convertible isocyanide **179** [148] in combination with readily available primary amines, aldehydes and *N*-Boc-protected amino acids [140]. It was shown that treat-



Scheme 52: UDC-approach to obtain 2,5-DKPs, either using Armstrong's isocyanide or via ethylglyoxalate.



Scheme 53: a) Ugi reaction in water gave either 2,5-DKP structures or spiro compounds. b) The Ugi reaction in DCM gave tricyclic lactams.

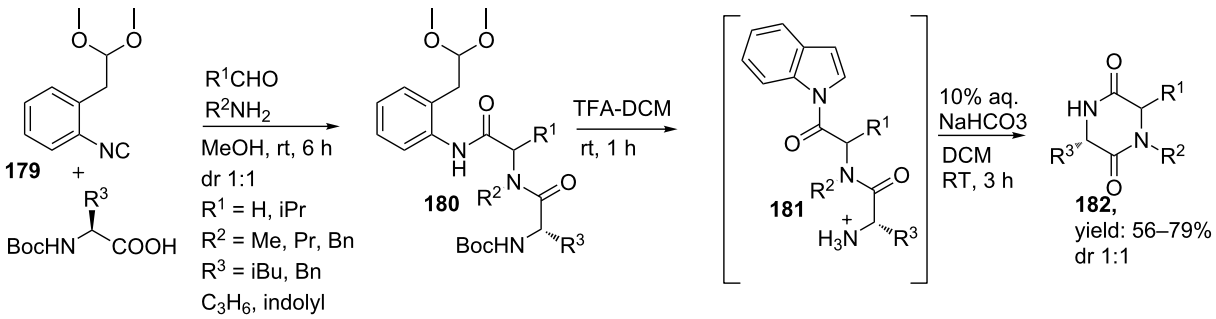


Scheme 54: Solid-phase approach towards diketopiperazines.

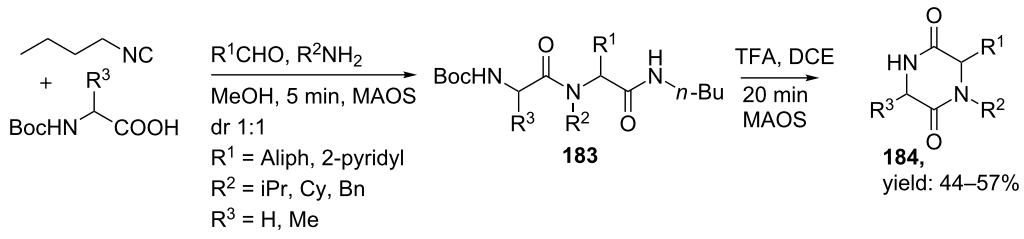
ment of the Ugi-adduct **180** with acid both cleaved the *N*-Boc-protecting group and activated the nitrile amide. Subsequent addition of a base induced cyclization and resulted in the DKP-scaffolds (**182,** Scheme 55). In total seven compounds were synthesized based on this UDAC-protocol with yields varying from 56 to 79%.

Recently, another UDC-based synthesis of DKP scaffolds using the cheaper and commercial available *n*-butylisocyanide as convertible component was reported [149]. The scaffolds were obtained in good yields in a 1:1 diastereomeric ratio. However, microwave heating was required to induce cyclization (Scheme 56).

In addition the UDC-approach was also used for a small library of orally active diketopiperazines active against the oxytocin receptor [150,151]. Rapid access towards these antagonists is highly desirable since inhibition of this receptor delays preterm labour in newborns [152]. The UDC-approach started with an Ugi reaction of aryl aldehydes, isonitriles, D-leucine methyl



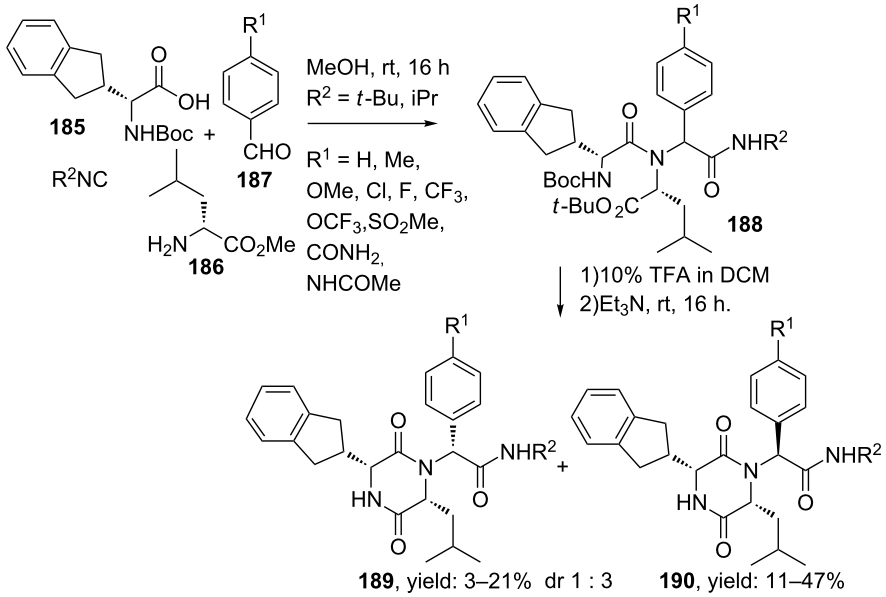
Scheme 55: UDAC-approach towards DKPs.



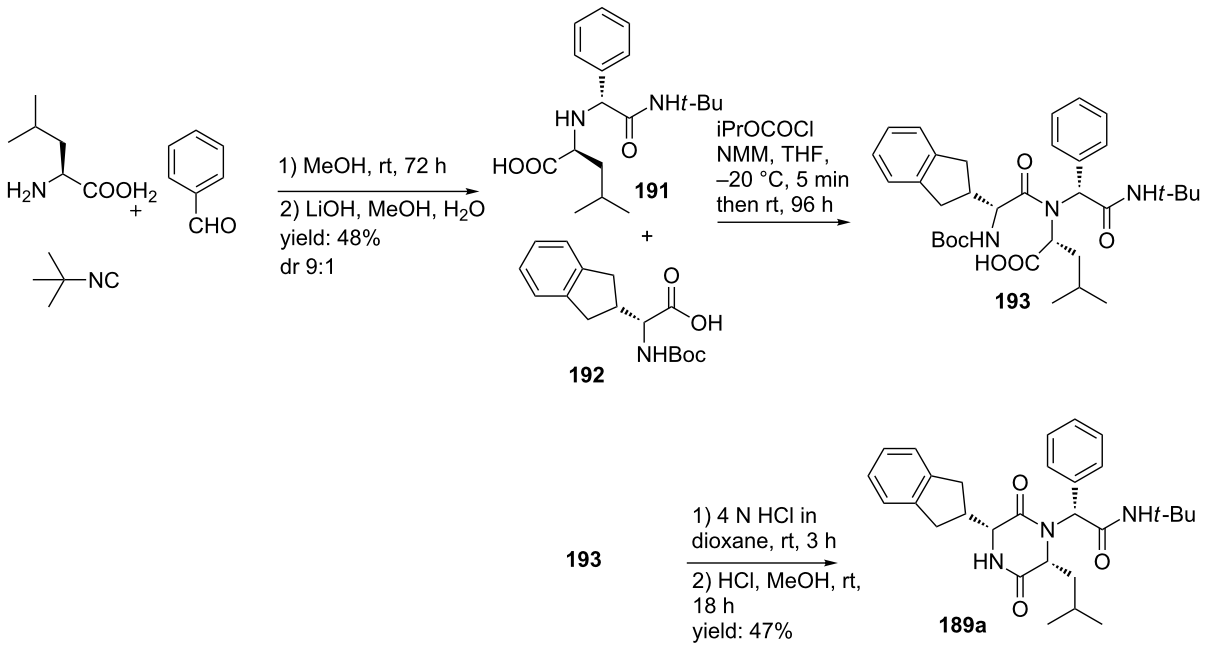
Scheme 56: The intermediate amide is activated as leaving group by acid and microwave assisted organic synthesis (MAOS).

ester and *N*-Boc-D-indanylglycine (derived from the benzhydrylimine of *N*-Boc-glycine, ee >99%) in methanol and afforded linear dipeptide **188** (Scheme 57). Subsequent treatment with TFA followed by base catalyzed cyclization provided both (3*R*,6*R*,7*R*)- and (3*R*,6*R*,7*S*)-isomers, in favour of the latter (dr 1:3). However, the minor *RRR*-isomers **189** showed to have the highest potency and were obtained in yields up to 21%.

In a variation, improved stereoselective reaction for the *RRR*-isomer **189** was observed. After an Ugi 4C-3-CR of benzalde-



Scheme 57: UDC-procedure towards active oxytocin inhibitors.



Scheme 58: An improved stereoselective MCR-approach towards the oxytocin inhibitor.

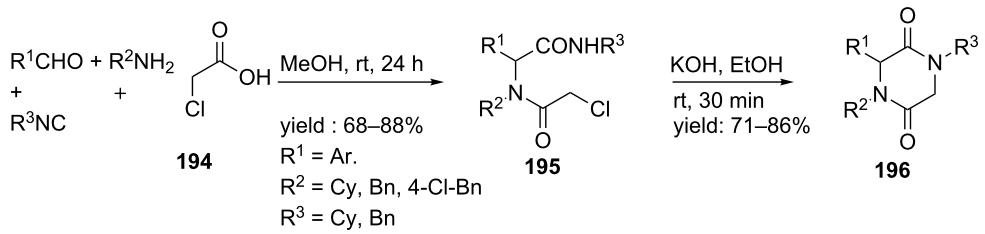
hyde, L-leucine, *t*-butylisonitrile in methanol followed by subsequent hydrolysis of the ester the *RS*-acid **191** was formed in 48% yield (Scheme 58) [153]. The acid was then combined with the in situ-formed anhydride derivative of (*R*)-Boc-indanyl glycine (**192**) and subsequent cyclization resulted in **187** in 47% yield. It is noteworthy that via this particular route, the configuration of the leucyl amide is inverted during the coupling reaction, whereas the chirality of phenyl glycine and the indanyl glycine are retained.

A less common approach was developed by Marcaccini and co-workers [154]. They obtained 2,5-DKPs in high yields by reacting 2-chloroacetic acid **194** with different aromatic amines, isocyanides and aldehydes in methanol followed by cyclization in ethanolic KOH under ultrasonic conditions (Scheme 59).

Bicyclic diketopiperazines

The development of bicyclic diketopiperazines has received special interest since these scaffolds force the molecule into a similar conformation as the type I β-turn in native peptides [142,155]. Therefore, β-turn mimetics based on this bicyclic core can reveal important information about the biologically active conformation of the native peptide [69,155]. β-Turns are characterized as any tetrapeptide sequence which is stabilized by an intramolecular H-bond between residue *i* and *i*+3 forming a pseudo-ten-membered ring [10,156]. The distance between the α-carbons of these two residues is ≤ 7 Å (Figure 2) [157].

There are two different types of β-turn mimetics possible, external and internal mimics [159]. The former includes turn-inducing-scaffolds that in most cases replace the *i*+1 and *i*+2



Scheme 59: The less common Ugi reaction towards DKPs, involving a S_n2-substitution.

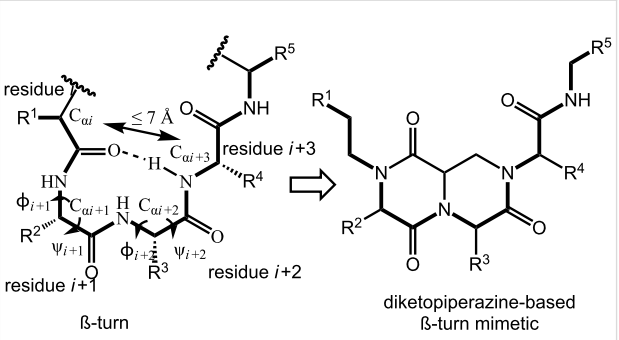
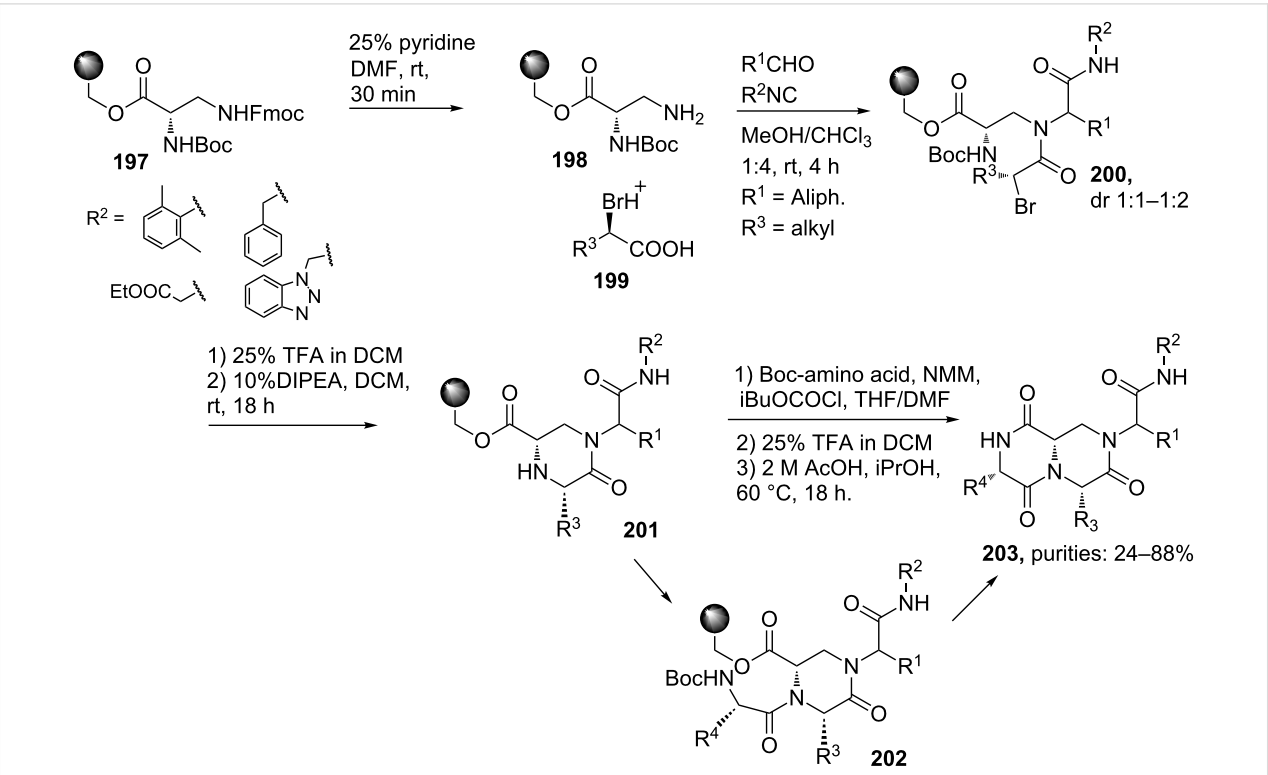


Figure 2: Spatial similarities between a natural β-turn conformation and a DKP based β-turn mimetic [158].

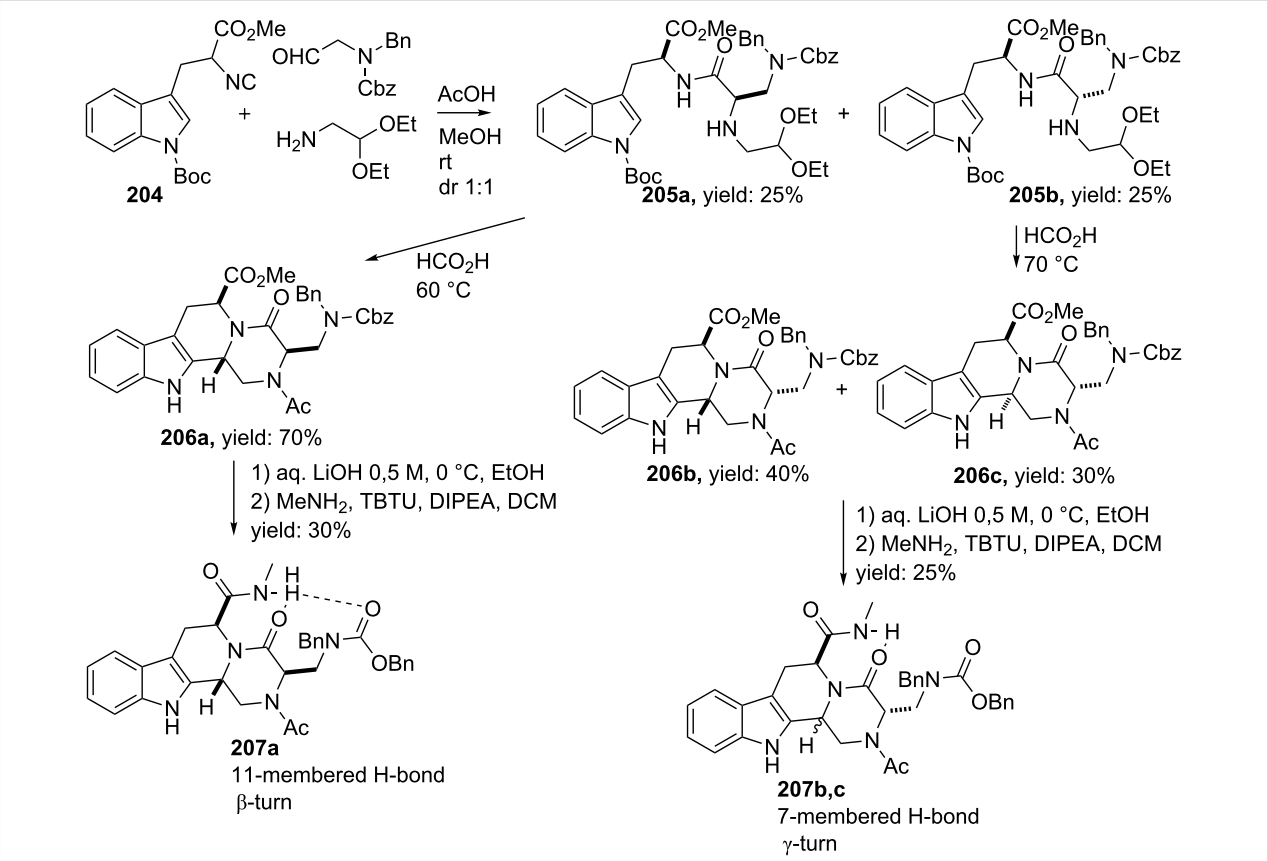
residues and have their rigidifying moiety lying outside the hydrogen bonded ring. Examples are lactams and dihydropyridimidinones .In contrast, internal mimics have their rigidifying part lying in the pseudo-ten-membered ring. Examples are bicyclic scaffolds such as diketopiperazines. A multicomponent approach to these latter scaffolds is described by Golebiowski et al. (Scheme 60) [156,160]. Herein, the Ugi reaction involving resin-bound amine **198** and an excess of *R*-(+)-2-bromoalkyl acid **199**, isocyanide and aldehyde (5 equiv) afforded the linear dipeptide **200** that after acidic Boc-removal and base-catalyzed S_n2-cyclization was converted to the monocyclic ketopiperazine **201**. The authors coupled this modified Ugi-adduct to different *N*-Boc-amino acids, in which TFA treatment and subsequent cyclization in acetic acid furnished the bicyclic diketopiperazines **203**. During the Ugi reaction, inversion of configuration was observed at the R^3-position (from bromine displacement by a S_n2-mechanism), whereas the stereochemistry at the central bridging carbon originates from the chirality of diaminopropionic acid, derived from either L- or D-asparagine. The scope of the Ugi reaction includes several aliphatic and aromatic aldehydes, in which the former gave higher conversions. However, only a limited set of isocyanides were tolerated in this approach.

Other bicyclic derivatives

As an alternative to (bicyclic) DKPs, the group of Silvani reported a tetracyclic tetrahydro-β-carboline (THBC)-based turn-mimic via an Ugi/Pictet–Spengler combination [16]. The Ugi reaction provided two diastereomers (**205a**,**b**, dr 1:1), both in 25% yield by reacting *N*-diprotected-2-aminoacetaldehyde (used for the first time in an Ugi-like reaction), *N*-protected tryptophan derived isocyanide **204**, aminoacetaldehyde diethyl acetal and acetic acid (Scheme 61). The subsequent Pictet–Spengler reaction provided three steroisomers **206a**,**c**. To investigate the turn-properties, the authors converted the products to the corresponding carboxamide *N*-acetyl analogues via a



Scheme 60: Ugi-based syntheses of bicyclic DKPs. The amine component is derived from a coupling between (*R*)-*N*-Boc-α-*N*-Fmoc-*L*-diaminopropionic acid and Merrifield's hydroxymethyl resin under Mitsunobu conditions, followed by a standard Fmoc deprotection.



Scheme 61: Ugi-based synthesis of β-turn and γ-turn mimetics.

hydrolysis and subsequent condensation with $MeNH_2$. Both NMR and modelling studies confirmed the formation of a β-turn like conformation for the *cis*-isomer **207a** and γ-turns for the *trans*-isomers **207b**,**c**.

3,4-Dihydropyridin-2-ones

Another interesting class of 6-membered heterocyclic rings that can be used in peptidomimetics is the 3,4-dihydropyridin-2-one. Conformationally, dihydropyridin-2-ones can be compared to dihydropyridines (DHP), which in turn have shown potential as calcium channel modulators [161,162]. Furthermore, these scaffolds have structural similarities with Freidinger lactams (Figure 3) [161,162].

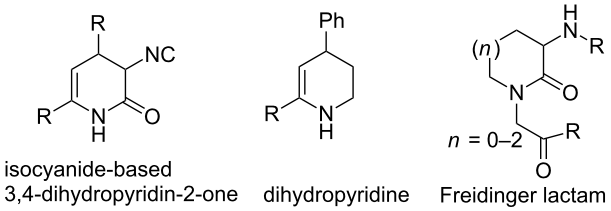
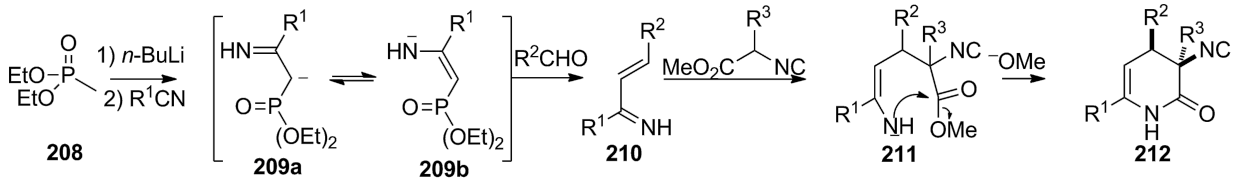


Figure 3: Isocyanide substituted 3,4-dihydropyridin-2-ones, dihydropyridines and the Freidinger lactams. Bio-active calcium channel modulators, the dihydropyridines should contain an axial phenyl substituent at the C4-center adopting a boat conformation.

In 2007, our group reported the synthesis of 3,4-dihydropyridin-2-ones via a double MCR approach [163,164]. The first MCR provided the 3,4-dihydropyridin-2-one core by reacting phosphonate **208** with various nitriles, aldehydes and α-aryl isocyanoacetates. This particular 4-CR involves a Horner–Wadsworth–Emmons (HWE) reaction, in which first the phosphonate is deprotonated [125]. Subsequent addition to the nitrile-component resulted in the ketimine intermediate **209a**,**b** which is more nucleophilic at carbon than at nitrogen and reacts with the aldehyde, generating an in situ 1-azadiene intermediate **210**. A subsequent Michael attack by the isocyanide α-carbon atom, followed by a lactonization resulted in the core structure containing an isocyanide moiety (**212,** Scheme 62).

Variation of all substrates except the phosphonate proved the possible formation of the isonitrile-functionalized 3,4-dihydropyridin-2-ones in good yields, in which aromatic isocyanoacetates exclusively gave the *cis*-diastereomer. In addition, aliphatic isocyanoacetates only show a preference for the *cis*-



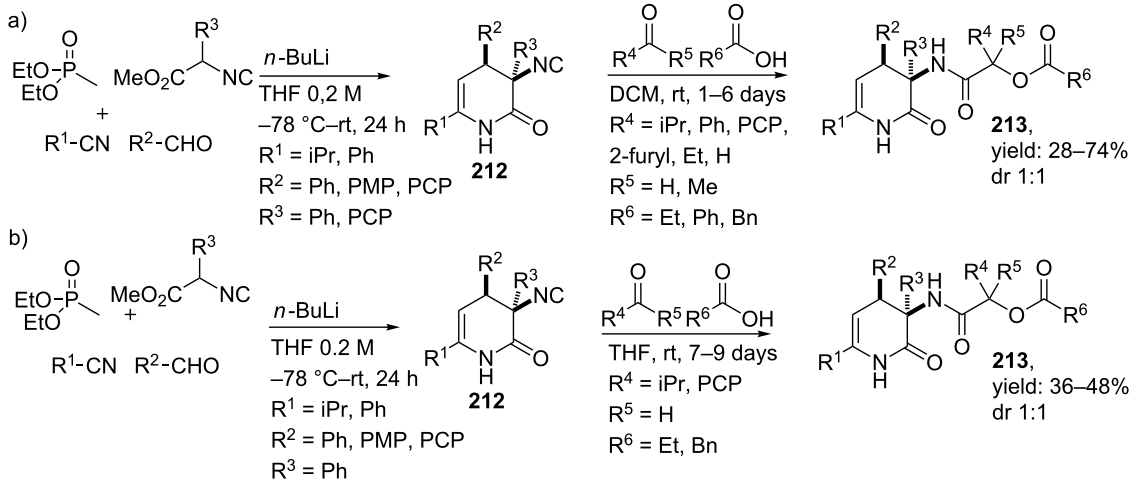
Scheme 62: The mechanism of the 4-CR towards 3,4-dihydropyridine-2-ones **212**.

diastereomer if the cyclization step was performed at higher temperatures [12]. We argued that epimerization (of the C4-center) to the more thermodynamically stable isomer was the reason for this. More interestingly, the isocyanide moiety did not react and was left intact during the initial 1-azadiene-based multicomponent reaction. This opened the way for an additional Passerini 3-CR (Scheme 63), in which a wide variety of aldehydes/ketones and acids successfully reacted with the isocyanide to obtain depsipeptides **213** in overall yields of 28–74% (dr 1:1). In a variation, we combined both MCRs to a one-pot 6-CR, and obtained the depsipeptides in comparable yields as the two-step procedure.

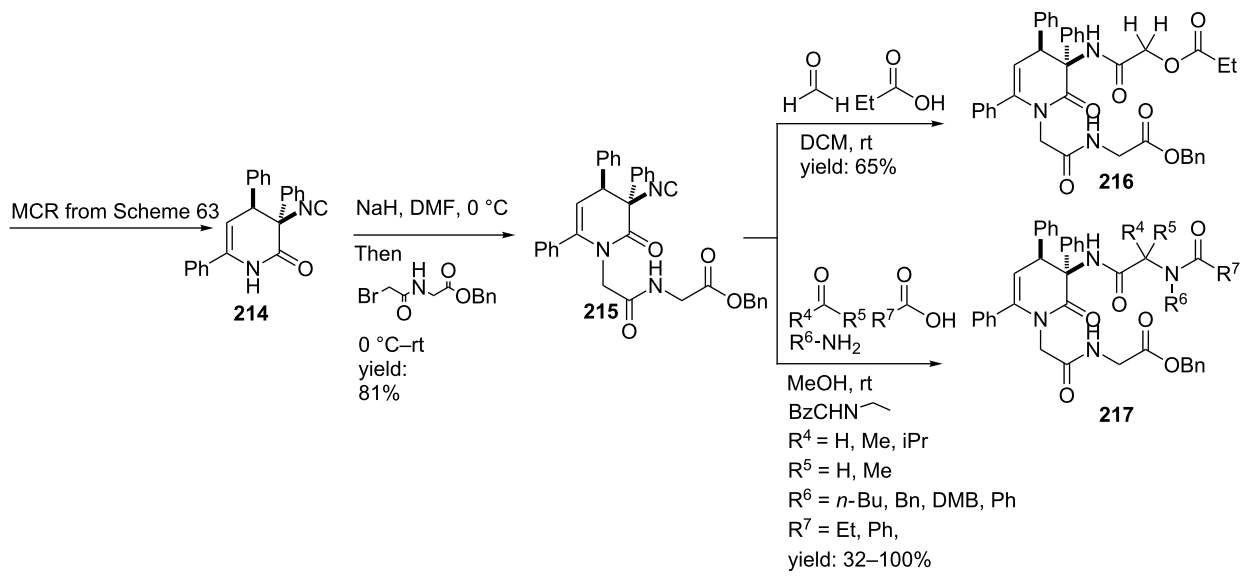
Moreover, the structural similarities of C3-substituted 3,4-dihydropyridin-2-ones with Freidinger lactams inspired our group to investigate possible turn properties of this restricted core element [10]. Since modelling studies confirmed that these scaffolds can adopt type IV β-turn structures, we developed constrained tetra/penta (depsi) peptides via a quick MCR–alkylation–MCR approach. It is noteworthy that both the Passerini and the Ugi reaction could be applied as second MCR, providing the cyclic constrained peptide-like structures in good yields (Scheme 64). As an extension, we also incorporated *N*-protected amino acids as acid input in order to provide penta(depsi)peptides **216** and **217**. Unfortunately, based on spectroscopic analyzes (X-ray crystallography and ^{1}H NMR) none of these penta or tetra mimics adopted a true β-turn conformation. Nevertheless, these scaffolds consist of rigidifying properties and can be used as conformationally constrained building blocks in the design of peptidomimetics.

Triazines

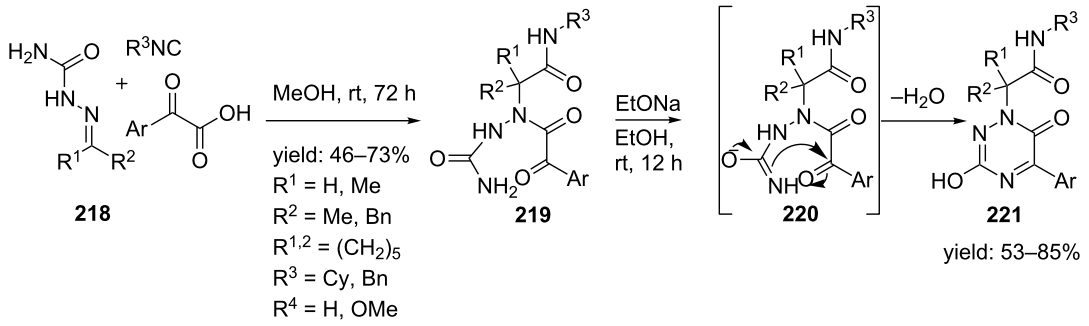
Aza- and urea-based peptidomimetics have shown to be useful peptide isosteres in several therapeutic applications [166-168]. In addition, their cyclic constraints such as 1,2,4-triazines can induce peptide-turns and according to literature 1,2,4-triazines are active as selective herbicides [169], HIV-protease inhibitors [170] and anti-cancer agents [171-173]. However, multicomponent reactions towards them are scarce. The group of Torroba and Marcacinni reported an interesting Ugi 3-CR/cyclization approach towards pseudopeptidic 6-oxo-[1,2,4]-triazines (Scheme 65) [174]. The linear Ugi-adducts **219** were obtained from a reaction between phenylglyoxalic acid, several isocyanides and semicarbazone **218** as imine component, in



Scheme 63: a) Multiple MCR-approach to provide DHP-peptidomimetic in two-steps. b) A one-pot 6-CR providing the same compounds.



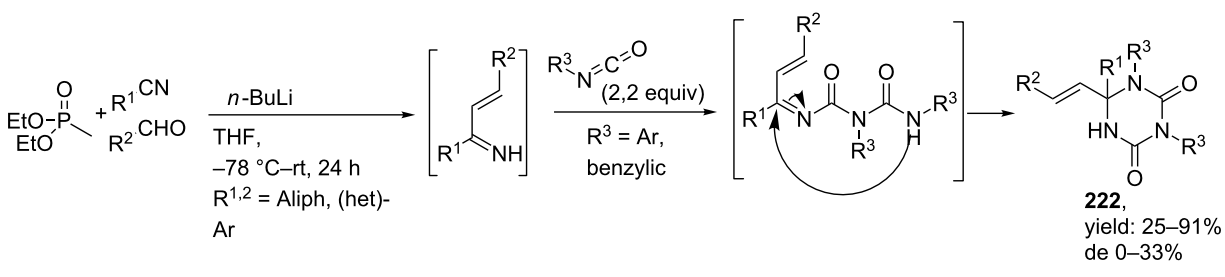
Scheme 64: The MCR–alkylation–MCR procedure to obtain either tetrapeptoids or depsipeptides.



Scheme 65: U-3CR/cyclization employing semicarbazone as imine component gave triazine based peptidomimetics.

which the incorporation of the latter was not reported before. Addition of sodium ethoxide in ethanol promoted cyclization and afforded the triazines **221** in good overall yields.

Our group published the synthesis of triazinane diones as novel cyclic urea derivatives via a 4-CR-alkylation-IMCR sequence [165,175-177]. The 4-CR involves the HWE reaction described above between a phosphonate, nitrile and aldehyde, in which the in situ-formed 1-azadiene is trapped by an isocyanate (instead of an isocyanoacetate) to afford the triazinane dione core (**222**, Scheme 66). For the scope of this reaction a wide range of aliphatic and (hetero)aromatic nitriles and aldehydes and several benzylic and aromatic isocyanates were tolerated, whereas for the phosphonate input only diethyl methyl- or

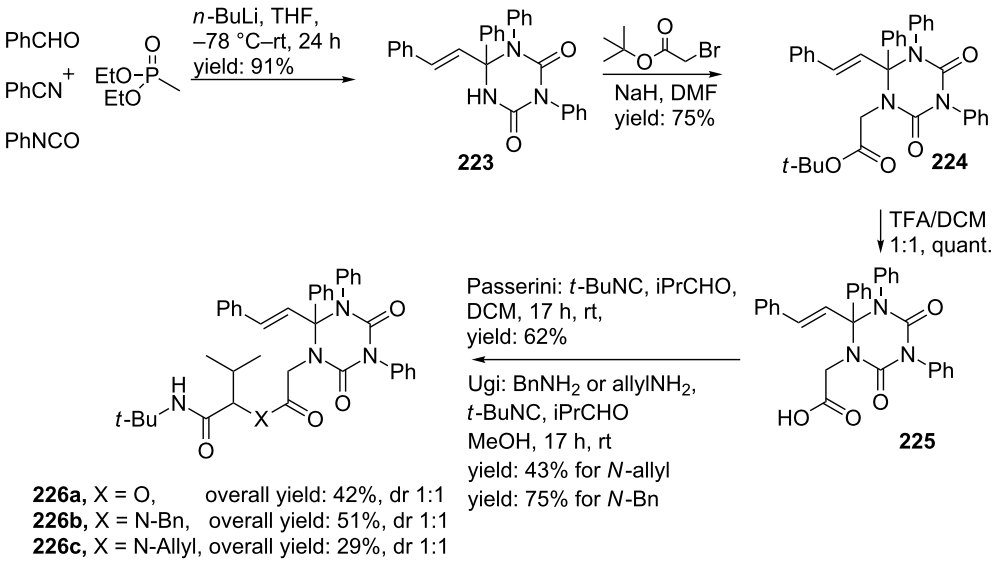


Scheme 66: 4CR towards triazinane-diones.

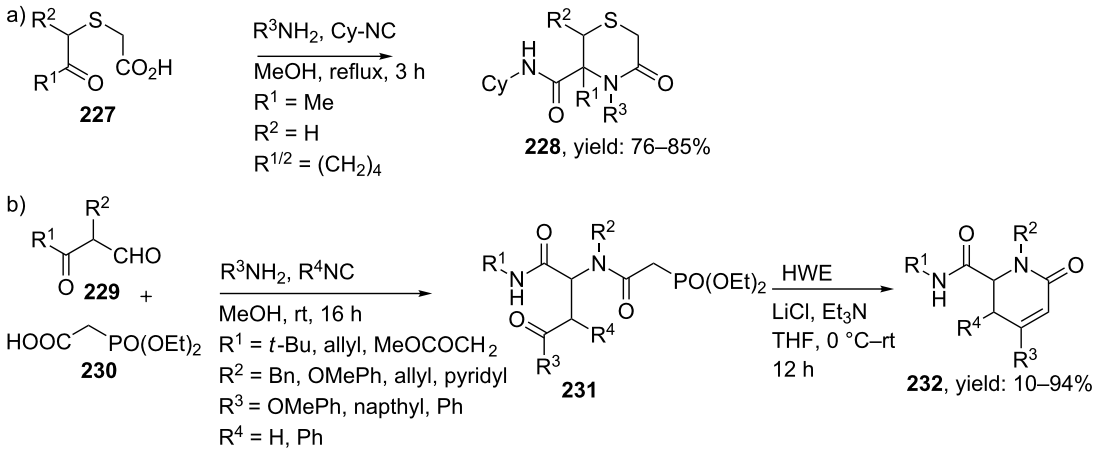
ethylphosphonate were compatible. From the results it became clear, that addition of 2,2 equivalents of the isocyanate was favourable for the reaction and increased the yield of **223** up to 91%. A subsequent *N*-alkylation with *tert*-butyl 2-bromoacetate followed by deprotection of the *tert*-butyl group furnished the carboxylic acid **225** which could further react in an additional Ugi or Passerini reaction (Scheme 67). The Passerini reaction was performed with isobutyraldehyde, acid **225** and *tert*-butyl isocyanide to provide the depsipeptide-like product **226a** in 62% yield, whereas the Ugi reaction was employed with the same substrates and benzyl– or allyl amine as fourth component to provide two peptidoyl triazinane diones **226b,c** in 43% and 75% yield for the last step, respectively [176].

Other 6-membered ring constraints

In addition to a range of MCR-based protocols available for the above discussed six-membered ring constraints, a few other types of (hetero) cyclic peptidomimetics containing a six membered ring have been reported. Among them, the thiomorpholin-3-one heterocycle is used in several therapeutic applications [178,179] and an Ugi-based MCR was reported by the group of Marcaccini (Scheme 68) [180]. In this work, monocyclic and bicyclic 5-oxothiomorpholine-3-carboxamides **228** were obtained in 76–85% yields (dr 1:1) by reacting bifunctional oxoacids **227**, benzylamines and cyclohexyl isocyanides in methanol. Pyrrolidone-constrained peptidomimetics can be obtained via an Ugi/HWE sequence as describe by Dömling et



Scheme 67: The MCR–alkylation–IMCR-sequence described by our group towards triazinane dione-based peptidomimetics.



Scheme 68: Ugi-4CR approaches followed by a cyclization to thiomorpholin-ones (a) and pyrrolidines (b).

al. [181]. They obtained the linear Ugi-products **231** by reacting α-keto aldehydes **229**, phosphono acetic acid **230** and a variety of isocyanides and primary amines in methanol. The following HWE reaction was performed under basic conditions and furnished the 6-oxo-1,2,3,6-tetrahydro-pyridine-2-carboxylic acid amides **232** in modest to excellent yields (10–94%).

Seven membered ring constraints

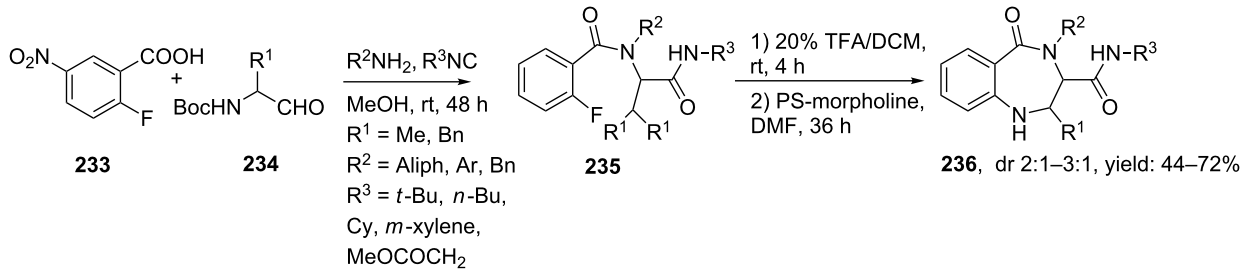
Benzodiazepines

Benzodiazepines (BDPs) represent an important class of small seven membered ring peptidomimetics. These BDPs demonstrate numerous therapeutic applications ranging from protease inhibitors against HIV [182] and malaria [183,184] to drugs with anticancer [185-187] or psychoactive properties [188]. In addition, the diazepinone ring also possesses turn and α-helix inducing properties 8 [189-191]. Multicomponent approaches towards BDPs usually comprise an Ugi reaction along with several cyclization strategies. Hulme and co-workers reported an UDC strategy involving a S_nAr cyclization (Scheme 69) [192]. The Ugi products herein were obtained in good yields by reacting 2-fluoro-5-nitrobenzoic acid **233** with *N*-Boc-α-amino aldehydes **234** and several isocyanides and amines. Subsequent TFA treatment and cyclization induced by a proton scavenger revealed a library of 80 BDPs (**236**, 44–72%, dr 2:1–3:1).

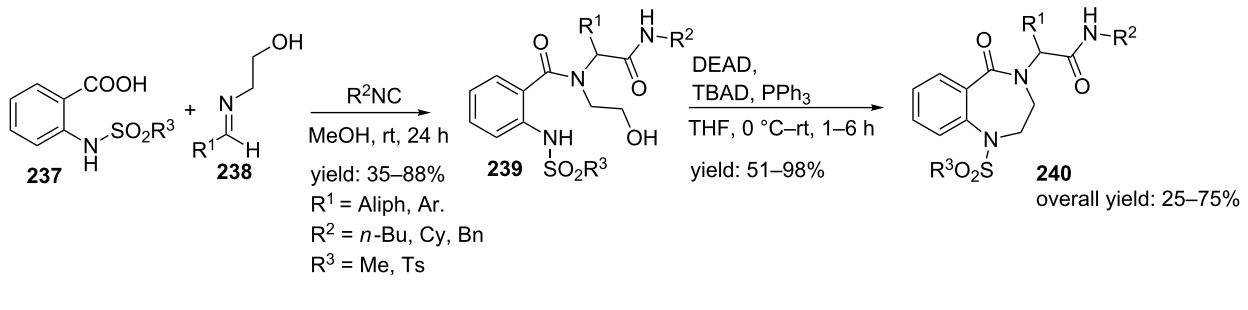
Banfi et al. published an Ugi/Mitsunobu combination towards sulfonamide-based BDPs, **240** which makes use of imines **238**, isocyanides and acid **237** [193]. Herein, the imines were obtained from aldehydes and ethanolamine. The subsequent cyclization using standard Mitsunobu conditions furnished the BDPs in good overall yields (Scheme 70).

A microwave-mediated UDAC-procedure employing convertible isocyanides was also reported (Scheme 71) [194]. The usually non-convertible cyclohexylamino- and methylacetylamino isocyanides proved in this case ideally suited as convertible substrates. The Ugi-products were obtained by combining these isocyanides with a variety of aromatic aldehydes, bifunctional acids and both aliphatic and benzylic amines. Subsequent *N*-Boc-deprotection and microwave-assisted cyclization furnished a small library of BDPs (**242**, yields 31–97%). In addition, it was also shown that fluoro-benzaldehydes allow further scaffold derivatization via a subsequent Suzuki coupling.

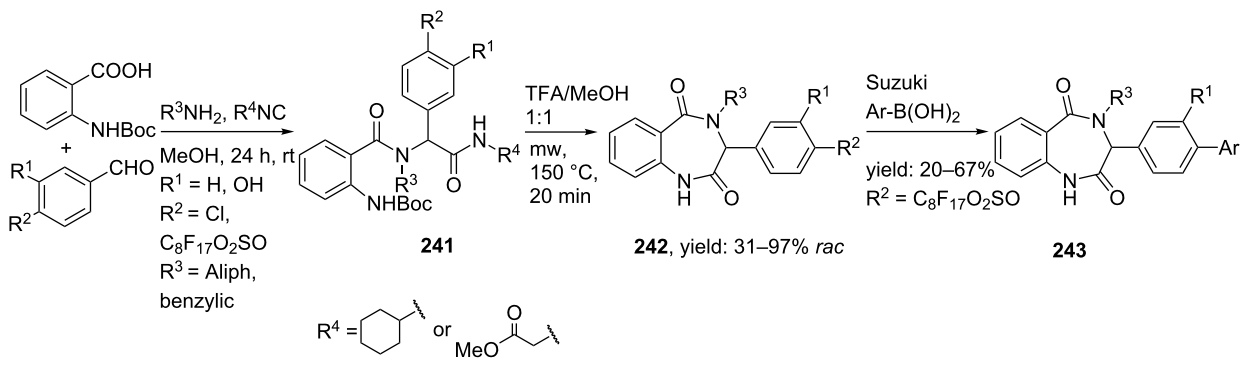
In a variation, Hulme et al. developed a similar approach utilizing two internal nucleophiles towards tetracyclic BDPs (Scheme 72) [195]. Deprotection of the Ugi-products activated the nitrile functionality and unmasked both amino-groups, in which microwave irradiation allowed a sequential double



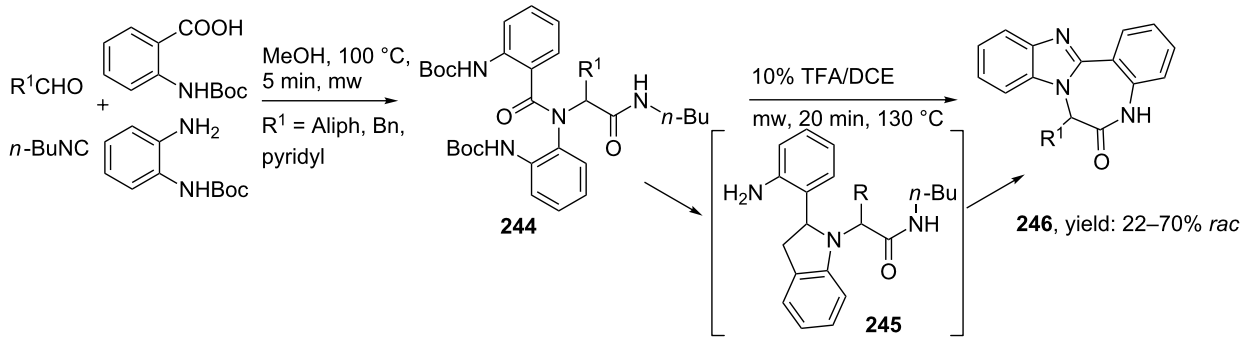
Scheme 69: UDC-approach for benzodiazepinones.



Scheme 70: Ugi/Mitsunobu sequence to BDPs.



Scheme 71: A UDAC-approach to BDPs with convertible isocyanides. The corresponding amide is cleaved by microwave heating, thereby providing the 7-membered ring.

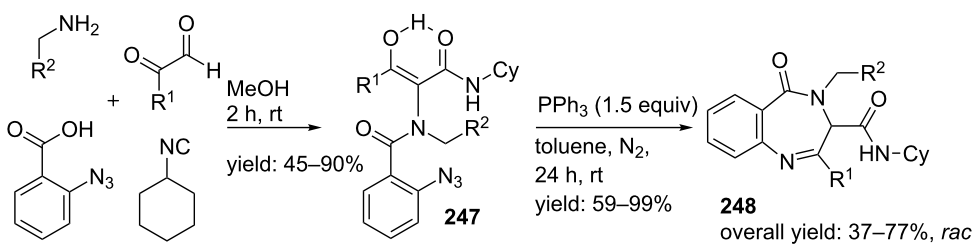


Scheme 72: microwave assisted post condensation Ugi reaction.

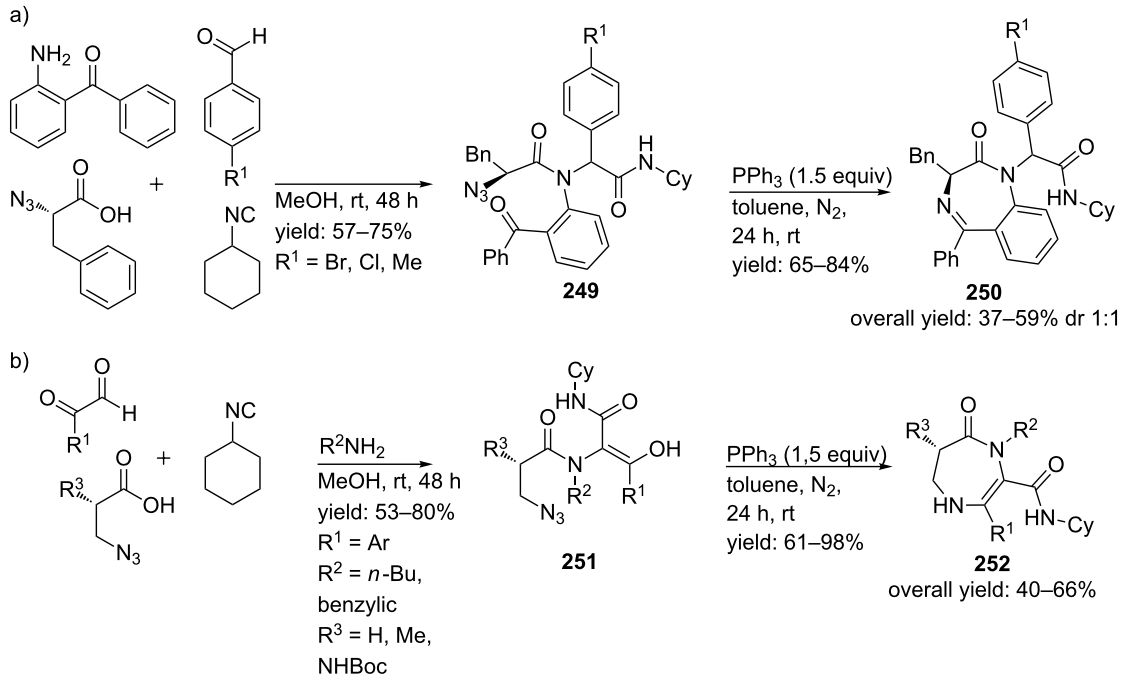
cyclization to the tetracyclic benzimidazole-benzodiazepines **246**. During these cyclizations the authors observed that the order of cyclization was in favour of the benzimidazole, nonetheless after 20 minutes of irradiation all the intermediates were converted to the tetracyclic scaffolds in modest to high yields (22–70%).

β-Turn mimetics of type **248** were developed by the groups of Marcaccini and Torroba [196] via an Ugi/Staudinger–Aza-Wittig sequence (Scheme 73). The Ugi reaction of arylglyoxals, *para*-substituted benzylamines, cyclohexyl isocyanide, and 2-azidobenzoic acid provided the linear dipeptides **247**. Subsequent addition of triphenylphopshine induced a Staudinger–aza-Wittig cyclization and furnished the BDPs **248** in 37–77% overall yields. From spectroscopic studies it became clear that these conformationally restricted peptidomimetics adopt type I, I', II and II' β-turn conformations.

In 2010, the same groups performed the Ugi reaction with (*S*)-3-phenyl-2-azidopropionic acid (instead of 2-azidobenzoic acid) in order to control stereochemistry at the position of the aryl glycine moiety (Scheme 74) [197]. However, no stereoinduc-



Scheme 73: Benzodiazepinones synthesized via the post-condensation Ugi/ Staudinger–Aza-Wittig cyclization.

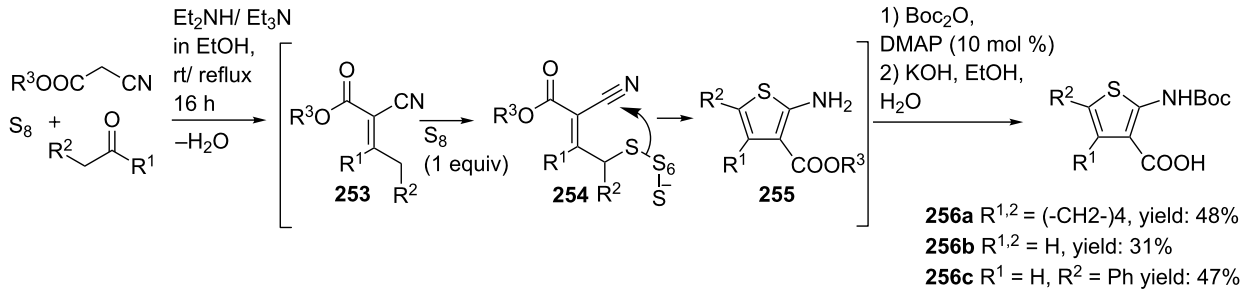


Scheme 74: Two Ugi/cyclization approaches utilizing chiral carboxylic acids. Reaction (a) provided the products in a diastereomeric mixture of 1:1, whereas reaction (b) yielded the products as single enantiomers.

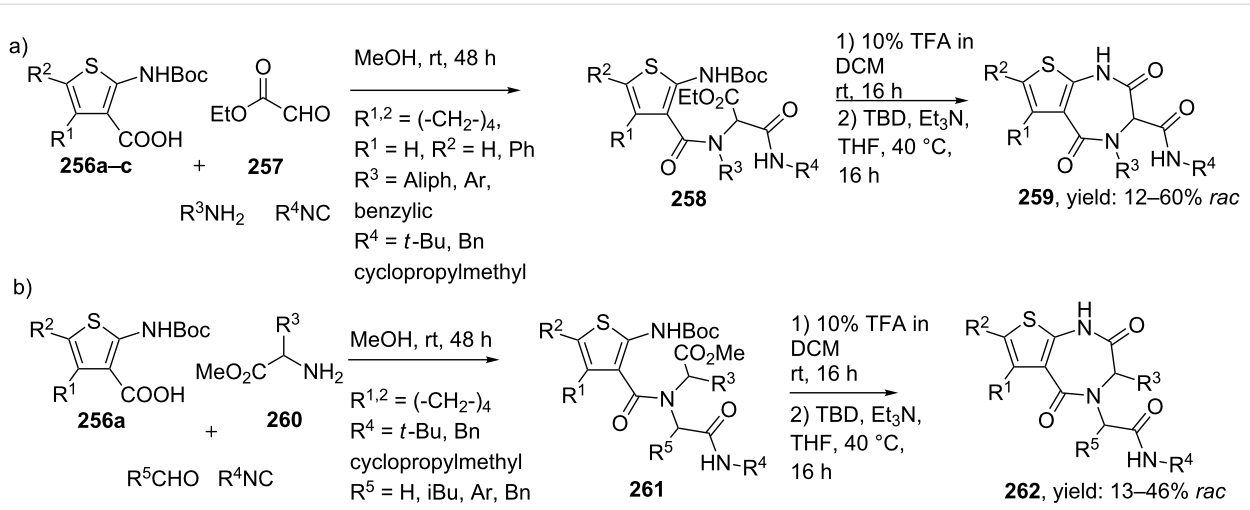
tion was observed at this stereocenter and the BDPs **250** were obtained as mixtures of diastereomers (dr 1:1, 37–59%). In the same report, they described an enantioselective Ugi/cyclization reaction in which monocyclic diazepinones **252** were obtained as single *S*-enantiomers (40–66%). In this approach the Ugi reaction was performed with optically pure (*S*)-3-azidopropionic acids and 2-aminobenzophenone (Scheme 74).

Other seven membered ring derivatives

Dömling and co-workers reported a convenient route towards 1,4-thienodiazepine-2,5-diones [198]. Thiophenes can be synthesized via the Gewald 3-CR, providing 2-aminothiophenes, which in turn have shown to be suitable derivatives of anthranilic acids (Scheme 75) [199,200]. This inspired the researchers to combine the Gewald 3-CR with a sequential Ugi-deprotection–cyclization in order to obtain 1,4-thienodiazepine-2,5-diones. The Ugi reaction of **256**, **257** and a variety of amines and isocyanides gave access to the linear dipeptides **258**. Subsequent TFA-deprotection and cyclization catalyzed by the strong guanidine base triazabicyclodecene (TBD) afforded the 1,4-thienodiazepine-2,5-diones **259** in moderate to excellent overall yields (12–60%, Scheme 76). Additional modelling studies showed that these mimics consist of α-helix-inducing properties and that they can be used as potent tumor suppressors. In a variation, the authors shifted the (*exo*-) peptide chain



Scheme 75: The mechanism of the Gewald-3CR includes three base-catalysed steps involving first a Knoevnagel–Cope condensation between α-methylene carbonyls and α-activated acetonitriles, second an addition of sulfur to the α-β-unsaturated intermediate and third a cyclization towards the 2-aminothiophene.



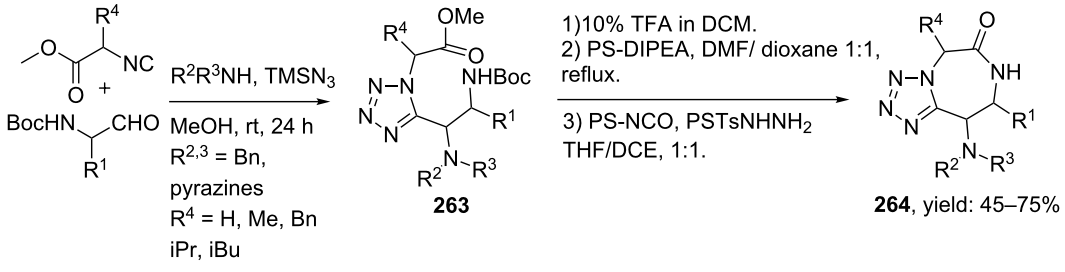
Scheme 76: Two structural 1,4-thienodiazepine-2,5-dione isomers by U-4CR/cyclization.

from carbon to the neighbouring nitrogen by performing the Ugi reaction with different amino esters as amine source (Scheme 76) [201].

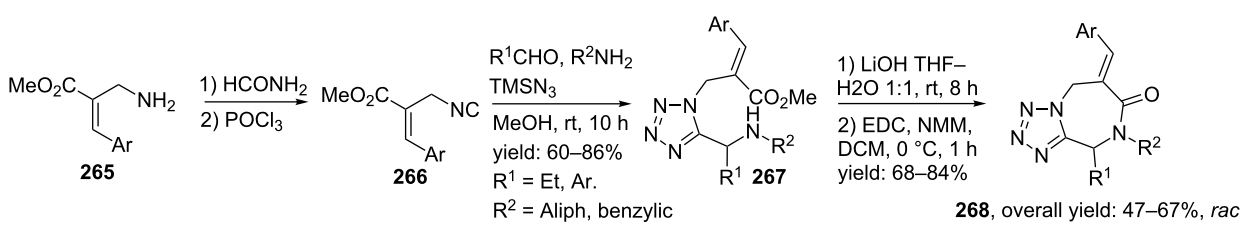
Tetrazole-based diazepinones were obtained via a $TMSN_3$-modified UDC protocol reported by Hulme and co-workers (Scheme 77) [202]. A variety of secondary amines, *N*-Boc-amino-aldehydes, and substituted methylisocyanoacetates were tolerated and provided the tetrazoles **263** in good yields. TFA treatment and the addition of a proton scavenger allowed cyclization and furnished the tetrazole-diazepine-ones **264** in 45–75% yield.

In a variation, Nayak and Batra reported an Ugi/hydrolysis/coupling sequence starting from allyl isonitrile **266** that was synthesized from its corresponding primary allyl amine **265**, which in turn was derived from Baylis–Hillsman acrylates [203]. The tetrazole-based Ugi adducts **267** were obtained in high to excellent yields (60–86%), that via subsequent ester-hydrolysis and coupling with EDC and NMM resulted in the tetrazole-based BDPs **268** in overall yields of 47–67% (Scheme 78).

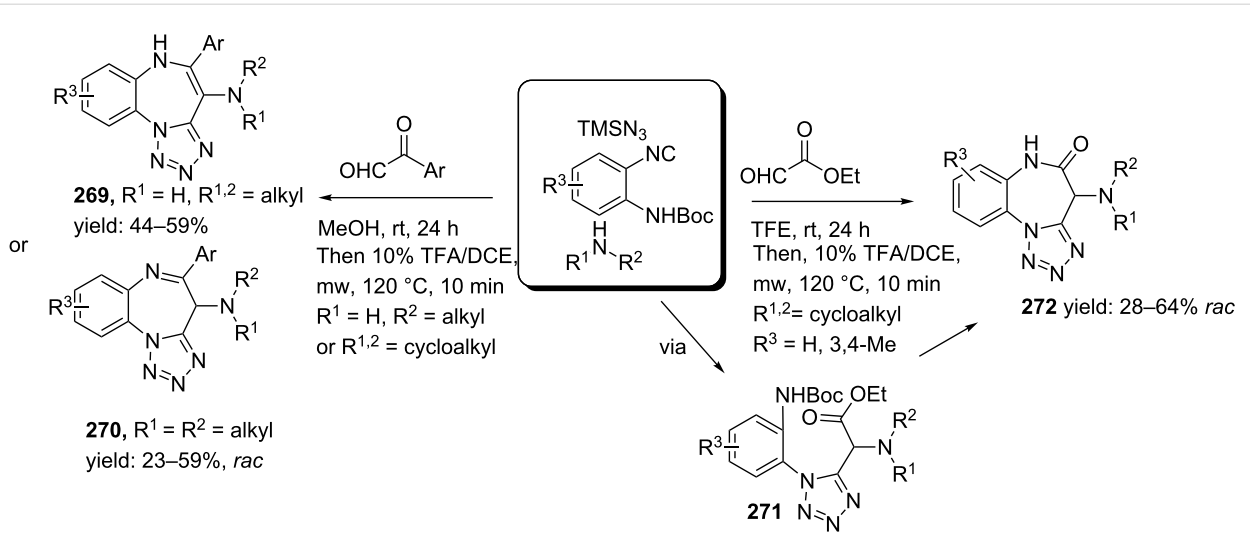
Tricyclic tetrazole-fused BDP derivatives were reported as well (Scheme 79) [204]. In this case an Ugi-Azide reaction using



Scheme 77: Tetrazole-based diazepinones by UDC-procedure.



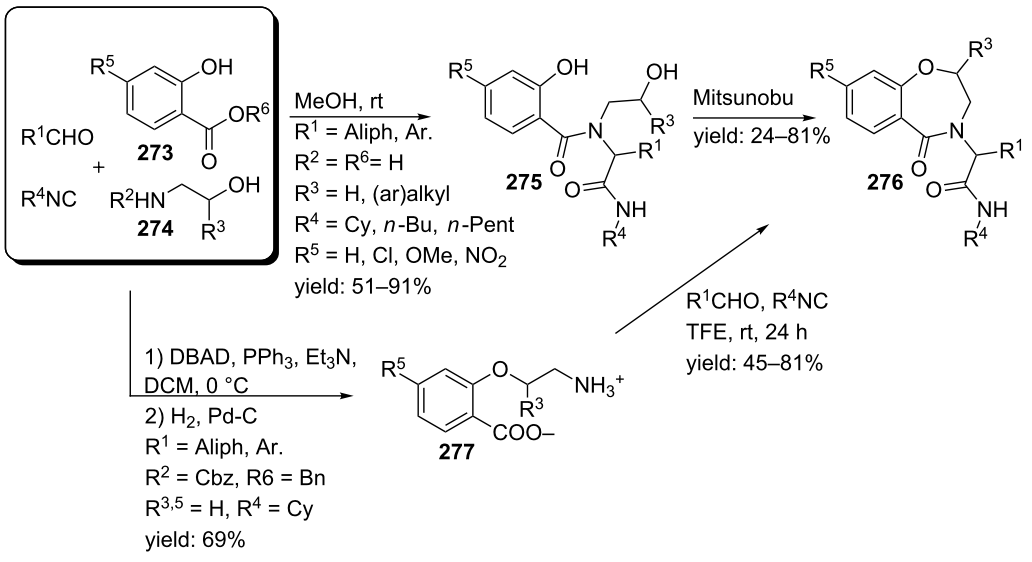
Scheme 78: Tetrazole-based BDPs via a sequential Ugi/hydrolysis/coupling.



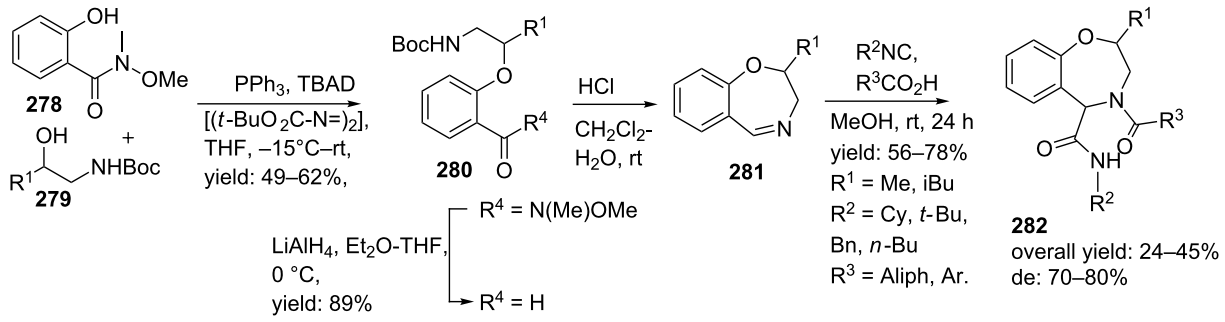
Scheme 79: MCR synthesis of three different tricyclic BPDs.

amines with ethylglyoxalate, $TMSN_3$ and bifunctional isocyanide in trifluoroethanol were employed to obtain **271**. An additional Boc-cleavage and cyclization under microwave conditions afforded the benzotetrazolediazepinones **272**. As an extension, the authors also performed the Ugi reaction with arylglyoxaldehydes together with either primary or secondary amines, in which the primary amines exclusively led to benzotetrazolodiazepines **269**, whereas incorporation of secondary amines afforded either benzotetrazolodiazepines **269** or **270**. However, these latter analogues are prone to hydrolysis and oxidation at room temperature.

Another important structural motif that can constrain peptides is the 1,4-oxazepine [205-208]. Only a few multicomponent approaches have been described towards 1,4-oxazepine analogues. For example, dihydro-1,4-benzoxazepines and dihydro-1,4-benzoxazepin-5-ones have been reported by Banfi et al. [209]. The dihydro-1,4-benzoxazepin-5-ones **276** were synthesized by either a sequential Ugi–Mitsunobu cyclization or employing a reversed version of the sequence (Mitsunobu–Ugi). Both procedures gave similar results, however, the latter one required an additional deprotection step (Scheme 80). In addition, the Mitsunobu reactions were performed with PPh_3 and



Scheme 80: Two similar approaches both involving an Ugi reaction and a Mitsunobu cyclization.



Scheme 81: Mitsunobu–Ugi-approach towards dihydro-1,4-benzoxazepines.

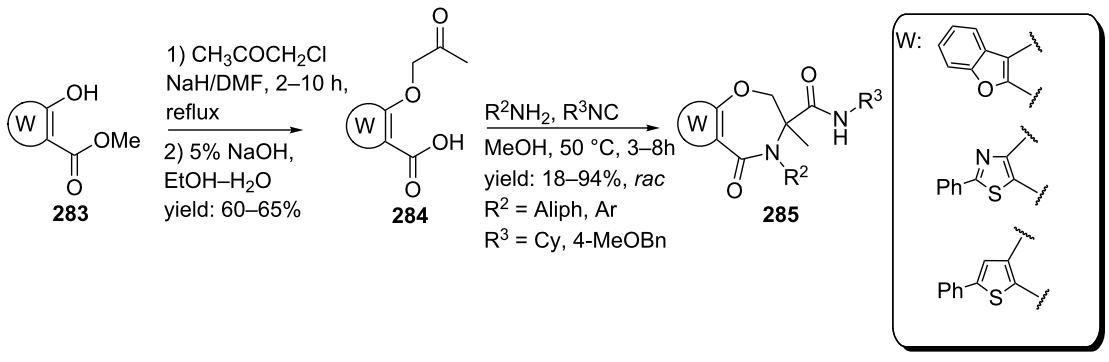
DBAD. The scope of the Ugi reaction tolerated a wide variety of isocyanides and aldehydes, affording the bicyclic scaffolds in good yields. Furthermore, additional modelling studies revealed that these mimics could induce α-helix-conformations, when the R^1, R^3, R^5 substituents contains (aryl)alkylchains [190].

In contrast, dihydro-1,4-benzoxazepines **282** (Scheme 81) could be obtained in four-steps by first performing the Mitsunobu reaction with racemic alcohols and the Weinreb hydroxamate **278**. Subsequent reduction and deprotection resulted in the cyclic imines **281** [210]. Then an additional Joullié–Ugi reaction provided the final bicyclic mimics **282** in good to excellent yields, (24–45%) with a preference for the *cis*-isomer. Steric arguments account for the observed selectivities.

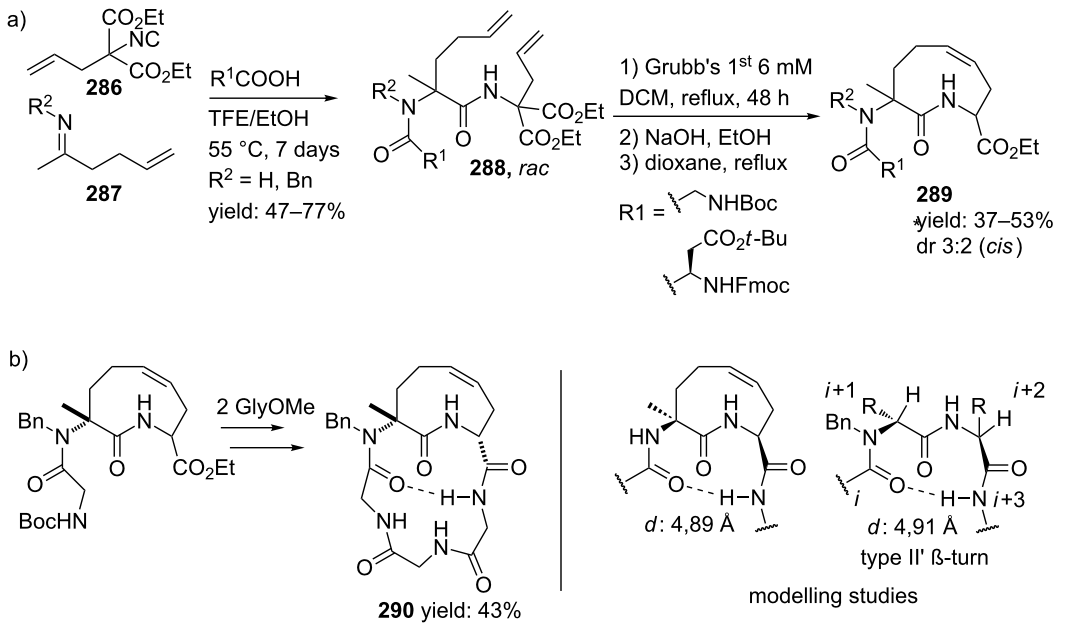
Heteroaryl-fused 5-oxo-1,4-oxazepines have been reported by Ivachtchenko and co-workers (Scheme 82) [211]. The key substrate in their approach employs the bifunctional keto-acid **284**, derived from hydroxy-substituted heteroaryl carboxylates **283**, which in turn were commercially or synthetically available. In total a medium-sized library of 23 heteroaryl-derivatives **285** was developed using three different hetero-aryl keto-acids and a wide variety of amines (18–94%).

Nine-membered ring constraints

Multicomponent reactions towards medium-sized cyclic peptidomimics (9–12 membered) usually involve two unsaturated components that can be cyclized via a post ring closing metathesis (RCM). Following this two-step sequence, Banfi and co-workers [212] reported a small library of nine-membered lactams with potential turn-properties (Scheme 83). The isocyanoacetate **286** and the (preformed) imine **287** provided the olefin moieties in the racemic Ugi-products. Subsequent treatment of these Ugi-products **288** with Grubb's catalyst (first generation) provided the cyclic constructs exclusively in the *Z*-conformation, along with several acyclic dimers as byproducts. Final saponification and decarboxylation, furnished the nine-membered lactams **289** in good yields (37–53%, dr 3:2 for the *cis*-isomer). In order to investigate the turn-properties, the authors coupled the lactam (R^1 = (Boc)NHCH$_2$) analogues with two glycine methylesters that after deprotection and a final peptide-coupling with BOP afforded the pentacyclic structure **290** as shown in Scheme 83. It is noteworthy that only the *cis*-isomer was able to cyclize and was obtained in a reasonable overall yield (43%). In addition, modelling and spectroscopic studies of the structures revealed that these bicyclic scaffolds can adopt a type II' β-turn motif, in which a hydrogen bond between residue *i* and *i*+3 is formed [11].



Scheme 82: Ugi reaction towards hetero-aryl fused 5-oxo-1,4-oxazepines.

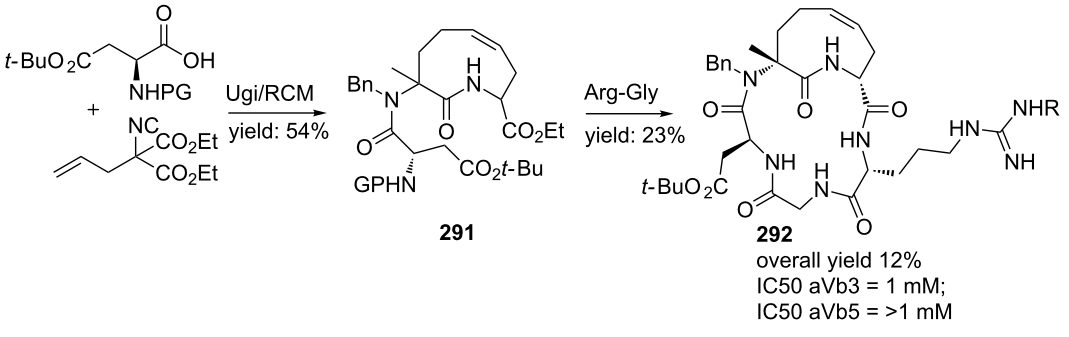


Scheme 83: a) Ugi/RCM-approach towards nine-membered peptidomimetics b) Sequential peptide-coupling, deprotection, peptide coupling revealed the GGG-pentacyclic structure that adopts a β-turn conformation.

A second application extended the scope to cyclic RGD pentapeptides (Scheme 84). Peptides containing the RGD-sequence (arginine-glycine-apartic acid) are of great pharmaceutical interest since this tripeptide sequence can be recognized by a special category of receptors, the so-called integrins. Integrins consist of one α- and one β-subunit that play key roles in several biological functions of mammals, for example in cell–cell interactions. Some of them are also involved in the regulation processes of diseases, in which the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrins are believed to be involved in tumor induced angiogenesis [213-216]. Therefore, inhibition of these integrins by small peptides that contain a RGD-sequence is of high interest [217]. For the development of the cyclic RGD-pentapeptides the authors employed the Ugi/RCM/decarboxylation/coupling sequence, in which the RGD mimics **291** were obtained in overall yields of 12%. In this procedure, the final peptide-coupling was performed with protected Arg-Gly-dipeptide and HATU as couplings reagent [218]. To validate the potency of these mimics, the authors screened their mimics against $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrins and it was shown that the *cis*-isomer was a potent inhibitor of the $\alpha_V\beta_3$ (IC_{50} = 1 μM) and very weak against $\alpha_V\beta_5$ (>1 mM).

Macrocycles

An alternative approach to reduce the flexibility in a peptide backbone and thus limit the number of possible active conformations employs macrocyclization (>12 membered rings) strategies. Such macrocyclic peptides have the additional



Scheme 84: Ugi-based synthesis towards cyclic RGD-pentapeptides.

advantage that no terminal groups are present, which makes them more stable (compared to linear analogues) towards degradation i.e. terminal groups are usually required for efficient protease-binding. In addition, the increased conformational order also reduces the folding-energy required for binding as compared to the flexible linear peptide or mimics [26,219-222]. In order to obtain such peptidic macrocycles via multicomponent reactions, several research groups have utilized post-MCR cyclization reactions such as RCMs, macrolactonizations or nucleophilic aromatic substitutions (S_nAr). Alternatively, macrocycle synthesis via cyclizing multiple MCRs have been reported. In this part of the review first the post-MCR-condensations via RCM, lactonization and S_nAr will be considered, after that the multiple MCR-approaches will be discussed.

Macrocycles via MCR-RCM-approaches

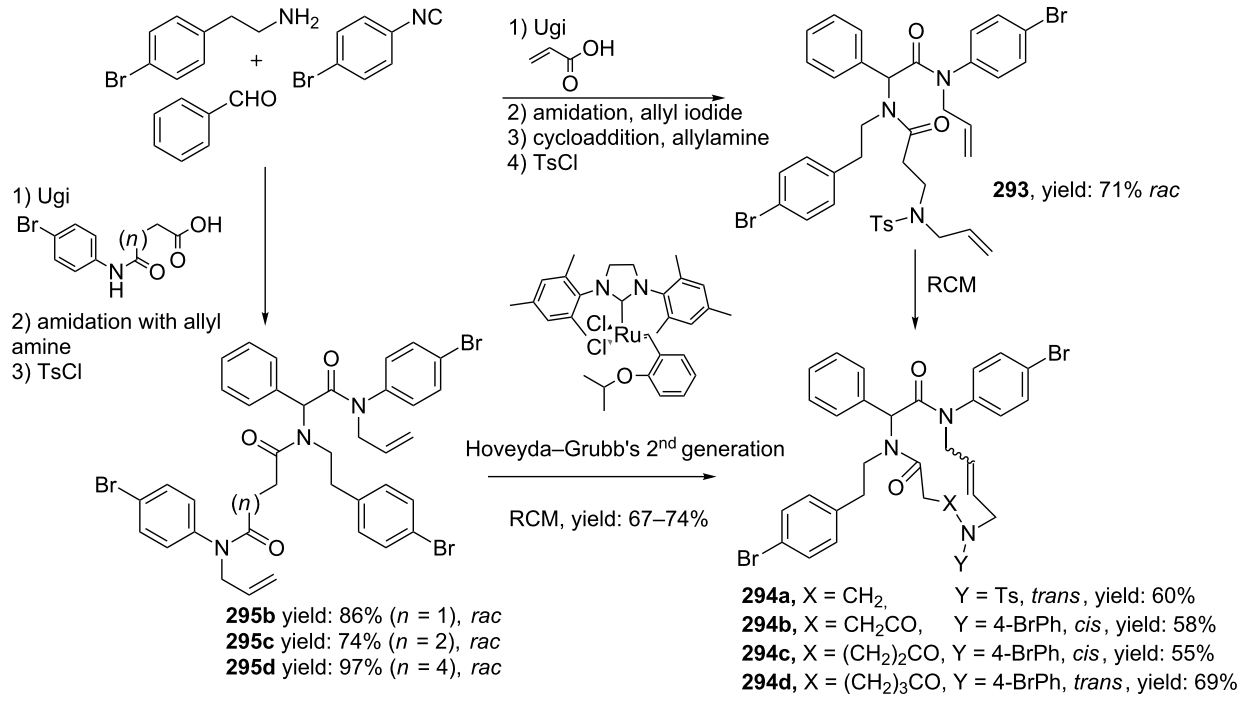
In the past decade three research groups have developed peptide-like macrocycles via a MCR-RCM-sequence. Oikawa et al. reported a small library consisting of 12–15 membered cyclic peptidomimetics [223]. These mimics were synthesized in good yields via a three-step procedure involving an Ugi 4-CR, incorporation of the alkene functionalities and a subsequent RCM assisted by the second generation Hoveyda-Grubb's catalyst (Scheme 85). Depending on the acid component, the alkene moieties could be introduced by performing either a double amidation with allyl iodide yielding **295** or via a sequential cycloaddition/amidation with allyl amine and allyliodide, respectively, to afford **293**. The follow-up RCM yielded the macrocycles as *trans*-isomer for the 12- and 15-membered cycles and as *cis*-isomer for the 13- and 14-membered cycles **294a–d**.

Kazmaier et al, also active in this area, reported a stereoselective Ugi/RCM-approach by utilizing allyl isocyanoacetate and (four) different Alloc-amino acids as bifunctional substrates (Scheme 86) [224]. Whith (*S*)-amino acids and (*S*)-2,2-(*m*-methoxyphenyl)ethylamine as chiral components, the Ugi-products **296** were obtained mainly as the (*S,S,S*)-diastereomers (de 44–90%). Subsequent RCM with Grubb's 1st generation catalyst afforded the 16-membered macrocycles **297** in good overall yields, favouring the *E*-isomer.

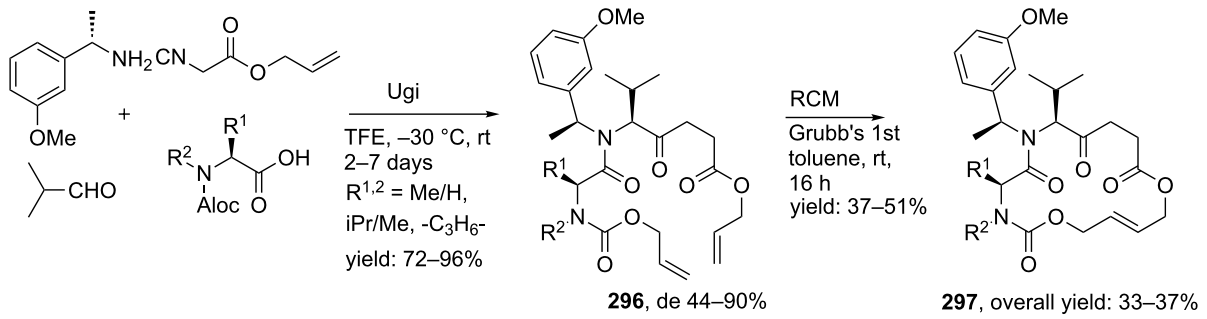
As an alternative, Dömling et al. applied a Passerini/RCM-approach for the construction of macrocycle **299** (Scheme 87) [225]. Both the carboxylic acid and the isocyanide substrate bear the alkene moiety and were derived from commercially available precursors. The addition of paraformaldehyde provided the linear Passerini-adduct in 67% yield, in which the post-RCM with Grubb's catalyst afforded the 22-membered macrocycle **299** in 17% overall yield.

Macrocycles via MCR-macrolactonization protocols

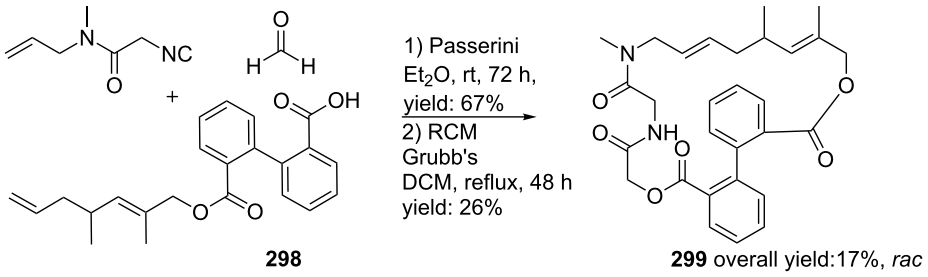
Macrolactonization was employed by Zhu and co-workers after the MCR described above in Scheme 43 generating oxazole



Scheme 85: Ugi/MCR-approach towards 12–15 membered macrocycles.



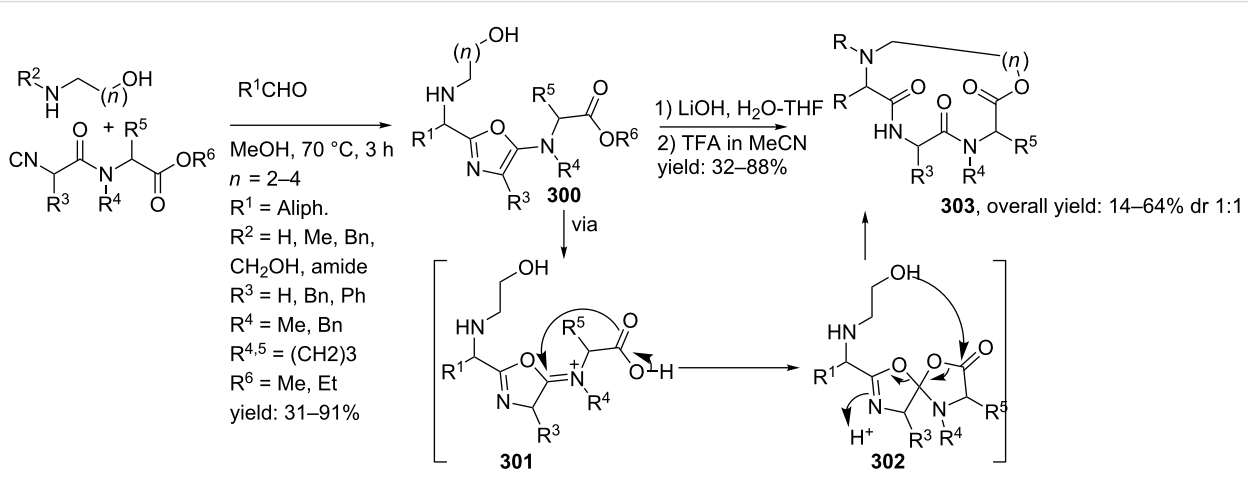
Scheme 86: Stereoselective Ugi/RCM approach towards 16-membered macrocycles.



Scheme 87: Passerini/RCM-sequence to 22-membered macrocycles.

peptidomimetics. The procedure is based on the instability under acidic conditions of the initially formed amino oxazole [226,227]. The modification includes a hydrolysis/activation/cyclization sequence to provide 12–18-membered cyclic depsipeptides in good overall yields (upto 64%). As shown in Scheme 88, the process starts with a base catalyzed hydrolysis of the alkyl ester followed by protonation of the oxazole-scaffold to provide imminium cation **301**. Subsequent intramolecular cyclization induced by the carboxylate yielded the spiro-intermediate that via a nucleophilic attack of the tethered alcohol to the activated ester resulted in the macrocyclic depsipeptides **303**.

Another interesting procedure involves a MCR/macrolactonization strategy in order to obtain two structural derivatives of the in vivo active antibiotic acyldepsipeptide, ADEP-4 [228]. It is noteworthy that the pipecolic acid moiety in ADEP-4 enhances the in vitro and in vivo antibiotic activity as compared to its



Scheme 88: UDAC-approach towards 12–18-membered depsipeptides.

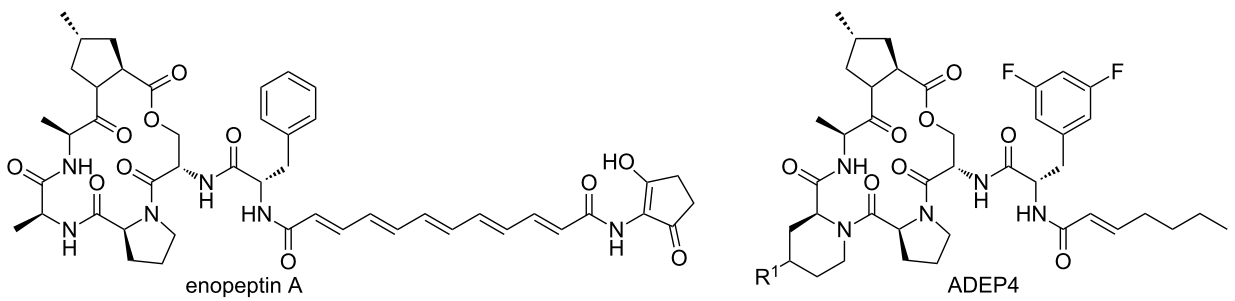
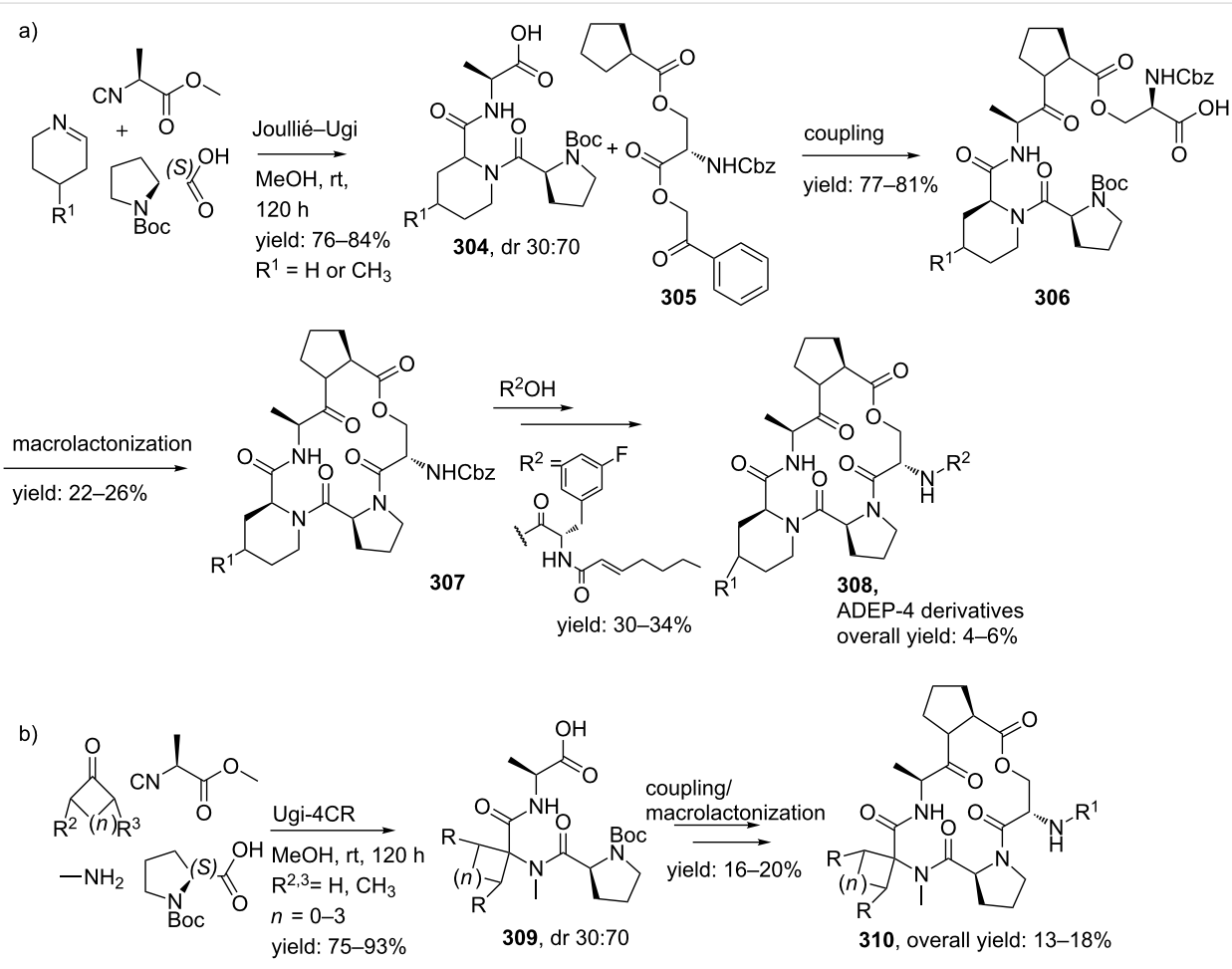


Figure 4: Enopeptin A with its more active derivative ADEP-4.

N-methylaniline precursor enopeptin A, thereby reflecting the importance of conformationally restricted elements (Figure 4).

For these ADEP-4 derivatives, a Joullié–Ugi 3CR of cyclic imines, *N*-Boc-proline and isocyanopropanoate (derived from aniline methylester), followed by coupling with **305** and subsequent TFA-promoted saponification gave the macrocycle **307** (Scheme 89). Under these conditions the Ugi reaction proceeds in a diastereoselective fashion and for unclear reasons formation of the less active isomer (dr 30:70) was favoured. Chromatographic separation followed by an additional peptide coupling provided the final compounds **308** in 4–6% overall yield. In a variation an Ugi 4-CR was employed to construct α,α-dimethylated derivatives. Herein, the Ugi reaction of



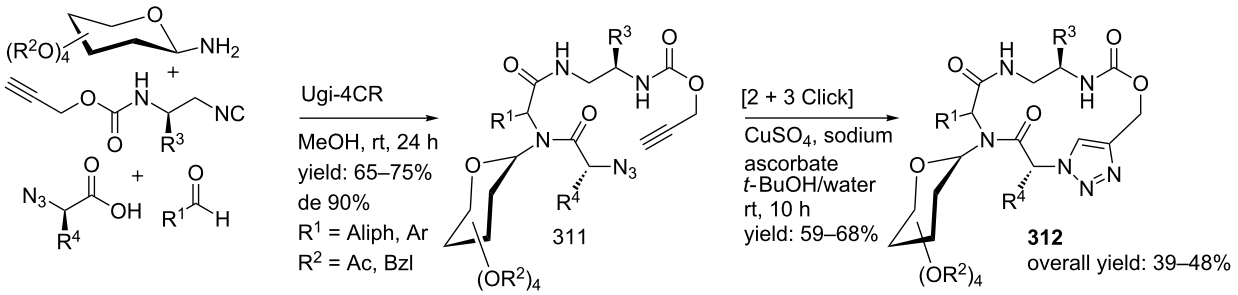
Scheme 89: a) The Joullié–Ugi-approach towards ADEP-4 derivatives b) Ugi-approach for the α,α-dimethylated derivatives.

methylamine, *N*-Boc-proline, isocyanopropanoate and different ketones gave the desired tripeptides **309** in good to excellent yields (Scheme 89). The subsequent post-modification reactions provided macrocyclic analogues **310** in overall yields of 13–18%. To validate the antibacterial activity, the different scaffolds were screened against several drug-resistant bacterial strains, however, only the pipecolic derivatives showed antibacterial activity.

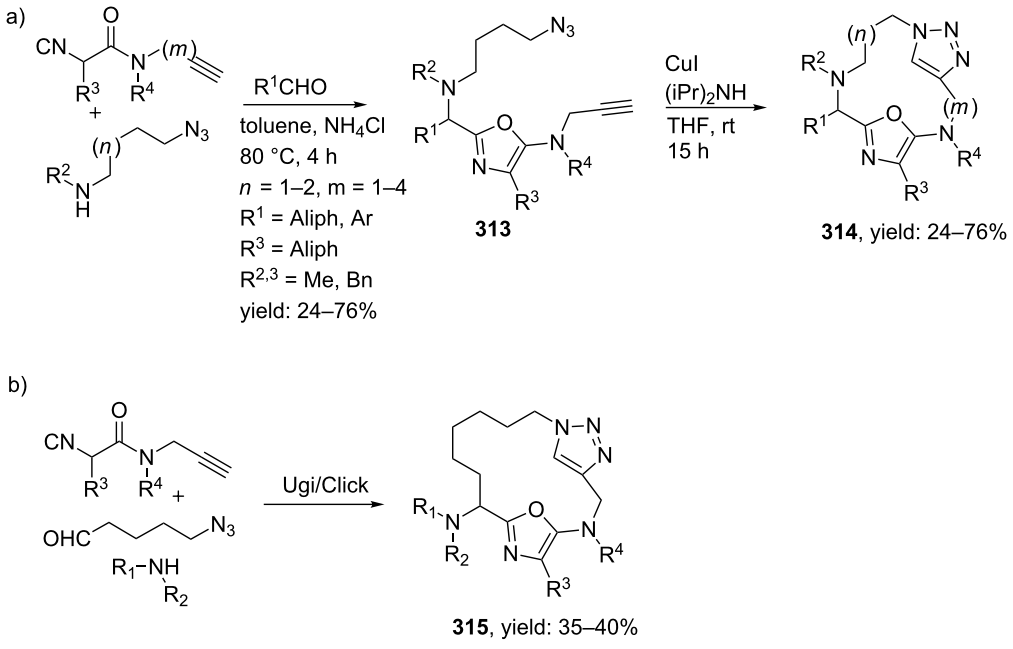
Macrocycles via MCR-Click-combinations

A third approach that can be utilized to construct macrocyclic peptidomimetics is a sequential Ugi–Click-combination. Via this approach the cyclic mimics are linked via a triazole-unit. Recently, Sureshbabu and co-workers used such a two-step sequence for a small library of 15-membered cyclic glyco-peptidomimetics [229]. In this approach, the Ugi reaction was performed with a variety of sugar-1-amines, aldehydes, azido acids and Poc-amino methyl isocyanide and afforded the linear Ugi-products as a mixture of two diastereomers in a ratio of 95:5. The Poc-group functions as protecting group in the Ugi reaction while being reactive in the subsequent Click reaction (Scheme 90). The Click reaction gave the macrocycles **312** in 39–48% overall yield. It is noteworthy that the cyclization was performed at mM concentrations to minimize dimerization processes.

In a variation to the aforementioned 5-amino-oxazole Ugi MCR/macrolactonization, the group of Zhu also synthesized macrocycles via a subsequent [3 + 2] cycloaddition reaction that contained both a triazole and an oxazole unit (Scheme 91)



Scheme 90: Ugi–Click-strategy for 15-membered macrocyclic glyco-peptidomimetics.



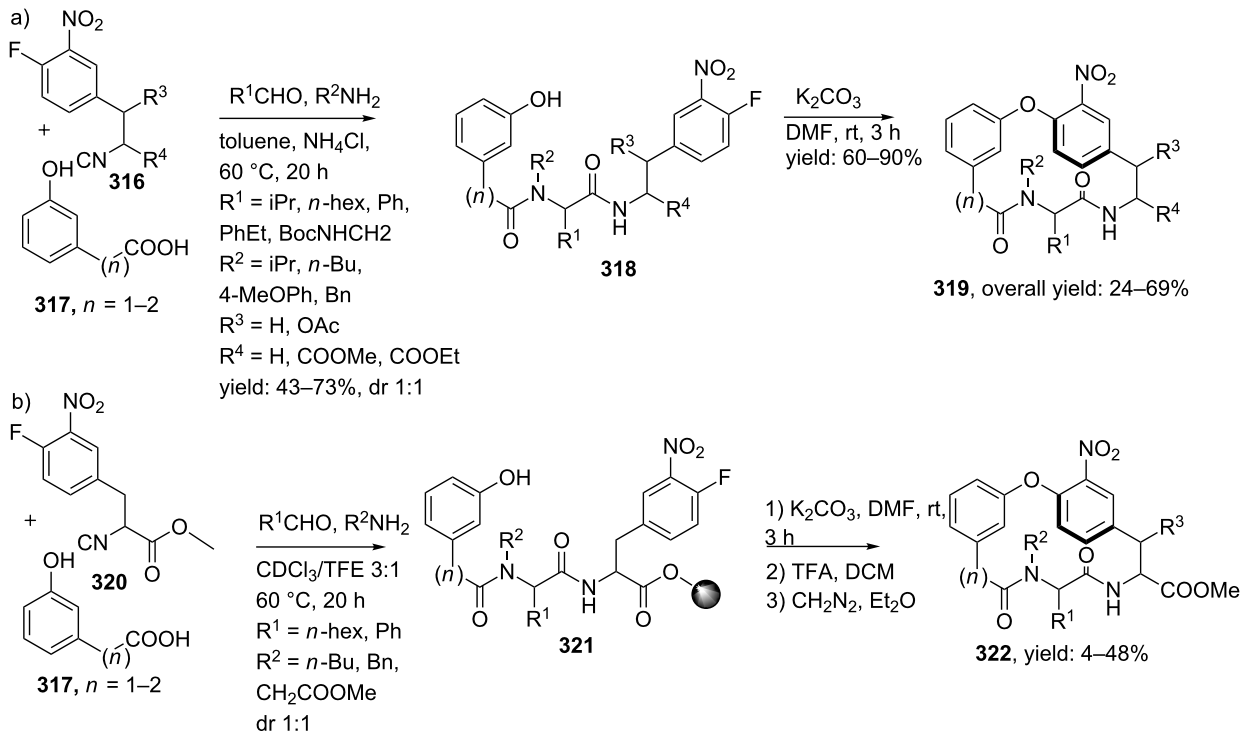
Scheme 91: Ugi/Click combinations provided macrocycles containing both a triazole and an oxazole moiety.

[230]. The Ugi reaction was performed in toluene and a variety of isocyanoacetamides and amines were employed as bifunctional inputs containing either a terminal alkyne or azide moiety. Herein, the isocyanoacetamides were derived from formylated amino acids via an azide-coupling and dehydration sequence. The subsequent cycloaddition was catalyzed by copper iodide, furnishing 14–16-membered macrocycles **314** in good yields (24–76%) that all contain a triazole (as amide biosteres) and an oxazole moiety (as dipeptide surrogate). In addition, it is worth noting that the reaction sequence could also be performed with tethered azide and alkyne moieties in the aldehyde and isocyanide inputs, thereby providing macrocycles with an *exo*-tertiary amine (**315**, 35–40%).

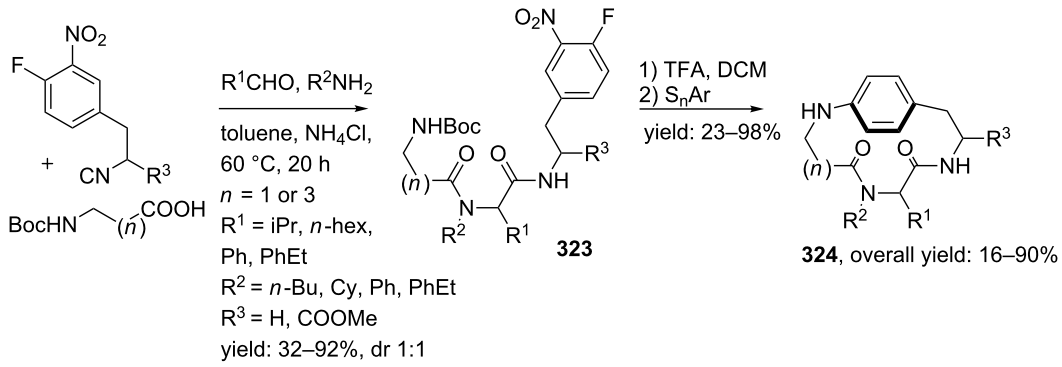
Macrocycles via MCR-S_nAr-procedures

Macrocycles containing an aryl-ether bridge can be obtained via a combination of the Ugi reaction and a sequential aromatic substitution (S_nAr). In Nature, these particular macrocycles have been found and some of them possess interesting antibiotic [231,232], antitumor [233], or antifungal activities [234,235]. In addition, they are also found as potent ACE-inhibitors [236]. The most leading example is the antibiotic vancomycin, which found application as last remedy against multi-drug resistant microbial strains [237]. Zhu and co-workers designed both a solution and solid-phase synthesis of biaryl-ether-linked macrocycles (Scheme 92) [238,239]. In the solution-phase approach, they performed an Ugi reaction with a variety of aliphatic and aromatic amines and aldehydes, two acids and two isocyanides (synthetically derived) to arrive at the linear Ugi-products **318** in good yields (43–73%, dr 1:1). During the reaction no formation of Passerini-like or ammonia derived side products were observed. The solid-phase synthesis afforded the linear precursors by reacting resin-bound isocyanide **320** with a variety of different amines, aldehydes and acids in $CDCl_3$/TFE [240]. The subsequent ring closure reaction was performed under basic conditions, providing the 16–17 membered macrocycles as two atropisomers for each diastereomer in moderate to high yields. Slightly better overall yields were observed for the solution-phase process (**319**, 24–69%), compared to the solid-phase route (**322**, 4–48%) [238].

The same authors also published a similar solution-phase sequence towards cyclophane based-macrocycles having an aryl-*N*-alkyl bridge (Scheme 93) [241]. In this route the Ugi reaction was performed with aliphatic carboxylic acids, furnishing the dipeptides **323** in 32–92% yield. Subsequent TFA treatment followed by S_nAr-cyclization provided the 15-membered macrocycles **324** in 16–90% overall yield, again as two atropisomers.



Scheme 92: a) A solution-phase procedure towards macrocycles. b) Alternative solid-phase synthesis as was reported by Zhu et al. [238,239].



Scheme 93: Ugi/cyclization towards cyclophane based macrocycles.

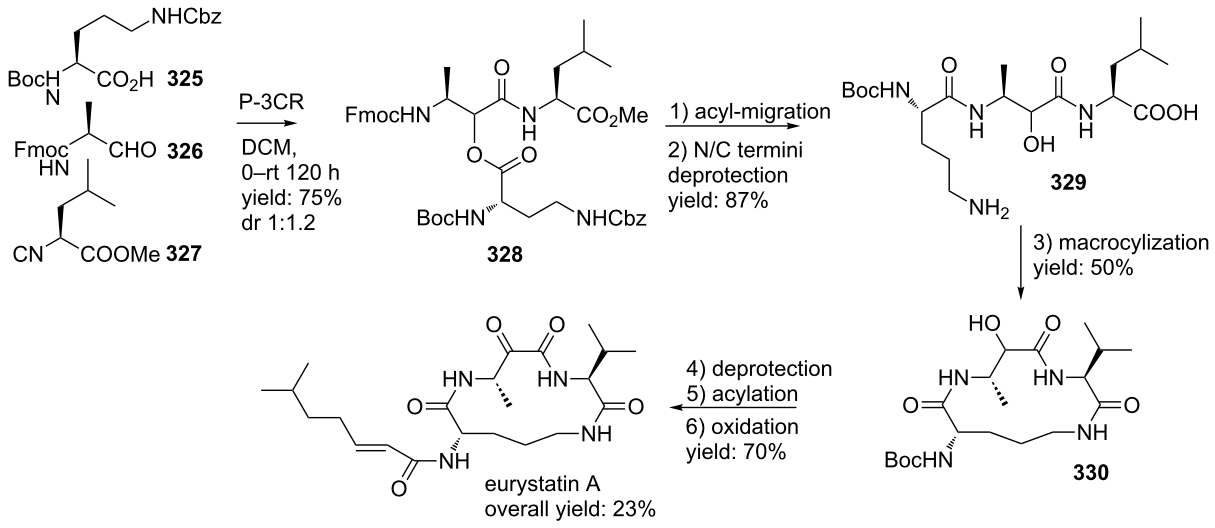
Passerini-amine deprotection-acyl migration procedures

The Passerini-amine-deprotection-acyl migration (PADAM) strategy is a useful alternative to provide dipeptides that can be cyclized to the corresponding macrocycles via a subsequent peptide-coupling. The PADAM-strategy has been used for the total synthesis of eurystatin A and cyclotheanamide C, both are potent α-keto-amide-based protease inhibitors. Synthesis of eurystatin A was developed by Semple and co-workers and included *N*-protected amino acid **325,** enantiopure aldehyde **326** and leucine isonitrile **327** as MCR-substrates (Scheme 94) [242]. Subsequent *N*-Fmoc deprotection of the resulting linear adduct induced acyl-migration, in which deprotection and hydrolysis of the two N/C-termini provided the cyclization substrate **329**. A sequential *N*-Boc deprotection, acylation and oxidation provided the macrocyclic eurystatin A in 23% yield over 8 steps.

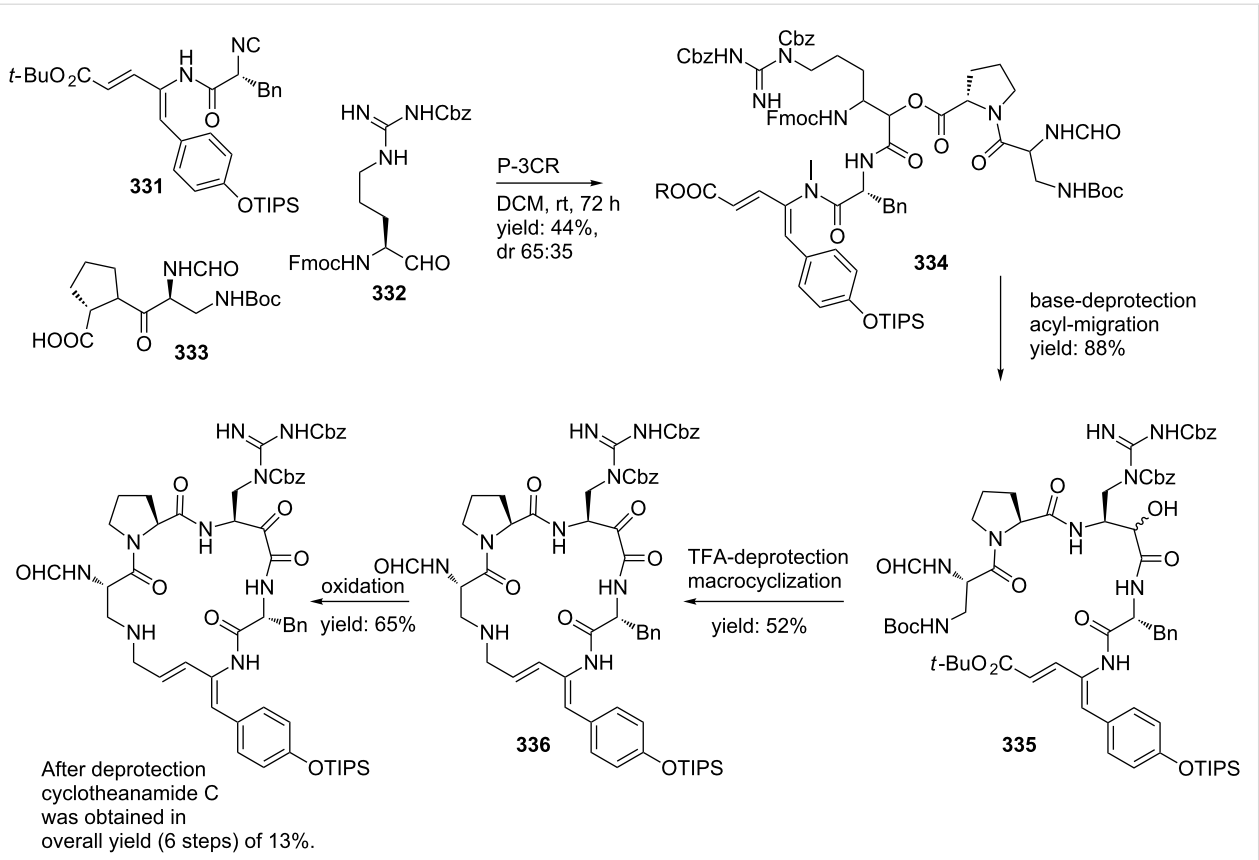
The PADAM-based synthesis of cyclotheanamide C was published by Aitken et al. (Scheme 95) [243]. In this report, the α-acyloxyamide precursor was obtained in 44% yield by reacting isocyanide **331** with a small excess of both Fmoc-amino aldehyde **332** and *N*-Boc dipeptide **333** (1.2 equiv). Again base promoted *N*-Fmoc deprotection induced acyl-migration, in which TFA treatment and subsequent peptide-coupling using TBTU/HOBt furnished macrocycle **336**. Final oxidation with DMP and base-catalyzed Cbz-removal gave the cyclotheanamide C-compound in 13% yield over 6 steps.

MCR-MCR cyclizations

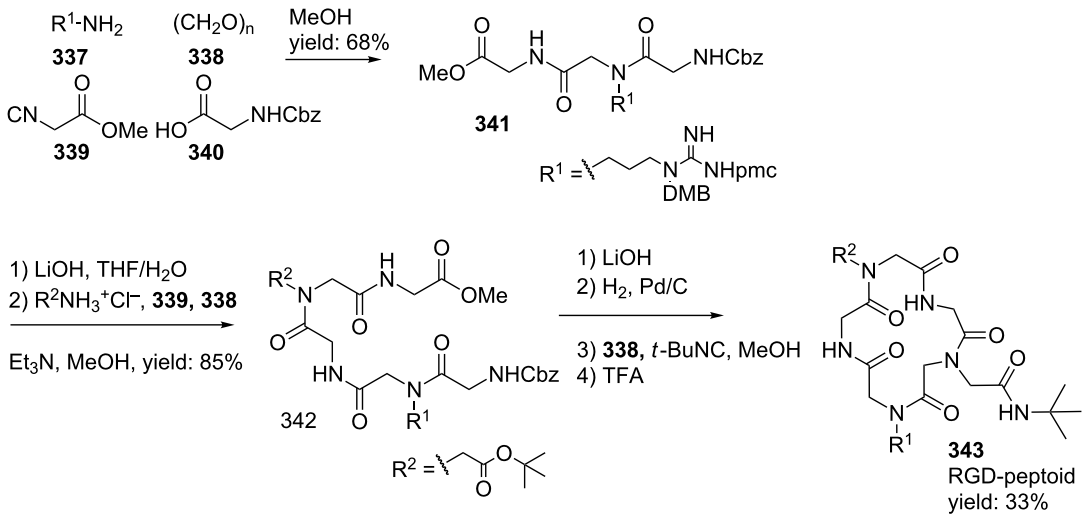
Even more challenging is the construction of macrocycles in which the cyclization step is also performed by a multicomponent reaction. Wessjohann and co-workers reported a combination of three sequential Ugi-MCRs towards RGD-pentapeptoids (Scheme 96) [244]. All three MCRs involved an Ugi-



Scheme 94: PADAM-strategy towards eurystatin A.



Scheme 95: PADAM-approach for cyclotheanamide.



Scheme 96: A triple MCR-approach affording RGD-pentapeptoids.

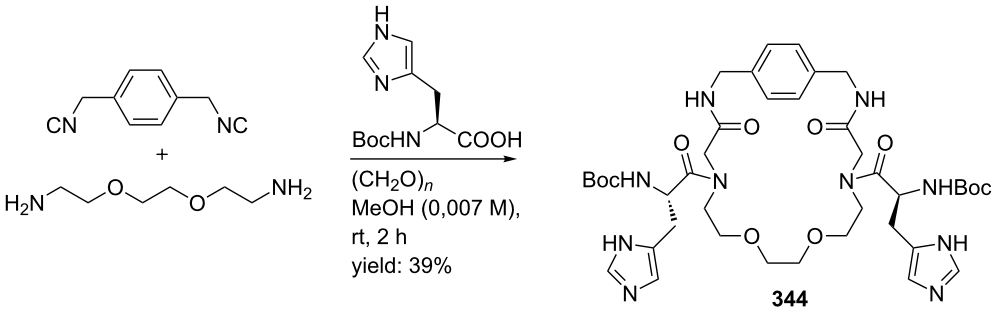
MCR, in which the first two provided linear products **341** and **342**, whereas the third MCR resulted in the ultimate macrocyclic peptoid structure. The final RGD-macrocycles **343** were obtained after TFA-deprotection in 33% overall yield. It was shown by the authors that a wide range of cyclic peptoids could be obtained by alternating the MCR-substrates. In particular, interchange of the amine component in the first two MCRs resulted in (retro)-peptoids consisting of a DGR-sequence.

A second powerful strategy to obtain macrocycles exclusively from combinations of multicomponent reactions is the MiB-approach (*m*ultiple multicomponent macrocyclizations *i*ncluding *b*ifunctional building blocks). Similar to the previous described MCR-MCR approach, macrocycles are in this approach obtained from two or more MCRs. However, in this particular process, the MCRs include two or more *unprotected* bifunctional groups such as diisonitriles, diamines or amino acids. The incorporation of these unprotected bifunctional substrates makes the construction of highly complex macrocycles even more straightforward and also allows scaffold diversification. In the literature, several Ugi or Passerini-based MiB-approaches have been reported and only two examples will be given in this review since they already have been extensively reviewed by the groups of Wessjohann and Rivera. For more details see also references [24,27-29,245,246].

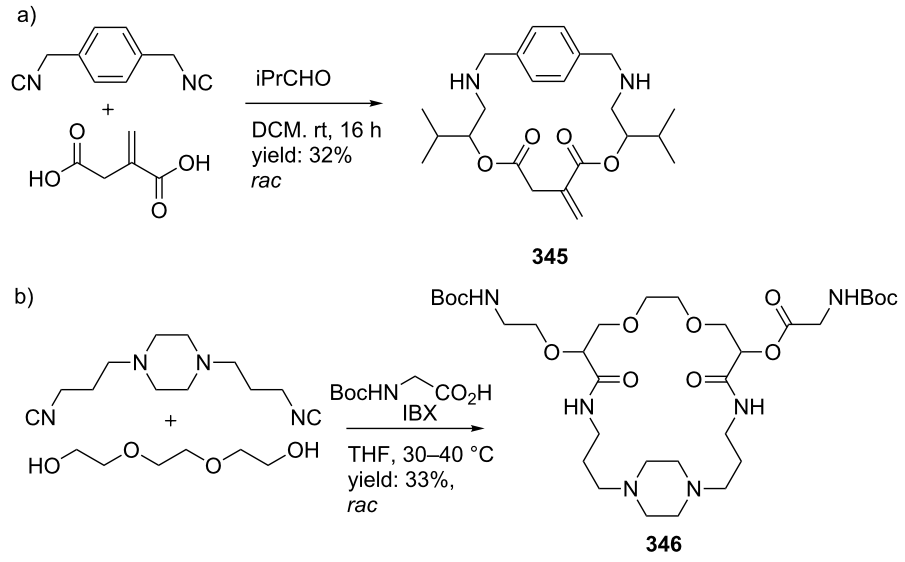
An example of an Ugi-approach by Rivera and Wessjohann included symmetric diamines and diisonitriles in combination with formaldehyde and (protected) α-amino acids (Scheme 97). Via this procedure peptoid-based macrocycles **344** were obtained that contain biologically relevant side chains [245].

The same group also reported a Passerini-based MiB-approach (Scheme 98) [247]. The multicomponent reactions were either performed with diacid/diisonitrile combinations or with diisonitrile/dialdehyde bifunctional groups, providing the macrocycles **345** and **346** in 32% and 33% yield, respectively. It was shown that the latter combination requires in situ-generation of the dialdehydes from dialcohols via an oxidative Passerini reaction. One reason for this in situ generation was the acid-instability of aldehydes [248].

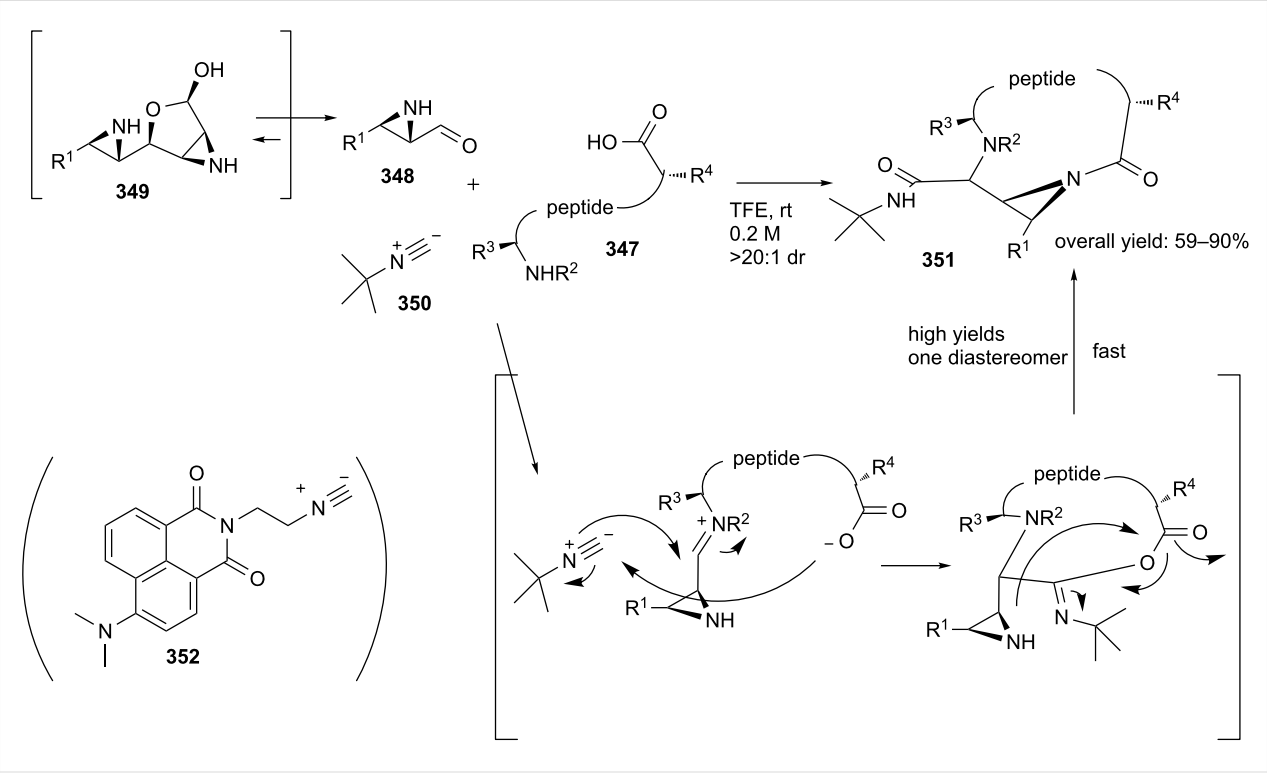
Finally, Yudin et al. [219,249] developed interesting and very effective strategies to construct macrocyclic peptidomimetics through an MCR-induced cyclization. Their approach includes macrocyclization of peptides of type **347** using so-called amphoteric aziridine-based aldehydes **348** (used as the corres-



Scheme 97: Ugi-MiBs-approach towards peptoid macrocycles.



Scheme 98: Passerini-based MiB approaches towards macrocycles **345** and **346**.



Scheme 99: Macrocyclic peptide formation by the use of amphoteric aziridine-based aldehydes.

ponding dimer **349**) in combination with isocyanides **350** (Scheme 99). As became clear from discussions in this review, the use of the Ugi reaction in a "traditional" sense to induce macrocyclization of peptidic α-amino acids (as bifunctional inputs), aldehydes and isocyanides usually produces mixtures of diastereoisomers of macrocyclic peptides and requires high dilution conditions to minimize overall dominant formation of cyclo di- or oligomerization products. The amphoteric aldehydes **348** in the Yudin macrocyclization strategy can be applied under conventional reactant conencentrations and overcomes both the stereoselectivity and oligomerization issues producing in good yields and excellent diastereoselectivities macrocyclic peptides **351** avoiding epimerization. In follow-up work a number of interesting applications were discussed [250] including the use of solvatochromic isocyanides **352** to access cell permeable macrocyclic peptide vectors [251] and RGD fluorescent probes [252]. In addition, the macrocyclization tool proved very useful in the exocyclic control over turn induction in macrocyclic petides [253].

Conclusion

Isocyanide-based multicomponent reactions in combination with subsequent cyclization reactions have become valuable tools in the design and synthesis of cyclic constrained peptidomimetics. These IMCRs give rapid access to these complex target molecules from relatively simple starting materials addressing both structural diversity and complexity. Furthermore, after the initial MCRs several post-cyclization condensations can be utilized, since a variety of unreactive or monoprotected functionalities are tolerated in the initial MCRs. This ultimately leads to cyclic constrained peptidomimetics in only a few steps as compared to often much longer more traditional sequential procedures.

We discussed many examples of four to seven membered (bi)cyclic dipeptide isosteres such as lactams, triazoles, oxazoles and thiazoles that can be easily incorporated via these IMCR/cyclization protocols, in which it was even possible to provide triazole based peptidomimetics. Incorporating dipeptide mimics into peptides introduces conformational order, improves stability against enzymatic degradation and allows the peptidic structures to adopt secondary structures such as turns and α-helices. A nice example of this was the bicyclic diketopiperazines as they perfectly force the peptide-like structure into a type I β-turn.

In addition, the IMCR/cyclization strategies have also shown to be highly suitable for the synthesis of macrocyclic peptidomimetics. The interest for macrocycles is based on two important properties. These macrocyclic peptoids combine conformational order with flexibility and they are stable against terminal group degradation by proteases. As discussed here, the

IMCR-based synthesis of such macrocycles usually requires a subsequent head-to-tail cyclization such as ring-closing-metatheses, cycloadditions, lactonizations, peptide-couplings or nucleophilic substitutions. Even more interestingly is the synthesis of cyclic peptidomimetics via multiple MCRs as was described for macrocyclic RGD-peptoids. These multiple MCR-approaches have the advantages to also introduce structural diversity and complexity at the cyclization step.

However, still a main flaw of MCR-based strategies for the synthesis of constrained peptidomimetics is the often poor stereocontrol in these reactions. This is crucial since optically pure peptide-like products are essential for proper study of peptide-peptide interactions, therefore, for the future of this chemistry in this field the design of (dia)stereoselective multicomponent reactions is highly desirable. Several research groups have indeed realized this challenge and are developing such asymmetric multicomponent reactions. Perhaps a prominent example is the bio-catalytic synthesis of optically active pyrrolidines that can be used in a MCR-based synthesis of telaprevir. Further developments may rely on the use of these asymmetric approaches and will make the multicomponent reaction an even more useful tool for the design of novel conformationally constrained peptidomimetics.

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One-pot three-component synthesis and photophysical characteristics of novel triene merocyanines

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Full Research Paper

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Abstract

Novel triene merocyanines, i.e. 1-styryleth-2-enylidene and 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones are obtained in good to excellent yields in a consecutive three-component insertion Sonogashira coupling–addition sequence. The selectivity of either series is remarkable and has its origin in the stepwise character of the terminal addition step as shown by extensive computations on the DFT level. All merocyanines display intense absorption bands in solution and the film spectra indicate *J*-aggregation. While 1-styryleth-2-enylideneindolones show an intense deep red emission in films, 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones are essentially nonemissive in films or in the solid state. TD-DFT computations rationalize the charge-transfer nature of the characteristic broad long-wavelength absorptions bands.

Introduction

Functional organic materials [1], such as chromophores, fluorophores, and electrophores, constitute the active components in molecular electronics [2], photonics [3], and bioanalytics [4-6]. Among many chromophores the class of merocyanines [7-9], i.e. α-donor-ω-acceptor-substituted polyenes, has become increasingly interesting due to their fine-tunable electronic distribution [10]. For instance, merocyanines are perfectly suited for developing molecule-based non-linear optical materials and photovoltaic chromophores [11]. Classically, these push–pull chromophores always have been accessed by Knoevenagel condensations [12-14] or substitution reactions [15-18]. Still the quest for new synthetic strategies, novel substitution patterns, and eventually unusual properties and effects has become an ongoing challenge for organic synthesis, physical organic chemistry, and photophysics.

Inspired by the concept of a diversity-oriented synthetic approach to chromophores [19-26] we have launched a program to

apply transition metal-catalyzed processes as an entry to consecutive multicomponent [27,28] and domino reactions [29]. These highly convergent strategies paved the way to luminescent push–pull dienes **1**–**4** with conformationally flexible and fixed acceptor units (Figure 1) [30-32], pyrazoles [33,34], benzodiazepines [35], furans and pyrroles [36,37] by consecutive multicomponent reactions and to highly emissive spirocycles [38-40] and pyranoindoles [41] via domino sequences. Interestingly, our versatile three-component enaminone synthesis [42,43] could be readily extended in a vinylogous fashion with enamines furnishing orange or deep red diene chromophores **2** and **3** that display aggregation induced emission [31].

In particular, the electrophilic enyne intermediate [32,40], which is trespassed in the three-component synthesis of solid-state luminescent push–pull indolones **4**, intrigued our interest for accessing even triene push–pull systems and to study their electronic properties. Here we report our findings on the diversity-oriented and highly selective three-component synthesis of a new class of deeply colored triene merocyanines in a one-pot fashion. Furthermore, their absorption and emission characteristics are investigated.

Results and Discussion

After the coupling of the *N*-methyl-substituted alkynoyl *o*-iodoanilides **5a** and terminal arylalkynes **6** at room temperature under Sonogashira conditions forming ynylideneindolones as intermediates (the reaction was monitored by TLC to ensure complete conversion) [30-32], which were not isolated, an ethanolic solution of Fischer's base (**7**) was added and reacted at reflux temperature to give 1-styryleth-2-enylideneindolones **8** in good to excellent yields as violet solids with a metallic luster (Scheme 1, Table 1). In contrary to the reaction with secondary amines, where the *E*,*E*-configured butadiene chromophores are formed with excellent stereoselectivity [30-32], Fischer's base

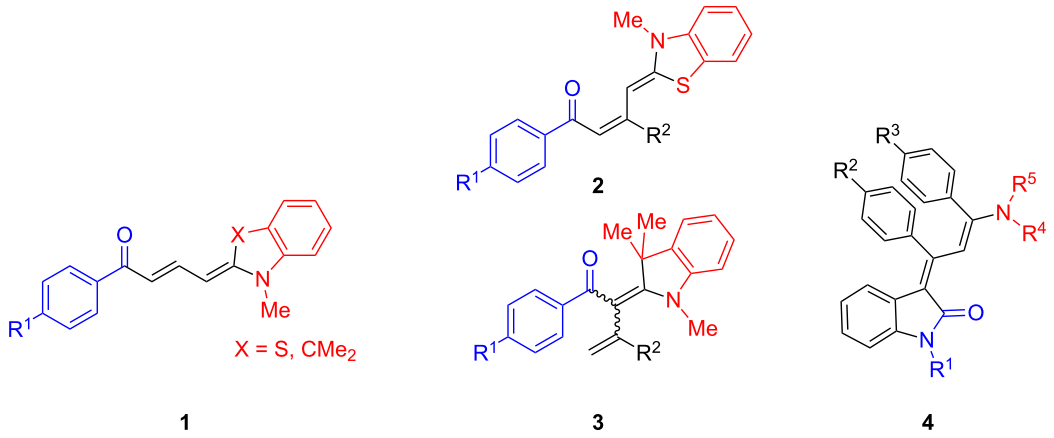
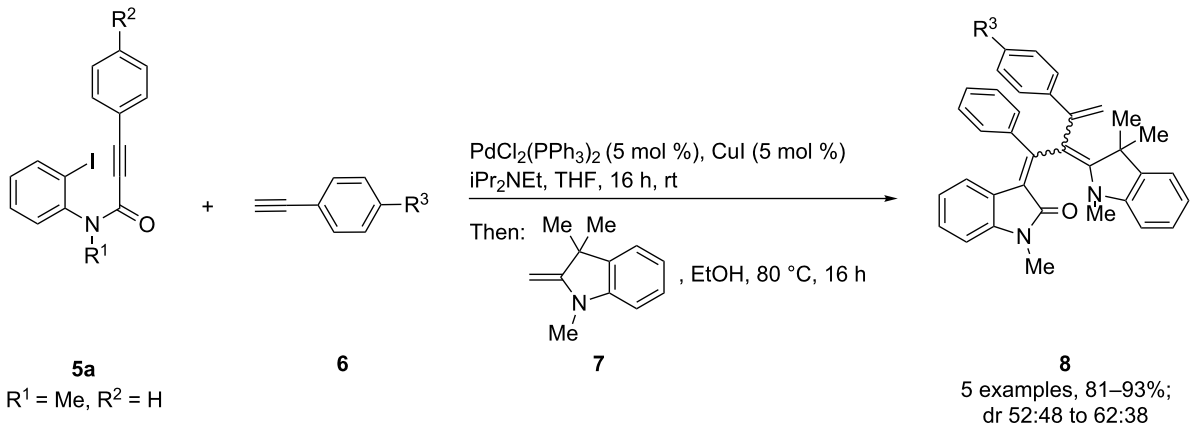
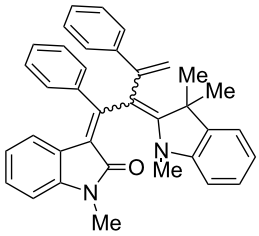
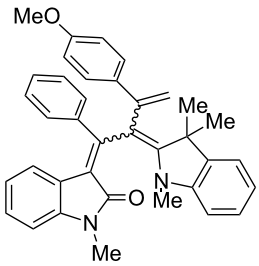
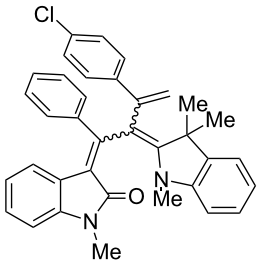
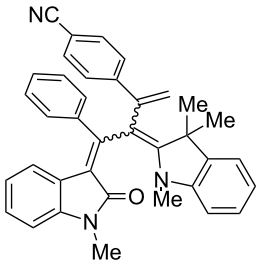
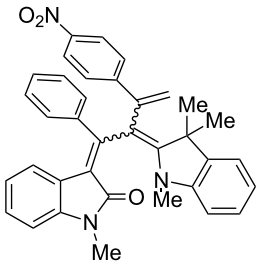


Figure 1: Linear push–pull solid-state diene lumophores with conformationally flexible and fixed acceptor moieties.



Scheme 1: Three-component synthesis of 1-styryleth-2-enylideneindolones **8**.

Table 1: Three-component synthesis of 1-styryleth-2-enylidene indolones **8**.

Entry	Alkyne **6**	1-Styryleth-2-enylideneindolones **8**	Yield [%][a]
1	R^3 = H (**6a**)	 **8a**	93 (d.r. = 56:44)[b]
2	R^3 = OMe (**6b**)	 **8b**	81 (d.r. = 62:38)[b]
3	R^3 = Cl (**6c**)	 **8c**	82 (d.r. = 56:44)[b]
4	R^3 = CN (**6d**)	 **8d**	87 (d.r. = 52:48)[b]
5	R^3 = NO_2 (**6e**)	 **8e**	91 (d.r. = 52:48)[b]

[a]The yields were determined after chromatography on silica gel. [b]The diastereomeric ratios were determined by ^{1}H NMR spectroscopy after chromatography on silica gel.

gives rise to the formation of a mixture of *E*,*E*- and *E*,*Z*-configured push–pull dienes with 3-styryl substituents in narrow diastereomeric ratios ranging from 52:48 to 62:38 (Table 1, entries 1–5) as indicated by the appearance of a second set of many signals in the proton and carbon NMR spectra.

The structures of the 1-styryleth-2-enylideneindolones **8** were assigned by NMR, mass spectrometry and by combustion analysis. The diastereomeric ratios of the *E*,*E*- and *E*,*Z*-configured push–pull dienes **8** were determined by integration of the distinct signals of the corresponding pairs of geminal olefinic protons appearing at δ 4.8–5.2 and δ 5.5–5.8 for the major diastereomer and at δ 4.5–4.8 and δ 5.3–5.5 for the minor diastereomer in the ^{1}H NMR spectra. The signals of the corresponding carbon nuclei are accordingly identified in the ^{13}C NMR spectra as methylene signals at δ 114.7–117.5 for the major diastereomer and at δ 118.1–123.5 for the minor diastereomer.

Based upon computations (B3LYP functional, 6-31G* basis set) [44] on geometry-optimized diastereomers 2*Z*,4*Z*-**8a** and 2*Z*,4*E*-**8a** the former is energetically favored by 1.5 kcal mol^{-1} over the latter (Figure 2), nicely reproducing the experimentally determined very similar diastereomeric distribution of the 1-styryleth-2-enylideneindolones **8**.

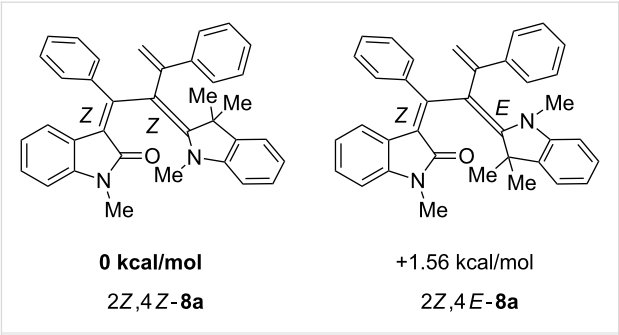
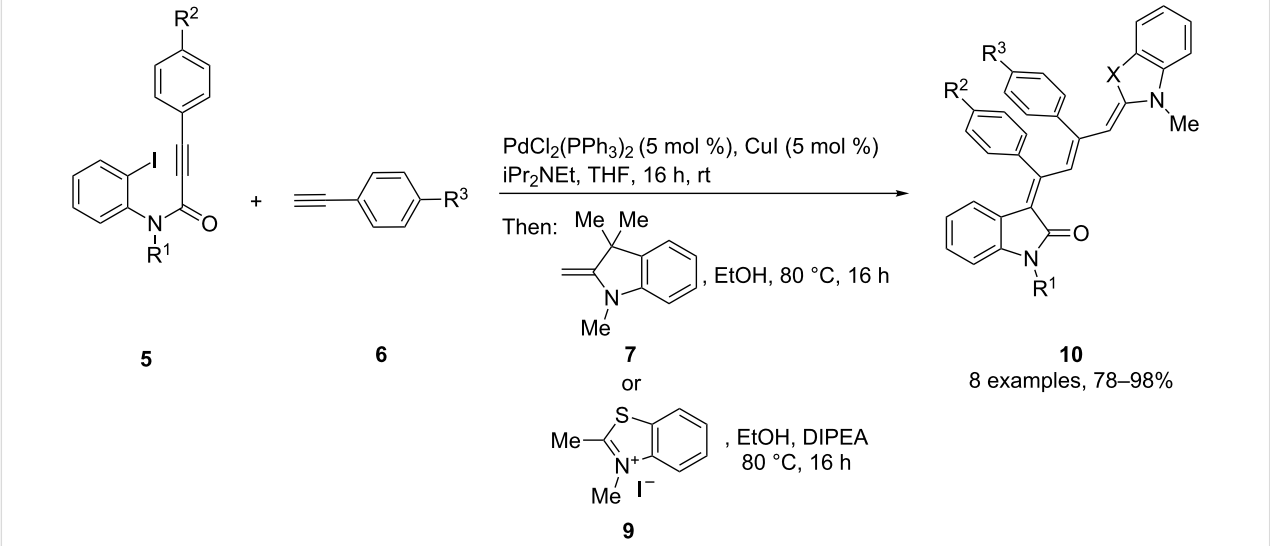


Figure 2: DFT-computed energy differences of the stereoisomers of 2*Z*,4*Z*-**8a** and 2*Z*,4*E*-**8a**.

Interestingly, upon coupling of the *N*-tosyl-substituted alkynoyl *o*-iodoanilides **5b** and **5c** with terminal arylalkynes **6** at room temperature under Sonogashira conditions and reacting the ynylideneindolone intermediates (complete conversion monitored by TLC) [30-32] under the same conditions as above with an ethanolic solution of Fischer's base (**7**), the 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10a–g** (X = CMe_2) were isolated in good to excellent yields as bluish-black solids with a metallic luster (Scheme 2, Table 2, entries 1–7). The sequence starting from the *N*-methyl-substituted alkynoyl *o*-iodoanilide **5a** surprisingly furnishes after coupling and reaction with an ethanolic solution of benzothiazolium iodide **9** in the presence of diisopropylethylamine (DIPEA) the 4-(3-methylbenzo[*d*]thiazol-2(3*H*)-ylidene)but-2-en-1-ylideneindolone **10h** (X = S) as a greenish-black solid and not the corresponding 1-styryleth-2-enylideneindolones **8** (Table 2, entry 8).

The structures of the 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10** were unambiguously assigned by NMR, mass spectrometry and by combustion analysis. The appearance of only a single set of signals in the NMR spectra indicates that the process is highly stereoselective. The occur-



Scheme 2: Three-component synthesis of 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10**.

rence of deep-colored products indicates the presence of a chromophore with extended π-electron conjugation where the terminal acceptor and donor functionalities are connected via an essentially coplanar methine bridge. Based upon analogy to the 4-aminoprop-3-enylideneindolones [30-32] and computations (B3LYP functional, 6-31G* basis set) [44] on geometry-optimized 2*E*,4*Z*,6*Z*- and 2*E*,4*Z*,6*E*-diastereomers of **10a** and **10h** the stereochemistry of the most stable isomers of these novel

Table 2: Three-component synthesis of of 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10**.

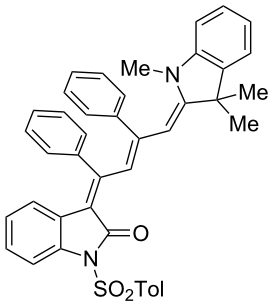
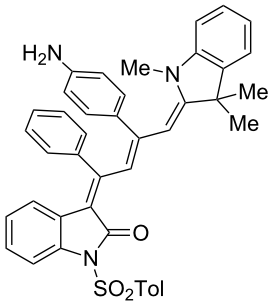
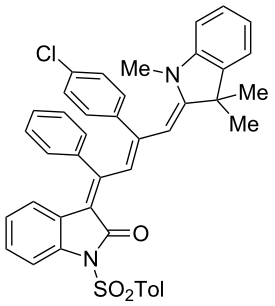
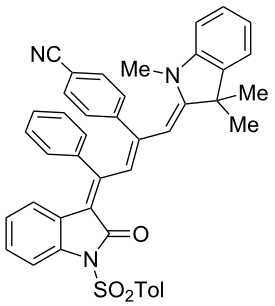
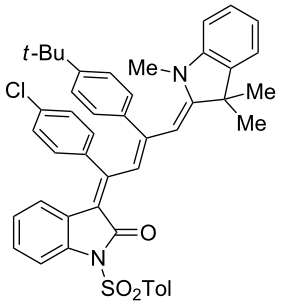
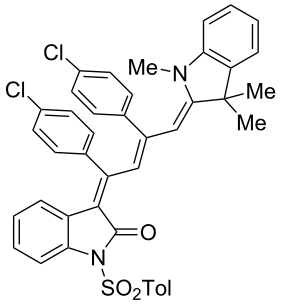
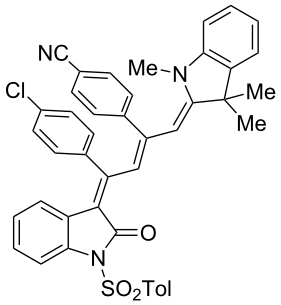
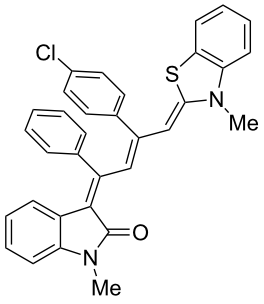
Entry	Alkynoyl *o*-iodoanilides **5**	Alkyne **6**	Enamine **7** or benzothiazolium salt **9**	4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10**	Yield [%][a]
1	R^1 = *p*Tos, R^2 = H (**5b**)	**6a**	**7**	 **10a**	98
2	**5b**	**6e**	**7**	 **10b**	90[b]
3	**5b**	**6c**	**7**	 **10c**	78
4	**5b**	**6d**	**7**	 **10d**	82

Table 2: Three-component synthesis of of 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10**. (continued)

5	R^1 = *p*Tos, R^2 = Cl (**5c**)	R^3 = *t*-Bu (**6e**)	**7**	 **10e**	82
6	**5c**	**6c**	**7**	 **10f**	92
7	**5c**	**6d**	**7**	 **10g**	90
8	**5a**	**6c**	**9**[c]	 **10h**	84

[a]The yields were determined after chromatography on silica gel. [b]The nitro group was reduced to an amino group under the reaction conditions. [c]Diisopropylethylamine was added for in situ generation of the *S*,*N*-ketene acetal.

triene merocyanines was assigned to be 2*E*,4*Z*,6*Z* for both the Fischer's base derivatives **10a–g** (X = CMe_2) and the benzothiazole derivative **10h** (X = S) (Figure 3). Since the stereoconvergent-product formation (only single sets of signals are obtained in the NMR spectra for all representatives of **10**) occurs at elevated temperatures (boiling ethanol in the terminal step) it can be assumed that the assigned structures represent the thermodynamically and kinetically controlled products in this series.

Mechanistically the observed unusual selectivity for the formation of 1-styryleth-2-enylideneindolones **8** vs 4-(1,3,3-

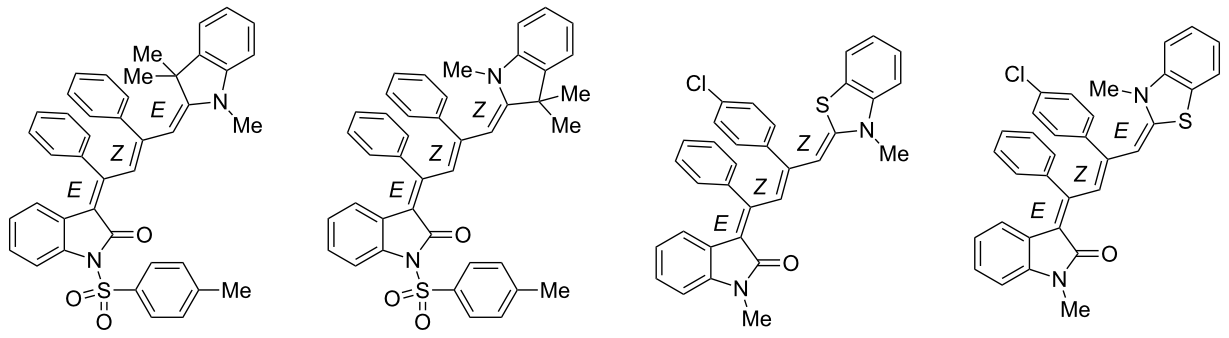
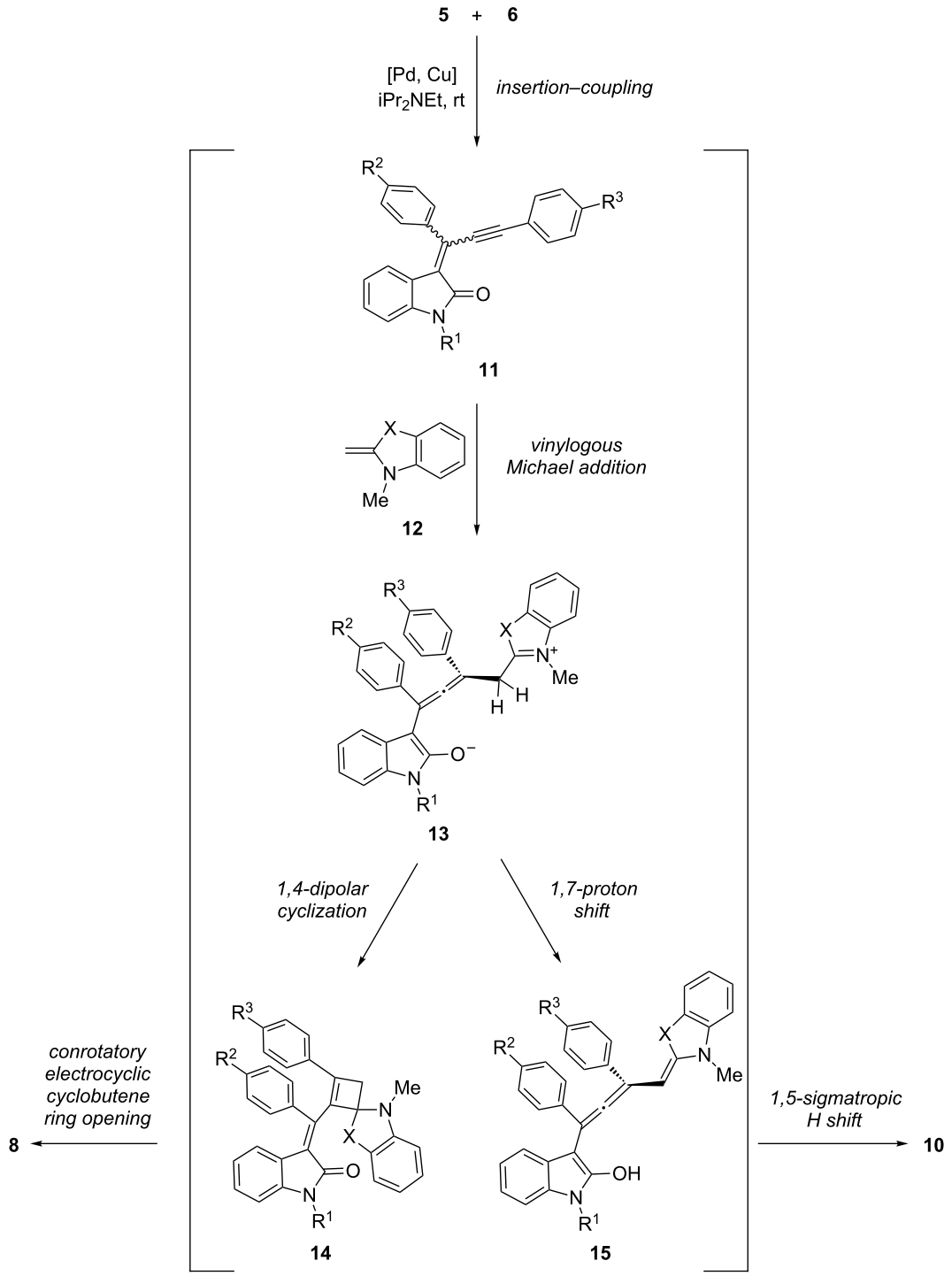


Figure 3: DFT-computed energy differences of the stereoisomers of **10a** and **10h**.

trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10** obviously originates from minute electronic differences in the ynylideneindolone intermediate **11**. This species was previously isolated and unambiguously structurally identified [40]. In the case of amine additions to ynylideneindolone intermediates **11** we recently could show by experimental and computational studies that the terminal Michael addition proceeds in a stepwise fashion with the intermediacy of an allenyl enol that undergoes a rapid, irreversible 1,5-sigmatropic hydride shift triggering the allenyl enol–dienone tautomerism [30]. Therefore, we propose a similar mechanism for the formation of the merocyanines **8** and **10** (Scheme 3). The sequences commence after oxidative addition of the Pd species in the carbon–iodine bond of **5** with a 5-*exo*-*dig* insertion of the appended alkynoyl moiety, which is coupled by transmetallation with the alkyne **6** and reductive elimination to give the ynylideneindolone intermediate **11**. The ynylideneindolone **11** is a vinylogous Michael system, and therefore, it is reasonable to assume a 1,4-addition of the nucleophilic enamine **12**, which is employed directly (as in the case of Fischer's base (**7**)) or generated in situ by deprotonation of the benzothiazolium salt **9**. Hence, in both cases a resonance-stabilized iminium–allenyl enolate **13** is formed. Here, the bifurcation of the sequences takes over. Based upon product analysis the pathway to the formation of the merocyanines **8** begins with a 1,4-dipolar cyclization of **13** furnishing the highly substituted cyclobutene intermediate **14**. Finally, the conrotatory electrocyclic ring opening of the cyclobutene occurs under thermodynamic control, which is obviously only governed by steric effects as reflected by very similar levels of diastereoselectivity of the double-bond formation. In contrast the formation of the merocyanines **10** starts with a proton transfer from the CH-acidic α-position of the iminium moiety of **13** to the amide enolate part. The resulting enol **15** is part of an allenyl enol, which is just perfectly suited for undergoing a 1,5-sigmatropic H-shift, giving directly rise to the formation of the conjugated push–pull triene **10**.

This mechanistic rationale suggests that the observed remarkable chemoselectivity in the formation of two different triene merocyanines could originate from minute electronic distributions in the zwitterionic key intermediate, which is controlled in the allenyl enolate moiety by the indolyl nitrogen substituent R^1 and by the fragment X on the iminium part, which participates in the stabilization on that side of the zwitterion. The former hypothesis is supported by the fact that only methyl-substituted ynylideneindolone intermediates **11** enable the cyclobutene pathway, whereas all *N*-tosyl derivatives exclusively give the merocyanines **10** via the allenyl enol pathway. All other remote substituents on the ynylideneindolone intermediates **11** do not influence the outcome of the sequence. The latter hypothesis of the iminium-ion stabilization obviously influences the lifetime of the zwitterion **13**. Furthermore the enamine formed by deprotonation of **9** is a *S*,*N*-ketene acetal, which is significantly more nucleophilic than Fischer's base (**7**). The higher reactivity of the latter enamine and the higher thermodynamic stability of the iminium intermediate both account for a stepwise pathway that proceeds via the intermediacy of zwitterion **13**. Therefore, if intermediate **13** is long lived enough to undergo the prototropy the merocyanines **10** will be the obvious product. Therefore, the local charge density in **13** is most crucial for the bifurcation and, hence, for the product formation.

For scrutinizing this rationale we computed the electrostatic charges on the atoms 1–7 of the allenyl enolate moiety of model zwitterions **16**, which only differ by the *N*-substituent, on the density functional level of theory (B3LYP functional, 6-31G* basis set) [40]. For a stepwise cyclobutene formation via 1,4-dipolar cyclization the negative partial charge on the central

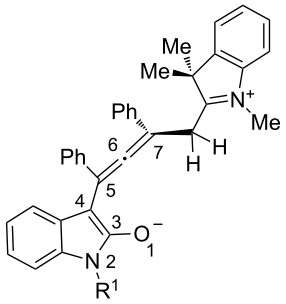


Scheme 3: Mechanistic rationale of the three-component sequence furnishing the 1-styryleth-2-enylideneindolones **8** and 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10**.

allenyl carbon atom 6 should be relatively high. The computations of the electrostatic charges for an *N*-methyl (**16a**) and an *N*-tosyl intermediate (**16b**) clearly shows charge density differences at five distinct atoms (Table 3).

All merocyanines **8** and **10** are expectedly deeply colored both in the solid state and in solution. For further investigation of the photophysical properties the absorption spectra were recorded in dichloromethane solution and of thin films prepared by drop-

Table 3: Selected computed electrostatic charges of zwitterion intermediates **16** (DFT computations with B3LYP functional and the 6-31G* basis set).



16a (R^1 = Me)
16b (R^1 = Tos)

Atom	**16a** (R^1 = Me)	**16b** (R^1 = *p*Tos)
O1	−0.564	−0.520
N2	−0.107	−0.299
C3	0.480	0.416
C4	−0.296	−0.209
C5	0.035	−0.060
C6	−0.162	−0.119
C7	−0.070	−0.089

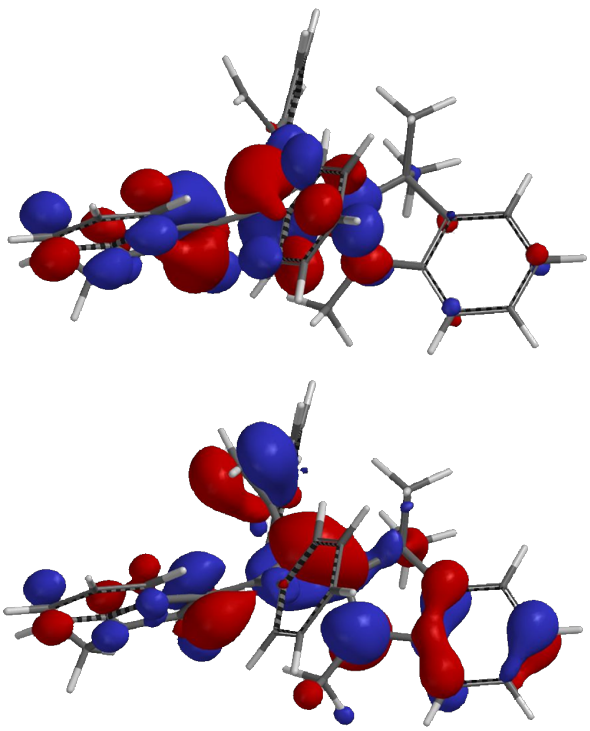


Figure 4: DFT-computed (B3LYP functional, 6-31G* basis set) HOMO (left) and LUMO (right) of merocyanine **8a**.

casting of concentrated dichloromethane solutions on glass-probe cuvettes (Table 4). For the powders and films of the merocyanines **8** intense deep-red luminescence was detected upon eyesight. The emission spectra of the films of **8** were recorded, whereas the films of the merocyanines **10** did not display emission upon eyesight.

The 1-styryleth-2-enylideneindolones **8** are deep red in solution and in the films with intense, broad unstructured absorption bands between 510 and 522 nm in dichloromethane solutions, whereas the maxima of the films are slightly red-shifted and appear between 519 and 532 nm as a result of a *J*-aggregation [45]. Apparently, the aryl substitution on the triene moiety only affects the absorption bands to a minor extent. The merocyanine character of the 1-styryleth-2-enylideneindolones **8** is additionally supported by quantum chemical calculations on the DFT level (B3LYP functional, 6-31G* basis set) [40]. The computed Kohn–Sham frontier molecular orbitals of compound **8a** clearly indicate a charge transfer from the aminovinyl dominated donor fragment in the HOMO to the indolone-centered LUMO, which is generally responsible for the intense longest-wavelength absorption band upon optical excitation (Figure 4).

In contrast to the deep-red luminescence of both amorphous films and dyes in the solid state with sharp bands between 644 and 665 nm (Figure 5), the emission in solution is completely quenched. As already witnessed for the film absorption maxima of the 4-amino-prop-3-enylideneindolones **4** [30,32] the *J*-aggregation results in an induced emission [46,47] by Davydov splitting of the vibrationally relaxed lowest excited-state energy level [48,49] and causes a significant red shift of the sharp emission bands.

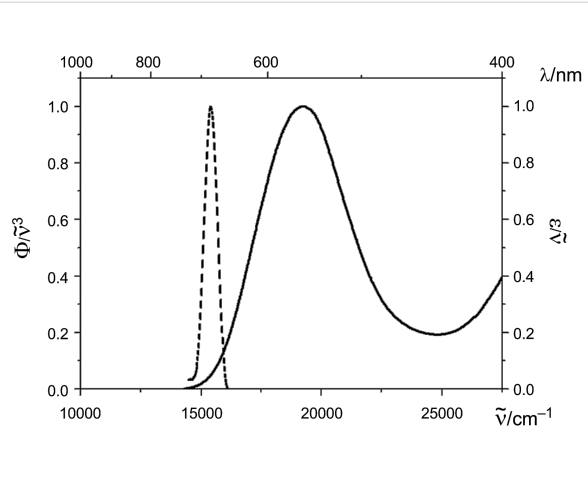


Figure 5: Absorption and emission spectrum of the dropcasted film of compound **8a** (recorded at room temperature, normalized spectra, $\lambda_{max,exc}$ = 490 nm).

Table 4: Selected absorption and emission data of the 1-styryleth-2-enylidene indolones **8** and the 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylidene indolones **10**.

Entry	Compound	Absorption		Emission	Stokes shift
		$\lambda_{max,abs}$ [nm] (ε, L·mol^{-1}·cm^{-1})[a]	$\lambda_{max,abs}$ [nm] (film)[b]	$\lambda_{max,em}$ [nm] (film)[b]	$\Delta\tilde{\nu}$ [cm^{-1}][c] (film)
1	**8a**	510 (23600) 330 (20100) 290 (33200)	519	655	4000
2	**8b**	513 (24200) 327 (25800) 267 (56300)	523	662	4000
3	**8c**	513 (17900) 259 (40200)	525	665	4000
4	**8d**	517 (21500) 298 (39700) 265 (51300)	527	665	3900
5	**8e**	522 (14900) 317 (29300)	532	665	3800
6	**10a**	587 (33600) 290 (20400)	601	–	–
7	**10b**	592 (57500) 276 (51400)	623	–	–
8	**10c**	577 (30200) 257 (66400)	599	–	–
9	**10d**	592 (34000) 375 (15200) 269 (36100)	604	–	–
10	**10e**	597 (50900) 373 (40300) 266 (37300)	609	–	–
11	**10f**	591 (28700)	604	–	–
12	**10g**	597 (39400) 376 (20400) 276 (40700)	607	–	–
13	**10h**	563 (68900) 345 (24500)	617 572 (sh)	–	–

[a]Recorded in dichloromethane. [b]Prepared by dropcasting. [c]$\Delta\tilde{\nu} = \lambda_{max,abs}^{-1} - \lambda_{max,em}^{-1}$ [cm^{-1}].

The 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylidene-indolones **10a–g** are dark-blue to black solids and display in dichloromethane solutions broad unstructured longest wavelength absorption bands in a range from 577 to 597 nm with high molar extinction coefficients. As a consequence of *J*-aggregation the absorption bands of the films are red-shifted and appear between 599 and 623 nm (Table 4, Figure 6). The benzothiazol-terminated merocyanine **10h** displays in dichloromethane solution a hypsochromically shifted absorption band at 563 nm with the highest molar extinction coefficient (Table 4, entry 13), yet for the amorphous film the most pronounced bathochromic shift in the series of the merocyanines **10** (Figure 7). In the solid state a merocyanine characteristic metallic green luster can be seen. Again, the aryl substitution on the triene moiety only affects the absorption bands to a minor extent.

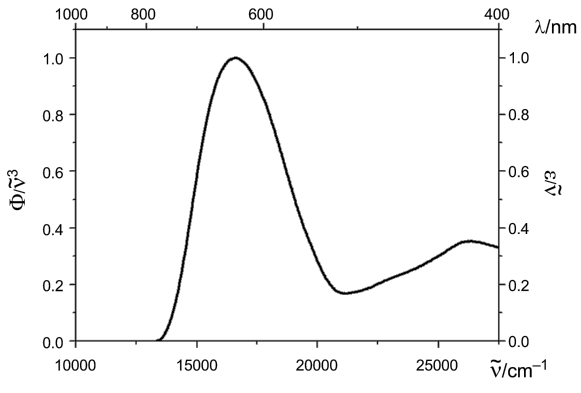


Figure 6: Absorption spectrum of the dropcasted film of compound **10d** (recorded at room temperature, normalized spectrum).

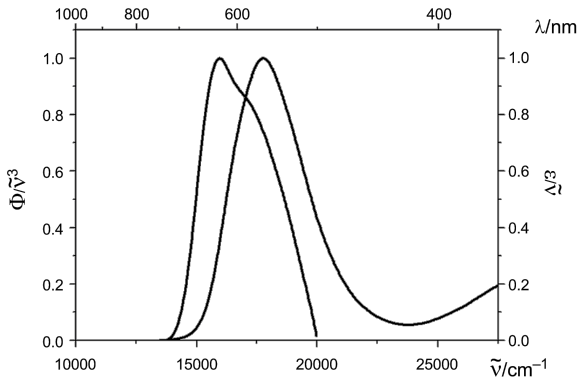


Figure 7: Absorption spectra of compound **10h** in dichloromethane (right trace) and of the dropcasted film (left trace) (recorded at room temperature, normalized spectrum).

For elucidation of the absorption characteristics of the 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones **10**, a thorough geometry optimization of the ground-state structure of compound **10a** was performed using Gaussian09 [50] with the B3LYP functional [51-55] and the Pople 6-311G(d,p) basis set [56]. For a better comparison with the experimentally determined solution spectrum the calculation was carried out using the Polarizable Continuum Model (PCM) applying dichloromethane as a solvent [57]. The minimum structure of **10a** was unambiguously confirmed by an analytical frequency analysis.

The optimized structure of **10a** was submitted to a TD-DFT calculation for assigning the experimentally determined absorption characteristics (Table 5). Therefore, the hybrid exchange–correlation functional CAM-B3LYP [58] was implemented and a non-equilibrium solvation [59-63] for the state-specific solvation of the vertical excitation was included.

The computations reveal that the longest wavelength absorption maximum appears at 541 nm, i.e., at a comparable energy as in the experimental spectrum. This transition is exclusively dominated by the HOMO–LUMO transition. The computed Kohn–Sham frontier molecular orbitals of structure **10a** clearly indicate the charge-transfer character from HOMO to LUMO along the triene axis in the molecule, which generates the intense longest wavelength absorption band upon optical excitation (Figure 8). While the phenyl substituents on the triene chromophore largely contribute to shorter wavelength absorption bands, the tosyl moiety does not display any coefficient density in the FMOs and, therefore, qualifies as a favorable electronic innocent bridge for ligating other chromophores to this novel class of merocyanines.

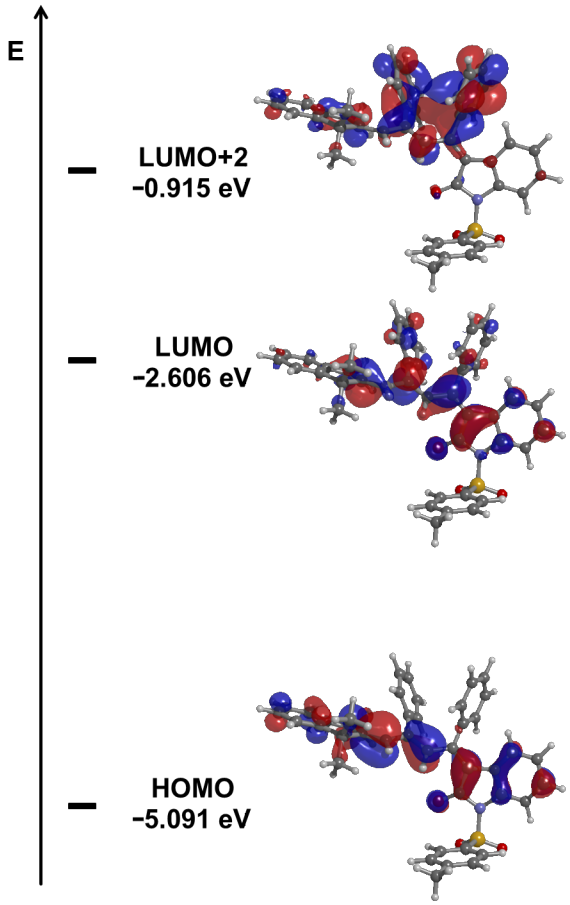


Figure 8: DFT-computed (B3LYP functional, 6-311G(d,p) basis set) FMOs (HOMO, bottom; LUMO (center), and LUMO+2 (top)) of merocyanine 2*E*,4*Z*,6*Z*-**10a**.

Table 5: Experimental and TD-DFT computed (CAM-B3LYP 6-311G(d,p)) absorption maxima of the 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolone 2*E*,4*Z*,6*Z*-**10a**.

Structure	Experimental $\lambda_{max,abs}$ [nm][a]	Computed $\lambda_{max,abs}$ [nm]	Dominant contributions
2*E*,4*Z*,6*Z*-**10a**	290	286	HOMO → LUMO+2 (56%)
	–	345	HOMO−1 → LUMO (89%)
	587	541	HOMO → LUMO (96%)

[a]Recorded in dichloromethane.

Conclusion

In conclusion, we enabled the diversity-oriented synthesis of novel triene merocyanines with intense bathochromic absorption by a consecutive three-component insertion–coupling–addition sequence in good to excellent yields. While the *N*-substituent on the indolone moiety exerts minute electronic differences in the dipolar intermediate, which is responsible for the bifurcation as supported by computational studies, enamine nucleophiles favorably lead to 1-styryleth-2-enylideneindolones diastereomers for *N*-methyl-substituted anilides. The *S*,*N*-ketene acetal derived from dimethyl benzothiazolium favors the formation of the corresponding 4-(3-methylbenzo[*d*]thiazol-2(3*H*)-ylidene)but-2-en-1-ylideneindolone. 4-(1,3,3-Trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones are also the exclusive products for *N*-tosylanilides as starting materials. As a result of aggregation-induced luminescence, 1-styryleth-2-enylideneindolones display in films and in the solid state distinct and intensive deep-red emission upon excitation of the longest wavelength absorption band. 4-(1,3,3-Trimethylindolin-2-ylidene)but-2-en-1-ylideneindolones neither luminesce in solution nor in the solid state upon electronic excitation, yet, they display broad absorption bands and computations suggest, that novel types of panchromatic absorbing bichromophores should be readily available by ligating the second chromophore via the electronically nonperturbing *N*-sulfonyl moiety. Synthetic, photophysical, and computational studies addressing aggregating broad-band absorbing bichromophores are currently underway.

Experimental

8c: In a flame-dried and argon-flushed Schlenk tube the iodophenylanilide **5a** (361 mg, 1.00 mmol), alkyne **6c** (150 mg, 1.10 mmol), and dry, degassed THF (5 mL) were placed. After the addition of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (10 mg, 0.05 mmol), diisopropylethylamine (1.7 mL, 10 mmol) was added and the reaction mixture was stirred at rt for 16 h. Then, Fischer's base (**7**, 346 mg, 2.00 mmol), and EtOH (2 mL) were added. The sealed reaction vessel was placed in a thermostatted oil bath at 80 °C and stirred for 48 h. After cooling to rt the solvents were removed in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc 9:1) to give the 1-styryleth-2-enylideneindolone **8c** (441 mg, 0.82 mmol, 82%) as violet solid, dr = 56:44. Mp 228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46–1.58 (m, 6H), 2.75–3.29 (m, 6H), 4.92 (0.56H), 5.61 (s, 0.56H), 5.78 (s, 0.56H), 6.25 (d, *J* = 7.8 Hz, 0.56H), 6.40–6.56 (m, 2H), 6.60–6.67 (m, 1H), 6.80–7.29 (m, 11H), 7.32 (d, *J* = 7.4 Hz, 0.56H); additional signals for the minor diastereomer: δ 4.61 (s, 0.44H), 5.33 (s, 0.44H), 6.73 (d, *J* = 7.5 Hz, 0.88H), 7.49 (d, *J* = 7.1 Hz, 0.44H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2 (CH_3), 26.2 (CH_3), 36.2 (CH_3), 49.4 (C_{quat}), 106.8 (C_{quat}), 107.1 (CH), 107.9 (CH), 115.0 (CH_2), 120.4 (CH), 121.3 (CH), 122.2 (CH), 124.3 (C_{quat}), 124.8 (C_{quat}), 126.4 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 128.9 (CH), 129.5 (CH), 130.0 (CH), 131.2 (CH), 132.9 (C_{quat}), 133.2 (C_{quat}), 140.2 (C_{quat}), 140.4 (C_{quat}), 140.5 (C_{quat}), 141.4 (C_{quat}), 144.4 (C_{quat}), 145.5 (C_{quat}), 153.9 (C_{quat}), 165.4 (C_{quat}); additional signals for the minor diastereomer: δ 26.3 (CH_3), 37.4 (CH_3), 50.1 (C_{quat}), 107.2 (C_{quat}), 107.2 (CH), 120.1 (CH_2), 120.8 (CH), 121.6 (CH), 122.5 (CH), 126.5 (CH), 127.5 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 129.0 (CH), 129.5 (CH), 132.5 (CH), 154.4 (C_{quat}), 167.5 (C_{quat}); EIMS (70 eV) *m*/*z* (% relative intensity): 544 ($[^{37}Cl–M]^+$, 23), 542 ($[^{35}Cl–M]^+$, 100), 382 ($[C_{25}H_{18}{}^{35}ClNO]^+$, 22), 158 ($[C_{11}H_{12}N]^+$, 38); IR (KBr) $\tilde{\nu}$: 3080, 3053, 2968, 2924, 2862, 1654, 1598, 1541, 1471, 1456, 1438, 1413, 1373, 1352, 1336, 1288, 1263, 1236, 1203, 1138, 1122, 1085, 1074, 1024, 1009, 958, 925, 893, 846, 825, 799, 732, 711, 693, 650, 619 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (ε): 259 (40200), 513 (17900); HRMS (*m*/*z*) calcd for $C_{36}H_{31}{}^{35}ClN_2O$: 542.2125; found: 542.2119; Anal. calcd for $C_{36}H_{31}ClN_2O$ (543.1): C, 79.61; H, 5.75; N, 5.16; found: C, 79.80; H, 6.02; N, 5.16.

10a: In a flame-dried and argon-flushed Schlenk tube iodophenylanilide **5b** (501 mg, 1.00 mmol), alkyne **6a** (112 mg, 1.10 mmol), and dry, degassed THF (5 mL) were placed. After the addition of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (10 mg, 0.05 mmol), diisopropylethylamine (1.7 mL, 10 mmol) was added and the reaction mixture was stirred at rt for 16 h. Then, the enamine **7** (346 mg, 2.00 mmol) and EtOH (2 mL) were added. The sealed reaction vessel was placed in a thermostatted oil bath at 80 °C and stirred for 48 h. After cooling to rt the solvents were removed in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc 4:1) to give the 4-(1,3,3-trimethylindolin-2-ylidene)but-2-en-1-ylideneindolone **10a** (636 mg, 98%) as bluish-black solid. Mp 141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 6H), 2.30 (s, 3H), 2.31 (s, 3H), 4.68 (d, *J* = 1.4 Hz, 1H), 5.70 (d, *J* = 7.3 Hz, 1H), 6.27 (d, *J* = 7.8 Hz, 1H), 6.56 (t, *J* = 7.8 Hz, 1H), 6.74 (dt, *J* = 7.3, 0.7 Hz, 1H), 6.90–7.22 (m, 12H), 7.32 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.66 (d, *J* = 1.4 Hz, 1H), 7.80 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (CH_3), 29.4 (CH_3), 34.4 (CH_3), 46.7 (C_{quat}), 94.3 (CH), 107.4 (CH), 113.0 (CH), 118.2 (C_{quat}), 120.8 (CH), 121.8 (CH), 122.7 (CH), 123.4 (CH), 124.6 (CH), 125.4 (C_{quat}), 127.3 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 128.9 (CH), 129.1 (CH), 129.3 (CH), 129.5 (CH), 129.8 (CH), 136.4 (C_{quat}), 137.1 (C_{quat}), 138.2 (C_{quat}), 140.7 (C_{quat}), 144.4 (C_{quat}), 145.1 (C_{quat}), 146.4 (C_{quat}), 153.9 (C_{quat}), 155.9 (C_{quat}), 161.8 (C_{quat}), 165.9 (C_{quat}). EIMS (70 eV) *m/z* (% relative intensity): 648 ($[M]^+$, 4), 493 ($[C_{35}H_{29}N_2O]^+$, 6), 334 (31), 321 (11), 306 (11), 291 (12), 222 (11), 218 (37), 144 (33), 142 (47), 132 (27), 127 (22), 117 (16), 105 (53), 91 (100); IR (KBr)

$\tilde{\nu}$: 3051, 2964, 2924, 2862, 1691, 1577, 1504, 1485, 1465, 1454, 1442, 1400, 1367, 1334, 1315, 1290, 1246, 1217, 1176, 1161, 1130, 1161, 1130, 1116, 1085, 1076, 1060, 1018, 1001, 960, 943, 925, 873, 854, 815, 773, 742, 725, 686, 663, 651, 611 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max}, nm (ε): 290 nm (20400), 587 (33600); Anal. calcd for $C_{42}H_{36}N_2O_3S$ (648.8): C, 77.75; H, 5.59; N, 4.32; found: C, 77.58; H, 5.41; N, 4.29.

Supporting Information

Supporting Information File 1

Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of compounds **8** and **10**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-51-S1.pdf]

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Rapid pseudo five-component synthesis of intensively blue luminescent 2,5-di(hetero)arylfurans via a Sonogashira–Glaser cyclization sequence

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Full Research Paper

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Abstract

2,5-Di(hetero)arylfurans are readily accessible in a pseudo five-component reaction via a Sonogashira–Glaser coupling sequence followed by a superbase-mediated (KOH/DMSO) cyclization in a consecutive one-pot fashion. Besides the straightforward synthesis of natural products and biologically active molecules all representatives are particularly interesting due to their bright blue luminescence with remarkably high quantum yields. The electronic structure of the title compounds is additionally studied with DFT computations.

Introduction

Multicomponent reactions (MCRs) [1-5] are conceptually diversity-oriented syntheses (DOS) [6,7] and have been developed to powerful tools for exploring broad ranges of different structural and functional characteristics. In addition, MCRs address the very fundamental principles of reaction efficiency and atom economy. Besides lead finding in pharmaceutical and medicinal chemistry [8-10] MCRs have also been recognized as a DOS tool for approaching functional π-systems [11] such as luminescent chromophores [6].

Interestingly, multicomponent syntheses of symmetrically substituted furans have remained rare [12,13], although furans are ubiquitous in nature [14]. In particular, 2,5-di(hetero)arylfurans are structural units with pronounced biological activities [15] and besides in natural products [16,17] they are also present in potential pharmaceuticals for the treatment of human African trypanosomiasis [18-20], and against human renal cancer cells [21-23]. Furthermore, 2,5-di(hetero)arylfurans have been reported as photonic chromophores [24]. However, the

electronic and photophysical properties of 2,5-di(hetero)aryl furans have only been occasionally studied [25-27].

The classical synthesis of symmetrical 2,5-disubstituted furans proceeds via Paal–Knorr synthesis [28]. Due to sophisticated starting materials this very general pathway is often not suitable for a DOS approach. In addition, some starting materials are either not readily available or quite expensive. 2,5-dihalogenated furans can be in principle employed in cross-coupling reactions, however, the poor stability of these dihalogenated precursors renders this approach very tedious [29]. Recent publications report gold-catalyzed syntheses of di(hetero)arylfurans starting from arylbutadiynes [30,31]. However, the major drawback of this approach is the complex, time-consuming preparation of the complicated gold catalyst and the separate synthesis of the butadiyne substrates. In a similar study arylbutadiynes prepared by Glaser homocoupling were converted into symmetrical 2,5-di(hetero)arylfurans [32] employing the superbase system DMSO/KOH/H_2O in the terminal cyclization step [33]. The same approach was applied to butadiynes that were formed by oxidative dimerization of arylalkynes with a Cu/Fe catalyst [34]. Apart from using reactive terminal alkynes as starting materials the major drawbacks of this approach are clearly the extended reaction times (3–6 d) and the removal of the catalyst after the coupling step.

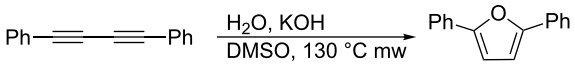
Recently, we became particularly interested in sequentially Pd-catalyzed processes [35] starting from (hetero)aryl iodides [36]. In particular, the Pd–Cu-catalyzed Sonogashira–Glaser sequence represents a highly intriguing combination of a cross-coupling and an oxidation reaction in a one-pot fashion [37]. By this approach we can efficiently avoid the major disadvantage of starting from terminal alkynes, which are occasionally unstable and tend to undergo polymerization. Based upon the Sonogashira–Glaser sequence we recently presented a straightforward one-pot sequence for the synthesis of 2,5-di(hetero)arylthiophenes [38]. Here, we report the methodological development of a novel multicomponent synthesis of symmetrical 2,5-(hetero)arylfurans in the sense of a consecutive one-pot sequence. In addition, the photophysical and electronical properties are studied and the electronic structure is investigated by DFT calculations.

Results and Discussion

Synthesis

Prior to setting up the one-pot sequence we first optimized the conditions of the terminal cyclization step for the formation of 2,5-diphenylfuran (**2a**, Table 1) starting from 1,4-diphenylbutadiyne (**1a**) as a substrate. Just upon eyesight a remarkable luminescence of **2a** caught our attention and we were encouraged to perform photophysical studies with these products as well (vide infra). In a set of experiments the reaction times under microwave heating (the temperature optimum of 130 °C was quickly identified by screening experiments), the water/KOH ratio, and the concentrations were varied.

Table 1: Evaluation of different reaction conditions.



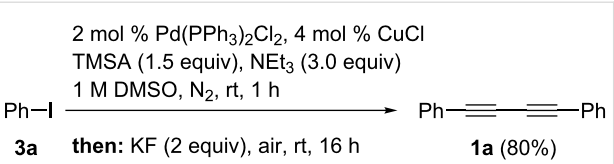
1a **2a**

Entry	H_2O [equiv]	KOH [equiv]	DMSO [mL/mmol]	Time [h]	Yield[a] [%]
1	2	2	4	1	53
2	2	2	4	3	24
3	10	2	4	1	25
4[b]	2	2	4	1	34
5[c]	2	2	4	1	36
6[c]	16	10	4	1	50
7[d]	8	10	4	1	40
8[d,e]	8	10	4	6	43
9	2	2	8	1	58
10	4	4	8	1	64
11	2	8	16	1	13
12	**8**	**8**	**16**	**1**	**84**
13	12	12	16	1	79

[a]Isolated yield after chromatography on silica gel. [b]In the presence of 2 mol % $PdCl_2(PPh_3)_2$. [c]In the presence of 5 mol % CuI, 15 mol % DMEDA. [d]In the presence of 5 mol % CuI, 15 mol % 1,10-phenanthroline. [e]Conductive heating (oilbath at 130 °C).

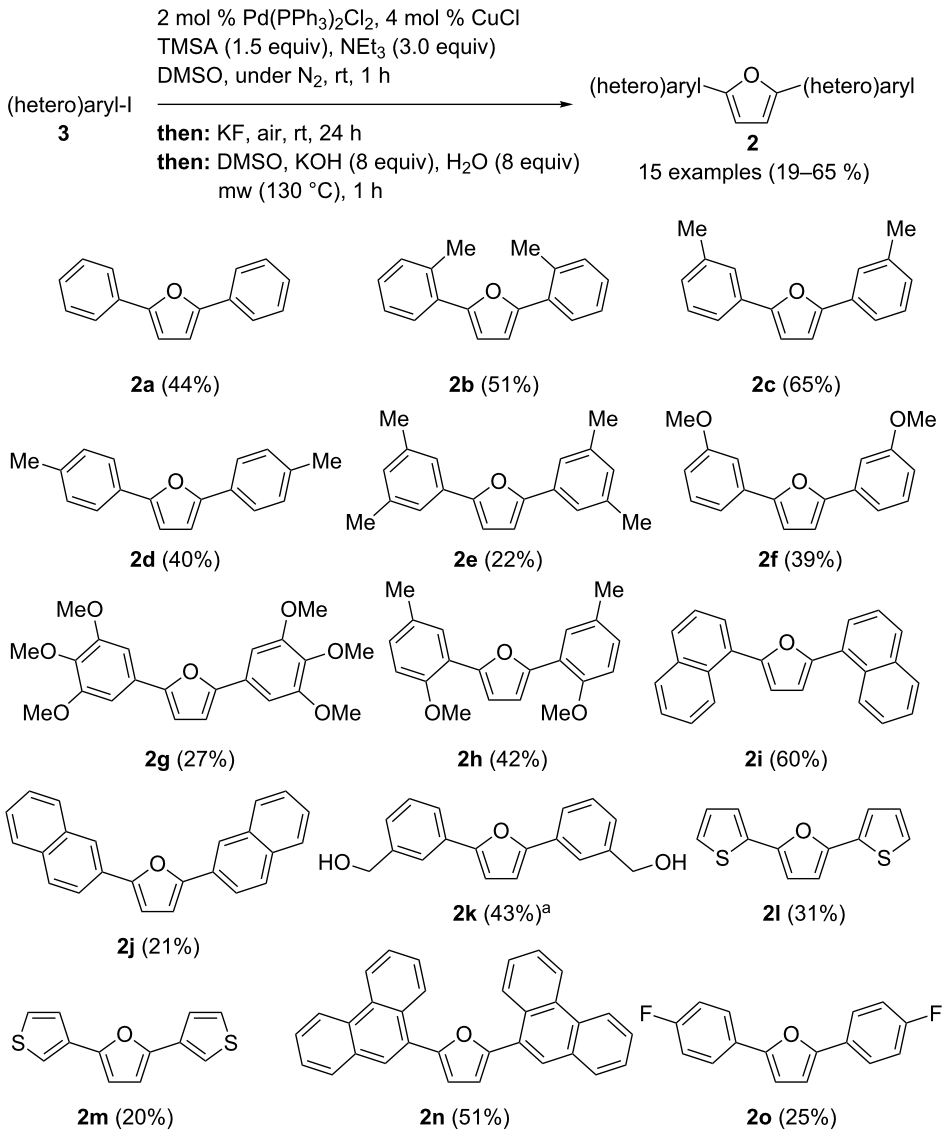
In the course of our studies a related work using copper catalysts with the electronrich DMEDA (*N,N'*-dimethylethylenediamine) or the electronpoor 1,10-phenanthroline as ligands was published [32], however, in our hands no favorable effect on the isolated yields of **2a** was found (Table 1, entries 4–8). The cyclization works equally well with conductive heating in an oil bath instead of microwave heating (Table 1, entry 8). At higher concentrations we always observed the formation of byproducts that were not detectable by GC, although **1a** was completely consumed. An isolated black solid with an elemental analysis matching with the elemental composition of **2a** was partially soluble in acetone and THF. The supernatant of the THF extraction was analyzed by MALDI–TOF mass spectrometry indicating the formation of oligomers with m/z = 422 to 1046. We could efficiently suppress this oligo- and polymerization by increasing the amount of solvent, i.e. by dilution (Table 1, entries 9–13). Additionally increasing the concentration of KOH and water also proved to be beneficial (Table 1, entries 10–13). The optimal conditions for this cyclization are marked in entry 12 of Table 1.

With these optimized conditions in hand we started to concatenate the one-pot sequence by generating the required 1,4-butadiynes from (hetero)aryl iodides. First, the Sonogashira–Glaser sequence had to be performed in DMSO as a solvent and in the presence of atmospheric oxygen for the Glaser step. Starting from iodobenzene (**3a**) and trimethylsilylacetylene (TMSA) the cross-coupling in DMSO proceeded uneventfully and the yield of the Glaser product **1a** was found to be 80%, i.e. approximately the same yield as for the sequence in THF as a solvent (Scheme 1) [37]. Most favorably no additional cosolvent was needed for increasing the solubility of the fluoride source [38]. For an optimal Glaser step vigorous stirring is required to ensure an efficient air saturation of the solvent.



Scheme 1: Sonogashira–Glaser sequence in DMSO as a solvent.

Finally, starting from (hetero)aryl iodides **3** and TMSA we combined the Sonogashira–Glaser sequence with the cyclization step into a one-pot sequence and studied the substrate scope of this pseudo five-component synthesis of 2,5-di(hetero)arylfurans **2** (Scheme 2). All reactions were performed on a 2 mmol scale.



Scheme 2: Pseudo five-component Sonogashira–Glaser cyclisation synthesis of 2,5-di(hetero)arylfurans **2** ([a]obtained from the THP-protected precursor).

The structural assignments of all furans **2** were unambiguously supported by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and combustion analysis (HRMS in case of **2j** and **2m**). Due to the poor solubility of some compounds all spectra were recorded in DMSO at room temperature, whereas the compounds **2r** and **2p** were measured at 80 °C.

The yields of the obtained 2,5-di(hetero)arylfurans **2** are moderate to good and the employed (hetero)aryl substituents can be electroneutral (**2a**, **2i**, **2j**) and electronrich (**2b**–**2h**, **2k**, **2l, 2m**). Substituents in *ortho*- (**2b, 2h**), *meta*- (**2c**, **2e**–**2h**, **2k**) and *para*-position (**2d**, **2g**, **2o**) are well tolerated. Polar substituents like alcohols (**2k**) can also be employed in the sequence. From the literature it is known that the naturally occurring compound **2h** [16,17] and 2,5-bis(3,4,5-trimethoxyphenyl)furan (**2g**) are highly biological active [39]. Compound **2k** is structurally related to small molecule inhibitors of p53-HDM-2 [21-23].

Electronic properties and computational studies

All title compounds **2** display strong fluorescence in solution and in the solid state upon UV excitation (Figure 1). Therefore, the absorption and emission spectra of all compounds **2** were recorded in dichloromethane and the fluorescence quantum yields Φ_f were determined with coumarin 1 or *p*-terphenyl as references (Table 2).

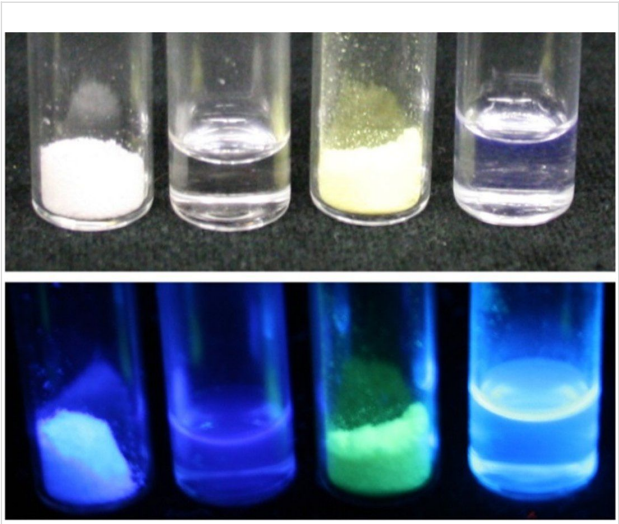


Figure 1: Compounds **2d** (solid and THF solution) and **2n** (solid and THF solution) (from left to right) under daylight (top) and under UV light (bottom, $\lambda_{max,exc}$ = 366 nm).

The most furans display intense, broad absorption bands between 321 and 358 nm with molar extinction coefficients between 21000 to 35000 L/mol cm^{-1}. In addition redshifted shoulders appear between 336 and 377 nm. Likewise the emission maxima are found between 367 and 439 nm and blueshifted shoulders appear between 351 and 424 nm. The Stokes shifts $\tilde{\nu}$ determined from the absorption and emission

Table 2: Selected absorption and emission data (recorded in dichloromethane at *T* = 293 K).

Compound	$\lambda_{max, abs}$ [nm][a] ([L·mol·cm^{-1}])	$\lambda_{max, em}$ [nm]	$\Delta\tilde{\nu}$ [cm^{-1}][b]	Φ_f
2a	**327** (35000), 342 sh	358 sh, **373**	3800	83%[c]
2b	**314** (23000), 342 sh	359 sh, **375**	5200	59%[c]
2c	**329** (33000), 344 sh	360 sh ,**376**	3800	72%[c]
2d	**331** (33000), 348 sh	360 sh, **379**	3800	64%[c]
2e	**331** (28000), 347 sh	362 sh, **379**	3800	55%[c]
2f	**331** (29000), 347 sh	362 sh, **381**	4000	95%[c]
2g	**340** (33000), 356 sh	378 sh, **391**	3800	80%[c]
2h	**347** (33000), 364 sh	377 sh, **395**	3500	47%[c]
2i	**347** (29000)	424 sh, **436**	5900	75%[d]
2j	**358** (26000), 377 sh	393 sh, **411**	3600	100%[d]
2k	**329** (32000), 345 sh	362 sh, **377**	3900	80%[c]
2l	**353** (24000), 371 sh	389 sh, **407**	3800	42%[c,e]
2m	**321** (23000), 336 sh	351 sh, **367**	3900	29%[c]
2n	**343** (23000)	**439**	6400	69%[d]
2o	**323** (21000), 338 sh	353 sh, **368**	3800	76%[c]

[a]sh = shoulder. [b]The boldfaced absorption and emission maxima were used to calculate the Stokes shifts. [c]*p*-Terphenyl (Φ_f = 93% in cyclohexane) as a reference [40]. [d]Coumarin 1 (Φ_f = 73% in EtOH) as a reference [41]. [e]Ref. [26]: Φ_f = 33% in acetonitrile.

maxima range from 3500 to 6400 cm^{-1} and the quantum yields are quite large in a range from Φ_f = 29 to 100%. The compounds **2b**, **2i** and **2n** display unstructured broad absorption and emission bands and possess the largest Stokes shifts.

This peculiar effect could arise from considerable geometrical differences between the electronic ground state and the vibrationally relaxed excited state caused by significant distortion of the aryl substituents from coplanarity in the ground state [42]. Therefore, the geometries of the ground state structures of the compounds **2a**,**2b**,**2i**,**2j,** and **2n** were optimized on the DFT level of theory (B3LYP functional [43-46] and the Pople 6-311G(d,p) basis set [47]) as implemented in Gaussian09 [48]. The computations applied the Polarizable Continuum Model (PCM) using dichloromethane as solvent [49]. All minima were confirmed by analytical frequency analyses. In conclusion, the computations clearly reveal that the *ortho*-aryl substituted compounds **2b**, **2h**, **2i** and **2n** are twisted from coplanarity while the other compounds are coplanar (Figure 2).

In the UV–vis spectra the similar planar structures **2a** and **2c** are bathochromically shifted in comparison to the twisted structure **2b**. The twisting from coplanarity also results in a lower fluorescence quantum yield Φ_f. The same holds true for the comparison of the constitutional isomers **2i** and **2j**. Therefore, the twisted structure of **2j** causes a larger Stokes shift and a much lower fluorescence quantum yield Φ_f. The huge Stokes shift originates from a considerable planarization in the excited state [42]. The absorption maximum of **2h** is considerably shifted bathochromically in comparison to those of **2c**, **2e**, and **2f**. The DFT calculation on structure **2h** reveals a twisted ground state structure. In the whole series compound **2j** shows the most redshifted absorption maximum and the highest fluorescence quantum yield Φ_f. This finding correlates well with the planar ground state structure and an associated low Stokes shift. All studied representatives are potentially interesting singlet blue-light emitters.

In addition, the electronic properties of the furans **2** have been studied by cyclic voltammetry (Table 3). Most cyclovoltammograms display reversible Nernstian one-electron oxidations in the anodic region between 1.06 and 1.25 V (vs Ag/AgCl) (Table 3). Expectedly, with increasing electron density the oxidative potential diminishes. The compounds **2f**, **2g**, **2l**, and **2n** could not be measured by cyclic voltammetry due to precipitation on the electrode. The determined oxidation potentials $E_{1/2}^{0/+1}$ vs Ag/AgCl were recalculated vs the normal hydrogen electrode (NHE) and then transformed into eV [50]. The reduction potentials were calculated by subtraction of the S_1–S_0 energy gap (in eV) from the first oxidation potential $E_{1/2}^{0/+1}$. This gap was estimated by the cross-section of the absorption and emission spectra. For the missing oxidation potentials of **2f**, **2g**, **2m**, and **2l** the HOMO and LUMO energies were determined by DFT calculations [48]. For validation of the experimental and computational data the oxidation and reduction potentials were converted into the corresponding experimental HOMO and LUMO energies (for details see Supporting Information File 1). The plot of measured and calculated HOMO energies gives a reasonable linear correlation (r^2 = 0.815, omitting the twisted compounds **2b**, **2h**, **2i** and **2n**) with a mean deviation of 0.05 eV (see Supporting Information File 1). Roughly a similar trend can be found for the HOMO–LUMO gap.

The inspection of the coefficient densities in the Kohn–Sham frontier molecular orbitals of the compounds **2i**, **2j**, and **2n** underlines that the HOMO and the LUMO are delocalized over the whole molecule (Figure 3), which plausibly rationalizes the high extinction coefficient of the longest wavelength absorptions bands.

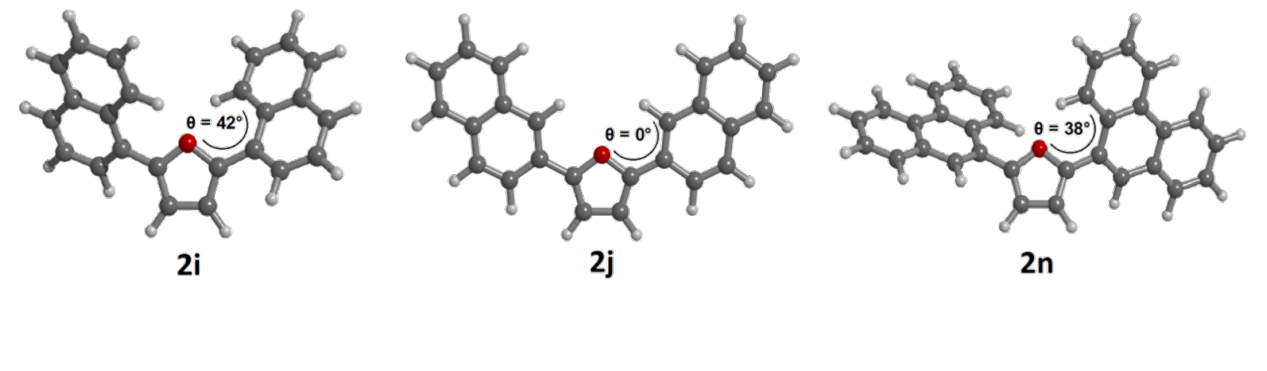


Figure 2: Selected computed minimum conformations of the 2,5-diarylfurans **2i**, **2j**, and **2n**.

Table 3: Selected cyclovoltammetric[a] (recorded in dichloromethane at 293 K) and computational[b] data.

Compound	$E_0^{0/+1}$ [V][c]	$E_{1/2}^{0/+1}$ [V] vs NHE[c]	$E_{1/2}^{0/-1}$ [V] vs NHE[d]	HOMO [eV]		LUMO [eV]		$\Delta E_{HOMO-LUMO}$	
				exp.[e]	calcd.[d]	exp.[f]	calcd.[b]	exp.	calcd.[b]
2a	1.25	1.45	−2.11	−5.60	−5.57	−2.04	−1.60	3.56	3.97
2b	1.19	1.39	−2.18	−5.54	−5.59	−1.97	−1.51	3.57	4.08
2c	1.19	1.39	−2.15	−5.54	−5.50	−2.00	−1.57	3.54	3.93
2d	1.09	1.29	−2.22	−5.44	−5.41	−1.93	−1.49	3.51	3.92
2e	1.06	1.26	−2.24	−5.41	−5.46	−1.91	−1.51	3.50	3.95
2f	–	–	–	–	−5.55	–	−1.57	–	3.98
2g	–	–	–	–	−5.44	–	−1.58	–	3.86
2h	1.24	1.44	−2.22	−5.59	−5.41	−1.93	−1.16	3.66	4.25
2i	1.15	1.35	−1.81	−5.50	−5.54	−2.34	−1.81	3.16	3.73
2j	1.10	1.30	−1.94	−5.45	−5.46	−2.21	−1.93	3.24	3.53
2k	1.16	1.36	−2.17	−5.51	−5.53	−1.98	−1.56	3.53	3.97
2l	–	–	–	–	−5.37	–	−1.70	–	3.67
2m	–	–	–	–	−5.44	–	−1.38	–	4.06
2n	1.14	1.34	−1.82	−5.49	−5.59	−2.33	−1.81	3.16	3.78
2o	1.24	1.44	−2.17	−5.59	−5.57	−1.98	−1.60	3.61	3.97

[a] 0.1 M electrolyte: $[Bu_4N][PF_6]$ (120 mg in 3 mL dichloromethane), Pt working electrode, Pt counter electrode, Ag/AgCl (in KCl) reference electrode. [b]Calculated with Gaussian09, B3LYP/6-311G(d,p). [c] $E_{1/2} = E_0 + NHE$ (with NHE (3 M KCl Ag/Ag^+) = 0.198 V).
[d] $E_{0-1/20/-10} = E_{1/2} - \frac{h\nu}{\lambda_{cross}}$ (with cross-section of absorption and emission spectra).
[e] $E_{HOMO} = -\left(E_{\frac{1}{2}}(Ox1) - E_{\frac{Fc}{Fc+}}\right) - 4.6eV8\cdot$ [f] $E_{LUMO} = -\left(E_{0-0} - E_{\frac{Fc}{Fc+}}\right) - 4.6eV\cdot$

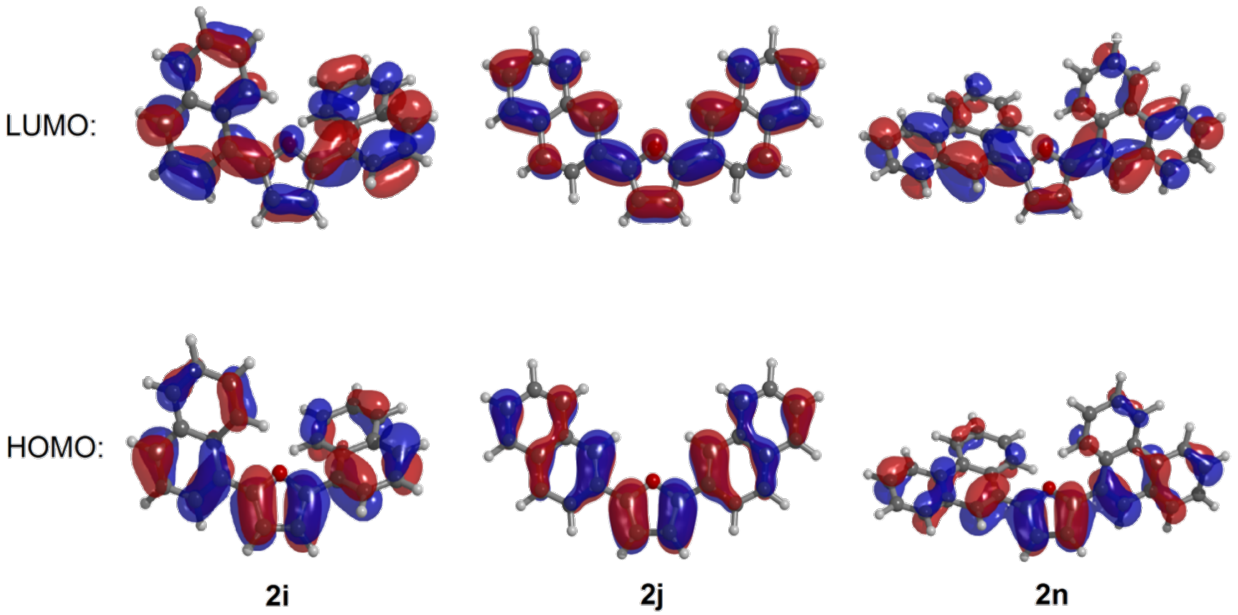


Figure 3: Kohn–Sham HOMOs (bottom) and LUMOs (top) of the compounds **2i**, **2j**, and **2n** (calculated on the DFT level of theory (B3LYP/6-311G(d,p)).

Conclusion

In summary we have disclosed a concise and efficient microwave-assisted pseudo five-component synthesis of symmetrical 2,5-di(hetero)arylfurans in a one-pot fashion, which opens a ready access to biologically active furan derivatives. In addition the investigation of the photophysical properties of these compounds reveals an intense blue luminescence in solution approaching unity for the fluorescence quantum yield Φ_f of distinct derivatives. Computations account for significant distortions from coplanarity in the electronic ground state and the computed HOMO energies correlate with the first reversible oxidation potentials determined by cyclic voltammetry.

Experimental

Pseudo five-component synthesis of 2a [51] **in a manner similar to** [38]**:** A mixture of iodobenzene (**3a**, 408 mg, 2.00 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol, 2 mol %), and CuCl (7.92 mg, 0.08 mmol, 4 mol %) was dissolved in DMSO (2.00 mL) in a 80 mL microwave vessel equipped with a stirring bar and a septum and was degassed with N_2 for 5 min. After addition of trimethylsilylacetylene (0.42 mL, 3.00 mmol) and dry triethylamine (0.55 mL, 4.00 mmol) the solution was stirred at room temperature for 1 h. Then, KF (232 mg, 4.00 mmol) was added and the reaction mixture was vigorously stirred under air in the open reaction vessel at room temperature for 16 h. After the addition of H_2O (144 mg, 8.00 mmol), potassium hydroxide (449 mg, 16 mmol), and DMSO (14.0 mL) the mixture was heated in the microwave cavity at 130 °C for 1 h. After cooling to room temperature the mixture was extracted with methylene chloride (300 mL) and brine (500 mL). The organic phase was dried with anhydrous Na_2SO_4 and the solvents were removed under reduced pressure. The residue was absorbed on Celite® and purified by column chromatography on silica gel with *n*-hexane as an eluent to give 96.0 mg (0.44 mmol, 44%) of the desired product as colorless crystals. R_f: = 0.31 (*n*-hexane). Mp 84 °C (66–68 °C [51]). ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.08 (s, 2H), 7.31 (t, ^3J = 7.4 Hz, 2H), 7.46 (t, ^3J = 7.8 Hz, 4H), 7.82 (d, ^3J = 7.3 Hz, 4H); ^{13}C NMR (DMSO, 150 MHz) δ 108.2 (CH), 123.4 (CH), 127.5 (CH), 128.9 (CH), 130.0 (C_{quat}), 152.6 (C_{quat}). GC–MS (*m/z* (%)): 220 (M^+, 100), 191 (13), 115 ($(M\text{-}C_7H_5O)^+$, 41), 105 ($(C_7H_5O)^+$, 22), 89 (14), 77 ($(C_6H_5)^+$, 51), 63 (13), 51 (22); IR (KBr): $\tilde{\nu}$ = 1479 (w) cm^{-1}, 1446 (w), 1155 (w), 1022 (m), 925 (w), 910 (w), 794 (m), 756 (s), 689 (s), 671 (m). Anal. calcd for $C_{16}H_{12}O$ (220.3): C 87.25, H 5.49; Found: C 87.09, H 5.42; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$: 327 nm (35000 L·mol^{-1}·cm^{-1}), 342 (22000). Fluorescence (CH_2Cl_2): λ_{max}: 358 nm. Stokes shift $\Delta\tilde{\nu}$ = 3800 cm^{-1}. Quantum yield: Φ_f = 83% (Ref.: *p*-terphenyl (Φ_f = 93% in cyclohexane)). Cyclic voltammetry (CH_2Cl_2): $E_{1/2}^{0/+1}$ = 1.25 V.

Supporting Information

For experimental details of the optimization studies of the cyclization step (compound **2a**), of general procedure of the Sonogashira–Glaser cyclization synthesis of the 2,5-di(hetero)arylfurans **2**, for UV–vis, fluorescence, and NMR spectra and cyclovoltammograms of the compounds **2**, and for computational data of the DFT calculations on the structures **2** of see Supporting Information.

Supporting Information File 1

Experimental procedures, spectroscopic and analytical data of all compounds **2**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-60-S1.pdf]

Acknowledgements

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The Ugi four-component reaction as a concise modular synthetic tool for photo-induced electron transfer donor-anthraquinone dyads

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Abstract

Phenothiazinyl and carbazolyl-donor moieties can be covalently coupled to an anthraquinone acceptor unit through an Ugi four-component reaction in a rapid, highly convergent fashion and with moderate to good yields. These novel donor–acceptor dyads are electronically decoupled in the electronic ground state according to UV–vis spectroscopy and cyclic voltammetry. However, in the excited state the inherent donor luminescence is efficiently quenched. Previously performed femtosecond spectroscopic measurements account for a rapid exergonic depopulation of the excited singlet states into a charge-separated state. Calculations of the Gibbs energy of photo-induced electron transfer from readily available UV–vis spectroscopic and cyclovoltammetric data applying the Weller approximation enables a quick evaluation of these novel donor–acceptor dyads. In addition, the X-ray structure of a phenothiazinyl–anthraquinone dyad supports short donor–acceptor distances by an intramolecular π-stacking conformation, an important assumption also implied in the calculations of the Gibbs energies according to the Weller approximation.

Introduction

Chromophores, fluorophores, and electrophores, are functional organic materials [1] and constitute active components in molecular electronics [2], photonics [3], and bioanalytics [4-6]. Therefore, the design of well-defined monomolecular structures with electron-donor (Do) and acceptor (Acc) substitution, so called Do–Acc dyads, is a topical field with a paramount academic and technological interest [7,8]. Tailor-made Do–Acc systems represent the fundamental basis for application in molecular electronics and optoelectronics [9-14] and they are employed in organic light-emitting diodes (OLEDs) for a

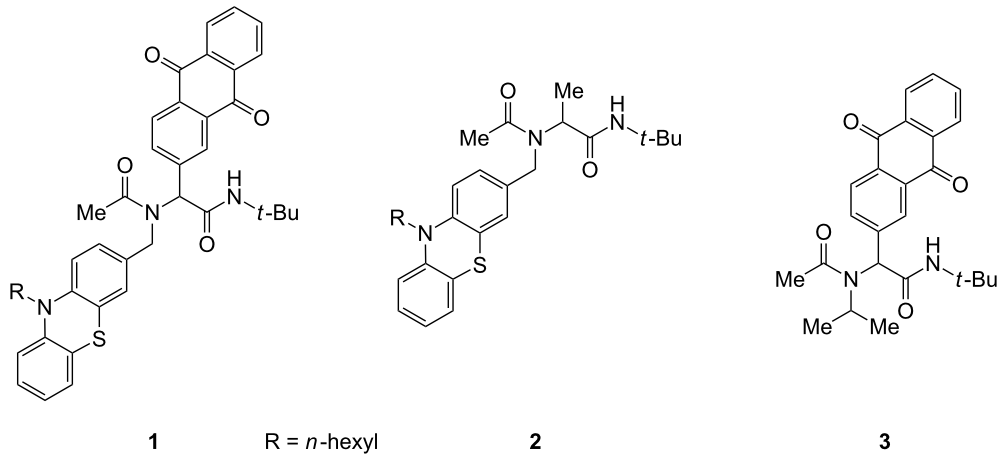
balanced charge transport [15-20] and photovoltaic devices [21-25]. The concept of persistent light-induced charge separation between a donor and an acceptor originates from photosynthesis, nature's most important process to convert sunlight into chemical energy. One of the most challenging endeavors of mankind is the unlimited generation of electrical energy from sunlight, with great efforts to mimicking photosynthesis by creation of artificial photosynthetic systems [26,27]. The simulation of relevant processes has reached a high level of understanding and the primary process of light-induced charge separation in various types of Do–Acc dyads has been intensively studied [28,29]. This photo-induced electron transfer (PET) [30-34] has been investigated with donors such as porphyrines, polycyclic aromatic hydrocarbons, perylenediimides and (oligo)thiophenes [35,36], tetrathiafulvalenes [37], as well as phenothiazine and its derivatives [22,38-40]. The latter have become attractive electrophores due to their reversible and tunable oxidation potential. Interestingly quenching of the phenothiazine inherent fluorescence offers a facile evidence for the occurrence of intramolecular PET in phenothiazine-containing Do–Acc dyads [41,42]. As suitable acceptor moieties C_{60} fullerene [43-45], and quinones, such as 9,10-anthraquinone as a potential two electron acceptor, have been commonly used in Do–Acc arrangements [46-51]. In previous studies phenothiazine–anthraquinone couples have been introduced into peptide scaffolds [52-54] and rigid Do–Acc dyads [55]. Nevertheless, a modular and rapid access by multicomponent reactions to these types of functional targets has never been explored prior to our recent studies [56]. For instance, the Ugi four-component reaction (Ugi 4CR) [57-60] establishes the chemically robust α-aminoacylamide backbone in one step and with high diversity. Therefore, it is also extensively used in medicinal and combinatorial chemistry for lead finding and optimization [61]. We have recently employed the Ugi 4CR as a one-step process to simultaneously introduce a phenothiazine-functionalized amine and an anthraquinone-substituted aldehyde together with acetic acid and *tert*-butyl isocyanide for rapidly assembling a donor–acceptor conjugate **1** displaying a photo-induced electron transfer leading to a charge-separated state with a lifetime of >2 ns (Figure 1), as elucidated by femtosecond transient absorption spectroscopy [56]. The donor-only (**2**) and acceptor-only (**3**) models for spectroscopic comparison were obtained analogously.

For enabling rapid accesses to functional π-systems, such as Do–Acc dyads for photo-induced charge separation, besides a robust, flexible diversity-oriented one-pot reaction, such as the Ugi 4CR, a quick semiquantitative estimation of the feasibility of the charge-separated state based upon inexpensive analytical methods is highly desirable. Here we present the synthetic versatility of this multicomponent approach to Do–anthraquinone dyads, as exemplified by phenothiazinyl and carbazole moieties as donors, and comprehensive physical organic studies of electronic and electrochemical properties investigated by steady state UV–vis and fluorescence spectroscopy as well as cyclic voltammetry. The obtained data are interpreted in the light of the Weller approximation to estimate the probability for charge separation by photo-induced electron transfer based upon its Gibbs energy calculated from the analytical data and donor–acceptor distances of lowest energy conformers from inexpensive force field computations.

Results and Discussion

Synthesis and structure

Within the concept of diversity-oriented syntheses of chromophores [62-69] we have established accesses to chromophores in a one-pot fashion based upon transition metal catalysis as an entry to consecutive multicomponent [70,71] and



1 R = *n*-hexyl **2** **3**

Figure 1: Phenothiazine–anthraquinone dyad **1**, donor-only (**2**) and acceptor-only (**3**) models assembled by Ugi 4CR.

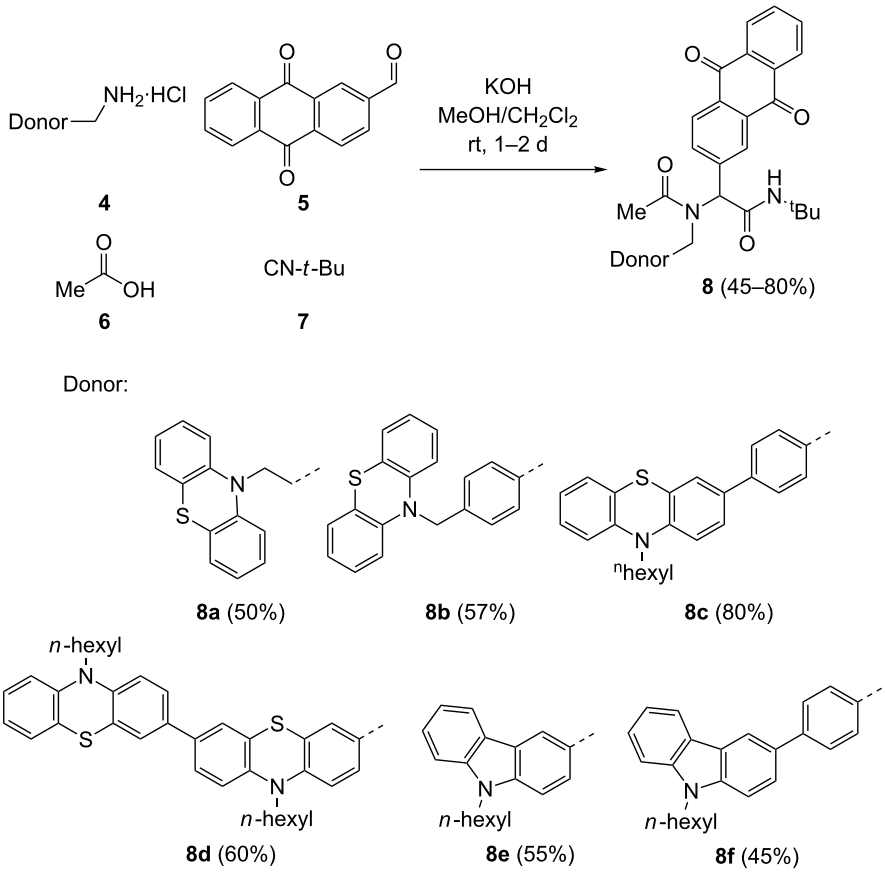
domino reactions [72]. The highly convergent synthetic approach by multicomponent reactions should as well be applicable to functional Do–Acc dyads. Therefore, we set out to place electron-rich phenothiazinyl and carbazolyl derivatives **4** as amino component in the Ugi 4CR, whereas the electron acceptor was introduced as anthraquinone-2-carbaldehyde (**5**). Acetic acid (**6**) and *tert*-butyl isocyanide (**7**) were the two residual components (Scheme 1) [56].

The most favorable solvent for Ugi 4CR is methanol. However, to increase solubility portions of dichloromethane were added to assure a homogeneous solution. For liberating the free base from methylamine hydrochlorides **4**, potassium hydroxide was employed as a base. The methylamine hydrochlorides **4**, in turn, were readily available from the corresponding cyano compounds [73] by lithium alanate reduction in diethyl ether [74]. The corresponding donor–anthraquinone dyads **8** were isolated in moderate to good yields. For reference, donor-only systems **10** were also prepared by Ugi 4CR from the amino derivatives **4** and acetaldehyde (**9**), in moderate to good yield, with acetic acid (**6**) and *tert*-butyl isocyanide (**7**) as the corresponding acid and isonitrile components (Scheme 2).

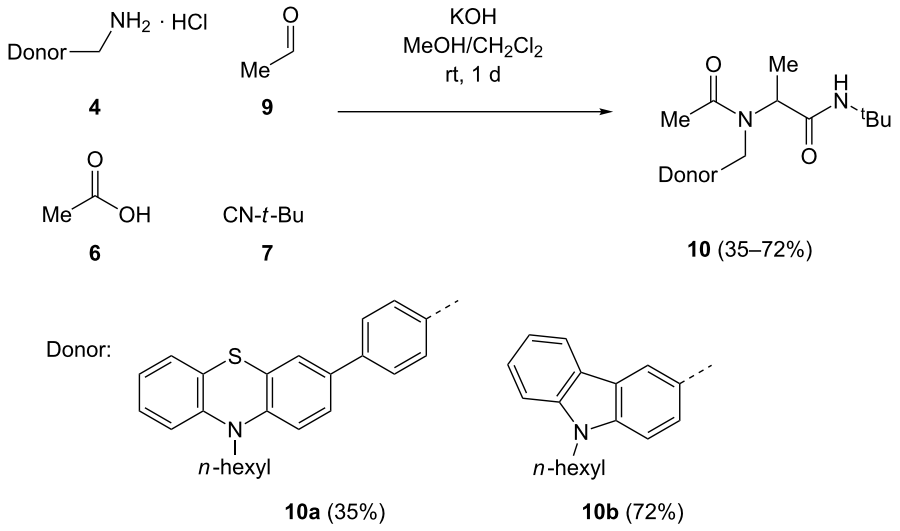
The appearance of single signal sets in the ^{1}H and ^{13}C NMR spectra of **8** and **10** unambiguously supports the structural assignment and that isomeric mixtures due to restricted amide-bond rotation can be excluded. Besides mass spectrometry and combustion analysis the structure of phenothiazine–anthraquinone dyads **8a–d** was additionally supported by an X-ray structure analysis of the partially oxidized derivative of compound S(O)-**1** (Figure 2) [75]. The phenothiazine and anthraquinone moieties are aligned by intramolecular π-stacking with an average distance of ~3.9 Å [76,77]. In the unit cell the *R*- and *S*-enantiomers of a single diastereomer (S-oxide) are arranged in pairs resulting in four stacked (hetero)aromatic units (Figure 2), so that the anthraquinone moieties of two molecules display an average distance of ~3.8 Å. Based upon the X-ray data quantum mechanical computations on this conformer were envisioned (vide infra).

Electronic properties and electronic structure

All dyads **8** and **1** as well as the reference systems **2**, **3**, and **10** were studied by cyclic voltammetry in dichloromethane at room temperature (Table 1, Figure 3).



Scheme 1: Ugi 4CR synthesis of donor–anthraquinone dyads **8**.



Scheme 2: Ugi 4CR synthesis of donor-only reference systems **10**.

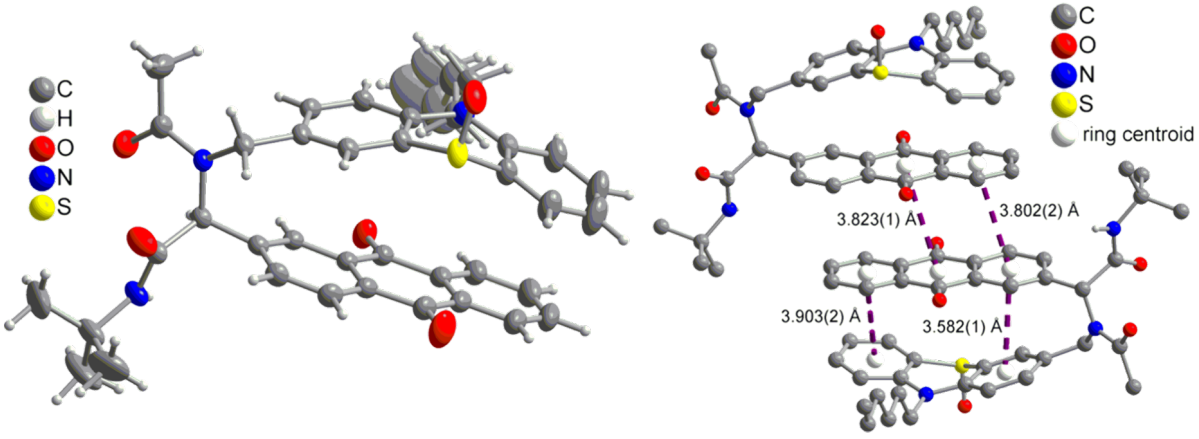


Figure 2: Molecular structure of S(O)-**1** (left) (30% ellipsoids, except for the CH_3CH_2 end of the hexyl group, the disordered water molecules were omitted for clarity) and the intra- and intermolecular π–π-stacking interactions between an inversion symmetry related pair (right, hydrogen atoms were omitted for clarity).

The cyclic voltammograms were recorded at scan rates v of 100, 250, 500 and 1000 mV·s^{-1} and the differences of anodic and cathodic peak potentials were plotted against $\sqrt{v}$ for extrapolating the half-wave potentials $E_{1/2}$ for a scan rate v = 0 mV·s^{-1} assuming an ideal Nernstian behavior. In the cyclic voltammograms of the phenothiazine–anthraquinone dyads **8a**–**d**, typical for phenothiazine derivatives [41,42,78], first reversible oxidations $E_{1/2}{}^{0/+1}$ between 630 and 780 mV are found, and in addition the cyclic voltammograms of **8c** and **8d** display second oxidation waves $E_{1/2}{}^{+1/+2}$ at 1450 (**8c**) and 800 mV (**8d**). The direct comparison of the 3-phenyl derivative **8c** with the donor-only reference **10a** clearly indicates that the proximity of the electron-withdrawing anthraquinone moiety does not affect the first and second reversible oxidations of the phenothiazinyl moiety in the Do–Acc dyad **8c**. The system **8d** containing two conjugated phenothiazinyl moieties is particular since the second oxidation wave originates from the electronic coupling within the diphenothiazine unit [79,80]. These values for first and second oxidation can also be found in the donor-only reference compound **10a**. Furthermore two quasi-reversible reductions stemming from the anthraquinone core can be detected for $E_{1/2}{}^{-1/0}$ between −850 to −900 mV and for $E_{1/2}{}^{-2/-1}$ between −1370 and −1500 mV, in good agreement with literature data [81,82]. Within a margin of 70 mV both reduction waves fall into the same region as for the anthraquinone-only reference **3** with $E_{1/2}{}^{-1/0}$ at −920 mV and

Table 1: Cyclovoltammetric data of the dyads **8** and the reference systems **1**, **2**, **3** and **10** (recorded in CH_2Cl_2, T = 298 K, c = 0.1 mol·L^{-1}, Pt working electrode, Pt counter electrode, Ag/AgCl reference electrode, electrolyte N(n-Bu)$_4$PF$_6$, scan rates v of 100, 250, 500 and 1000 mV·s^{-1})[a,b].

Compound	$E_{1/2}^{0/+1}$ [mV]	$E_{1/2}^{+1/+2}$ [mV]	$E_{1/2}^{-1/0}$ [mV]	$E_{1/2}^{-2/-1}$ [mV]
8a	780	–	−850[c]	−1500[c]
8b	780	–	−870[c]	−1370[c]
8c	710	1450	−900[c]	−1390[c]
8d	630	800	−880[c]	−1380[c]
8e	1220[c]	–	−940[c]	−1420[c]
8f	1170[c]	–	−920[c]	–
1	710	–	−870[c]	−1430[c]
3	–	–	−920[c]	−1430[c]
2	730	–	–	–
10a	710	1430	–	–
10b	1320[c]	–	–	–

[a]Calibrated against ferrocene as an internal standard ($E_0^{0/+1}$ = 450 mV). [b]The half-wave potentials $E_{1/2}$ were extrapolated to a scan rate of v = 0 mV·s^{-1} from the linear correlation plot of the differences of the anodic and cathodic peak potentials against $\sqrt{v}$. [c]Quasi-reversible redox wave.

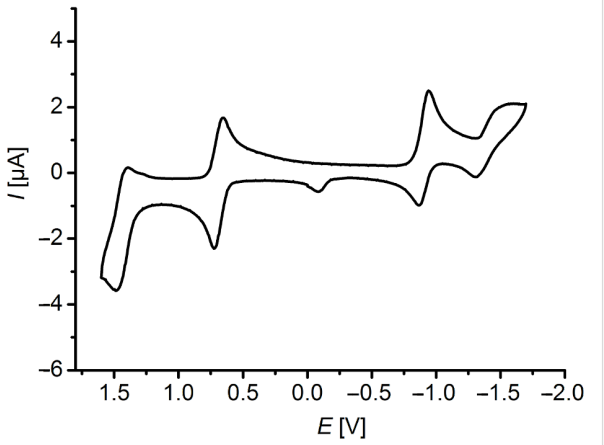


Figure 3: Cyclic voltammogram of dyad **8c** (recorded in CH_2Cl_2, T = 298 K, c (**8c**) = 0.1 mol·L^{-1}, Pt working electrode, Pt counter electrode, Ag/AgCl reference electrode, electrolyte N(n-Bu)$_4$PF$_6$, scan rate of 250 mV·s^{-1}).

$E_{1/2}^{-2/-1}$ at −1430 mV. Cum grano salis the electrochemical behavior of the novel dyads **8a–d** are very similar to the parent system **1**. The carbazole-based dyads **8e** and **8f** only show quasi-reversible oxidation waves at an estimated $E_{1/2}^{0/+1}$ of 1220 and 1170 mV, yet in good agreement with the behavior of the carbazole-only reference **10b** with an estimated $E_{1/2}^{0/+1}$ at 1320 mV. The carbazole–anthraquinone dyads **8e** and **8f** display the anthraquinone-centered first quasi-reversible reduction wave $E_{1/2}^{-1/0}$ at −940 (**8e**) and −920 mV (**8f**), the second quasi-reversible reduction wave is only found for dyad **8e** and appears at $E_{1/2}^{-2/-1}$ = −1420 mV. The comparison of the cyclic voltammograms between all dyads **8** and the reference systems **2**, **3**, and **10** clearly shows that the donor and anthraquinone moieties are essentially electronically decoupled in the electronic ground state. Therefore, in the electronic ground state the electronic effects should behave additively, i.e., as if the donors and anthraquinones were placed at large distances.

Based on the starting geometry from the X-ray structure analysis of S(O)-**1** the frontier molecular orbitals (FMO) of **1** were calculated on the DFT level of theory with the B3LYP functional and the Pople basis set 6-311G* (Figure 4) [83-86]. It is noticeable that the coefficient density of the HOMO is almost completely localized on the phenothiazine unit whereas the coefficient density of the LUMO resides on the anthraquinone core, supporting the electronic decoupling of the donor and the acceptor in the electronic ground state. In conclusion the computation underlines that in dyad **1** an electronic prerequisite for electronically favored electron-transfer processes in donor–acceptor systems is the spatial proximity of PT and AQ. This conformer is additionally stabilized by π-stacking of the donor and the acceptor, which is adopted in the solid state and results in a strong bathochromically shifted absorption of the solid.

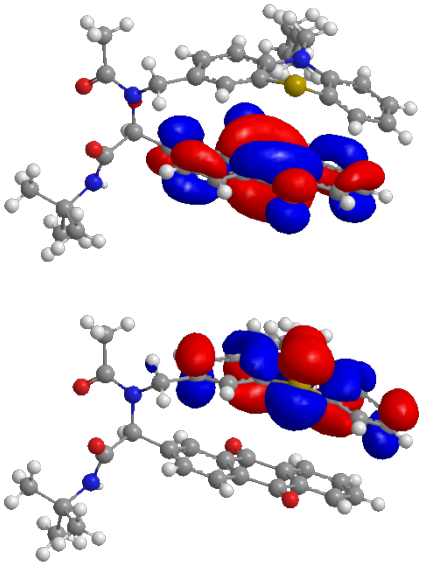


Figure 4: DFT-computed (B3LYP, 6-311G*) frontier molecular orbitals HOMO (bottom) and LUMO (top) of the phenothiazine–anthraquinone dyad **1**.

Furthermore, the electronic properties of the donor-anthraquinone dyads **8** were studied by absorption and emission spectroscopy (Table 2). All phenothiazine-based dyads **8a–d** show very similar absorption characteristics with a major

Table 2: Absorption and emission characteristics of the dyads **8**, **1**, and the reference systems **2**, **3**, and **10** (recorded in CH_2Cl_2, c = 1.4–3.1·10^{-5} mol·L^{-1}, T = 298 K).

Compound	Absorption $\lambda_{max,abs}$ [nm] (ε [L·mol·cm^{-1}])	Emission $\lambda_{max,em}$ [nm]	Stokes shift $\Delta\tilde{\nu}$ [cm^{-1}][a]
8a	257 (44000), 319 (5000)	–[b]	–
8b	258 (87000), 325 (10000)	–[b]	–
8c	258 (92000), 326 (19000)	–[b]	–
8d	259 (145000), 326 (40000)	–[b]	–
8e	250 (58000), 265 (69000), 298 (21000), 335 (11000)	–[b]	–
8f	255 (85000), 285 (62000)	–[b]	–
1	258 (69000), 323 (11000)	–[b]	–
3	259 (49000), 329 (6000)	–[b]	–
2	259 (39000), 311 (6000)	450[c]	9900
10a	269 (61000), 320 (18000)	463[d]	9700
10b	240 (47000), 267 (29000), 298 (17000), 336 (4000), 352 (4000)	362, 377[e]	800

[a]$\Delta\tilde{\nu}$ = 1/$\lambda_{max,abs}$ − 1/$\lambda_{max,em}$ [cm^{-1}]. [b]The residual fluorescence is only detectable in the base line, i.e., less than 5% in a.u., vide infra. [c]λ_{exc} = 311 nm. [d]λ_{exc} = 320 nm. [e]λ_{exc} = 298 nm.

absorption band around 259 nm and a lower intensity band around 325 nm (Figure 5). According to the phenothiazine-only (**10a**) and anthraquinone-only (**3**) references phenothiazine as well as anthraquinone absorb in the same region. In the spectrum of the carbazole dyad **8e** the carbazole-typical absorption maxima can be found (cf reference systems **3** and **10b**), whereas the spectrum of **8f** displays just two absorption bands at 255 and 285 nm, originating from the 3-phenylcarbazole moiety.

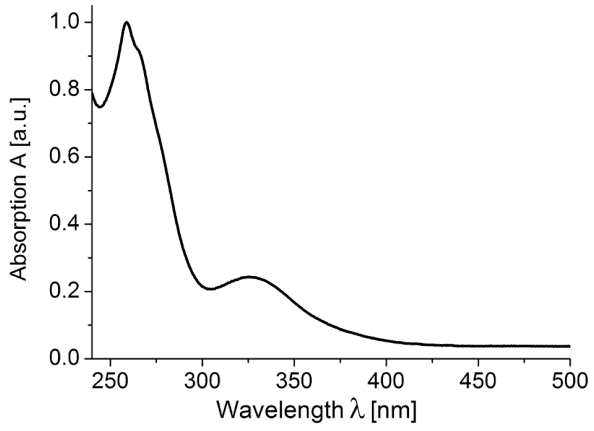


Figure 5: Normalized absorption spectra of the phenothiazine–anthraquinone dyad **8c** (recorded in CH_2Cl_2, c (**8c**) = 2.5·10^{-5} mol·L^{-1}, T = 298 K).

The extinction coefficients of the Do–anthraquinone dyads **8** are expectedly larger than those of the donor-only (**10**) or anthraquinone-only (**3**) compounds. Plotting the extinction coefficient against the wavelength it becomes evident that the Do–anthraquinone dyads behave additively with respect to the constituent reference chromophores (Figure 6). Absorption

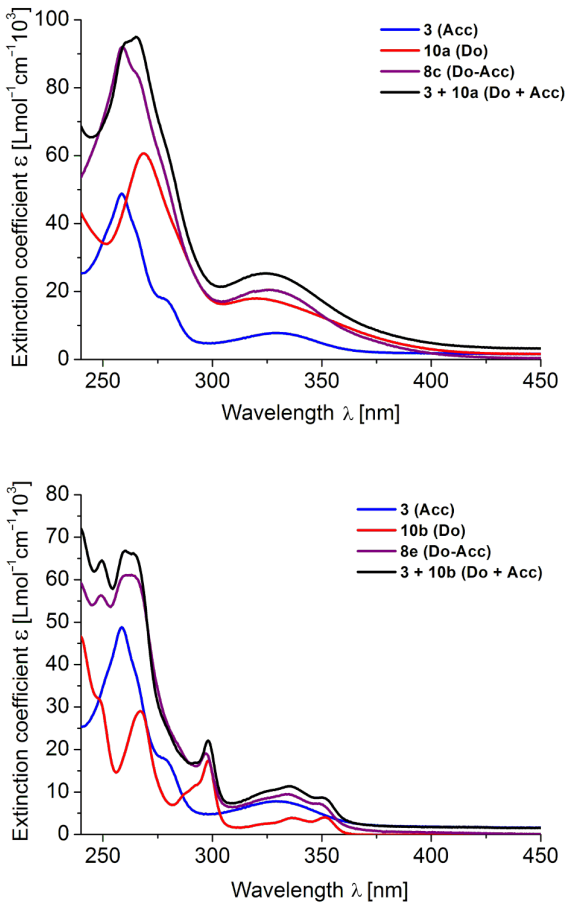


Figure 6: Absorption spectra of Do–anthraquinone dyads **8c** (top) and **8e** (bottom) with the corresponding references **3** and **10**, and their addition spectra (Do + Acc) (recorded in CH_2Cl_2, T = 298 K).

spectroscopy as a probe for the electronic ground state also supports that in Do–anthraquinone dyads **8** the donor and anthraquinone moieties are electronically decoupled in the electronic ground state.

Fluorescence is an excited-state phenomenon and, therefore, steady-state emission spectra of the donor-only reference systems **2** (Figure 7) and **10** and the donor–anthraquinone dyads **8** were recorded (Figure 8). For the donor–anthraquinone dyads **8** the emission is significantly quenched in comparison to the corresponding donor-only model systems **2** and **10** at the same concentrations according to relative fluorescence quantum yields $\Phi_{f,rel}$ (Table 3) and only residual weak emission traces from the donor and/or the anthraquinone excitations can be detected (for spectra of the residual emissions of the dyads **8** see Supporting Information File 1). Since the relative fluorescence quantum yields $\Phi_{f,rel}$ are attenuated by 95–99% in comparison to the donors' fluorescence an efficient and rapid nonradiative depopulation of the excited state can be assumed by an electron transfer. This rationale is additionally supported by our previous transient absorption spectroscopic study of the dyad **1** [56].

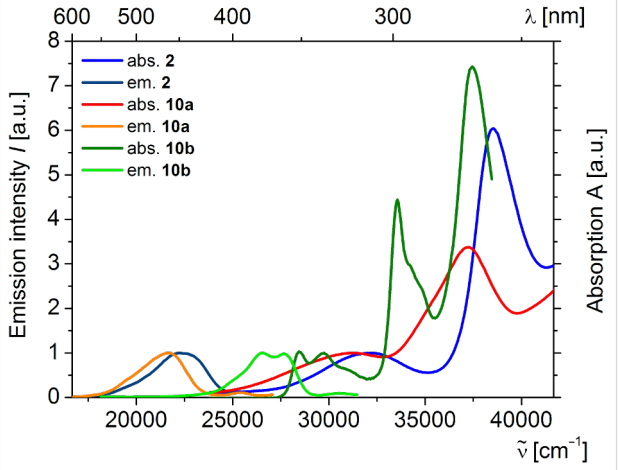


Figure 7: Normalized absorption and emission spectra of Ugi-donor compounds **2** and **10** (recorded in CH_2Cl_2, T = 298 K, $\lambda_{max,exc}$ (**2**) = 311 nm, $\lambda_{max,exc}$ (**10a**) = 320 nm, $\lambda_{max,exc}$ (**10b**) = 298 nm).

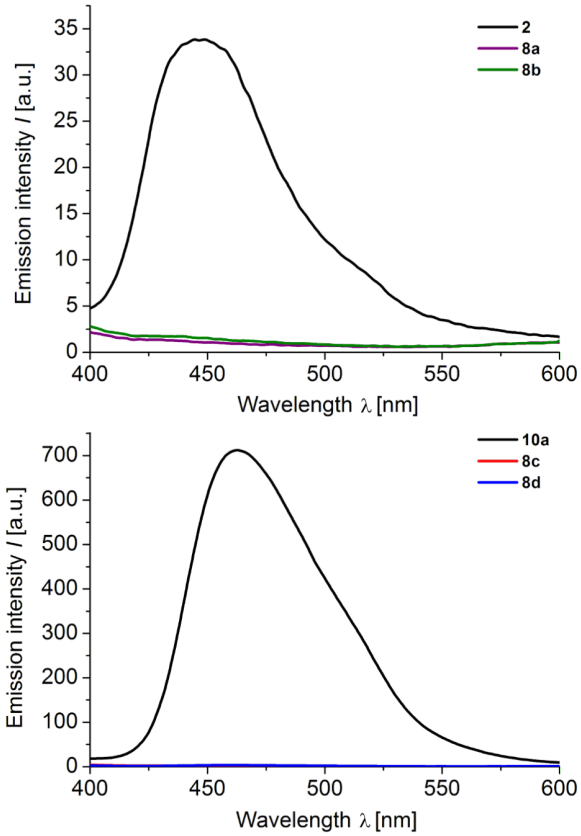


Figure 8: Emission spectra of donor-only system **2** phenothiazine–anthraquinone dyads **8a**,**b** (top), and the donor-only system **10a** and the phenothiazine–anthraquinone dyads **8c**,**d** (bottom) (recorded in CH_2Cl_2, T = 298 K, c = 0.7–2.9·10^{-6} mol·L^{-1}).

According to the Weller approximation [87] the driving force for a photo-induced electron transfer leading to a charge-separated state that is responsible for the observed fluorescence quenching can be calculated from the measured electrochemical and spectroscopic data. Among several representations for calculating the Gibbs free energy of the electron transfer ΔG^0_{ET} [88,89] can be described by Equation 1 [90]

$$\Delta G^0_{ET} = e\left[E^0_{ox}(\text{Do}) - E^0_{red}(\text{Acc})\right] - E_{00} - \frac{e^2}{4\pi\varepsilon_0\varepsilon_s R_{\text{Do-Acc}}} - \frac{e^2}{8\pi\varepsilon_0}\left(\frac{1}{r^+}+\frac{1}{r^-}\right)\left(\frac{1}{\varepsilon_{ref}}-\frac{1}{\varepsilon_s}\right) \quad (1)$$

Table 3: Relative quantum yields $\Phi_{f,rel}$ of Do-anthraquinone dyads **8** in comparison to their donor-only reference systems **2** and **10**.

Donor-only reference	**2**		**10a**		**10b**	
Donor-anthraquinone dyad	**8a**	**8b**	**8c**	**8d**	**8e**	**8f**
$\Phi_{f,rel}$[a]	0.04	0.05	<0.01	<0.01	0.01	0.04

[a]Determined in CH_2Cl_2, T = 298 K, the quantum yield of the corresponding reference was set to 1.0.

Where $E^0_{ox}(\text{Do}) - E^0_{red}(\text{Acc})$ is the difference of the first oxidation potential of the donor and first reduction potential of the acceptor, respectively, E_{00} expresses the energy of the photonic excitation, $R_{\text{Do–Acc}}$ delineates the distance between the centers of the donor and acceptor moieties, ε_s and ε_{ref} are the dielectric constants of the solvent applied in spectroscopy (ε_s) and reference solvent used in electrochemistry (ε_{ref}), and r^+ and r^- are indicating the effective ionic radii of the donor radical cation and acceptor radical anion, respectively. It is allowed to neglect the forth term, if spectroscopic and electrochemical measurements are performed in the same solvent. Therefore, Equation 1 simplifies to Equation 2 for calculating ΔG^0_{ET}

$$\Delta G^0_{ET} = e\left[E^0_{ox}(\text{Do}) - E^0_{red}(\text{Acc})\right] - E_{00} - \Delta G^0_{solv} \quad (2)$$

Where the first two terms indicate the free energy of the charge-separated state calculated from the spectroscopic and electrochemical measurements (in eV) and ΔG^0_{solv} represents the correction term of the solvent polarity and the effect of the distance of the donor and acceptor moieties according to $\Delta G^0_{solv} = \frac{e^2}{4\pi\varepsilon_0\varepsilon_s R_{\text{Do–Acc}}}$.

Indeed, for all Do-anthraquinone dyads **8** exergonic Gibbs free energies for the electron transfer are found, both for the simplified free enthalpy $\Delta G_{ET,simpl}$, i.e., the first two terms of Equation 2, and upon taking solvation into account with the term ΔG^0_{solv}. Therefore, the extent of the thermodynamically favored charge separation by an intramolecular photo-induced electron transfer (PET), plausibly explaining the observed fluorescence quenching, can be easily determined and compared within the series of related dyad systems (Table 4).

The negative free enthalpies of PET are numerically very similar for **8b**, **8c**, **8e**, and **8f**, however, larger in quantity for dyad **8a** and smaller for dyad **8d**. A diminishing of the distance between donor and anthraquinone, e.g., by adopting flexible close-contact conformations as for dyad **8a** causes an increase in the driving force of the PET. Smaller excitation energies E_{00} and lower oxidation potentials as for the diphenothiazine dyad **8d** cause a smaller PET driving force ΔG^0_{ET}. All phenothiazine systems **8a–d** are excited at longer wavelengths, i.e., at lower energies, than the carbazole dyads **8e** and **8f**. Eventually, the absorption characteristics of phenothiazine dyads can be more easily red-shifted and, therefore, charge separation by PET should be accessible with visible light by fine-tuning the donor chromophore towards lower HOMO–LUMO gaps.

Conclusion

The Ugi four-component reaction represents a rapid and excellent modular and diversity-oriented synthesis of donor-anthraquinone dyads with various phenothiazine and carbazole model donors. Cyclic voltammetry and UV–vis spectroscopy clearly indicate an electronic decoupling of the donor and the acceptor substituents in the electronic ground state, whereas the emission of the donor moieties is efficiently quenched according to static fluorescence spectroscopy. The observed peculiar fluorescence quenching was previously studied by femtosecond transient absorption spectroscopy of a related model dyad indicating a photo-induced electron transfer (PET) process into a dark, i.e., non-emissive, charge-separated state. The Gibbs free energies of the PET into the charge-separated states are exergonic and can be quickly calculated from absorption and electrochemical data applying the Weller approximation. The concise synthetic concept to donor–acceptor systems is very general, easy to perform and readily expandable to all

Table 4: Calculation of the Gibbs free energies for the simple electron transfer $\Delta G_{ET,simpl}$, for the solvation ΔG^0_{solv}, and the electron transfer ΔG^0_{ET} according to the Weller approximation of the dyads **8**.

Compound	$e[E^0_{ox}(\text{Do}) - E^0_{red}(\text{Acc})]$ [eV][a]	E_{00} [eV][b]	$\Delta G_{ET,simpl}$ [eV][c]	$R_{\text{Do–Acc}}$ [nm][d]	ΔG^0_{solv} [eV]	ΔG^0_{ET} [eV]
8a	1.60	3.08	−1.46	0.39	0.40	−1.78
8b	1.65	3.08	−1.43	0.43	0.37	−1.66
8c	1.51	2.93	−1.42	0.53	0.30	−1.68
8d	1.61	2.93	−1.32	0.38	0.41	−1.64
8e	2.16	3.49	−1.34	0.40	0.39	−1.70
8f	2.09	3.49	−1.41	0.46	0.34	−1.69

[a]Calculated from $(E_{1/2}{}^{0/+1} - E_{1/2}{}^{-1/0})$ [V] obtained from cyclic voltammetry (see Table 1). [b]E_{00} [eV] of donor-only reference compounds **2** (E_{00} = 402 nm), **10a** (E_{00} = 423 nm), and **10b** (E_{00} = 355 nm) were estimated by the intersection of normalized absorption and emission spectra. [c]$\Delta G_{ET,simpl} = e[E^0_{ox}(\text{Do}) - E^0_{red}(\text{Acc})] - E_{00}$. [d]The distances $R_{\text{Do–Acc}}$ [nm] of the donor and acceptor centers were estimated from lowest energy conformers by optimized MM2FF calculations [91] taking the distances between the centroid of the anthraquinone and the nitrogen atom of the donor moiety. For the diphenothiazine derivative **8d** the more electron-rich inner phenothiazine was assumed to be oxidized first.

kinds of functional π-electron systems. The Weller approximation of the Gibbs free energies of the PET allows a semiquantitative evaluation and optimization of photo-induced charge-separation systems. Studies directed towards multicomponent syntheses of more complex light harvesting and charge separation systems are currently underway.

Experimental

Synthesis of compounds **8** and **10** via Ugi four-component reaction (General Procedure) in a manner similar to [56])

In a 25 mL Schlenk tube 0.50 mmol of the donor hydrochloride **4** and potassium hydroxide (28 mg, 0.50 mmol) were dissolved in methanol and the mixture was stirred for 30 min (for experimental details see Table 5). A solution of aldehyde **5** (118 mg, 0.50 mmol) in dichloromethane (2 mL) or the neat aldehyde **9** (22 mg, 0.50 mmol) were added to the reaction mixture and the solution was stirred at rt for 1 h, followed by the addition of 1 equiv of acetic acid (**6**) (30 mg, 0.50 mmol) and 1 equiv of *tert*-butyl isocyanide (**7**) (42 mg, 0.50 mmol) by syringe. The reaction mixture was stirred overnight at rt. The solvents were removed in vacuo and the crude product was purified by column chromatography on silica gel to give the analytically pure Ugi products **8** and **10**.

Supporting Information

Supporting Information File 1

^{1}H NMR, ^{13}C NMR, UV–vis, fluorescence spectra and cyclic voltammograms of compounds **8** and **10**, a summary of the X-ray crystallographic data of S(O)-**1**, computed xyz-coordinates of the structure **1** and HOMO and LUMO energies.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-100-S1.pdf]

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Table 5: Experimental details for the synthesis of the Ugi products **8** and **10**.

Entry	MeOH [mL]	CH_2Cl_2 [mL]	Reaction time *t* [d]	Ugi 4CR products **8** or **10** (yield)
1	3	2	2	153 mg (50 %) of **8a**
2	2	2	1	193 mg(57 %) of **8b**
3	2	2	1	299 mg(80 %) of **8c**
4	2	2	1	287 mg (60 %) of **8d**
5	2	2.2	1	187 mg (55 %) of **8e**
6	2	2	1	162 mg (45 %) of **8f**
7	3	–	1	105 mg (35 %) of **10a**
8	2	–	1	162 mg (72 %) of **10b**

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Consecutive isocyanide-based multicomponent reactions: synthesis of cyclic pentadepsipeptoids

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Letter

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Abstract

The synthesis of six cyclic depsipeptoids inspired by the natural depsipeptide sansalvamide A is described. An efficient and fast synthetic strategy was developed using a combination of consecutive isocyanide-based multicomponent reactions (Ugi and Passerini reactions). This methodology can be used to access a variety of cyclic oligodepsipeptoids.

Introduction

Peptoids are an interesting class of non-natural compounds that have recently received much attention due to their wide range of biological activities, which makes them attractive candidates for drug discovery [1-7]. This family of oligomers comprising poly-*N*-substituted glycines mimics the primary natural structure of peptides and exhibits greater proteolytic stability and increased cellular permeabilities in comparison to peptides [5-7]. A powerful synthetic tool for the preparation of a peptoid backbone is the Ugi four-component reaction (U-4CR) [8-14]. It has been demonstrated that the combination of multicomponent reactions with the use of microwave irradiation is able to efficiently produce complex molecules with a reduced number of steps and short reaction times [15-18].

Depsipeptides are polymeric natural compounds, analogues of peptides, being formed by amino acids and hydroxy acids linked together by amide and ester bonds. These natural products show promising biological activities, especially regarding their therapeutic potential in cancer treatment [19]. An example of a cyclic depsipeptide is sansalvamide A (San A, Figure 1) [20-29], which was isolated from a marine fungus (*Fusarium spp.*) [20] and exhibits antitumor activity against multiple

cancer cell lines. It is cytotoxic against colon (HCT-116) [20,23,25,26], pancreatic (S2-013 and AsPC-1) [22,28,29], prostate (PC-3), breast (MDA-MB231) and melanoma cancers (WM-115) [24]. It has been reported that substitution of an ester group by an amide in the structure of a peptide provides an efficient way to evaluate the role of protein hydrogen bonding [30-34]. Recent works have discovered that some analogues of San A inhibit Hsp 90, a key protein that enables many proteins involved in tumor progression [35-39].

The Passerini three-component reaction (P-3CR) allows an easy access to depsipeptides using a convergent approach. It has become a powerful tool in combinatorial synthesis [40-43] and can be used strategically for the synthesis of depsipeptoids. By analogy to peptides and peptoids, a depsipeptoid would be a peptoid bearing an ester group instead of an amide group. Differences between peptide, peptoid, depsipeptide and depsipeptoid structures are outlined in Figure 2.

Results and Discussion

In continuing our research on the synthesis of peptoids with potential pharmacological activity [12,17,18,44,45] and using a fast and efficient microwave-assisted synthesis of peptoids [15,17,18], we decided to carry out the synthesis of depsipeptoid analogues of San A based on a strategy developed in our groups for the synthesis of cyclic RGD pentapeptoids [44]. This strategy was adapted by a combination of microwave-assisted Ugi and Passerini reactions. It is also important to highlight that the synthesis of cyclic depsipeptoids had not been explored yet. In this paper, we describe the synthesis of six pentadepsipeptoid analogues of San A (Figure 3).

The synthetic route for the synthesis of cyclic pentadepsipeptoids via consecutive Ugi reactions allows only three side chains connected to three nitrogen atoms. The pentapeptide of San A has in its structure five side chains attached to the α carbon atoms: one isopropyl, one benzyl and three isobutyl groups. To generate the pentapeptoid analogues of San A, the side chain groups isobutyl, isopropyl and benzyl linked to the α carbon atom present in the peptide were moved to the nitrogen atoms. It was decided to keep at least one benzyl group in the structure of the peptoids and vary the isopropyl and isobutyl groups, thus maintaining a greater similarity with the structure of the San A depsipeptide.

The retrosynthetic analysis of the depsipeptoids (Scheme 1) shows that the proposed compounds can be achieved using a strategy based on: (a) formation of a peptoid via Ugi reaction;

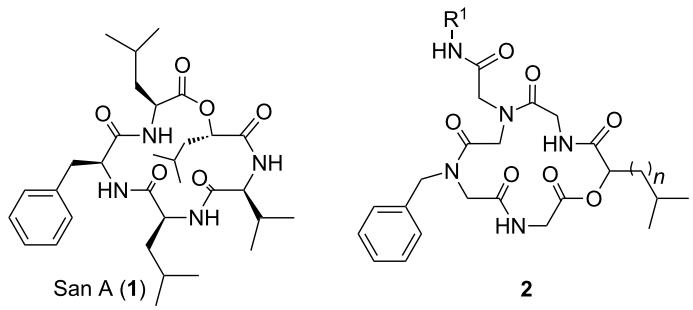


Figure 1: Sansalvamide A (**1**) and its depsipeptoid analogues (**2**).

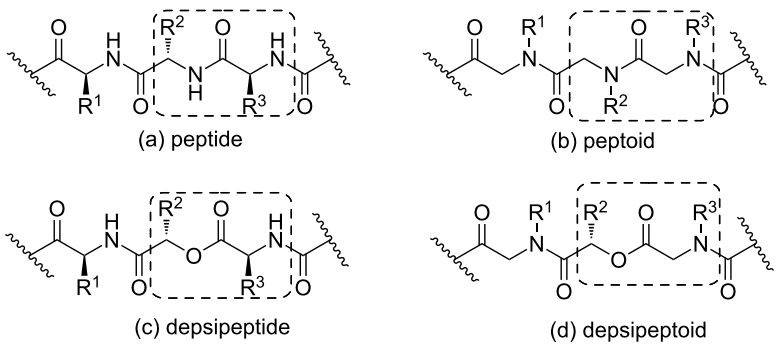


Figure 2: Generic structures of (a) peptide, (b) peptoid, (c) depsipeptide and (d) depsipeptoid.

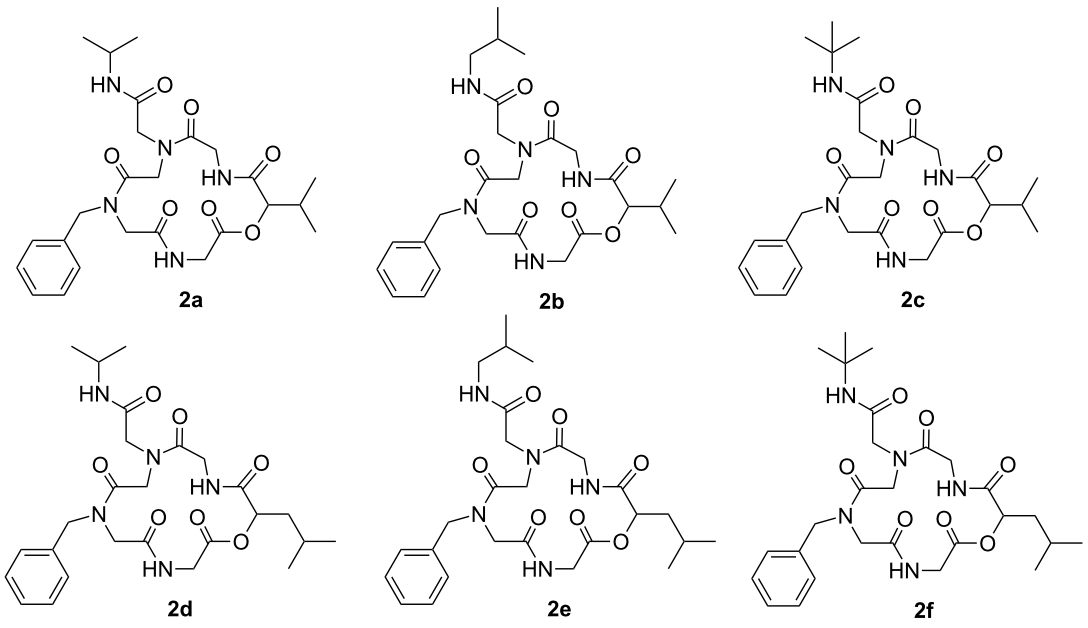
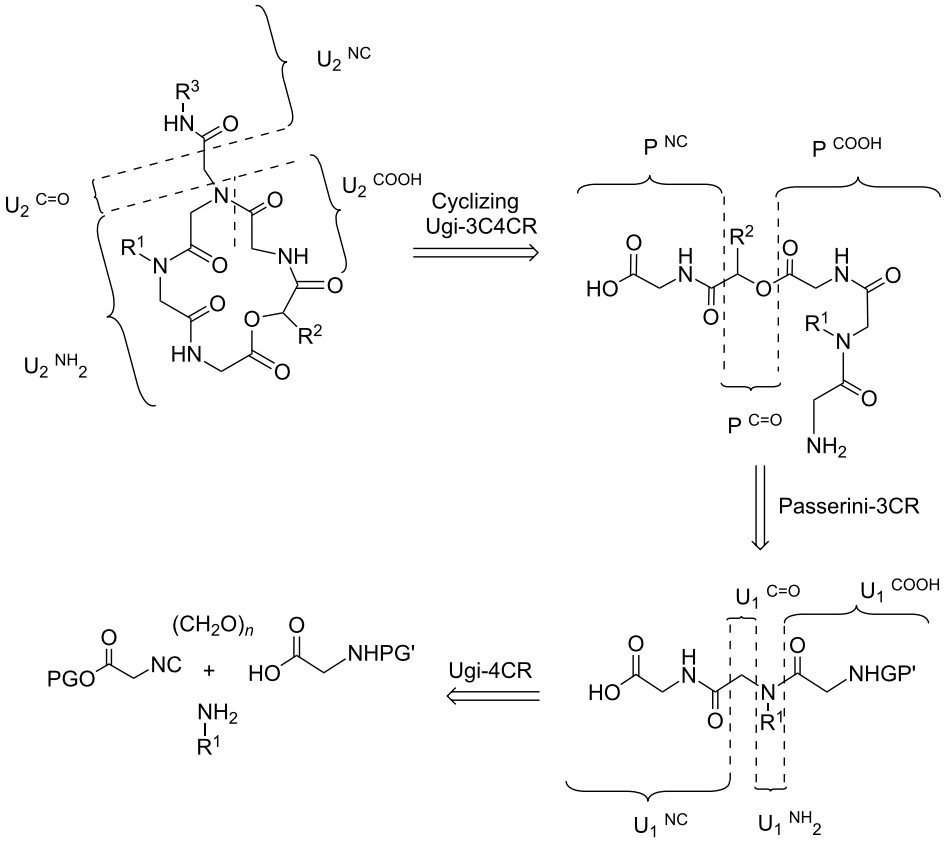


Figure 3: Structures of six pentadepsipeptoid analogues of San A.

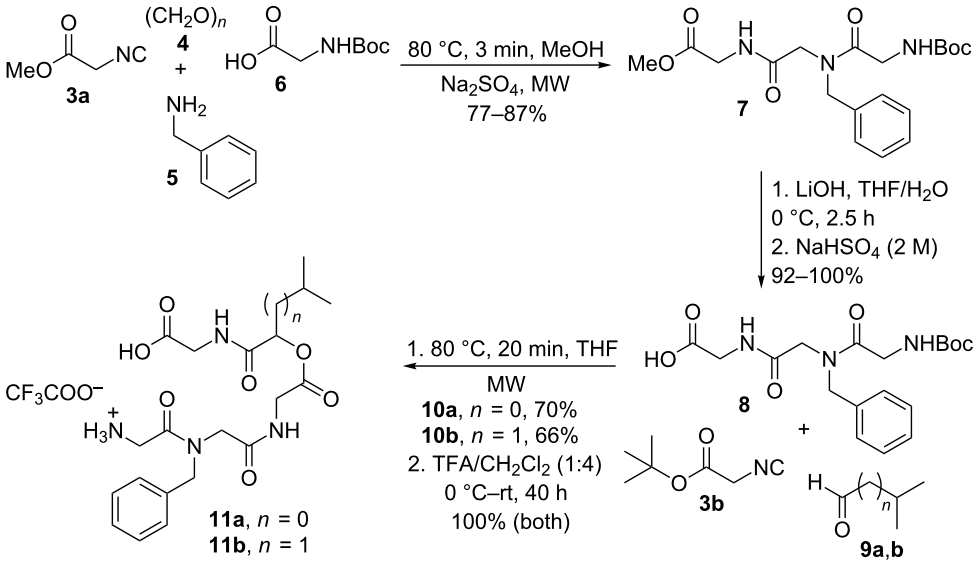


Scheme 1: Retrosynthetic analysis of the cyclic depsipeptoids.

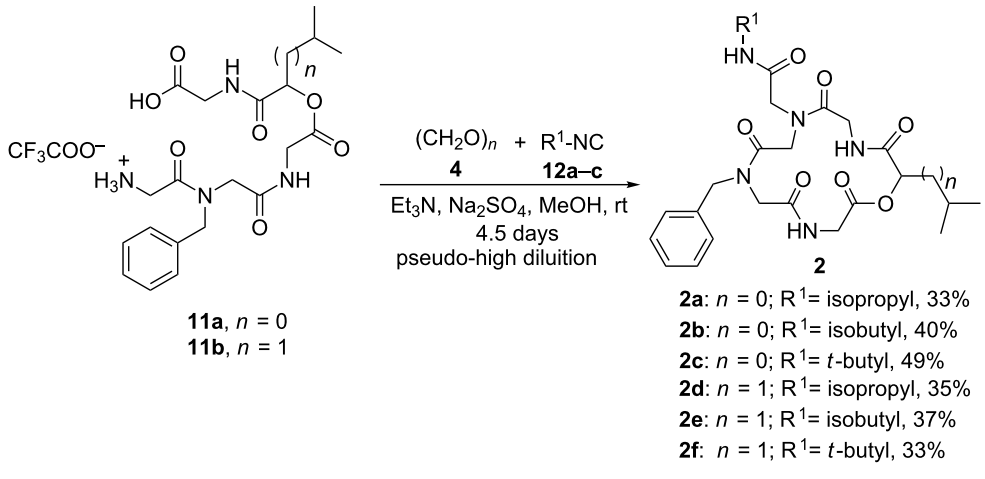
(b) ester hydrolysis; (c) formation of an acyclic depsipeptoid scaffold through a Passerini reaction; (d) deprotection of the amine/acid groups and (e) a macrocyclization step via an intramolecular Ugi reaction.

The general strategy for the synthesis of cyclic pentadepsipeptoids is depicted in Scheme 2. The synthesis of analogues **2** was initiated by an Ugi 4-component reaction (U-4CR) using methyl isocyanoacetate (**3a**), paraformaldehyde (**4**), benzylamine (**5**) and *N*-Boc-glycine (**6**) in MeOH (Scheme 2) in a microwave (MW) reactor (3 min at 80 °C) to provide the peptoid **7** in 77–87% yield. Peptoid **7** was subjected to hydrolysis in the presence of LiOH (THF/H_2O, 0 °C, 2.5 h) followed by treatment with 2 M $NaHSO_4$ providing the corresponding acid **8** in 92–100% yield. Acid **8** was then employed in a Passerini reaction with isobutyraldehyde (**9a**) or isovaleraldehyde (**9b**) and *tert*-butyl isocyanoacetate (**3b**), in a MW reactor (20 min at 80 °C) in THF, affording the acyclic depsipeptoids **10a** and **10b** in 70% and 66% yield, respectively. Removal of the *Boc* protecting group and ester hydrolysis were achieved after treatment of the acyclic depsipeptoids **10a**,**b** with TFA in CH_2Cl_2, giving the corresponding amino acids **11a**,**b** as TFA salt in quantitative yields.

In the last step, the depsipeptoid amino acid salts **11a**,**b** were subjected to an Ugi three-component four-center reaction (U-3C4CR) (Scheme 3). Compounds **11a**,**b** were added under pseudo-high dilution conditions (addition rate: 0.6 mL/h; addi-



Scheme 2: Synthesis of acyclic depsipeptoids **11a**,**b**.



Scheme 3: Synthesis of macrocycles **2a-f**.

tion time: 83 h; concentration: 0.80 mmol/L) to a suspension of paraformaldehyde **4**, triethylamine, sodium sulfate and isopropyl/isobutyl/*tert*-butyl isocyanide **12a–c** in methanol to yield the target cyclic pentadepsipeptoids **2a–f** after purification by column chromatography (yields ranged from 33–49% depending on the substrate). The structures of the final products obtained are shown in Figure 3.

Conclusion

In summary, the approach developed herein allows the synthesis of a wide range of cyclic depsipeptoids. Different structures can be obtained by changes in the amine component in the first Ugi reaction, in the carbonyl component in the Passerini reaction or in the isocyanide and carbonyl components in the macrocyclization step. The general route and procedure developed allows an easy access to complex molecules with a significantly reduced number of steps in short reaction times, and high yields in most of the steps. The strategic combination of two isocyanide-based multicomponent reactions and microwave irradiation makes this a very useful and attractive protocol. The obtained depsipeptoids will be tested for different biological activities.

Supporting Information

Supporting Information File 1

General procedures, NMR and mass spectra of all compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-101-S1.pdf]

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Microwave-assisted Cu(I)-catalyzed, three-component synthesis of 2-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1*H*-benzo[*d*]imidazoles

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Abstract

A microwave-assisted synthesis of 2-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1*H*-benzo[*d*]imidazoles from a phenyl-azide, propargyloxybenzaldehyde and a 1,2-diaminobenzene is proposed.

Introduction

Due to their structural range and biological importance nitrogen-containing heterocycles have been striking targets for many years. They are found in a variety of natural products and are characterized by an appreciable chemical and biological importance. The synthesis of nitrogen-containing heterocyclic compounds and their derivatives plays an important role in organic chemistry as they frequently exhibit therapeutic and pharmacological properties. They have emerged as an integral backbone of several existing drugs. Various medicinal agents are composed of several heterocyclic rings in which the benzimidazole and the 1,2,3-triazole constitute an important position. Benzimidazole derivatives have been shown to posses anticancer [1,2], antihypertensive [3], antibacterial [4] and enzyme inhibition activity [5,6]. They have also been used to synthesize dyes [7], chemosensitizers [8] and fluorophores [9]. Triazole derivatives have shown antifungal [10], anticancer [11] antituberculosis [12] and antimicrobial [13] activities. Recently, hybrid molecules, connecting two or more distinct drug entities

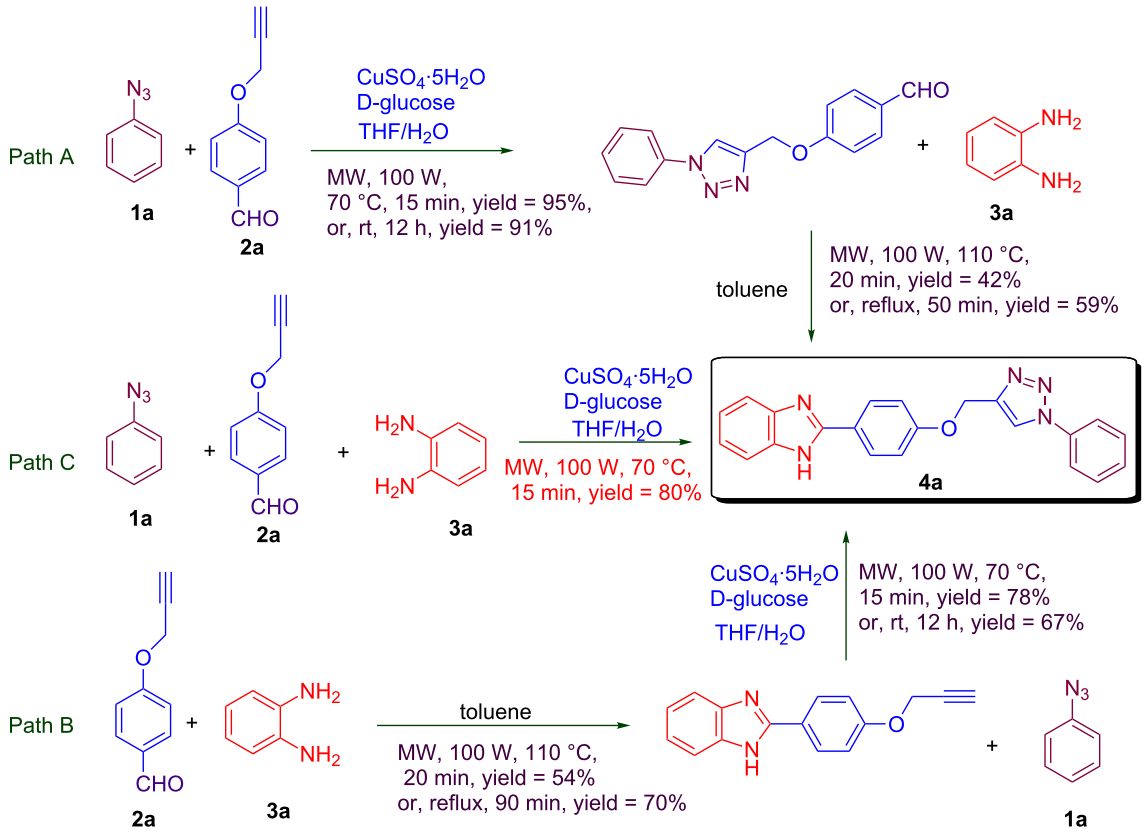
in one molecule, have drawn the attention of medicinal chemists [14-18]. This logical approach is a promising path for those drug molecules which can effectively and selectively target multifunctional diseases. It has also been found that hybrid molecules are sometimes much more effective than the sum of their individual components.

The therapeutic application of 2-(3-fluoro-phenyl)-1-[1-(substituted-phenyl)-1*H*-[1,2,3]-triazol-4-yl-methyl)-1*H*-benzo*[d]*imidazoles has been demonstrated by treating tuberculosis[19]. However, there has been little progress in the development of such hybrid molecules to date. An extensive literature survey revealed the existence of a multistep synthesis with low yields and long reaction times. This encouraged us to develop a new methodology for this synthesis.

Results and Discussion

Three different approaches for the construction of the proposed 2-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1*H*-benzo[*d*]imidazole are illustrated in Scheme 1. In a two-step process the triazole and imidazole ring are synthesized consecutively (Scheme 1, path A and B). However, we reasoned that the desired adduct could also be formed in a one-pot fashion (Scheme 1, path C) as a multicomponent reaction (MCR). The utility and importance of MCRs have been recognized by chemists [20-23]. Several MCRs are now well-established reactions, such as Ugi [24], Passerini [25], Van Leusen [26], Strecker [27], Hantzsch [28], and Biginelli [29-31].

However, when path A and path B were explored, the desired product was afforded in different yields (Scheme 1). The treatment of acetylene **2a** with phenylazide (**1a**) in the presence of copper sulfate and D-glucose as a reductant [32,33] in THF/H_2O (2:1) as a solvent under stirring at rt as well as under microwave irradiation resulted in the obtainment of the desired product in excellent yields of 91% and 95% in 12 h and 15 min, respectively. However, when the manufactured 4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde was treated with 1,2-diaminobenzene, the desired product was obtained in an inferior yield of 59% and 42% under conventional heating and microwave irradiation in 50 and 20 min, respectively (path A). On the other hand, when 4-(prop-2-yn-1-yloxy)benzaldehyde



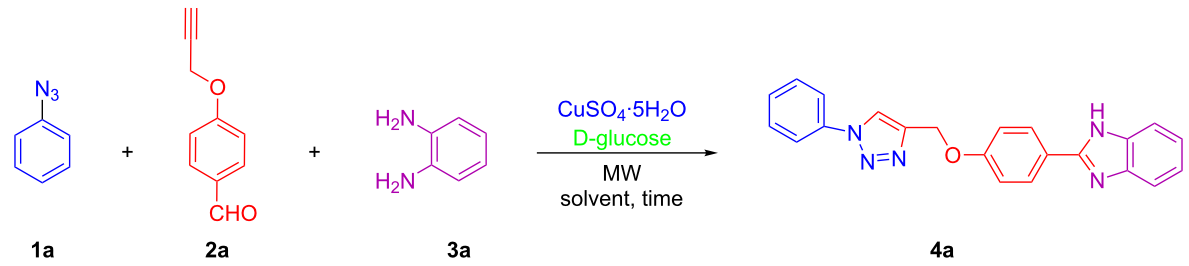
Scheme 1: Synthesis of 2-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1*H*-benzo[*d*]imidazoles.

(**2a**) was first treated with 1,2-diaminobenzene in the presence of copper sulfate and D-glucose in a THF/H_2O (2:1) mixture under conventional heating as well as microwave irradiation, the desired product was obtained in a better yield (70%) under conventional heating compared to microwave irradiation (54% yield). The compound was subsequently coupled with phenylazide (**1a**), which afforded the desired product in 67% and 78% yield upon stirring at rt and microwave irradiation, respectively (path B). However, in the MCR approach (Scheme 1, path C) the desired product was obtained in a good yield. The reaction proceeded smoothly in the presence of $CuSO_4{\cdot}5H_2O$ and D-glucose under microwave irradiation for 15 min and gave the desired compound in 80% yield. Surprisingly, under conventional heating with this MCR approach no product formation was observed, even after an extended period of time (24 h) with heating under reflux .

In order to optimize the reaction conditions for this protocol, we screened several organic solvents. We explored the reaction between phenylazide (**1a**), 4-(prop-2-yn-1-yloxy)benzaldehyde (**2a**) and 1,2-diaminobenzene (**3a**). It was found that when the reactions were carried out in polar solvents, such as acetonitrile, *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO) or 1,4-dioxane, no product formation was observed (Table 1, entries 1–4). However, upon microwave irridiation the reaction went to completion in a non-polar solvent, such as tetrahydrofuran (THF) or toulene, and the desired product was isolated in 20% and 25% yields (Table 1, entry 5 and entry 6) in THF and toluene, respectively. Moreover, when the reaction was carried out in an aqueous solvent system, decent improvements of the yields were observed (Table 1, entries 7–11). The best result was obtained with THF/H_2O 2:1 (Table 1, entry 8). It is believed that the higher solubility of $CuSO_4$ in this aqueous solvent system is responsible for the enhanced product formation. On the contrary, the formation of aggregates of the copper acetylide intermediate in polar solvents results in a failure of the reaction [34].

Various 1,2-diaminobenzenes **3a**,**b** and phenylazides **1a–j** were explored in order to estabilish the applicability of this protocol and the results are summarized in Table 2. Different azides **1a–j** with electron-donating groups (Table 2, entries 2–8, 12–17, 20–23), electron-withdrawing groups (Table 2, entries 9, 10, 18 and 19), two different 4-(prop-2-yn-1-yloxy)benzaldehydes

Table 1: Optimization of the solvent system.[a]

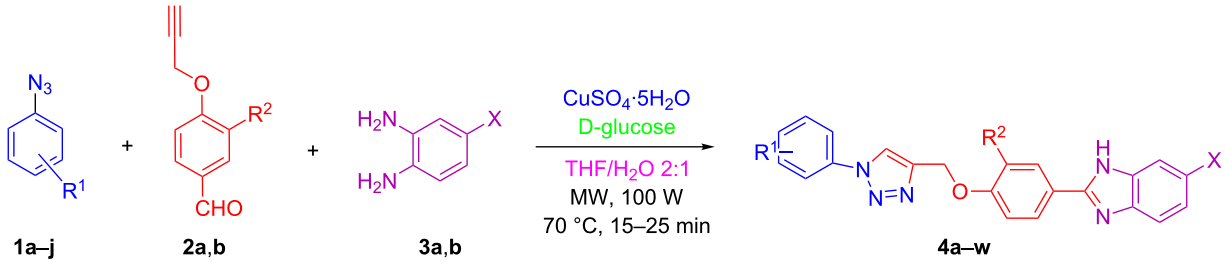


1a **2a** **3a** **4a**

Entry	Solvent	Time (min)/temperature (°C)	Yield (%)[b]
1	Acetonitrile	30/80	0
2	DMF	15/100	0
3	DMSO	15/100	0
4	1,4-Dioxane	15/110	0
5	THF	20/70	20
6	Toluene	20/100	25
7	Toluene/H_2O 2:1	20/100	56
8	**THF/H_2O 2:1**	**15/70**	**80**
9	DMF/H_2O 2:1	15/100	30
10	DMSO/H_2O 2:1	15/100	25
11	1,4-Dioxane/H_2O 2:1	15/100	40

[a]Phenylazide (**1a**, 1.0 mmol), 4-(prop-2-yn-1-yloxy)benzaldehyde (**2a**, 1.2 mmol), 1,2-diaminobenzene (**3a**, 2 mmol), $CuSO_4{\cdot}5H_2O$ (0.2 equiv), D-glucose (0.4 equiv) in different solvents were irradiated for the indicated time and temperature at 100 W maximum power; [b]isolated yields.

Table 2: Scope and limitations of the protocol employing different 4-(prop-2-yn-1-yloxy)benzaldehydes (**2**), phenylazides (**1**) and 1,2-diaminobenzenes (**3**)[a].



1a–j **2a,b** **3a,b** **4a–w**

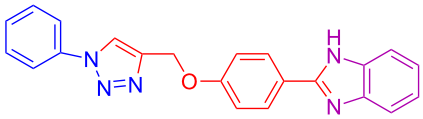
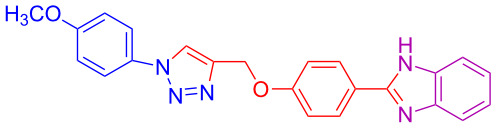
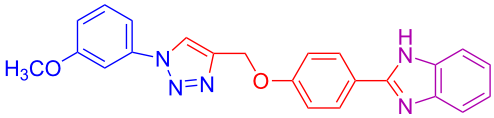
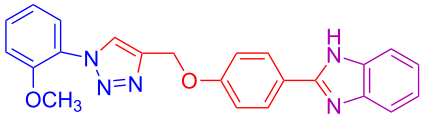
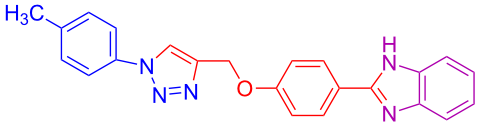
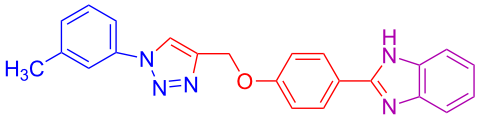
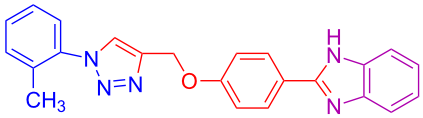
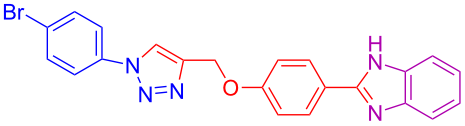
Entry	R^1	R^2	X	Product	Yield (%)[b]
1	H	H	H	 **4a**	80
2	4-OCH_3	H	H	 **4b**	92
3	3-OCH_3	H	H	 **4c**	83
4	2-OCH_3	H	H	 **4d**	75
5	4-CH_3	H	H	 **4e**	79
6	3-CH_3	H	H	 **4f**	68[c]
7	2-CH_3	H	H	 **4g**	60
8	4-Br	H	H	 **4h**	75

Table 2: Scope and limitations of the protocol employing different 4-(prop-2-yn-1-yloxy)benzaldehydes (**2**), phenylazides (**1**) and 1,2-diaminobenzenes (**3**)[a]. (continued)

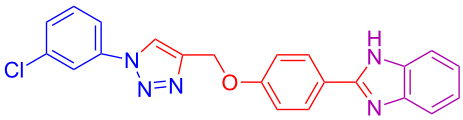
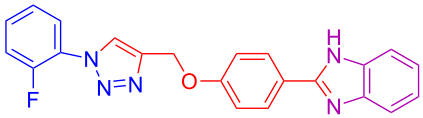
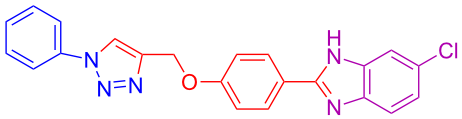
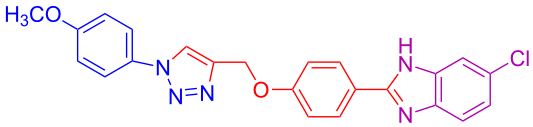
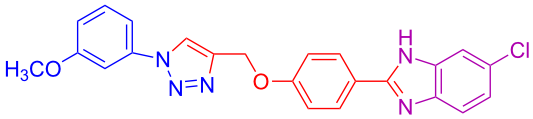
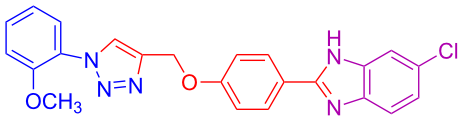
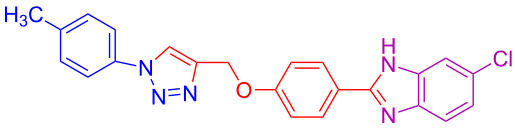
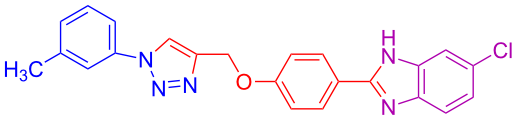
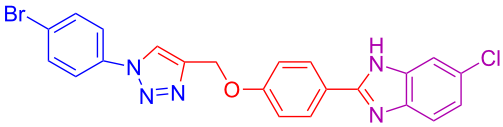
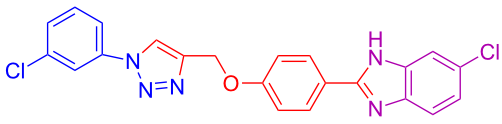
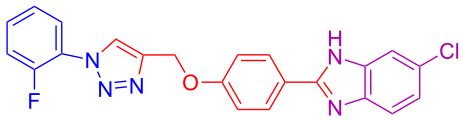
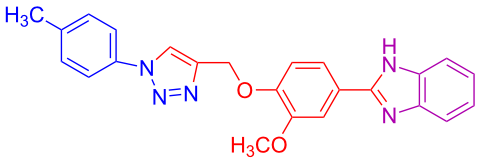
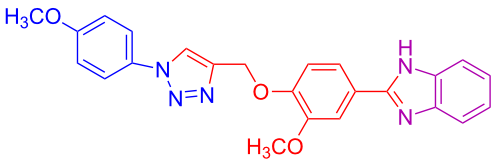
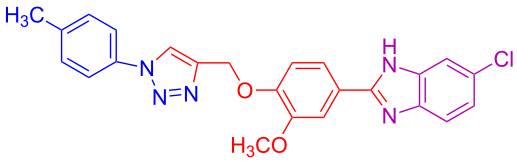
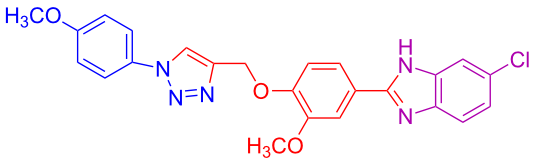
9	3-Cl	H	H	 **4i**	73
10	2-F	H	H	 **4j**	60[c]
11	H	H	Cl	 **4k**	90
12	4-OCH_3	H	Cl	 **4l**	91
13	3-OCH_3	H	Cl	 **4m**	73
14	2-OCH_3	H	Cl	 **4n**	76[c]
15	4-CH_3	H	Cl	 **4o**	82
16	3- CH_3	H	Cl	 **4p**	69
17	4-Br	H	Cl	 **4q**	78
18	3-Cl	H	Cl	 **4r**	77

Table 2: Scope and limitations of the protocol employing different 4-(prop-2-yn-1-yloxy)benzaldehydes (**2**), phenylazides (**1**) and 1,2-diaminobenzenes (**3**)[a]. (continued)

19	2-F	H	Cl	 **4s**	67[c]
20	4-CH_3	OCH_3	H	 **4t**	69
21	4-OCH_3	OCH_3	H	 **4u**	83[c]
22	4-CH_3	OCH_3	Cl	 **4v**	68
23	4-OCH_3	OCH_3	Cl	 **4w**	85

[a]Phenylazide **1** (1.0 mmol), propargyloxybenzaldehyde **2** (1.2 mmol), 1,2-diaminobenzene **3** (2 mmol), $CuSO_4·5H_2O$ (0.2 equiv), D-glucose (0.4 equiv) were irradiated at 70 °C and 100 W maximum power; [b]isolated yields after work-up, no further purification was required; [c]Isolated yields after column chromatography.

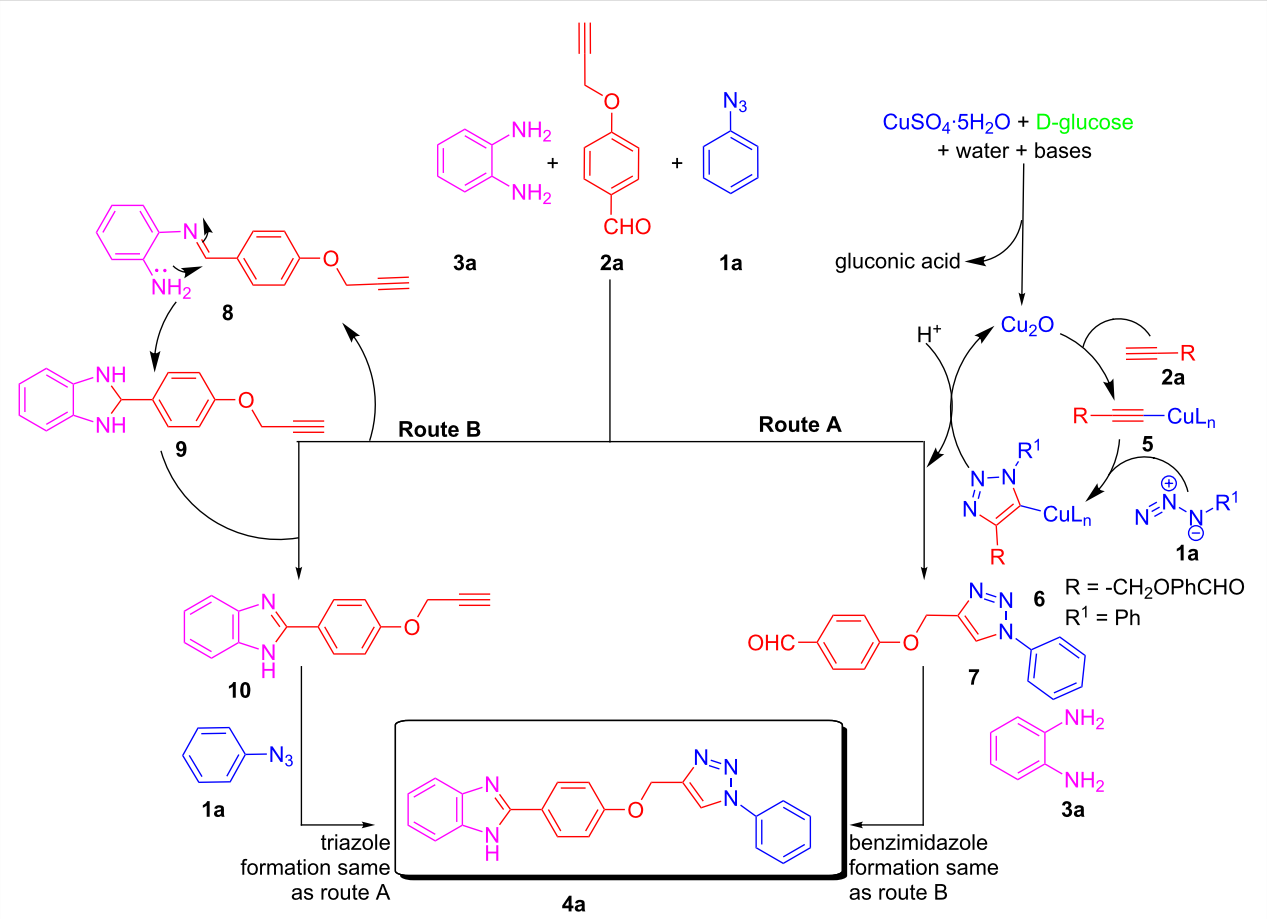
2a,**b**, and two different 1,2-diaminobenzenes **3a**,**b** were used. In general, good to excellent yields were obtained for the desired cyclized products.

Plausible mechanism

The desired product could be obtained by the two mechanistic pathways A and B as described in Scheme 2. The CuAAC could take place prior to or after benzimidazole formation and we do not have a clear mechanistic proof. However, we believe that if the reaction proceed via route A in situ generation of Cu(I) [32,33] from Cu(II) takes place first upon reduction with D-glucose. Then, this Cu(I) reacts with 4-(prop-2-yn-1-yloxy)benzaldehyde **2a** to form the copper acetylide [35,36] **5**, which reacts with azidobenzene **1a** affording intermediate **6** by a [3 + 2] cycloaddition reaction. The intermediate **6** yields 4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde intermediate **7** after protonolysis of the C–Cu bond. This intermediate reacts with 1,2-diaminobenzene (**3a**) under the formation of the corresponding Schiff' base, which further cyclizes to dihyrobenzimidazole. Finally, D-glucose [37] oxidizes the dihyrobenzimidazole to the benzimidazole. Moreover, if the reaction proceeds via route B the benzimidazole formation from 4-(prop-2-yn-1-yloxy)benzaldehyde **2a** and 1,2-diaminobenzene **3a** takes place first, followed by the formation of triazole by CuAAC reaction to give the desired product **4a**.

Conclusion

We developed a novel microwave-assisted, Cu(I)-catalyzed, three-component reaction for the synthesis of 2-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1*H*-benzo[*d*]imidazoles in good to excellent yields. This protocol is applicable to various phenylazides, propargyloxybenzaldehydes and 1,2-diaminobenzenes.



Scheme 2: Plausible mechanism for the synthesis of 2-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1*H*-benzo[*d*]imidazole.

Supporting Information

Supporting Information File 1

Experimental procedures and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-145-S1.pdf]

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Multicomponent reactions in nucleoside chemistry

Mariola Koszytkowska-Stawińska* and Włodzimierz Buchowicz

Review

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Abstract

This review covers sixty original publications dealing with the application of multicomponent reactions (MCRs) in the synthesis of novel nucleoside analogs. The reported approaches were employed for modifications of the parent nucleoside core or for de novo construction of a nucleoside scaffold from non-nucleoside substrates. The cited references are grouped according to the usually recognized types of the MCRs. Biochemical properties of the novel nucleoside analogs are also presented (if provided by the authors).

Introduction

Chemical modifications of natural ribose or 2'-deoxyribose nucleosides resulted in the development of a group of compounds referred to as nucleoside analogs (Figure 1). The essential role of nucleoside analogs in medicine is reflected by the fact that currently thirty-six compounds from this class are used throughout the world in the therapy of viral or cancer diseases [1]. Moreover, several novel nucleoside analogs (including those embedded in versatile conjugate or pronucleotide scaffolds) are under clinical or preclinical trials [1]. Recent studies have also revealed a potential of nucleoside analogs as radiopharmaceuticals [2-6], antibiotics [7-9], anti-infective agents [10-12], or molecular probes [13,14]. Taking into account the importance of nucleoside analogs in medicine and biotechnology, there is a considerable interest in the development of simple and efficient synthesis of these compounds.

Multicomponent reactions (MCRs) represent an excellent tool for the generation of libraries of small-molecule compounds, for instance they are indispensable for the structure–activity relationship (SAR) studies. Many excellent comprehensive reviews on MCRs have been published. The reviews have covered the significant topics in this field, such as: (a) the applications of MCRs in the drug discovery process [15-20], or in the total synthesis [21,22]; (b) strategies developed for the construction of new structural frameworks [23]; (c) the use of specific building blocks [24-28], reagents [29-32], catalysts [33], reaction conditions [34,35], or preparative techniques [36] in MCRs; (d) methods for the design of new MCRs [37,38]; or (e) higher-order MCRs [39]. However to date, the application of MCRs in the chemistry of nucleoside analogs has not been methodically discussed. To the best of our knowledge, the only review arti-

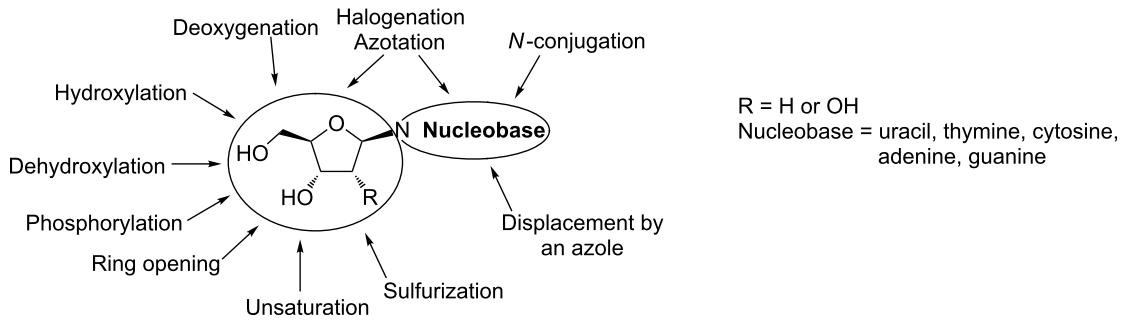


Figure 1: Selected chemical modifications of natural ribose or 2'-deoxyribose nucleosides leading to the development of medicinally important nucleoside analogs.

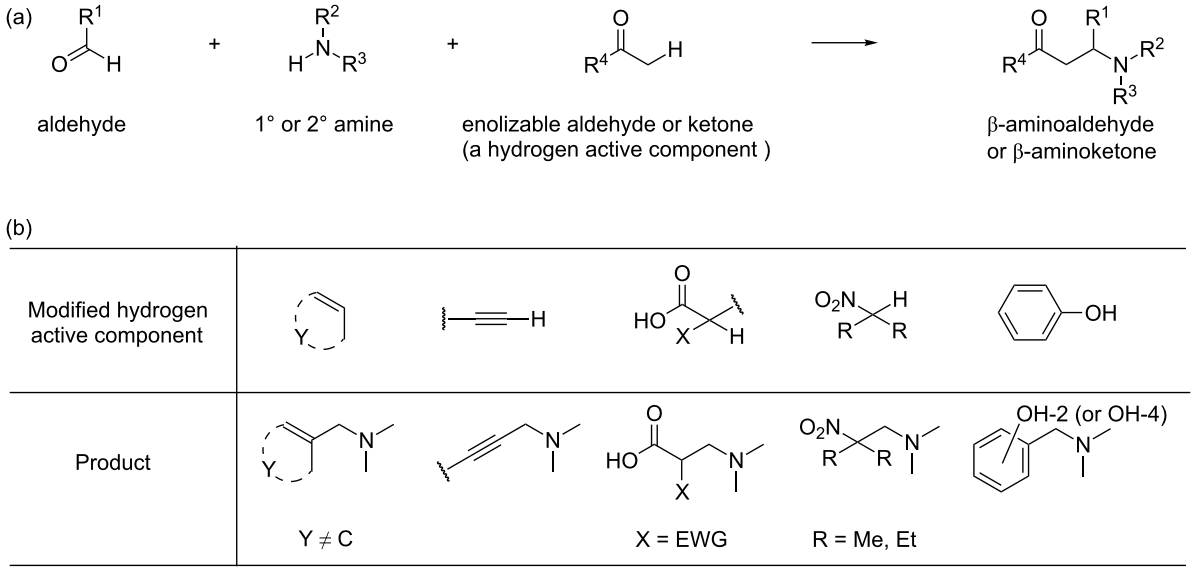
cles in this field were published from the Dondoni research group [40,41] or from the Torrence research group [42,43], and they were limited to the results obtained by these groups.

The present review covers reports published up to October 2013, and is devoted to the employment of MCRs in the synthesis of nucleoside analogs. The references were selected in accordance with the definition of a MCR given by Ugi et al.: "a multicomponent reaction comprises reactions with more than two starting materials participating in the reaction and, at the same time, the atoms of these educts contribute the majority of the novel skeleton of the product" [44]. In this review, we understand educts as compounds that contribute carbon atoms to the MCR product [45]. By the analogy to nucleosides included in the DNA/RNA nucleic acids, this review is limited to MCRs involving furanosyl nucleosides as (i) reaction components, or (ii) products obtained from non-nucleoside substrates. The cited references are grouped according to the usually recognized types of the MCRs [46].

Review

1. The Mannich reaction

The classical Mannich reaction yields β-aminoaldehydes or β-aminoketones and involves: an aldehyde, a primary (or a secondary) amine, and an enolizable aldehyde (or ketone) (Scheme 1a) [47,48]. The use of a hydrogen active component other than an enolizable aldehyde or ketone leads to a variety of structurally diverse products (Scheme 1b). The Mannich reaction products (commonly named as Mannich bases) can serve as starting materials in the syntheses of a variety of compounds.

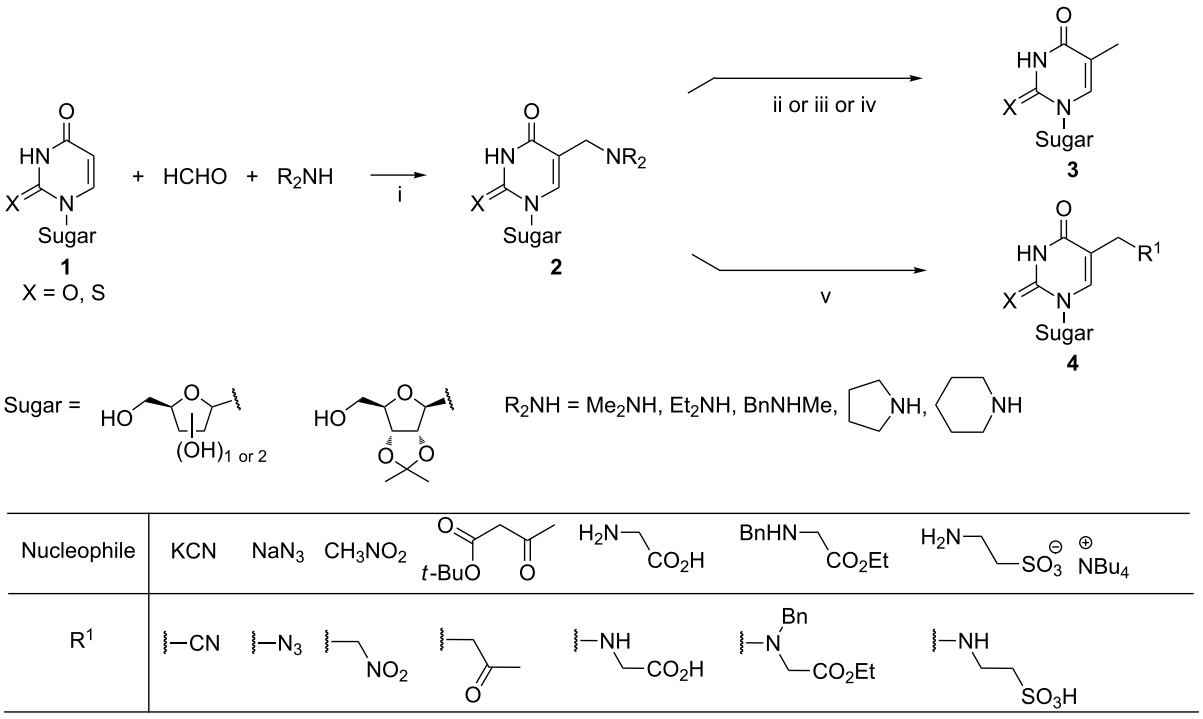


Scheme 1: (a) Classical Mannich reaction; (b) general structures of selected hydrogen active components and structures of the resulting Mannich reaction products.

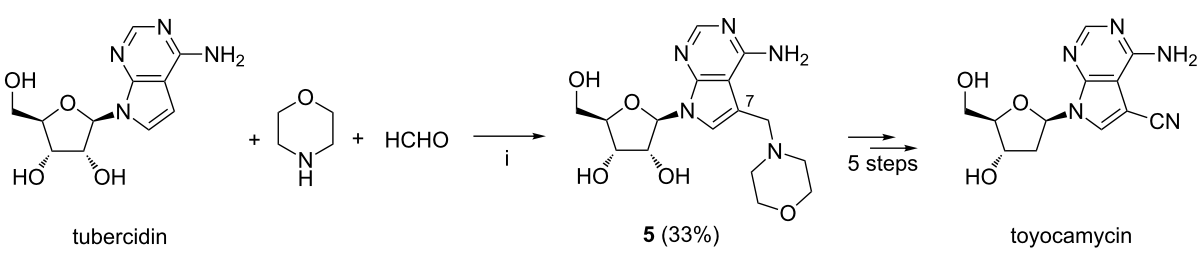
The employment of a nucleoside as the hydrogen active component has been one of the most common variants of the Mannich reaction. Treatment of uracil (or 2-thiouracil) nucleosides **1** with aq formaldehyde and a secondary amine (i.e., dimethylamine [49,50], diethylamine [51,52], *N*-methylbenzylamine [49], pyrrolidine [53,54], or piperidine [55,56]) at temperatures ranging from 60 °C to 100 °C afforded the corresponding 5-(alkylaminomethyl)pyrimidine nucleosides **2** (Scheme 2). Compounds **2** served as precursors to a variety of compounds. The transformations leading to thymidine or its derivatives **3** involved: (a) the metal-catalyzed hydrogenolysis of products **2** [51,52,54,55] (or their 5-(4-tolylthio)methyl derivatives [57]), or (b) the reduction of methylammonium iodides derived from compounds **2** with sodium borohydride [53]. Compounds **4** were achieved by treatment of the corresponding methylammonium iodides with an organic nucleophile [56,58-60]. As studies on the synthesis of 5-taurinomethyluridine showed [60], this two-step procedure was much more efficient than a direct Mannich reaction involving taurine, formaldehyde and 2',3'-*O*-isopropylideneuridine [61].

Watanabe et al. described the synthesis of 7-(morpholinomethyl)tubercidin **5** by heating tubercidin, 37% aq formaldehyde and morpholine at 90 °C overnight (Scheme 3) [62]. Compound **5** was converted into the natural nucleoside toyocamycin in five steps.

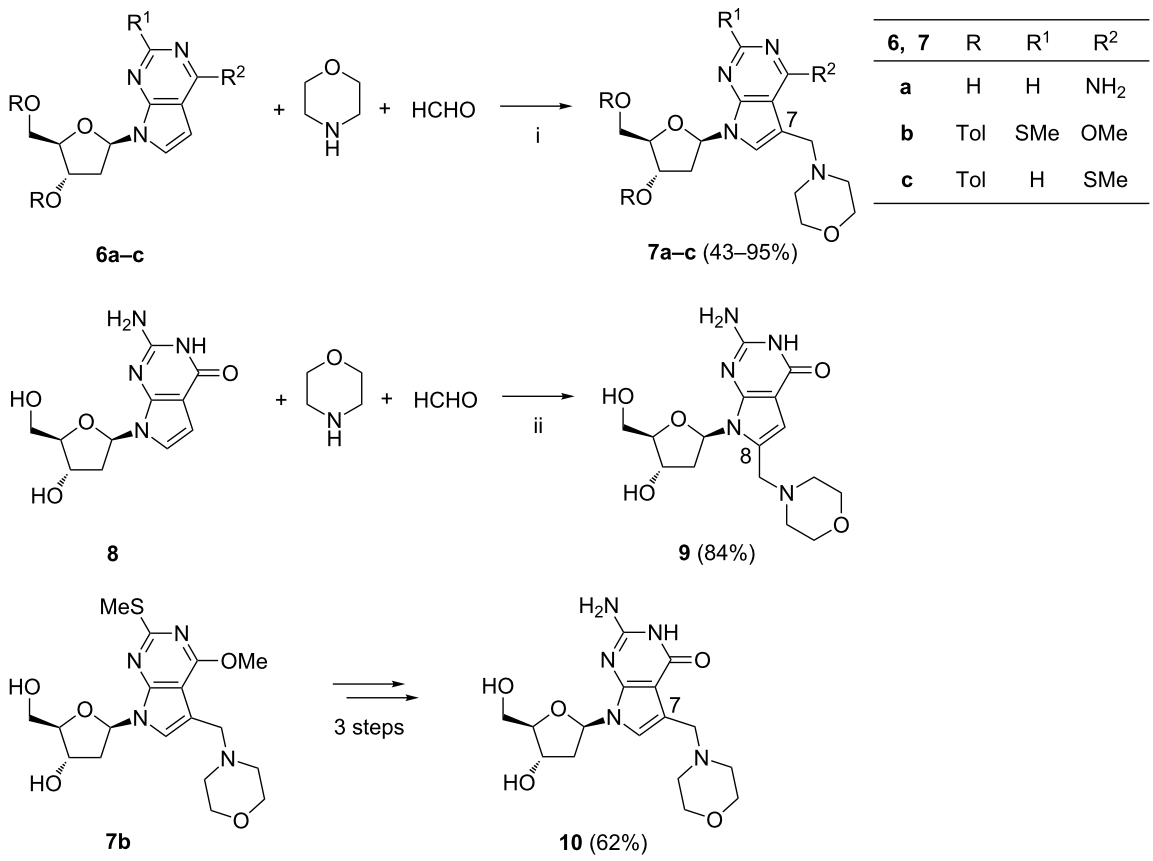
As Seela et al. reported, the reaction conditions developed for the preparation of compound **5** (Scheme 3) were ineffective when applied to 2'-deoxytubercidin **6a** (Scheme 4) [63]. The



Scheme 2: Reagents and reaction conditions: i. H_2O or H_2O/EtOH, 60–100 °C, 7 h–10 d; ii. H_2, Pd/C or PtO_2; iii. (1) 4-methylbenzenethiol, (2) Ni-Ra; iv. (1) MeI, (2) $NaBH_4$; v. (1) MeI, (2) nucleophile.



Scheme 3: Reagents and reaction conditions: i. H_2O, 90 °C, overnight.

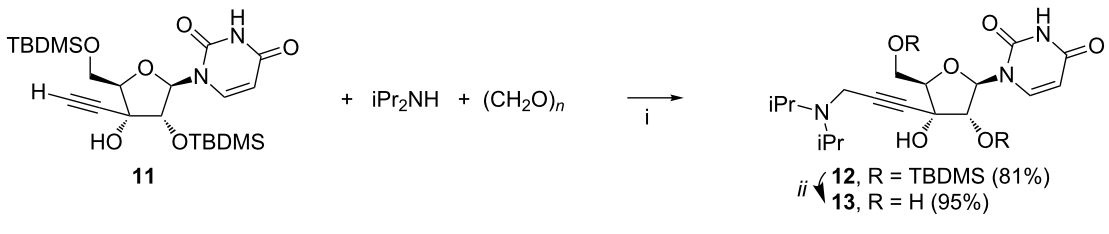


6, 7	R	R^1	R^2
a	H	H	NH_2
b	Tol	SMe	OMe
c	Tol	H	SMe

Scheme 4: Reagents and reaction conditions: i. AcOH, H_2O, 60 °C, 12 h-5 d; ii. AcOH, H_2O, 60 °C, 8 h.

efficient conversion of compounds **6** to the 7-(morpholinomethyl) derivatives **7** required the use of acetic acid as a co-solvent. However, in the case of 7-deaza-2'-deoxyguanosine (**8**) the regioselectivity of the reaction changed from the C-7 to the C-8 position of the 7-deazapurine system (Scheme 4). The formation of product **9** could be explained by the influence of the electron-donating properties of the C-2 amino group stabilizing the σ-complex formed during the electrophilic attack at the C-8 carbon atom. Since the attempted acylation of the guanine amino group of **8** did not succeeded in the formation of the C-7-substituted guanosine **10**, the compound was obtained in three steps from derivative **7b** by conventional protecting-group manipulations (Scheme 4).

The use of 3'-ethynylnucleoside **11** as the alkyne-derived hydrogen active component was described by Dauvergne et al. (Scheme 5) [64]. Treatment of compound **11** with paraformaldehyde and diisopropylamine in the presence of cuprous bromide in refluxing THF afforded the Mannich base **12** in 81% yield. The deprotection of compound **12** with tetrabutyl-



Scheme 5: Reagents and reaction conditions: i. CuBr, THF, reflux, 0.5 h; ii. *n*-$Bu_4NF{\cdot}3H_2O$, THF, rt, 2 h.

ammonium fluoride gave the final product **13**. Compound **13** showed antitumor activity (IC_{50} = 75 μM) against RDM4 tumor cells.

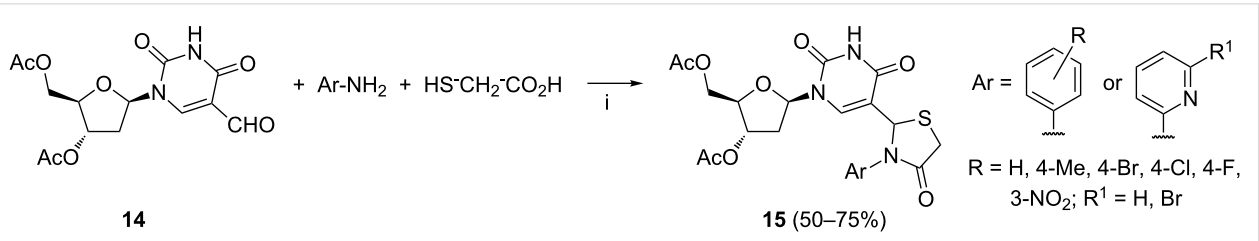
Examples of the Mannich reaction employing a nucleoside as the aldehyde-bearing component are rather limited. Zhang et al. obtained a series of pyrimidine nucleoside-thazolidinone hybrids **15** from 5-formyl-3',5'-di-*O*-acetyl-2'-deoxyuridine (**14**), an arylamine and mercaptoacetic acid (Scheme 6) [65]. The reactions were performed in a ionic liquid ([bmim]PF_6). Products **15** were obtained in good to moderate yields. Antiparasitic activities of the hybrid compounds **15** were evaluated; some of them showed moderate activities against trypomastigote forms of *Trypanosoma brucei brucei GVR 35* (e.g., IC_{50} = 25 μM for Ar = C_6H_4-Cl-4).

The Mannich reaction was also used to construct nucleoside scaffolds from non-nucleoside substrates (Schemes 7–9). Filichev et al. used pyrrolidine **16**, paraformaldehyde and uracil for the preparation of the Mannich base **17**, which is considered as an 1'-aza-analog of pseudouridine (Scheme 7) [66]. Information on application of compound **17** was not given.

By employing pyrrolidine hydrochlorides **16***HCl or **20a–c***HCl (Scheme 8), Evans et al. developed a concise synthesis of 1'-aza-analogs of immucilins, compounds **19** and **21** [67]. The amine hydrochlorides were treated in aq acetate buffer with aq formaldehyde and 9-deazaguanine **18a** or a variety of deazapurines **18b–e**. The acetate buffer was used to generate in situ the free amine **16**, i.e., the Mannich reagent. Reactions leading to products **19** or **21** were conducted for 1 h to 16 h. Among nucleosides **19** and **21**, the 9-deazahypoxanthine-derived compound **19a** (DADMe-Immucilin-H, ulodesine) and the 9-deazaguanine-derived compound **19b** (DADMe-Immucilin-G) were reported to be potent transition state analog inhibitors of human purine nucleoside phosphorylase (PNP). Ulodesine **19a** has completed two phase II clinical trials in 2013 [68,69].

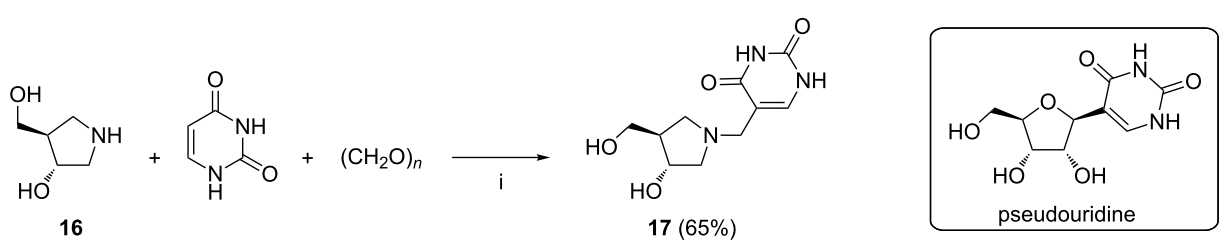
Using the fluorinated pyrrolidine (3*S*,4*S*)-**22** (Scheme 9), Mason et al. obtained azanucleoside (3*S*,4*S*)-**23**, that is an analog of ulodesine **19a** [70]. The two-step procedure leading to compound (3*S*,4*S*)-**23** involved: (i) *N*-Boc-deprotection of (3*S*,4*S*)-**22** with concentrated HCl in methanol, and (ii) treatment of the crude free pyrrolidine with 37% aq formaldehyde and 9-deazahypoxantine **18a** in the presence sodium acetate in dioxane at 100 °C. The compound was prepared on the 10 mg scale in 67% yield. In contrast to its (3*R*,4*R*)-enantiomer (not shown), compound (3*S*,4*S*)-**23** showed inhibitory activity toward human purine nucleoside phosphorylase (PNP) with a slow-onset binding constant K_i* = 0.032 nM. In comparison to ulodesine **19a**, compound (3*S*,4*S*)-**23** exhibited decreased oral availability in mice (0.2 mg/kg dose) and lower duration of action.

Compounds **25** and **26**, prepared by Chen et al. [71], can be considered as analogs of reversed nucleosides [72] with the thiazolidin-4-one mimic of a nucleobase (Scheme 10). The compounds were obtained from condensation of aminosugar **24**, arylaldehydes and mercaptoacetic acid in the presence of DMAP and DCC at room temperature. The reaction proceeded



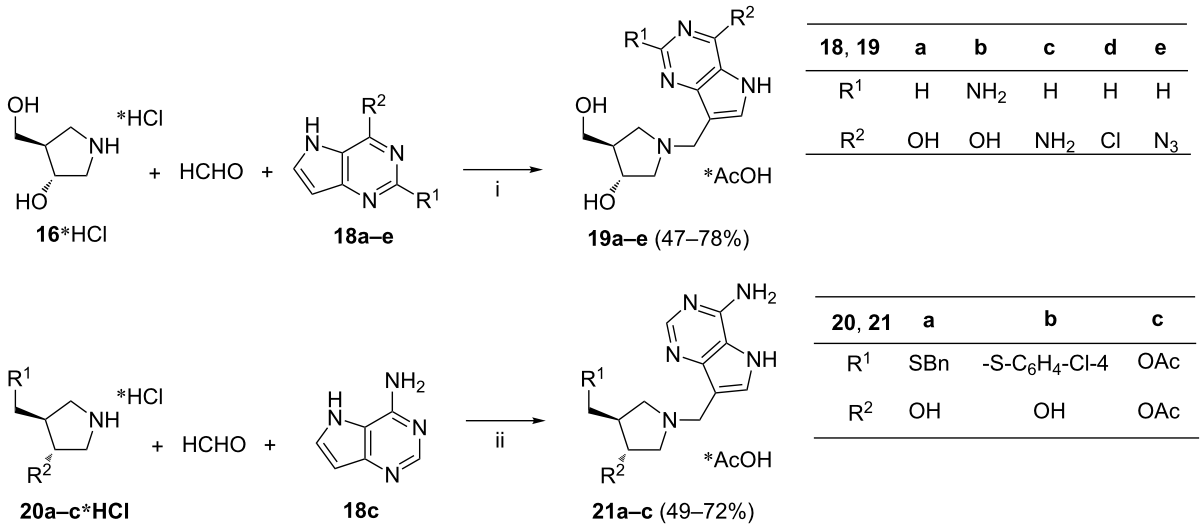
14 **15** (50–75%)

Scheme 6: Reagents and reaction conditions: i. [bmim][PF_6], 80 °C, 5–8 h.



16 **17** (65%)

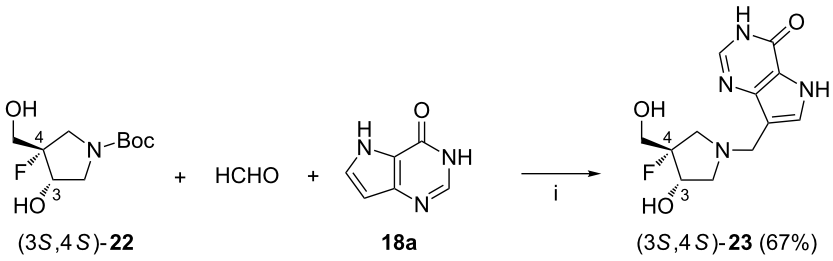
Scheme 7: Reagents and reaction conditions: i. EtOH, reflux, 24 h.



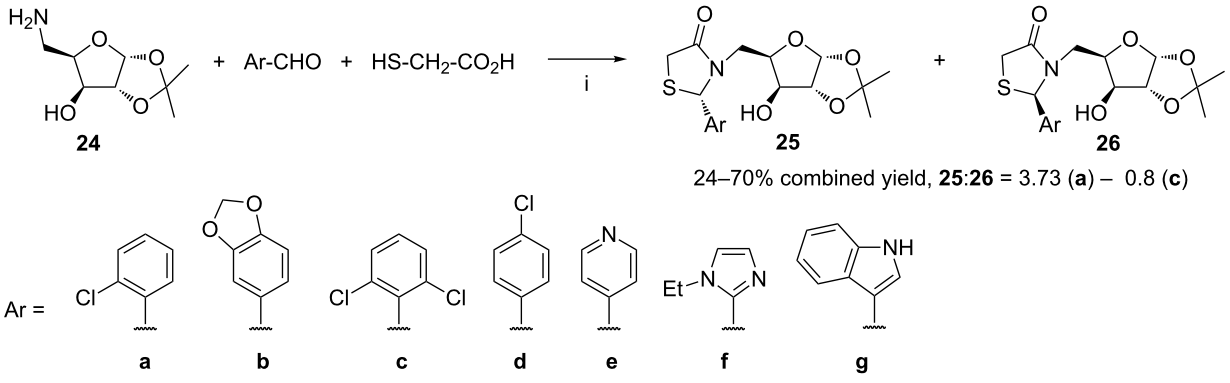
18, 19	a	b	c	d	e
R^1	H	NH_2	H	H	H
R^2	OH	OH	NH_2	Cl	N_3

20, 21	a	b	c
R^1	SBn	-S-C_6H_4-Cl-4	OAc
R^2	OH	OH	OAc

Scheme 8: Reagents and reaction conditions: i. NaOAc, H_2O, 95 °C, 1–16 h; ii. NaOAc, H_2O, 95 °C, 1 h.



Scheme 9: Reagents and reaction conditions: i. a. 37% aq HCl, MeOH; b. NaOAc, 1,4-dioxane, H_2O, 100 °C, overnight.



Scheme 10: Reagents and reaction conditions: i. DMAP, DCC, MeOH, rt, 1 h.

with almost no stereoselectivity for the majority of these aldehydes, i.e., two diasteroisomers were isolated in ratios from 0.8 to 1.35. A modest stereoselectivity was observed in the case of 2-chlorobenzaldehyde with the **25a**:**26a** ratio of 3.73. Compounds **25a** and **25b**, in contrast to their isomers **26**, showed moderate activity against human cervical cancer cells at the concentration of 100 μM. Recently, the same group has developed the synthesis of D-glucopyranose-derived counterparts of

compounds **25** and **26** [73]. The formation of an intermediate imine from a sugar azide and an aldehyde by Staudinger/aza-Wittig reaction was the key step of the synthesis.

2. The Kabachnik–Fields reaction

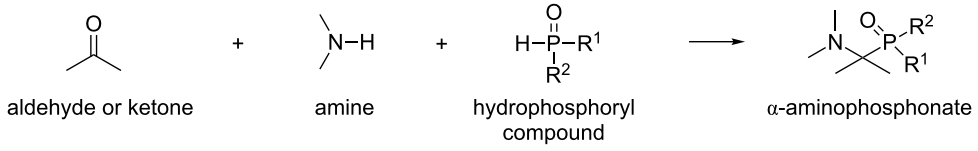
The Kabachnik–Fields reaction (Scheme 11) proceeds in a three-component system involving a carbonyl compound (aldehyde or ketone), amine, and a hydrophosphoryl compound (mainly alkyl/aryl phosphite) [74,75]. The reaction products, commonly termed as α-aminophoshonates, display properties of industrial and/or medical interest.

An example of the application of the Kabachnik–Fields reaction in nucleoside chemistry represents the preparation of α-arylaminophosphonates **28** and **29** by Zhang et al. (Scheme 12) [76]. The reactions between 5-formyl-2'-deoxyuridine **27** (or its 3',5'-di-*O*-acetyl derivative **14**), an aniline and dimethyl phosphite were carried out under solvent-free conditions at 60 °C (for **14**) or at 80 °C (for **27**). Products **28** and **29** were obtained in good to excellent yields as 1:1 diastereoisomeric mixtures arising from the generation of a stereogenic center at the aminophosphonate chain. The mixtures were not separated. Activity of hybrid compounds **28** and **29** against VZV and CMV viruses, as well as against Leishmania donovani promastigotes, was evaluated. Unfortunately, none of them showed any activity up to 250 μM.

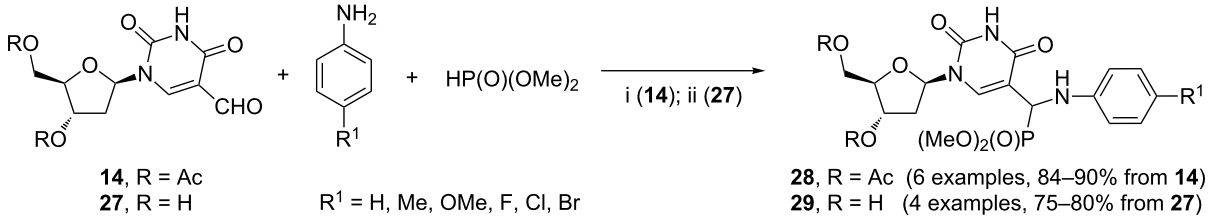
3. The Ugi reaction

The Ugi reaction allows for a facile synthesis of a bisamide from a ketone (or an aldehyde), an amine, an isocyanide, and a carboxylic acid (Scheme 13) [77,78]. The Ugi MCRs involving a nucleoside as the substrate bearing the formyl, amino, or isocyano group have been reported.

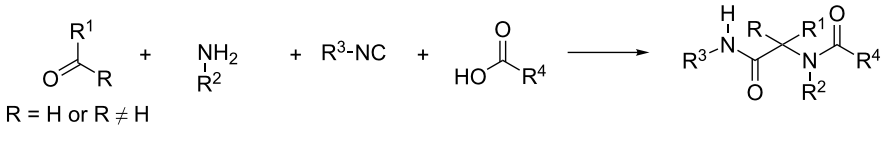
The four-component Ugi reaction employing 3',5'-di-*O*-acetyl-5-formyl-2'-deoxyuridine (**14**) as the key substrate afforded nucleosides **30** bearing a *N*-acyl α-amino acid amide moiety at the uracil C-5 carbon atom (Scheme 14) [79]. The variant of the reaction with trimethylsilyl azide (TMS-N_3) in place of the carboxylic acid gave the tetrazole-substituted nucleosides **31** [79]. Products **30** and **31** were obtained as 1:1 diastereoisomeric mixtures owing to the formation of the new stereogenic center at the amino acid residue. In most cases, the diastereoisomeric mixtures of compounds **30** were separated through column chromatography due to the large differences in the polarity of the diastereoisomers. Anti-leishmanial activity of



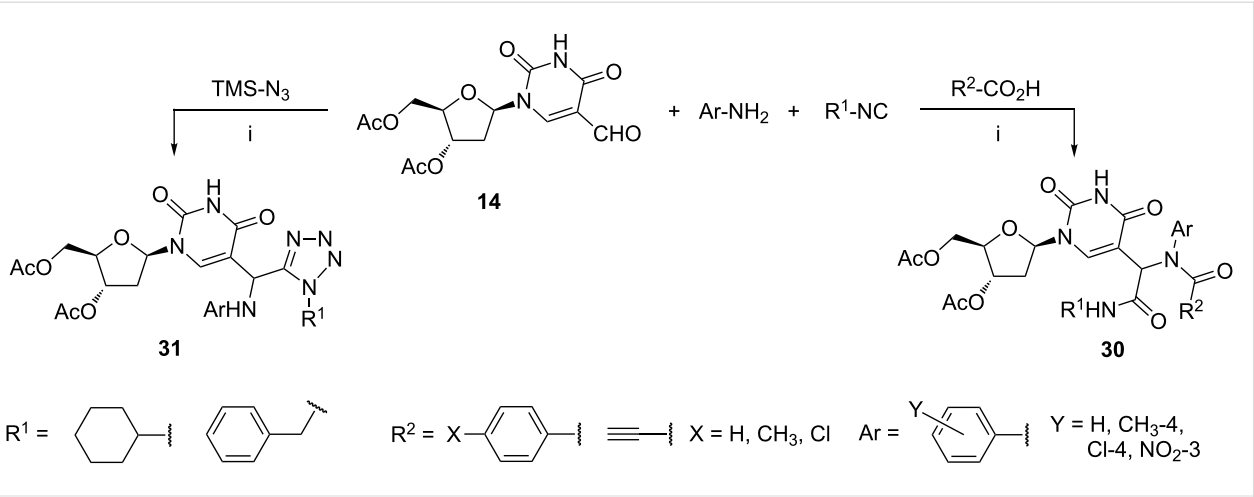
Scheme 11: The Kabachnik–Fields reaction.



Scheme 12: Reagents and reaction conditions: i. 60 °C, 3 h; ii. 80 °C, 2 h.



Scheme 13: The four-component Ugi reaction.

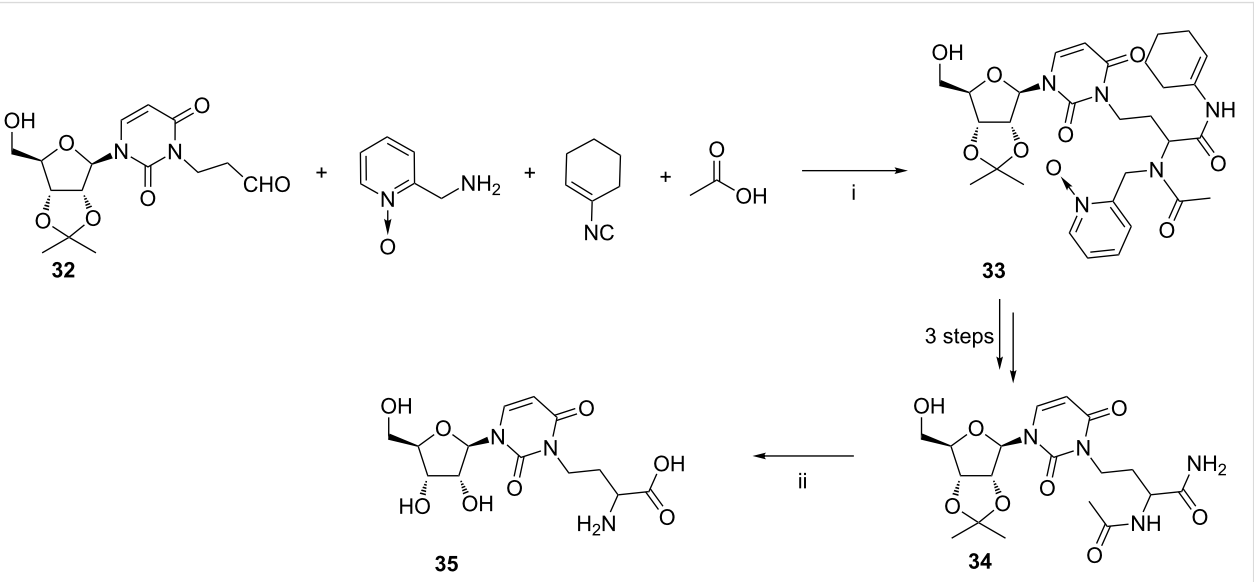


Scheme 14: Reagents and reaction conditions: i. MeOH, rt, 2–3 d, yields not given.

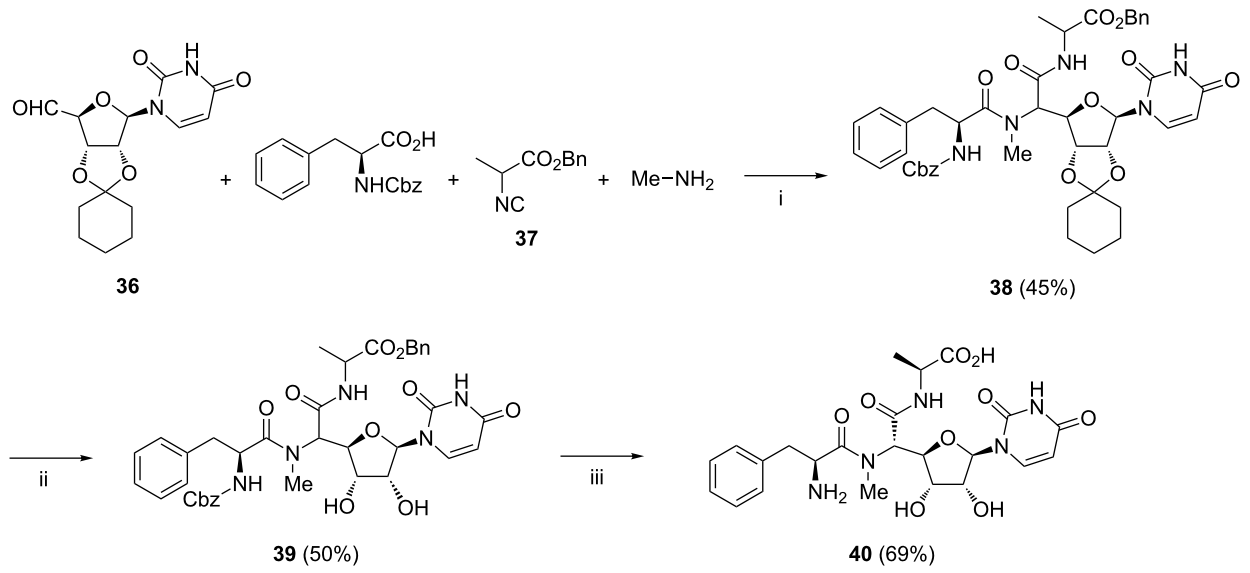
compounds **30** and **31**, as well as their activity against the vaccinia virus or cowpox virus, were evaluated. Several products **30** displayed moderate anti-leishmanial activity in the range of 12–44 μM.

The synthesis of the uridine derivative **35** involving the Ugi condensation as the key step was successfully accomplished by Tsuchida et al. (Scheme 15) [80]. The isopropylidene-protected 3-(2-formylethyl)uridine **32**, 2-(aminomethyl)pyridine 1-oxide, cyclohexenyl isocyanide, and acetic acid were allowed to react under ambient conditions for 24 h to yield the expected product **33**. Further conventional deprotection and acylation steps afforded the intermediate **34**. Upon treatment with 6 N HCl at 80 °C for 2 h the 3-(3-amino-3-carboxypropyl)uridine (**35**) was obtained in 80% yield. While this nucleoside was found in some transfer RNAs, no details of its application were disclosed.

Boehm and Kingsbury reported a facile synthesis of *N*-methylated di- and tri-peptide polyoxins by the Ugi reaction (Scheme 16) [81]. The aldehyde **36**, aq methylamine, racemic isonitrile **37**, and (*S*)-*N*-(benzyloxycarbonyl)phenylalanine were combined in MeOH to produce **38** as a mixture of four possible diastereoisomers in a total yield of 45%. The cyclohexylidene protecting group was then removed in refluxing aq AcOH. The resulting diastereoisomers **39** were separated by reversed phase HPLC to yield two pure isomers and the remaining two as an inseparable 1:1 mixture. These were further deprotected by hydrogenolysis under the hydrogen transfer conditions using the



Scheme 15: Reagents and reaction conditions: i. MeOH/CH_2Cl_2 (1:1), rt, 24 h, yield not given; ii. 6 N aq HCl, 80 °C, 2 h, 80%.

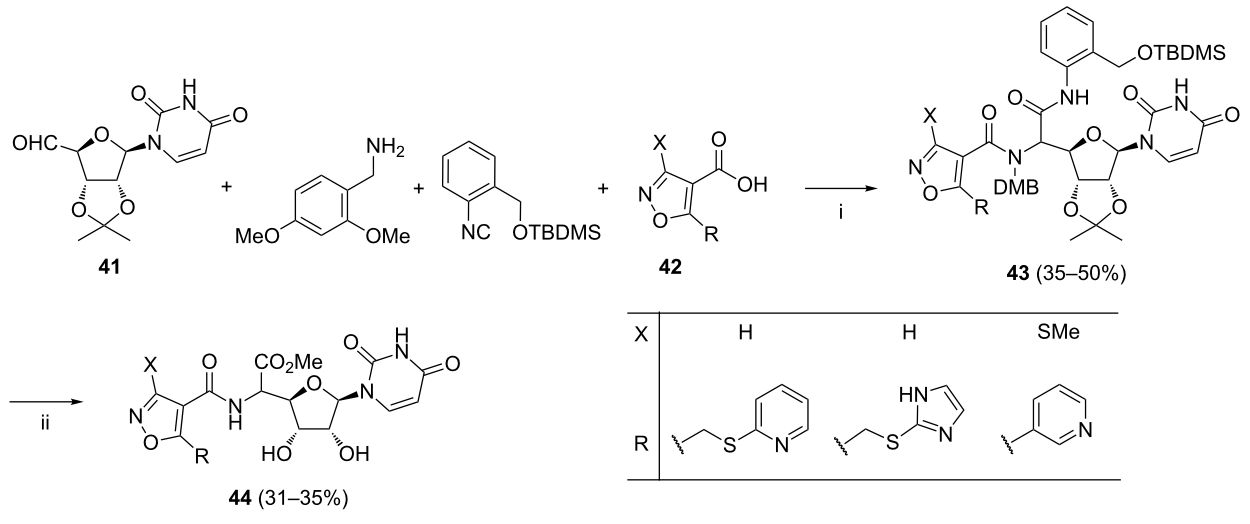


Scheme 16: Reagents and reaction conditions: i. MeOH/H_2O, rt, 26 h; ii. aq AcOH, reflux, 50%; iii. reversed phase HPLC, then MeOH, Pd black, formic acid, 1 h.

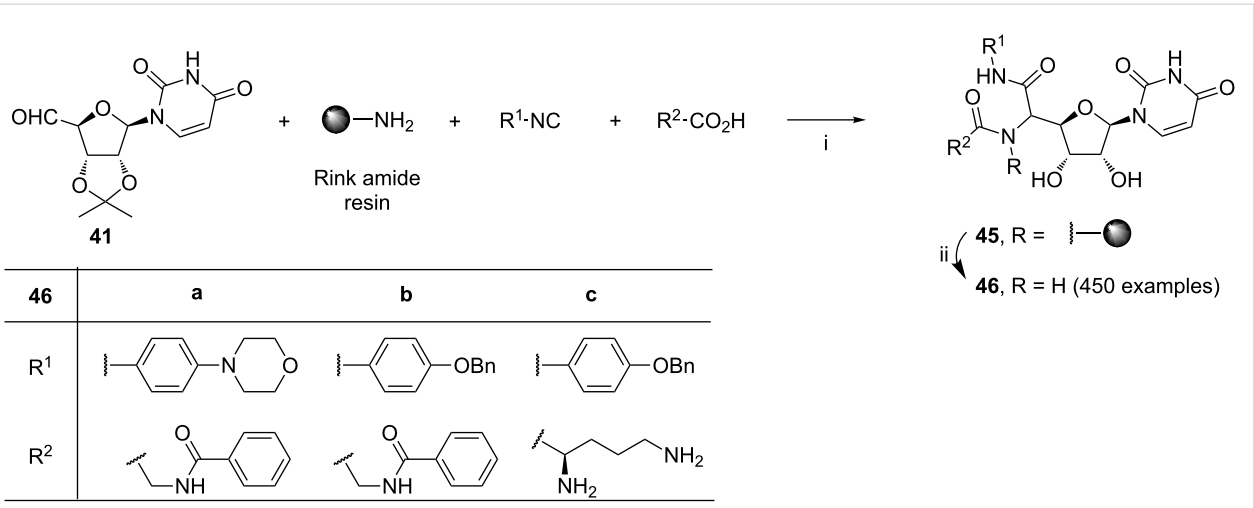
Pd black–formic acid system. Only one of the two pure isomers **40** was found to bind to chitin synthase.

Plant et al. reported another approach to uracil polyoxins via the Ugi reaction [82]. In this work, the desired products **44** were assembled from 2′,3′-protected uridine-5′-aldehyde **41**, 2,4-dimethoxybenzylamine, 2-((*tert*-butyldimethylsilyloxy)methyl)phenylisocyanide, and an isoxazolecarboxylic acid **42** (Scheme 17). Collectively, from three different isoxazolecarboxylic acids **42** three products **43** were obtained (each as ca. 1:1 mixture of diastereoisomers). Complete deprotection of **43** was accomplished in methanolic HCl to yield products **44** as mixtures of diastereoisomers.

The Ugi reaction has been often used in solid-phase synthesis of compound libraries [83]. Suda et al. developed the optimal reaction conditions of the solid-phase Ugi reaction involving Rink amide resin as the amine-bearing component (Scheme 18) [84]. The synthesis of nikkomycin Z analogs **46** aimed in an examination of their ability to inhibit *Candida albicans* chitin synthases. The library consisting of 450 analogs **46** was obtained from: (i) reactions involving nucleoside aldehyde **41**,



Scheme 17: Reagents and reaction conditions: i. MeOH, rt, 24 h; ii. HCl, MeOH, 0 °C to rt, 6 h, then H_2O, rt, 12 h.

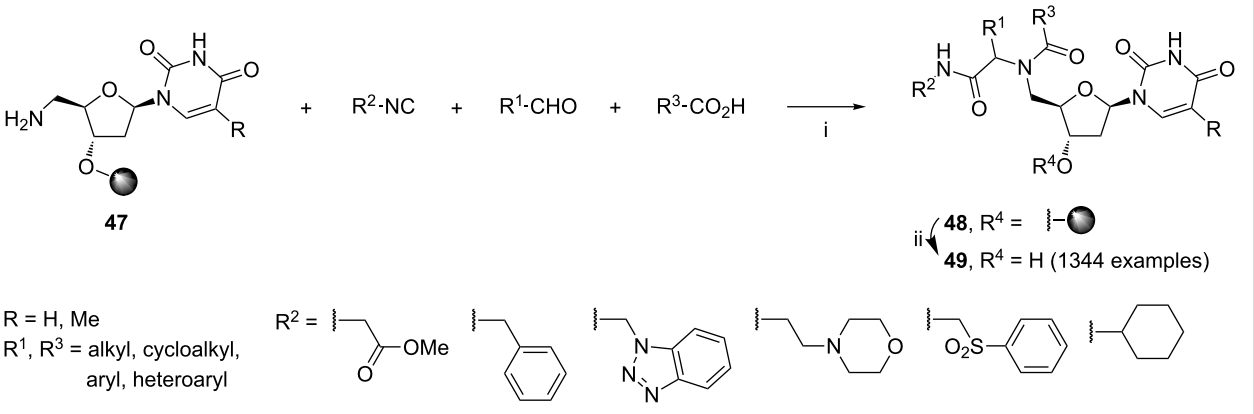


Scheme 18: Reagents and reaction conditions: i. DMF/Py/MeOH (1:1:1), rt, 48 h; ii. 10% HCl/MeOH, rt, 30 min.

Rink amide resin, one of 15 isocyanides and one of 59 carboxylic acids per reaction; (ii) treatment of the reaction mixtures with methanolic HCl. Products **46** were obtained as 1:1 mixtures of diastereoisomers. Within the library, 246 compounds showed higher than 50% inhibitory activity against *Candida albicans* chitin synthase 1 at the concentration of 10 μM. Among the most active analogs **46a–c**, compound **46a** showed a comparable activity (IC_{50} = 6.07 μM) as that determined for nikkomycin Z (IC_{50} = 9.49 μM). On the other hand, inhibitory activity of this compound toward *Candida albicans* chitin synthase 2 (IC_{50} = 4.78 μM) was significantly lower than that of nikkomycin Z (IC_{50} = 0.06 μM). The remaining compounds **46** were inactive toward *Candida albicans* chitin synthase 2.

Another approach to the solid-phase synthesis of nucleoside analogs was developed by Sun and Lee (Scheme 19) [85]. The library of 1344 compounds **49** was obtained for antibacterial screening. In this report, 5'-azidothymidine or 5'-azido-2'-deoxyuridine was linked to a polystyrene butyldiethylsilane resin and subsequently reduced to the polymer-supported thymidinyl (R = CH_3) or 2′-deoxyuridinyl (R = H) aminonucleoside **47**. The library synthesis was executed in 96-well plates, with one of the two amines **47**, 12 carboxylic acids, 8 aldehydes, and an isocyanide per plate. The products **49** were cleaved from the support with HF/pyridine in THF. As expected, the Ugi products **49** were obtained as ca. 1:1 mixtures of diasteroisomers (based on HPLC and ^{1}H NMR analysis). Members of this library were claimed to show promising biological activity, however details were not given.

Muraymycins (MRYs) are a class of naturally occurring nucleoside-lipopeptide antibiotics with excellent antibacterial activity. Matsuda and coworkers envisaged that MRYs complex molec-



Scheme 19: Reagents and reaction conditions (R = CH_3 or H): i. CH_2Cl_2/MeOH (2:1), 35–40 °C, 2 d; ii. HF/pyridine, THF, rt, 2.5 h, then MeOTMS, rt, 3.5 h.

ular structure could be efficiently assembled with the help of the Ugi reaction as the key step at the end of their synthesis. This approach was first exercised with a ring-opened muraymycin D2 analogue (Scheme 20) [86]. The reaction of carboxylic acid **50**, 2,4-dimethoxybenzylamine, isovaleraldehyde, and isonitrile-substituted nucleoside **51** in methanol yielded the desired product as a 1:1 mixture of diastereoisomers, which were fully deprotected using aq TFA to furnish the muraymycin analogue **52**.

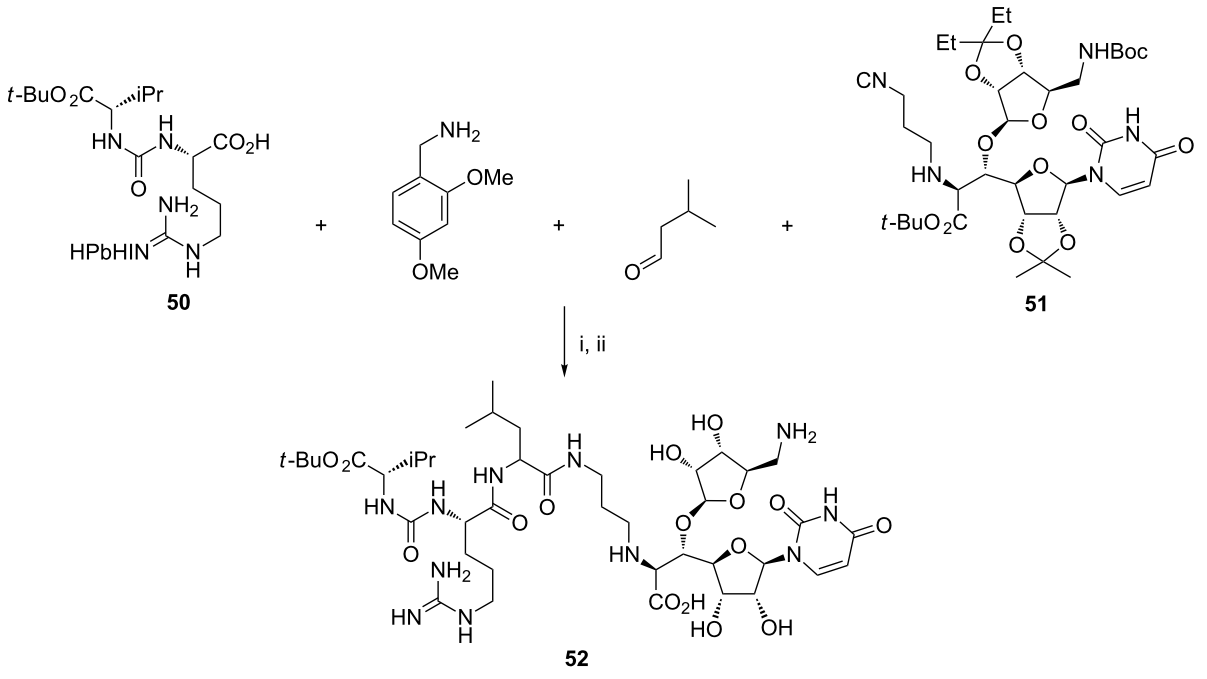
This successful route to the MRYs was then applied in the total synthesis of muraymycin D2 and its epimer (Scheme 21) [87]. After completion of the synthesis of the urea dipeptide **53** bearing the cyclic moiety found in muraymycin D2, the four-component condensation was performed similarly as in [86] to yield the protected product **54** as a 1:1 diastereomeric mixture. Functional group manipulation and HPLC separation completed the total synthesis. This approach was further developed in the synthesis of a number of MRY analogues in the following paper from the same research group [88].

More recently, the Ugi reaction was applied at a late stage of the synthesis of 3′-hydroxypacidamycin D (Scheme 22) [89]. The urea dipeptide **55**, 2,4-dimethoxybenzylamine, the protected (*S*)-2-(methylamino)propanal, and isonitrile **56** were simply combined in ethanol at ambient temperature for 48 h. The expected compound **57** and its epimer were obtained in reasonable yields, and were separated by column chromatography. The syntheses of 3′-hydroxypacidamycin D and its epimer were then accomplished in four steps from intermediates **57** or *epi*-**57**, including selective deprotection of the *N*-methyl-Boc group, coupling with *N*-Boc-L-alanine, and global deprotection. This strategy was also applicable to the synthesis of a considerable number of pacidamycin analogues.

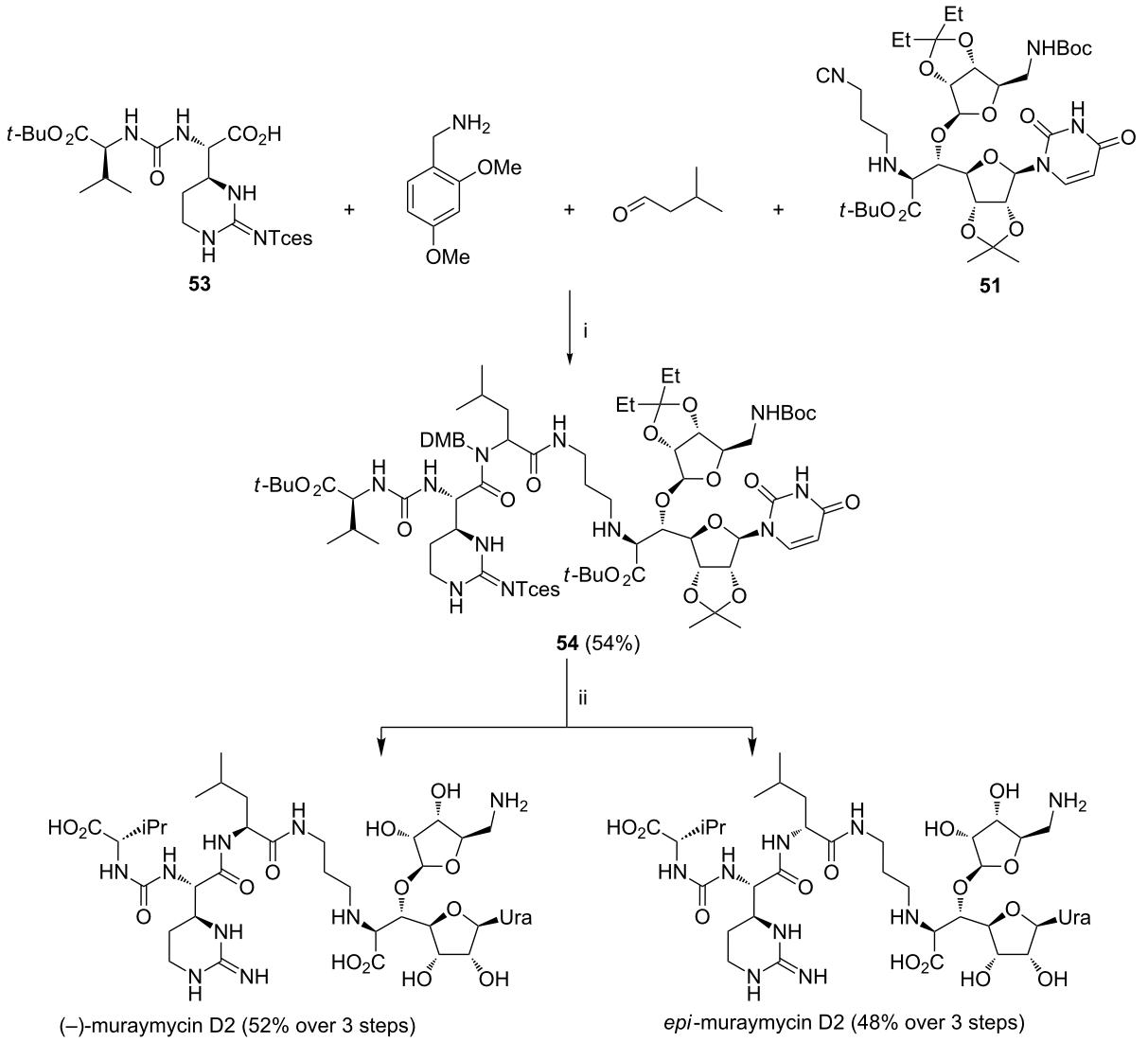
4. The multicomponent domino reactions initiated by the Knoevenagel condensation

The Knoevenagel condensation can be considered as one of the most useful tools for the formation of C=C double bonds. The condensation products, i.e., electron-deficient alkenes, readily act in subsequent reactions as Michael acceptors, Diels–Alder (hetero)dienes or dienophiles, or dipolarophiles. Multicomponent domino reactions initiated by the Knoevenagel condensation are a valuable tool for the construction of many compounds with complex molecular structures [90].

The syntheses shown in Scheme 23 and Scheme 24 represent examples of the Knoevenagel condensation-initiated domino reactions where the nucleoside aldehyde (i.e., 5-formyl-3',5'-di-*O*-acetyl-2'-deoxyuridine (**14**) or 5-formyl-2'-deoxyuridine (**27**)) acted as the Knoevenagel acceptor. Compounds **61** to **65** were prepared by the three-component process involving the Knoevenagel condensation, the Michael addition and the Thorpe–Ziegler heterocyclization (Scheme 23). Malonitrile

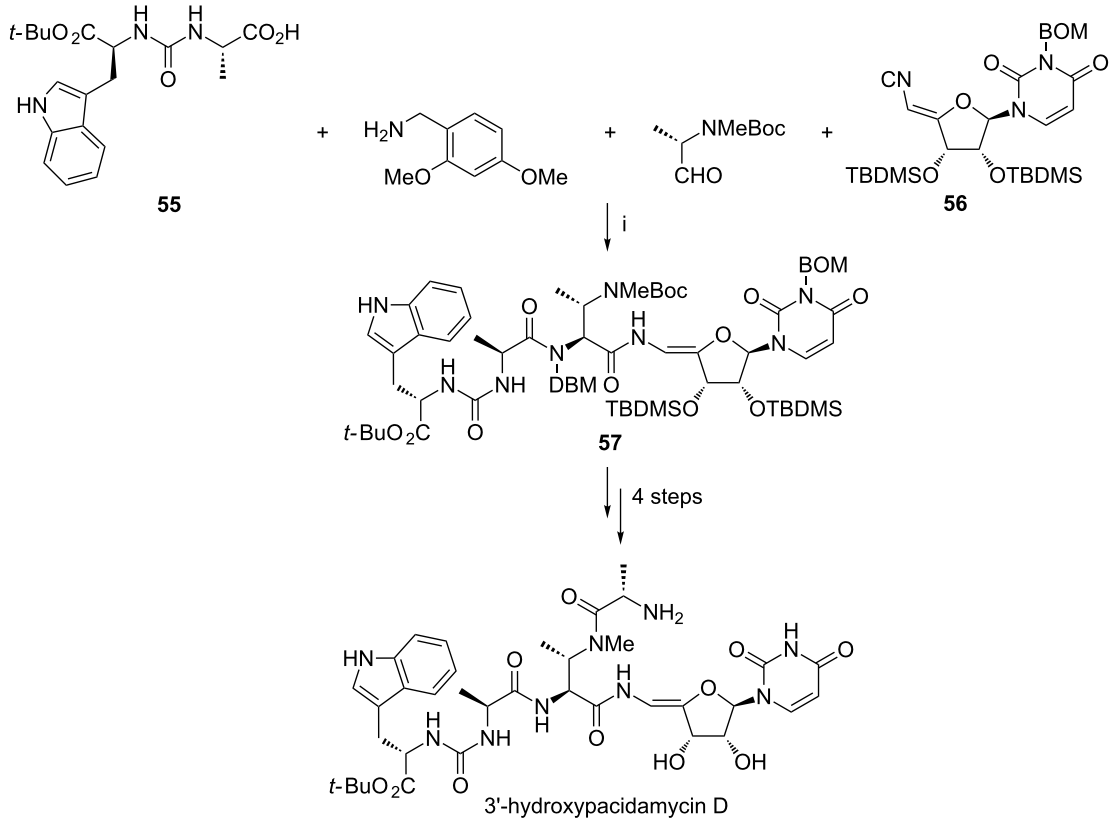


Scheme 20: Reagents and reaction conditions: i. MeOH, 76%; ii. 80% aq TFA, 100%.

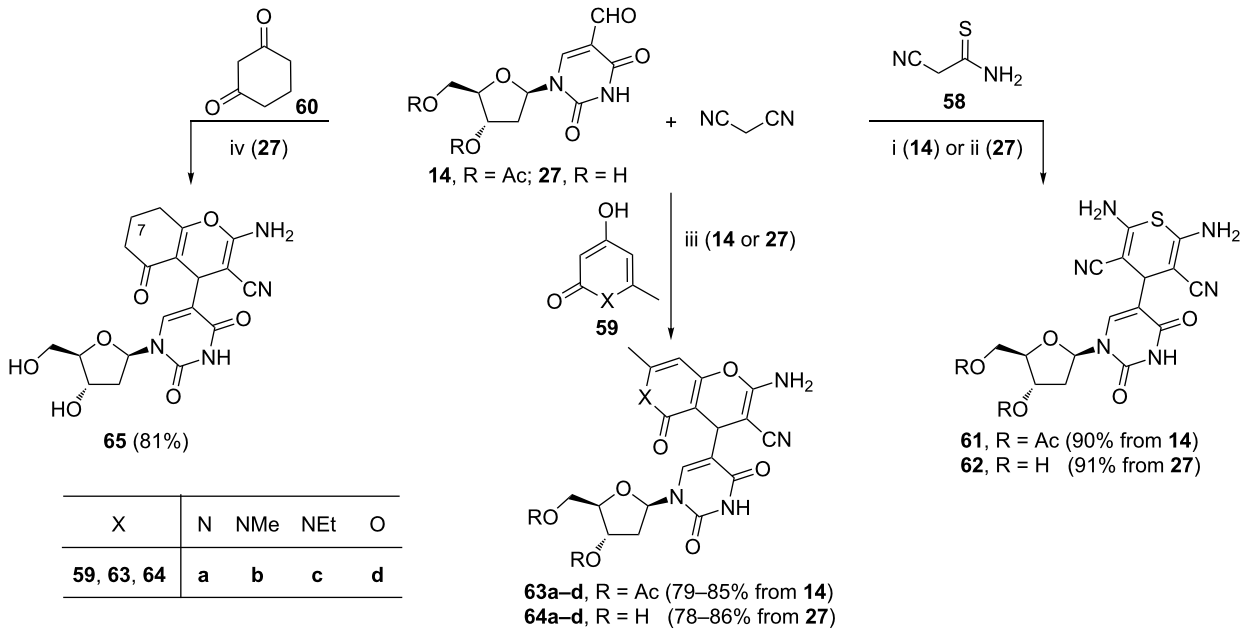


Scheme 21: Reagents and reaction conditions: i. EtOH, rt, 72 h; ii. Zn, aq NaH_2PO_4, THF, rt, 1 week; then 80% aq TFA, rt, 8 h; then HPLC separation.

acted as the Knoevenagel donor in all cases. The subsequent Michael addition steps involved: cyanothioacetamide [91], 4-hydroxy-6-methylpyridin-2(1*H*)-one (**59a**) (X = NH) [92], the *N*-methyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**59b**) (X = NMe) [92], *N*-ethyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**59c**) (X = NEt) [92], 4-hydroxy-6-methyl-2*H*-pyran-2-one (**59d**) (X = O) [92], or cyclohexane-1,3-dione (**60**) [93]. The syntheses of derivatives **61** to **64** represent a successful application of [bmim]BF_4 as a solvent [91,92]. The use of the ionic liquid allowed to shorten the reaction time and resulted in much higher yields of the final compounds than those obtained from the reactions performed in conventional organic solvents [91]. Studies on recovery and reuse of [bmim]BF_4 revealed that this solvent, when used in the fifth reaction cycle, still produced the target product in a good yield [92]. Biological activities of hybrids **63**, **64** and **65** were evaluated [91,92]. Among them, hybrid **63a** exhibited anti-leishmanian activity (IC_{50} = 10.6 ± 1.3 μM) [92]. The SAR study showed that the acetylation of the furanose hydroxy groups resulted in a dramatic decrease in anti-leishmanian activity from 10.6 ± 1.3 μM (**63a**) to 139 μM (**64b**). Compound **65** was active against the cowpox virus in human foreskin fibroblast cells (EC_{50} = 2.0 ± 0.3 μM) [93] and showed anti-leishmanian activity (IC_{50} = 1.4 ± 0.1 μM) [42]. Anti-leishmanian activities of the 7-substituted derivatives of compound **65** were also given [42]. Details concerning the preparation of those compounds were not given.



Scheme 22: Reagents and reaction conditions: i. EtOH, rt, 48 h, then silica gel chromatography, 33% for **57** (30% for *epi*-**57**).



X	N	NMe	NEt	O
59, **63**, **64**	**a**	**b**	**c**	**d**

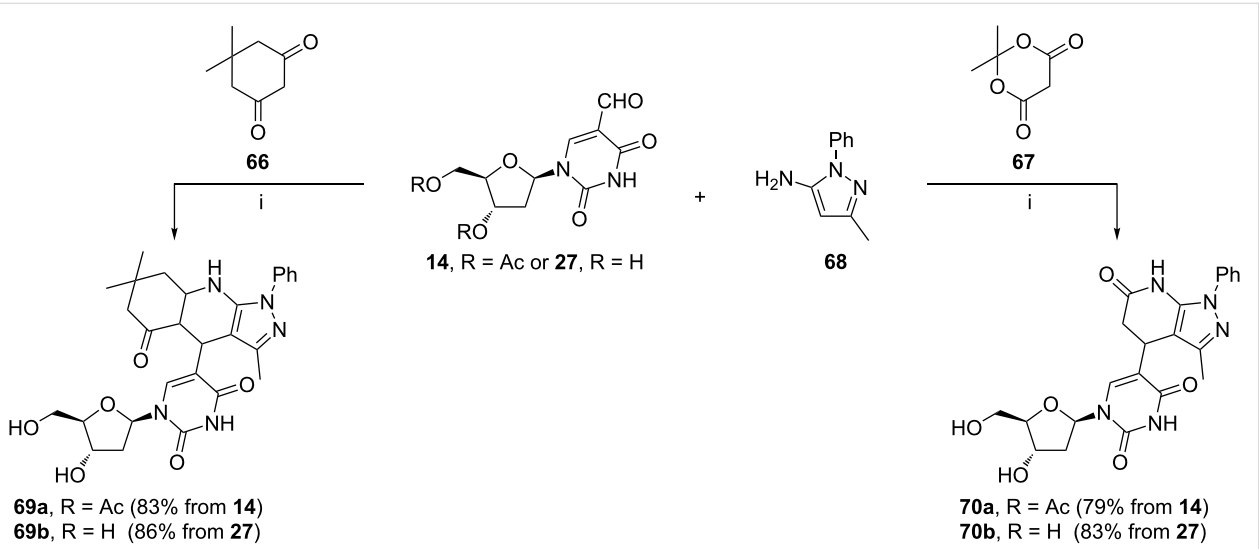
Scheme 23: Reagents and reaction conditions: i. [bmim]BF_4, 80 °C, 4 h; ii. [bmim]BF_4, 80 °C, 3 h; iii. [bmim]BF_4, 80 °C, 2–4 h; iv. EtOH, 50 °C, overnight.

The three-component synthesis of compounds **69** and **70** developed by Zhang et al. involved the Knoevenagel condensation, the Michael addition, and the *N*-nucleophilic cyclization (Scheme 24) [94]. Whereas 5,5-dimethylcyclohexane-1,3-dione (**66**) or Meldrum's acid (**67**) acted as the Knoevenagel donor, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**68**) played the role of the Michael donor in these reactions. The yields of products **69b** and **70b** derived from 5-formyl-2'-deoxyuridine (**27**) were slightly higher than yields of derivatives **69a** and **70a** obtained from the *O*-acetylated nucleoside **14**.

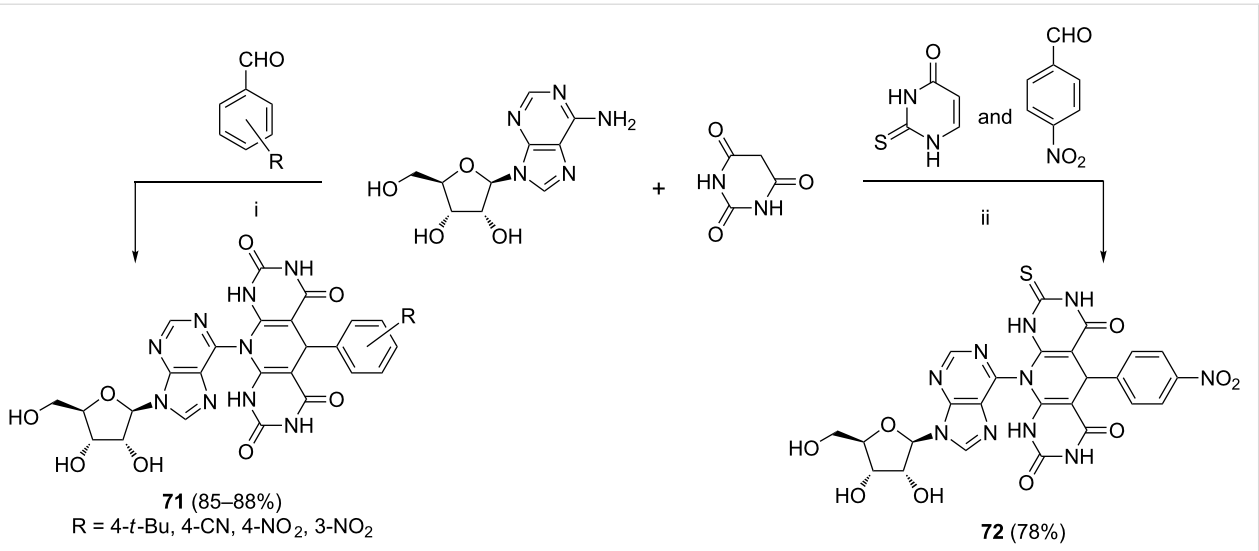
The syntheses of hybrids **71** [95] and **72** [96] represent examples of the Knoevenagel-initiated domino reactions where the purine nucleoside (i.e., adenosine) was modified (Scheme 25). Tungstophosphoric acid ($H_3PW_{12}O_{40}$) was employed as a catalyst (2 mol %). Hybrids **71** originated from the pseudo-four component cascade employing two equivalents of barbituric acid. The authors demonstrated that the method was applicable with both electron-poor and electron-rich aldehydes. The four-component variant of the reaction employing 2-thiouracil led to compound **72** with a slightly lower yield than those obtained from pseudo-four component cascade leading to compounds **71**.

5. The Biginelli reaction

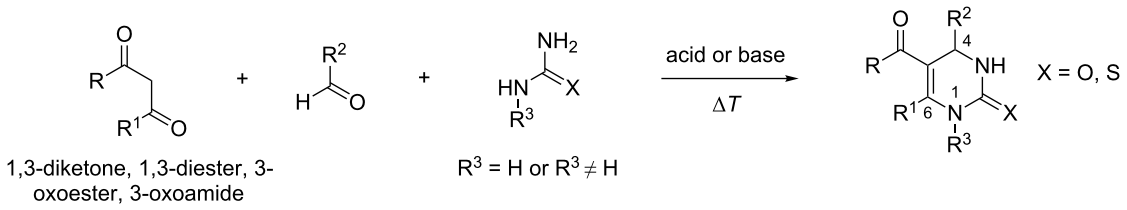
The Biginelli reaction (Scheme 26) consists in the three-component condensation of a 1,3-dicarbonyl compound, an aldehyde,



Scheme 24: Reagents and reaction conditions: i. [bmim]BF_4, 80 °C.



Scheme 25: Reagents and reaction conditions: i. $H_3PW_{12}O_{40}$ (2 mol %), EtOH, 50 °C, 2–15 h; ii. $H_3PW_{12}O_{40}$ (2 mol %), EtOH, 50 °C, 8 h.

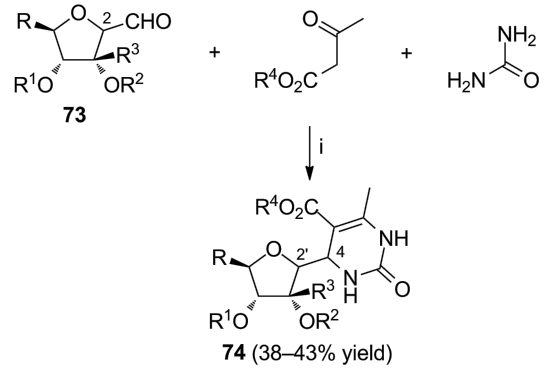


Scheme 26: General scheme of the Biginelli reaction.

and a nitrogen component, i.e., urea (X = O, R^3 = H) or thiourea (X = S, R^3 = H) [29]. The use of *N*-substituted derivatives of urea or thiourea ($R^3 \neq H$) has also been reported. Recently numerous advances in the asymmetric Biginelli reaction have been reviewed [97]. The reaction has been employed in the synthesis of C-nucleosides with 3,4-dihydropyrimidin-2(1*H*)-one or 3,4-dihydropyrimidin-2(1*H*)-thione as the nucleobase mimic. Up to date, depending on the role of the carbohydrate component in the reaction, C-nucleosides bearing the carbohydrate moiety at the position of N-1, C-4 or C-6 of the nucleobase mimic were synthesized.

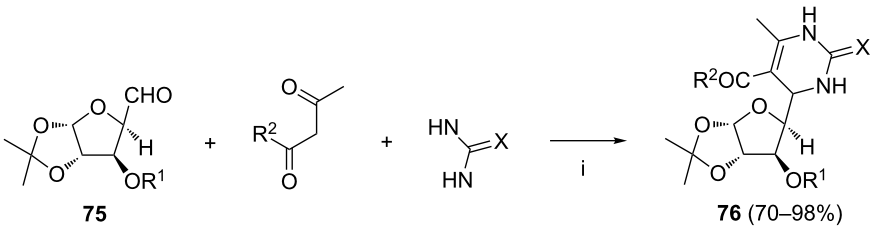
Starting from sugar aldehyde substrates **73**, Molina et al. synthesized a series of compounds **74** bearing the carbohydrate moiety at the C-4 carbon atom of the 3,4-dihydropyrimidin-2(1*H*)-one system (Scheme 27) [98,99]. Attempts to replace the aldehyde **73a** with its 3,4,6-hydroxylated counterpart failed to give the expected product [99].

Dwivedi et al. showed that the isopropylidene-protected sugars **75** reacted efficiently with urea (or thiourea) and 1,3-dicarbonyl compounds in diethylene glycol in the presence of tetrabutylammonium hydrogen sulfate as both an acid and a phase-transfer catalyst (Scheme 28) [100]. As the authors suggested, the formation of intermediate *N*-acyliminium ion from aldehyde **75** and (thio)urea was the key step of the reaction. Protonation of aldehyde **75** by tetrabutylammonium hydrogen sulfate facilitated the reaction. Galactose-6'-aldehyde counterparts of the urea-derived compounds **76** (X = O) were also prepared by this method.



73 or 74	C-2 (or 2')	R	R^1, R^2	R^3	R^4
a	α	CH_2OBz	Bz, H	OBz	Et
b	β	H	Bz, H	OBz	Et
c	β	H	Bn, H	OBn	Et
d	β	H	Bn, Bn	H	Et
e	α	H	$(CH_3)_2C$	H	Me

Scheme 27: Reagents and reaction conditions: i. EtOH, reflux.

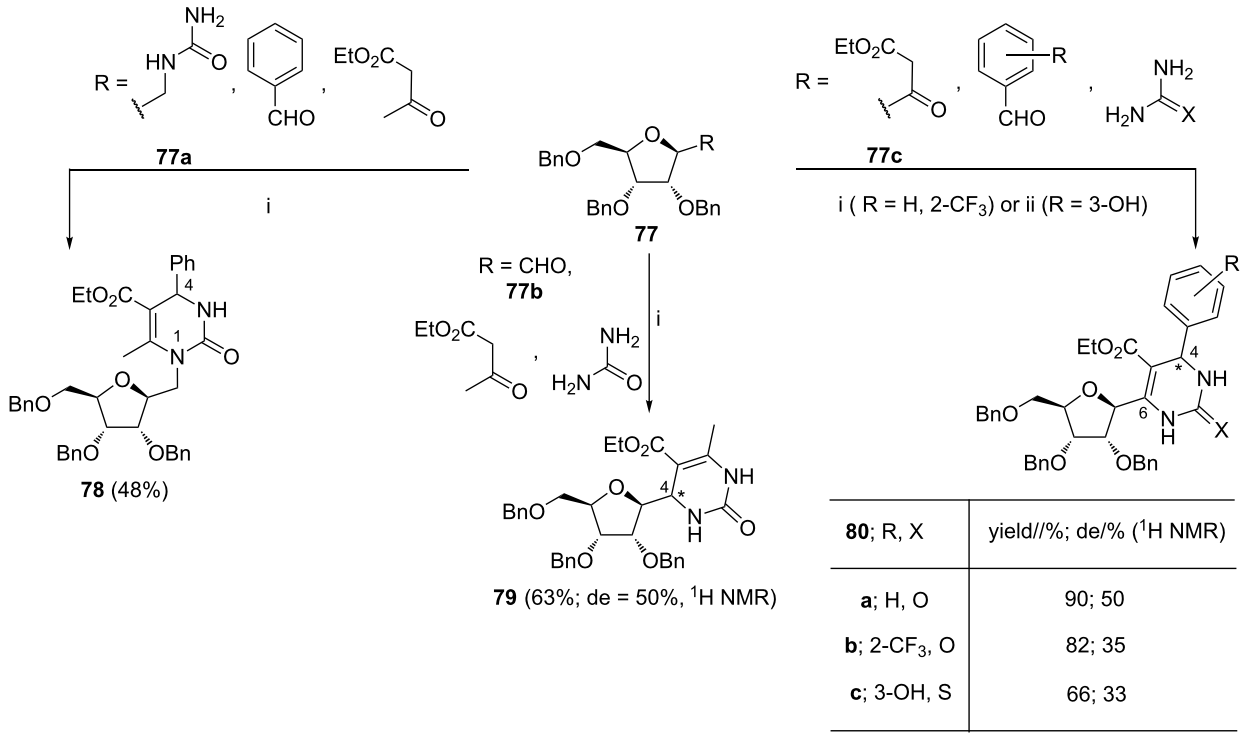


R^1	R^2	X
Me, Bn	Me, OEt	O
Me, Bn	OEt	S

Scheme 28: Reagents and reaction conditions: i. $Bu_4N^+HSO_4^-$, diethylene glycol, 120 °C, 1.5–3 h.

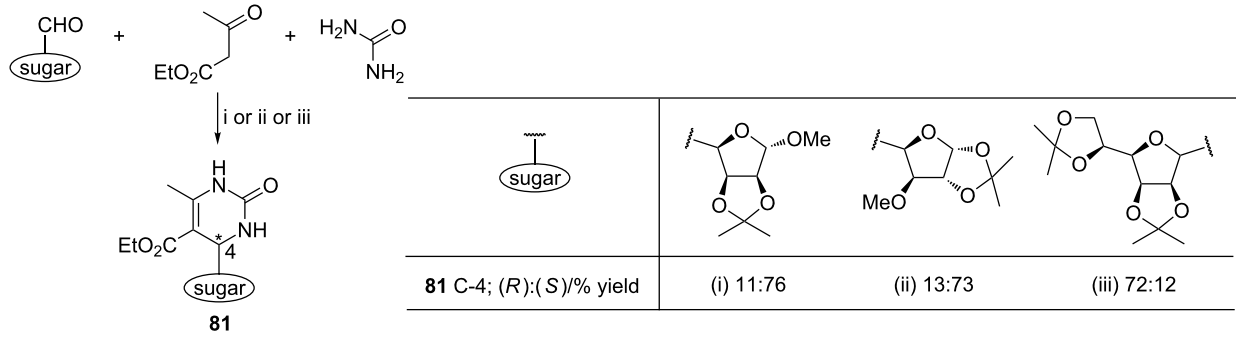
The Dondoni group developed Lewis acid-promoted reactions employing the sugar derivatives **77** acting as: the component bearing the urea function (**77a**), the aldehyde function (**77b**), or the β-ketoester function (**77c**) (Scheme 29) [101,102]. In contrast to the N-1-substituted homo-C-nucleosides **78**, the C-4 or C-6-substituted C-nucleosides (i.e., compounds **79** or **80**, respectively) were obtained with the diastereoisomeric excess varied from 33% to 50%. The diastereoisomers were separated and their absolute configuration was determined using X-ray crystallography and circular dichroism spectroscopy. The stereochemical outcome of the synthesis of compounds **79** and **80** was suggested to result from some internal asymmetric induction of the chiral residue of the sugar aldehyde **77b** or the sugar β-ketoester **77c**, respectively. The debenzylated forms of *C*-nucleosides **78**, **79** and **80** (as single diastereoisomers) were evaluated in vitro and in vivo as antimitotic agents [41]. They appeared to be less active than the reference (4*S*)-monastrol. Pyranose-derived nucleoside analogs were also prepared by these methods [101,102].

Sharma et al. used 2,4,6-trichloro[1,3,5]triazine (TCT) as the source of hydrogen chloride to promote the reactions leading to C-4-substituted C-nucleosides **81** with the high (ca. 7:1) diastereoisomeric ratio (Scheme 30) [103]. The products were



80; R, X	yield//%; de/% (^{1}H NMR)
a; H, O	90; 50
b; 2-CF_3, O	82; 35
c; 3-OH, S	66; 33

Scheme 29: Reagents and reaction conditions: i. $BF_3{\cdot}Et_2O$, CuCl, AcOH, THF, 65 °C, 24 h; ii. $Yb(OTf)_3$, THF, reflux, 20 h.



sugar			
81 C-4; (*R*):(*S*)/% yield	(i) 11:76	(ii) 13:73	(iii) 72:12

Scheme 30: Reagents and reaction conditions: TCT (10 mol %), rt: i. 100 min; ii. 150 min; iii. 140 min.

isolated as single diastereoisomers. Since the reactions conducted in the presence of molecular sieves (4Å) were unsuccessful, the authors suggested that traces of moisture present in the reaction system played the key role in the release of hydrogen chloride from TCT. A pyranose-derived nucleoside analog was also prepared by this method.

Very recently, Figueiredo et al. synthesized C-nucleosides **83** with the C-4 substituted 3,4-dihydropyrimidin-2(1*H*)-thione as a nucleobase (Scheme 31) [104]. The products were obtained as the C-4-(*R*) single diastereoisomers. The use of microwave irradiation allowed the authors to perform these reactions with ten times smaller volume of the solvent than that employed in the reactions carried out under conventional heating conditions. Compound **83b** showed promising activity against acetylcholinesterase at a concentration of 100 µmol/L.

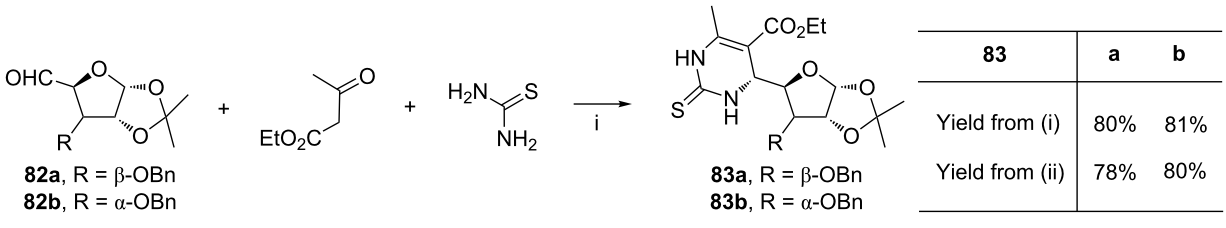
6. The Hantzsch reaction

The classical Hantzsch reaction provides 1,4-dihydropyrimidines (1,4-DHPs) from 1,3-dicarbonyl compounds, aldehydes and ammonia (Scheme 32) [19]. The reaction has attracted a considerable attention because of the therapeutic usefulness of drugs featuring the 1,4-DHP scaffold, i.e., nifedipine and olanzapine [105]. The preparation of unsymmetrical 1,4-DHPs by the Hantzsch reaction involving two different β-ketoesters has been reported [106]. The literature survey revealed that the Hantzsch reaction served as a tool for the preparation of C-nucleosides with the C-4-substituted 1,4-DHP moiety as a nucleobase (R^2 = sugar).

The Hantzsch reaction involving the sugar-derived aldehydes **84**, ethyl acetoacetate and ammonium acetate was applied by Sharma et al. in the synthesis of nucleoside analogs **85**, bearing the 1,4-DHP nucleobase at the C-4- or C-1 carbon atom of the sugar (Scheme 33) [107]. Analogously to the previously reported Biginelli reaction [103], compounds **85** were obtained in high yields under the TCT-catalysis conditions. A pyranose-derived nucleoside analog was also prepared by this method.

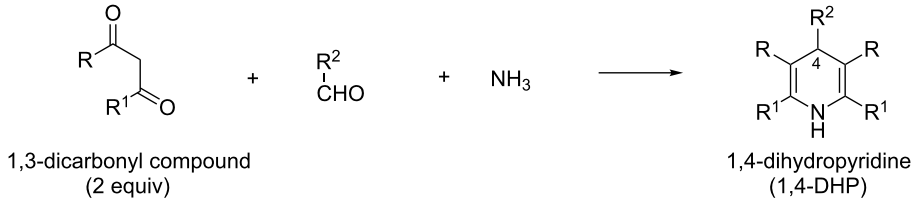
Using compound **87** as an example (Scheme 34), the Dondoni group demonstrated that the C-nucleosides with the C-4-substituted 1,4-DHP nucleobase can be efficiently obtained from the three-component reaction between the sugar aldehyde **86**, ethyl acetoacetate, and ethyl 3-aminocrotonate [108,109]. The course of the reaction in the presence of various additives was examined in detail. The best results were obtained in the presence of 4 Å molecular sieves. The analysis of the reaction products showed that ytterbium triflate induced partial 1,2-elimination of benzyl alcohol from the ribosyl residue of the starting aldehyde **86**, consequently leading to the 1',2'-didehydro-derivative of the target product **87**. Pyranose-derived nucleoside analogs were also prepared by this method [108,109].

This approach involving a sugar aldehyde, 3-oxoester, and an ester of 3-aminocrotonic acid was then extended by the Dondoni group to 2,5-deoxyhexose-derived aldehydes **88** (Scheme 35) [110]. The best results were obtained when the reaction was performed with an excess (1.5 equiv) of methyl acetoacetate and methyl 3-aminocrotonate under L-proline-

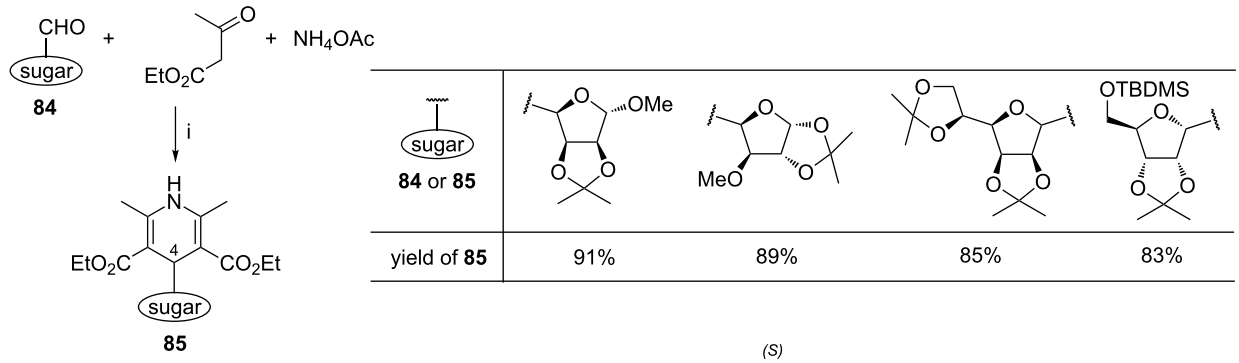


83	a	b
Yield from (i)	80%	81%
Yield from (ii)	78%	80%

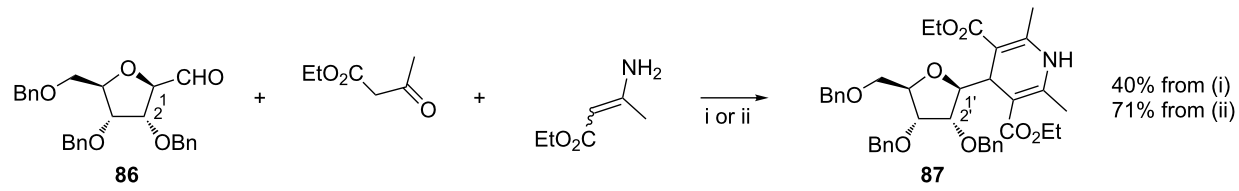
Scheme 31: Reagents and reaction conditions: i. EtOH, microwave irradiation (300 W), 10 min; ii. EtOH, 75 °C, 5 h and for 72 h, rt.



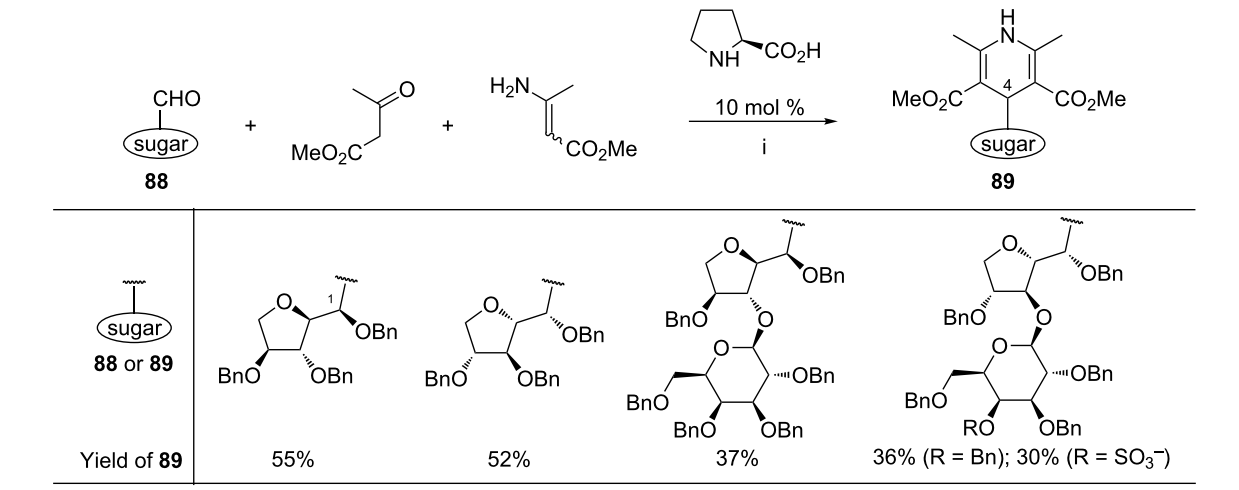
Scheme 32: The Hantzsch reaction.



Scheme 33: Reagents and reaction conditions: TCT (10 mol %), rt, 80–150 min.



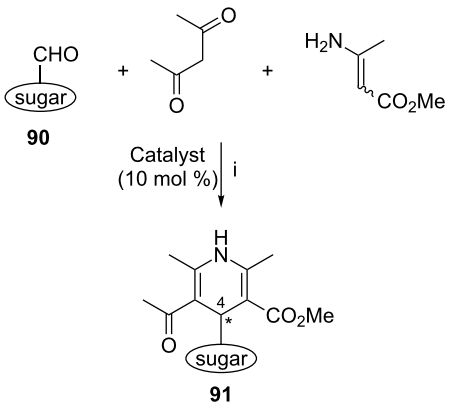
Scheme 34: Reagents and reaction conditions: i. $Yb(OTf)_3$, THF, 90 °C, 12 h; ii. 4 Å molecular sieves, EtOH, 90 °C, 48 h.



Scheme 35: Reagents and reaction conditions: i. MeOH, 50 °C, 48 h.

catalyzed conditions. In contrast to other catalysts tested (ytterbium triflate, D-proline, (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole, or (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine/TFA system), the catalytic effect of L-proline resulted in an increase in the reaction yield. Moreover, epimerization on the C-1 carbon atom of the starting aldehyde **88** was also suppressed. The latter effect was attributed to the preferential activation of methyl 3-aminocrotonate by L-proline via the corresponding enamine as compared to the activation of the sugar aldehyde.

The preliminary studies of the Dondoni group on the synthesis of C-nucleosides bearing the unsymmetrical 1,4-dihydropyridine nucleobase showed that the internal asymmetric induction by the sugar moiety played a crucial role in the formation of compounds **91** (Scheme 36) [110]. Regardless of the catalyst used, aldehyde **90** gave product **91** with a very high diastereomeric excess. Analogously to the reaction performed with aldehyde **90** in the presence of L-proline, aldehyde *ent*-**90** gave compound *ent*-**91** with the same diastereomeric excess under



sugar	Catalyst	Product yield	de (^{1}H NMR)
BnO, OBn (**90**, **91**)	L-proline	50%	>95%
	D-proline	48%	>95%
	pyrrolidine/AcOH	50%	>95%
BnO, OBn (*ent*-**90**, *ent*-**91**)	L-proline	47%	>95%

Scheme 36: Reagents and reaction conditions: i. MeOH, 25 °C, 5 d.

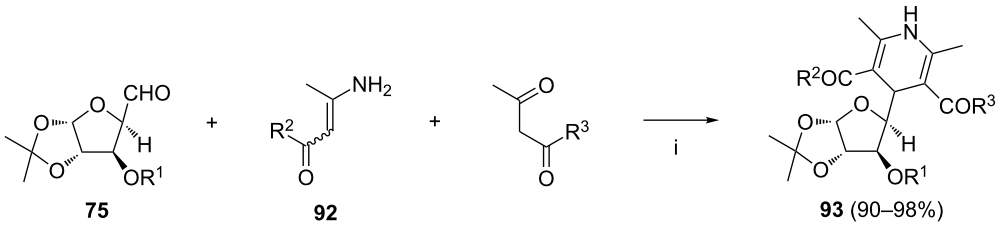
the same conditions. The absolute configuration of the C-4 carbon atom of compound **91** or *ent*-**91** was not determined.

The approach involving an enamine (i.e., compound **92**) as one of the reaction components was also used by Tewari et al. for the preparation of C-nucleosides **93** (Scheme 37) [111]. The reactions were carried out in the presence of tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst. The yield of products **93** varied from 90% to 98%. As the authors suggested on the basis of comparative experiments performed without the catalyst, tetrabutylammonium hydrogen sulfate facilitated dehydration and cyclization steps of the reaction owing to its acidic properties. The reaction variant involving the corresponding sugar aldehyde **75**, 4-aminopent-3-en-2-one and ethyl 3-oxobutanoate allowed to obtain unsymmetrical products **93**. Galactose-6'-aldehyde-derived counterparts of the symmetrical nucleosides **93** were also prepared by this method.

7. The carbopalladation of dienes

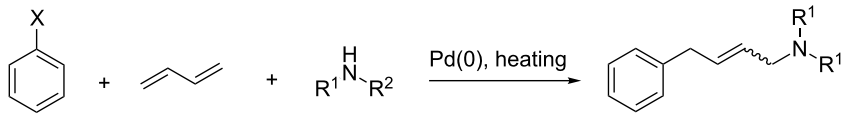
A reaction of an aryl halide, an unsaturated alkene (diene, allene), and an amine catalyzed by Pd(0) species, referred to as carbopalladation of dienes, results in the three-component assembly of an unsaturated amine (Scheme 38) [112].

The palladium-catalyzed reactions of 5-iodopyrimidines, various acyclic or cyclic dienes, and amines were optimized by Larock et al. [113]. Thus, coupling of 5-iodo-2'-deoxyuridine (**94a**) or 3',5'-di-*O*-acetyl-5-iodo-2'-deoxyuridine (**94b**) with 1,2-, 1,3- or 1,ω-dienes **95**, and morpholine afforded a considerable variety of the corresponding 5-(alkylallylamino)-2'-deoxyuridines **96** (Scheme 39, selected examples are shown). After an extensive search for optimal reaction conditions, the authors found that the best yields could be achieved in the presence of zinc salts, in particular with secondary amines. In some cases, protection of the hydroxy groups in **94a** was also neces-

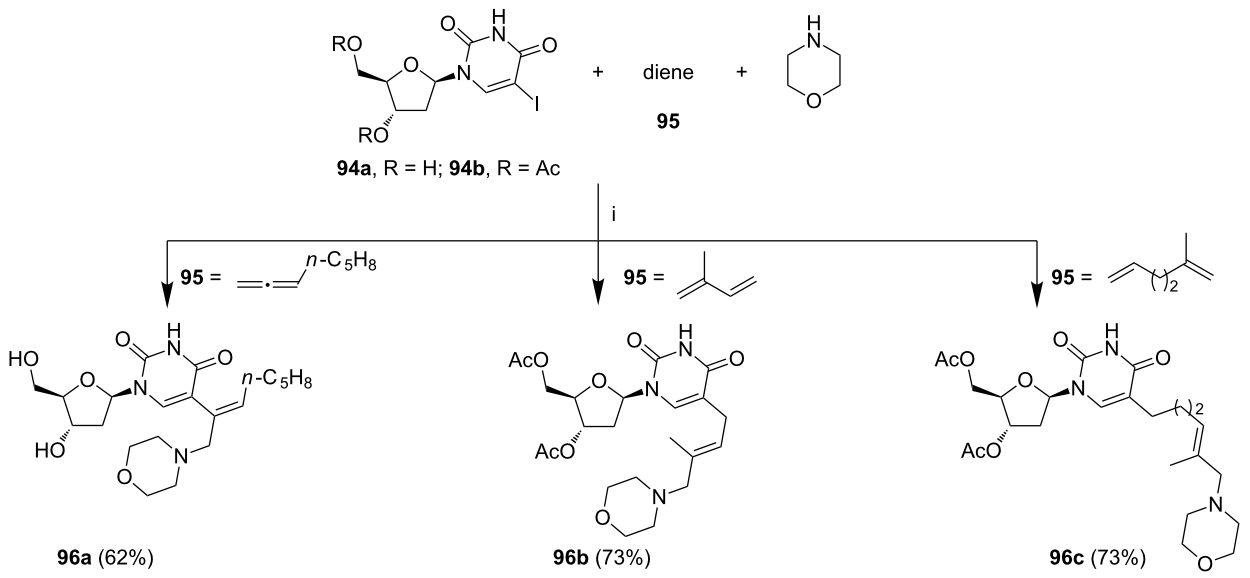


R^1	R^2	R^3
Me, Bn	Me	Me
Me, Bn	OEt	OEt
Me, Bn	Me	OEt

Scheme 37: $Bu_4N^+HSO_4^-$, diethylene glycol, 80 °C, 1–2 h.



Scheme 38: The three-component carbopalladation of dienes on the example of buta-1,3-diene.



Scheme 39: Reagents and reaction conditions: i. 5 mol % $Pd(dba)_2$, Bu_4NCl, $ZnCl_2$, acetonitrile or DMSO, 80 °C or 100 °C, 1–2 days.

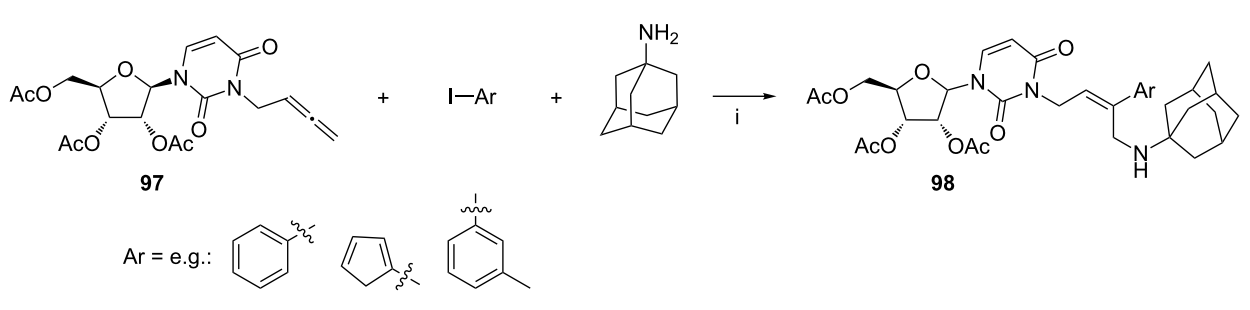
sary. The reactions between 3',5'-di-*O*-acetyl-5-iodo-2'-deoxyuridine (**94b**), long-chain 1,ω-dienes (e.g., deca-1,9-diene or tetradeca-1,13-diene) and morpholine afforded products as mixtures of regioisomers resulting from the addition of the nucleoside moiety to the C-1 or C-2 carbon atom of the C=C double bond.

The three-component reactions of nucleoside-derived (uridine or thymidine) allenes **97**, a range of aryl iodides, and 1-adamantylamine was accomplished smoothly under the palladium-catalyzed conditions (Scheme 40, the uridine example is shown) [114]. The coupling products **98** were obtained as (*Z*)-stereoisomers for studies related to the drug discovery against the hepatitis C virus.

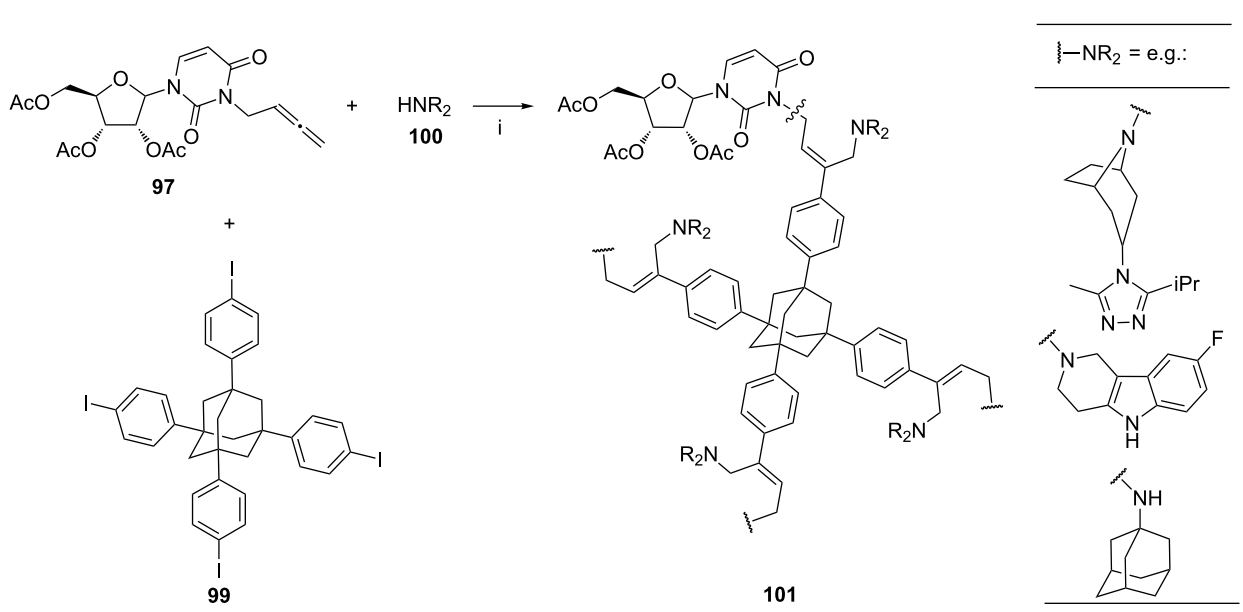
The methodology shown in Scheme 40 [114] was further elaborated on reactions of polyfunctional iodide **99** with four equivalents of nucleoside-derived allenes **97** (the uridine example shown), and a number of amines **100** (four equivalents, Scheme 41). The polyfunctional products **101** were obtained with excellent (*Z*)-stereoselectivity. The authors noticed a pronounced relationship between pK_a of the amine and the isolated yield of the product, i.e., 1-adamantylamine provided the highest yield.

8. The Bucherer–Bergs reaction

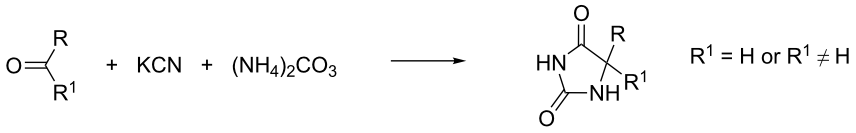
The three-component Bucherer–Bergs reaction provides 5-mono- or 5,5-disubstituted hydantoins from the condensation of a carbonyl compound with potassium cyanide and ammonium carbonate (Scheme 42) [115]. The chemistry of hydantoins attracted a considerable attention because of their importance in medicine and industry [116,117]. N-Nucleoside analogs with (thio)hydatantoin scaffold as a nucleobase mimic were also extensively investigated [118].



Scheme 40: Reagents and reaction conditions: i. 2.5 mol % $Pd_2(dba)_3$, tris(2-furyl)phosphine, K_2CO_3, MeCN or DMF, 80 °C, 3–24 h, 77–99%.



Scheme 41: Reagents and reaction conditions: i. 2.5 mol % $Pd_2(dba)_3$, tris(2-furyl)phosphine, K_2CO_3, MeCN or DMF, 80 °C, 3–24 h, 45–87%.

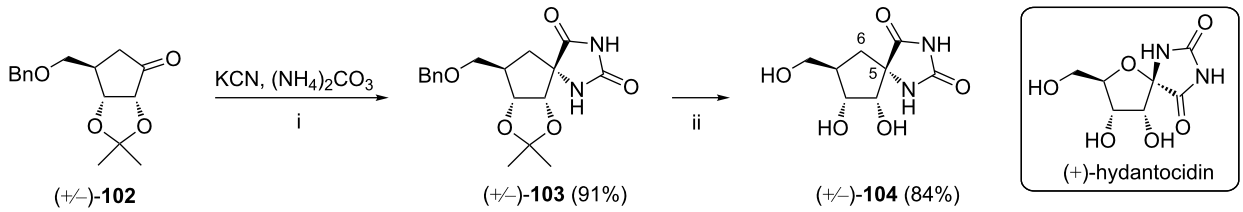


Scheme 42: The three-component Bucherer–Bergs reaction.

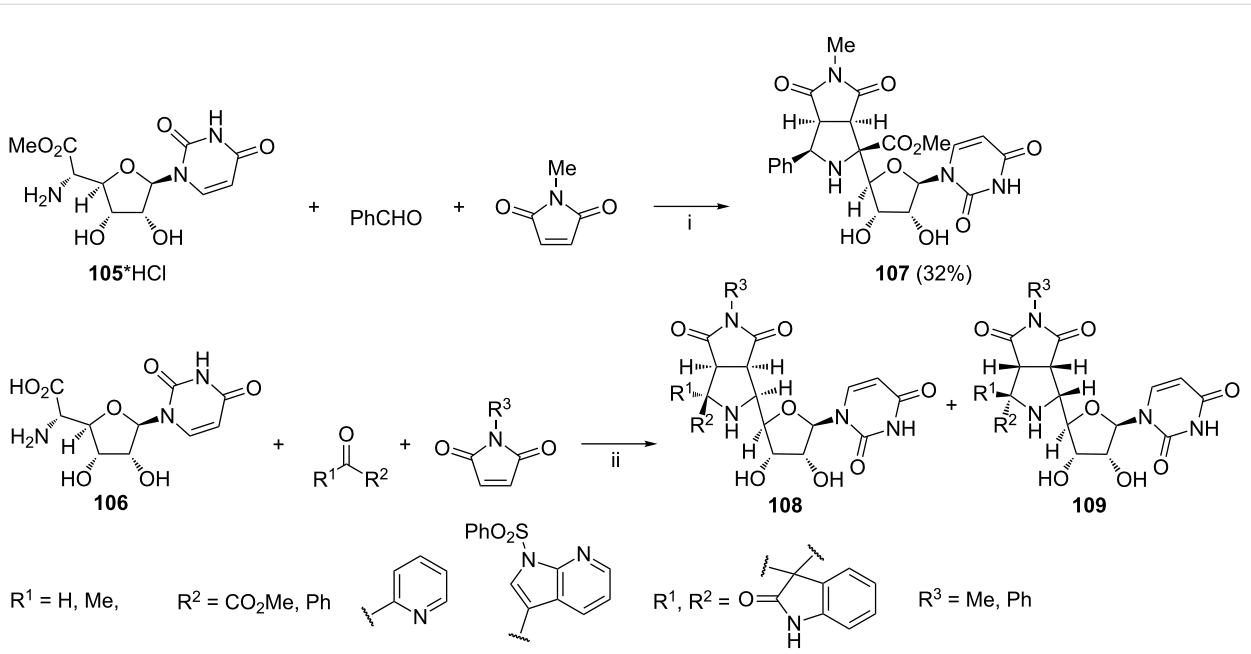
(+)-Hydantocidin (Scheme 43), isolated from *Streptomyces hygroscopicus*, is a unique nucleoside with a spirohydantoin ring at the anomeric carbon atom of D-ribofuranose. (+)-Hydantocidin has been identified as a herbicidal or a plant growth regulatory agent [119]. Using the Bucherer–Bergs reaction, Sano and Sugai accomplished the synthesis of a racemic 5-*epi*-6-carba-analog of (+)-hydantocidin (Scheme 43, compound (+/−)-**104**) [120]. The key step of the synthesis involved condensation of the racemic ketone (+/−)-**102** with potassium cyanide and ammonium carbonate in aq methanol at 70 °C. The 5-*epi* configuration of compound (+/−)-**103** was confirmed by NMR spectroscopy. In contrast to the (+/−)-6-carba-analog of (+)-hydantocidin, compound (+/−)-**103** was devoided of herbicidal activity at 1000 ppm concentration.

9. Miscellaneous reactions

Dondas et al. reported the synthesis of a derivative of compound **107** bearing the pyrrolo[3,4-*c*]pyrrole skeleton at the furanose C-4' position from uracil polyoxin C hydrochloride **105***HCl (Scheme 44) [121]. The reaction cascade involved thermal formation of the corresponding azomethine ylide from substrate **105***HCl and benzaldehyde, followed by 1,3-dipolar



Scheme 43: Reagents and reaction conditions: i. MeOH, H_2O, 70 °C, 4.5 h; ii. (1) H_2, 5% Pd/C, MeOH, 55 °C, 5 h; (2) Dowex 50 W, MeOH, H_2O, rt, 4 h.



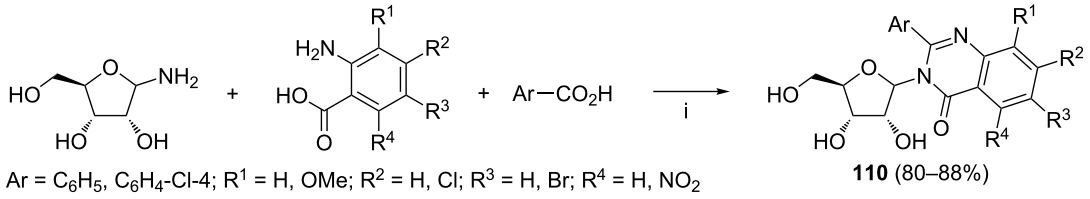
Scheme 44: Reagents and reaction conditions: i. pyridine, $MgSO_4$, 100 °C, 28 h, N_2; ii. DMF, 70–90 °C, 22–30 h, N_2, the cumulative yield of **108**/**109** from 55% to 96%.

cycloaddition of the ylide to *N*-methylmaleimide. The formation of compound **107** as the only product was rationalized using semi-empirical calculations. In the same contribution, the cascade reactions starting from uracil polyoxin C **106** were described (Scheme 44). Decarboxylative formation of azomethine ylides from **106** and an aldehyde (or ketone), followed by reaction of the ylide with maleimide afforded mixtures of cycloadducts **108** and **109** in molar ratios varied from 1:1 to 12:1. Compounds **108** were inactive against *Aspergillus fumigatus* or *Candida albicans* at concentration of 125 μg/mL.

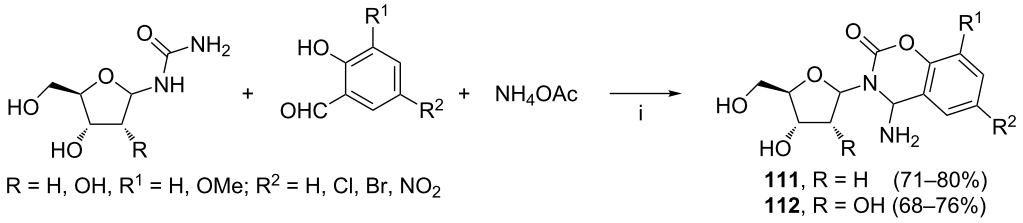
Nucleoside analogs **110** with the 3,4-dihydroquinazoline-derived nucleobase were obtained by Siddiqui et al. under microwave irradiation conditions with the substrates adsorbed onto Montmorillonite K-10 clay (Scheme 45) [122]. The formation of compounds **110** proceeded via: (a) N-acylation of aminosugar by the anthranilic acid derivative, and (b) N-acylation of the resulting amide at the aromatic amino group by benzoic acid (or 4-chlorobenzoic acid), followed by cyclization of the resulting diamide intermediate. After completion of the irradiation, products **110** were extracted with dichloromethane from the clay and crystallized from ethanol.

The Montmorillonite K-10 clay–microwave irradiation reaction system was also used by Yadav and Rai in the synthesis of nucleoside analogs **111** and **112** bearing novel nucleobase derived from benzo[*e*][1,3]oxazine (Scheme 46) [123]. The developed reactions were much more effective than those examined on other inorganic supports (i.e., silica gel, neutral or basic alumina). The conversion of the sugar urea to the corresponding isocyanate intermediate, accompanied by the loss of ammonia, was postulated to be the key step of the reaction cascade.

Another approach to nucleoside analogs bearing a nucleobase derived from benzo[*e*][1,3]oxazine was developed by Rai and



Scheme 45: Reagents and reaction conditions: i. Montmorillonite K-10 clay, microwave irradiation (600 W), 6–10 min (solvent-free conditions).

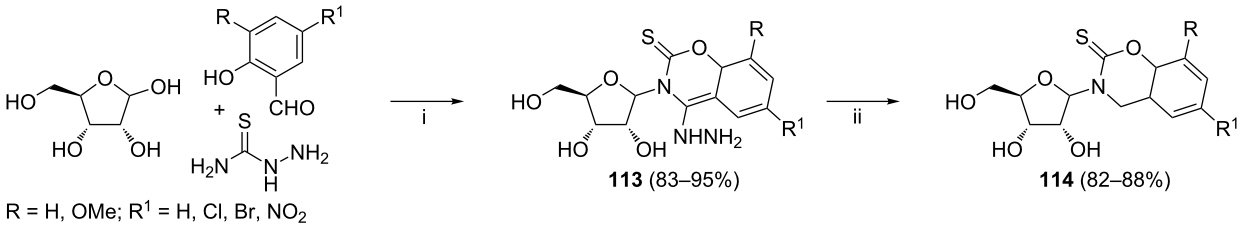


Scheme 46: Reagents and reaction conditions: i. Montmorillonite K-10 clay, microwave irradiation (560 W), 6–10 min (solvent-free conditions).

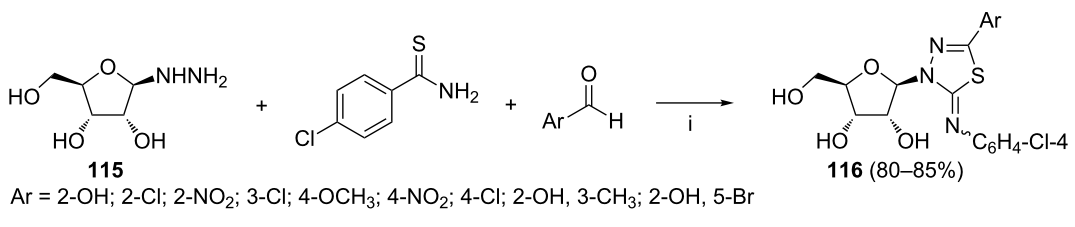
Singh (Scheme 47) [124]. The target compounds **113** and **114** were assembled from the three-component mixture of D-ribose, a derivative of salicylic aldehyde, and thiosemicarbazide under Lewis acid-catalysis and microwave irradiation. In comparison with analogous reactions carried out with mineral support (i.e., Montmorillonite K-10 clay or silica gel), the use of the $CeCl_3$/NaI catalyst system for the synthesis of intermediates **113** provided the best results in terms of reaction yield and time. The next step leading to final products **114**, i.e., the reductive dehydrazination of compounds **113** with alumina-supported copper(II) sulfate was conducted under solvent-free microwave irradiation conditions. Products **114** were isolated by crystallization in yields exceeding 80%.

Siddiqui et al. developed the method for the preparation of nucleoside analogs **116** with the 1,3,4-thiadiazole-derived nucleobase. This method involved the microwave irradiation-assisted condensation of sugar hydrazine **115**, 4-chlorobenzothioamide and an aromatic aldehyde in the presence of (diacetoxyiodo)benzene (Scheme 48) [125]. The conversion of 4-chlorobenzothioamide to 4-(chlorophenyl)isothiocyanate intermediate by (diacetoxyiodo)benzene was suggested to initiate the reported reaction sequence.

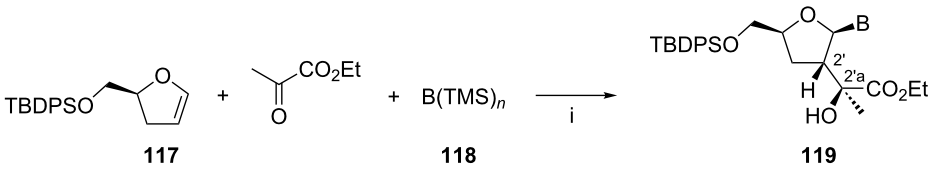
Ghosh and Kass synthesized nucleosides **119** from 2,3-dihydrofurane **117**, ethyl pyruvate, and the silylated nucleobase **118** (Scheme 49) [126]. This method does not strictly comply with the Ugi's definition of MCRs because of the sequential addition of the substrates. However, in our opinion the method is worth noting since it represents an interesting extension of the Vorbrüggen N-glycosylation process. Thus, the reaction sequence leading to nucleosides **119** was initiated by the titanium(IV) chloride-promoted alkylation of 2,3-dihydrofurane **117** with ethyl pyruvate at −78 °C (1 hour), followed by the coupling of the resulting oxocarbenium ion with the silylated nucleobase **118**. Compounds **119** were obtained as single diastereoisomers. The similar (not shown) reaction employing the silylated thymine and ethyl glyoxalate gave the corresponding product as 1:1 mixture of isomers at the *C*-2'a carbon atom.



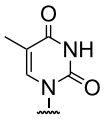
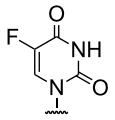
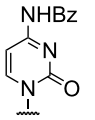
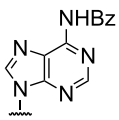
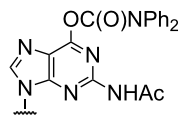
Scheme 47: Reagents and reaction conditions: i. $CeCl_3 \cdot 7H_2O$ (20 mol %), NaI (20 mol %), microwave irradiation (90 °C), 6–8 min; ii. $CuSO_4 \cdot 5H_2O$, Al_2O_3, microwave irradiation (90 °C), 3–3.5 min.



Scheme 48: Reagents and reaction conditions: i. $PhI(OAc)_2$ (3 mol %), microwave irradiation (45 °C), 6–9 min.



117 118 119

B					
					
Yield of **119**	70%	65%	53%	60%	42%

Scheme 49: Reagents and reaction conditions: i. **117**, ethyl pyruvate, $TiCl_4$, dichloromethane, −78 °C, 1 h; then **118**, −78 °C, 1 h; then 23 °C, 1 h.

Conclusion

In this comprehensive review application of multicomponent reactions (MCRs) in nucleoside chemistry has been presented. In recent years, growing interest in the construction of novel nucleoside scaffolds by MCR has been observed. This conclusion is supported by the fact that 23 out of 60 original works cited in this review appeared within the last five years. Up to date, much more efforts were devoted to the preparation of novel nucleoside scaffolds by a structural modification of the parent nucleosides (37 examples) than by their de novo construction from non-nucleoside substrates (23 examples). A majority of the reported modifications of the parent nucleosides concerned their nucleobase moiety (27 examples). However, the number of reports on modifications of the purine nucleobase was limited (4 examples). Among reports on the de novo construction of nucleosides from non-nucleoside substrates, the ones dealing with the construction of a non-natural nucleobase predominated (18 examples). Interestingly, a combinatorial solid-phase approach has not been extensively exploited (2 examples). The findings concerning the syntheses of nucleoside antibiotic analogs or 1'-aza-analogs of immucilins are interesting in view of both organic synthesis and potential applications. The trends of a great research potential in this field could be identified from the presented literature survey. The most recent reports were mainly directed to: (i) the employment of novel reaction techniques, such as microwave irradiation, ionic liquids or inorganic supports, or (ii) the development of novel MCRs leading to nucleoside analogs bearing an unconventional nucleobase. As reports dealing with these issues revealed, a combination of both these trends may result in the preparation of structurally interesting compounds. An intensification of studies on the structure–activity relationship of these compounds would provide valuable data on their potential applications. We hope that continued efforts in this field will result in novel nucleoside drug candidates.

Table 1: Abbreviations.

Abbreviation	Term
Ac	acetyl
Ar	aryl
[bmim]BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
[bmim]PF_6	1-butyl-3-methylimidazolium hexafluorophosphate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
Cbz	benzyloxycarbonyl
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMB	2,4-dimethoxybenzyl
Et	ethyl
EWG	electron withdrawing group
iPr	isopropyl
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
rt	room temperature
SAR	structure activity relationship
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
Tces	2,2,2-trichloroethoxysulfonyl
TCT	2,4,6-trichloro-1,2,3-triazine
Tf	(trifluoromethyl)sulfonyl
TFA	trifluoroacetic acid
TFP	tris(2-furyl)phosphine
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	4-methylbenzoyl
Ura	pyrimidine-2,4(1*H*,3*H*)-dion-1-yl

Acknowledgements

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Synthesis of trifluoromethyl-substituted pyrazolo[4,3-*c*]pyridines – sequential versus multicomponent reaction approach

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Full Research Paper

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Abstract

A straightforward synthesis of 6-substituted 1-phenyl-3-trifluoromethyl-1*H*-pyrazolo[4,3-*c*]pyridines and the corresponding 5-oxides is presented. Hence, microwave-assisted treatment of 5-chloro-1-phenyl-3-trifluoromethylpyrazole-4-carbaldehyde with various terminal alkynes in the presence of *tert*-butylamine under Sonogashira-type cross-coupling conditions affords the former title compounds in a one-pot multicomponent procedure. Oximes derived from (intermediate) 5-alkynyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazole-4-carbaldehydes were transformed into the corresponding 1*H*-pyrazolo[4,3-*c*]pyridine 5-oxides by silver triflate-catalyzed cyclization. Detailed NMR spectroscopic investigations (^{1}H, ^{13}C, ^{15}N and ^{19}F) were undertaken with all obtained products.

Introduction

Fluorine-containing compounds play an important role in medicinal and pharmaceutical chemistry as well as in agrochemistry [1-4]. A popular approach for the modulation of activity consists in the introduction of one or more fluorine atoms into the structure of a bioactive compound. This variation frequently leads to a higher metabolic stability and can modulate some physicochemical properties such as basicity or lipophilicity [1,2]. Moreover, incorporation of fluorine often results in an increase of the binding affinity of drug molecules to the target protein [1,2]. As a consequence, a considerable amount –

approximately 20% – of all the pharmaceuticals being currently on the market contain at least one fluorine substituent, including important drug molecules in different pharmaceutical classes [5]. Keeping in mind the above facts, the synthesis of fluorinated heterocyclic compounds, which can act as building blocks for the construction of biologically active fluorine-containing molecules, is of eminent interest. In the field of pyrazoles, pyridines and condensed systems thereof trifluoromethyl-substituted congeners can be found as partial structures in several pharmacologically active compounds. In the pyridine series the HIV protease inhibitor Tipranavir (Aptivus®) [6] may serve as an example, within the pyrazole-derived compounds the COX-2 inhibitor Celecoxib (Celebrex®) is an important representative (Figure 1) [7].

In continuation of our program regarding the synthesis of fluoro- and trifluoromethyl-substituted pyrazoles and annulated pyrazoles [8,9] we here present the synthesis of trifluoromethyl-substituted pyrazolo[4,3-*c*]pyridines. The latter heterocyclic system represents the core of several biologically active compounds, acting, for instance, as SSAO inhibitors [10], or inhibitors of different kinases (LRRK2 [11,12], TYK2 [13], JAK [14,15]).

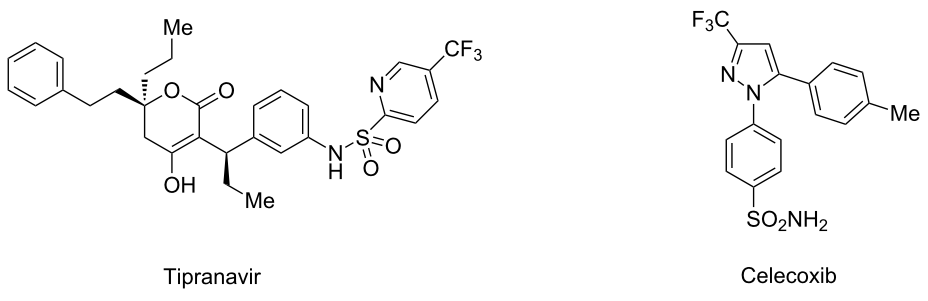
Results and Discussion

Chemistry

The construction of the pyrazolo[4,3-*c*]pyridine system can be mainly achieved through two different approaches. One strategy involves the annelation of a pyrazole ring onto an existing, suitable pyridine derivative [16]. Alternatively, the bicyclic system can be accessed by pyridine-ring formation with an accordant pyrazole precursor. Employing the latter approach we recently presented a novel method for the synthesis of the pyrazolo[4,3-*c*]pyridine system by Sonogashira-type cross-coupling reaction of easily obtainable 5-chloro-1-phenyl-1*H*-pyrazole-4-carbaldehydes with various alkynes and subsequent ring-closure reaction of the thus obtained 5-alkynyl-1*H*-pyrazole-4-carbaldehydes in the presence of *tert*-butylamine [17]. Furthermore, we showed that the oximes derived from the before mentioned 5-alkynylpyrazole-4-carbaldehydes can be transformed into the corresponding 1-phenylpyrazolo[4,3-*c*]pyridine 5-oxides [17].

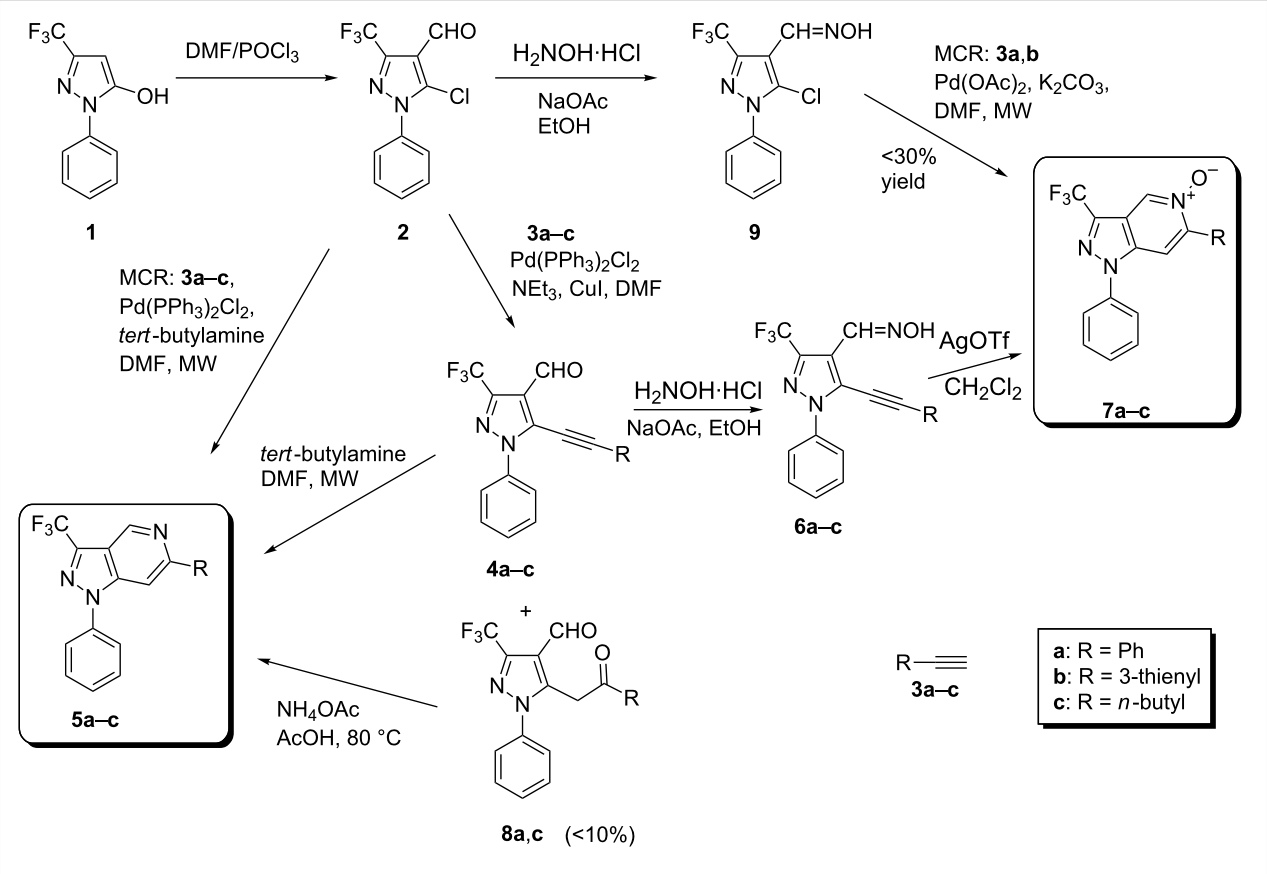
For the synthesis of the title compounds a similar approach was envisaged. As starting material the commercially available 1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol (**1**) was employed which, after Vilsmaier formylation [18] and concomitant transformation of the hydroxy function into a chloro substituent by treatment with excessive $POCl_3$, gave the chloroaldehyde **2** [19] (Scheme 1). Although Sonogashira-type cross-coupling reactions are preferably accomplished with iodo(hetero)arenes – considering the general reactivity I > Br/OTf >> Cl [20] – from related examples it was known that the chloro atom in 5-chloropyrazole-4-aldehydes is sufficiently activated to act as the leaving group in such kind of C–C linkages [17]. Indeed, reaction of chloroaldehyde **2** with different alkynes **3a**–**c** under typical Sonogashira reaction conditions afforded the corresponding cross-coupling products **4a**–**c** in good yields (Scheme 1). In some runs compounds of type **8** were determined as byproducts in differing yields, but mostly below 10%, obviously resulting from addition of water to the triple bond of **4** under the reaction conditions (or during work-up) and subsequent tautomerization of the thus formed enoles into the corresponding ketones. The hydration of C–C triple bonds under the influence of various catalytic systems, including also Pd-based catalysts, is a well-known reaction [21,22]. It should be emphasized that NMR investigations with compounds **8a**,**c** unambiguously revealed the methylene group adjacent to the pyrazole nucleus and the carbonyl moiety attached to the substituent R originating from the employed alkyne.

In the next reaction step, alkynylaldehydes **4a**,**b** were cyclized into the target pyrazolo[4,3-*c*]pyridines **5a**,**b** in 71%, resp. 52% yield by reaction with *tert*-butylamine under microwave assistance [17]. In view of the fact, that the two-step conversion **2**→**4a**,**b**→**5a**,**b** was characterized by only moderate overall yields (59%, resp. 43%) it was considered to merge these two steps into a one-pot multicomponent reaction. The latter type of reaction attracts increasing attention in organic chemistry due to



Tipranavir Celecoxib

Figure 1: Important drug molecules containing a trifluoromethylpyridine, respectively a trifluoromethylpyrazole moiety.



Scheme 1: Synthesis of the title compounds.

its preeminent synthetic efficiency, also in the construction of heterocyclic and condensed heterocyclic systems [23-27]. After testing different reaction conditions we found that microwave heating of the chloroaldehyde **2** with *tert*-butylamine in the presence of 6 mol % of $Pd(PPh_3)_2Cl_2$ afforded the desired pyrazolopyridines **5a**–**c** in high (**5a**: 89%, **5c**: 92%) respectively acceptable yields (**5b**: 51%) in a single one-pot and copper-free reaction step (Scheme 1). It should be mentioned that compounds **5** are also accessible by heating of ketones **8** with ammonium acetate in acetic acid according to a procedure described in [28]. Following this way, **5a** and **5c** were obtained in 70% yield from the corresponding ketones **8a** and **8c**. Although ketones **8** were only obtained as byproducts, the latter transformation allowed increasing the overall yield of compounds **5** through this 'bypass'.

In order to gain access to the corresponding *N*-oxides of type **7**, aldehydes **4a**–**c** were transformed into the corresponding oximes **6a**–**c** by reaction with hydroxylamine hydrochloride in ethanol in the presence of sodium acetate (Scheme 1). Subsequent treatment of the oximes with AgOTf in dichloromethane [29] finally afforded the corresponding pyrazolo[4,3-*c*]pyridine 5-oxides **7a**–**c** by a regioselective 6-*endo*-*dig* cyclisation [30] in high yields. Moreover, we tested an alternative approach to access compounds **7** through multicomponent reactions (MCR). Attempts to react chloroaldehyde **2** with hydroxylamine hydrochloride and an alkyne **3** in the presence of a suitable catalytic system were not successful. However, after conversion of **2** into the corresponding aldoxime **9** the latter could be transformed into the *N*-oxides **7a** and **7b** by reaction with alkynes **3a** and **3b**, respectively, employing $Pd(OAc)_2$ as the catalyst and under microwave irradiation (Scheme 1). Although a number of different reaction conditions were tested, we were not able to increase the yields in excess of 30%. Thus, with respect to the overall yields the successive approach **2**→**4**→**6**→**7** (overall yields: **6a**: 62%, **6b**: 43%) here is still advantageous compared to the multicomponent reaction following the path **2**→**9**→**7**. Azine *N*-oxides of type **7** are estimated to be of particular interest due to the possibility of further functionalization adjacent to the nitrogen atom (position 4), for instance by palladium-catalyzed direct arylation reactions [31].

NMR spectroscopic investigations

In Supporting Information File 1 the NMR spectroscopic data of all compounds treated within this study are indicated. Full and unambiguous assignment of all ^{1}H, ^{13}C, ^{15}N and ^{19}F NMR

resonances was achieved by combining standard NMR techniques [32], such as fully ^{1}H-coupled ^{13}C NMR spectra, APT, HMQC, gs-HSQC, gs-HMBC, COSY, TOCSY, NOESY and NOE-difference spectroscopy.

In compounds **4**–**7** the trifluoromethyl group exhibits very consistent chemical shifts, ranging from δ(F) −60.8 to −61.9 ppm. The fluorine resonance is split into a doublet by a small coupling (0.5–0.9 Hz) due to a through-space (or possibly ^{5}J) interaction with spatially close protons (**4**: CHO; **6**: CH=N; **5** and **7**: H-4). Reversely, the signals of the latter protons are split into a quartet (not always well resolved). The corresponding carbon resonance of CF_3 is located between 120.2 and 121.2 ppm with the relevant ^{1}J(C,F) coupling constants being approximately 270 Hz (269.6–270.6 Hz). As well, the signal of C-3 is always split into a quartet ($J \sim 40$ Hz) due to the ^{2}J(C,F_3) coupling.

As the ^{15}N NMR chemical shifts were determined by ^{15}N,^{1}H HMBC experiments the resonance of (pyrazole) N-2 was not captured owing to the fact that this nitrogen atom lacks of sufficient couplings to protons, thus disabling the necessary coherence transfer (^{19}F,^{15}N HMBC spectra were not possible with the equipment at hand). For N-1, with pyrazole derivatives **4** and **6** remarkably larger ^{15}N chemical shifts were detected (−158.8 to −160.2 ppm) compared to the corresponding signals for pyrazolopyridines **5** and **7** (−182.2 to −185.9 ppm). When switching from an azine to an azine oxide partial structure (**5**→**7**) the N-5 resonance exhibits an explicit upfield shift (15.6–18.3 ppm), being typical for the changeover from pyridine to pyridine *N*-oxide [33].

NMR experiments also allowed the determination of the stereochemistry of oximes **6**: considering the size of ^{1}J(N=C-H) which is strongly dependent on lone-pair effects [34] as well as the comparison of chemical shifts with those of related, unambiguously assigned oximes [17] reveals *E*-configuration at the C=N double bond.

With byproduct **8a** the position of the carbonyl group unequivocally follows from the correlations between phenyl protons and the carbonyl C-atom and, reversely, from those between the methylene protons with pyrazole C-4 and pyrazole C-5 (determined by ^{13}C,^{1}H HMBC).

In Figure 2 essential NMR data for the complete series of type **c** (**4c**, **5c**, **6c**, **7c**) are displayed, which easily enables to compare the notable chemical shifts and allows following the trends described above.

Full experimental details as well as spectral and microanalytical data of the obtained compounds are presented in Supporting Information File 1.

Conclusion

To sum up, the presented approach represents a simple method for the synthesis of 6-substituted 1-phenyl-3-trifluoromethyl-1*H*-pyrazolo[4,3-*c*]pyridines **5** and the analogous 5-oxides **7**

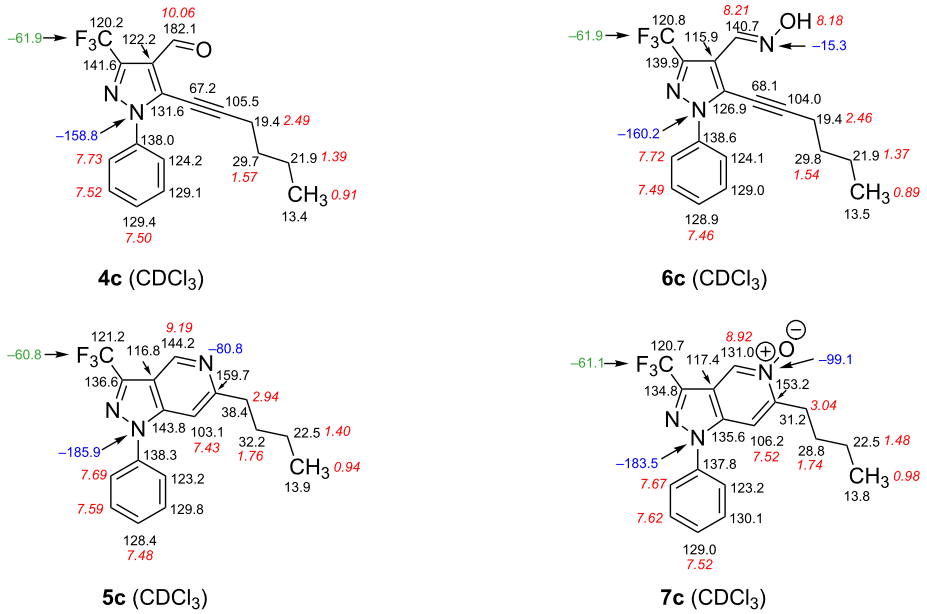


Figure 2: ^{1}H (in italics, red), ^{13}C (black), ^{15}N (in blue) and ^{19}F NMR (green) chemical shifts of compounds **4c**, **5c**, **6c** and **7c** (in $CDCl_3$).

starting from commercially available 1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol (**1**). In the case of the former (**5**) the described multicomponent reaction approach is superior compared to the sequential one, whereas the step-by-step synthesis of *N*-oxides **7** is still characterized by higher overall yields. In addition, in-depth NMR studies with all synthesized compounds were performed, affording full and unambiguous assignment of ^{1}H, ^{13}C, ^{15}N and ^{19}F resonances and the designation of ascertained heteronuclear spin-coupling constants.

Supporting Information

Supporting Information File 1

Experimental details and characterization data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-183-S1.pdf]

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Facile synthesis of 1*H*-imidazo[1,2-*b*]pyrazoles via a sequential one-pot synthetic approach

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Full Research Paper

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Groebke–Blackburn–Bienaymé reaction; 1*H*-imidazo[1,2-*b*]pyrazole; isocyanide; multicomponent reaction; *N*-heterocycles

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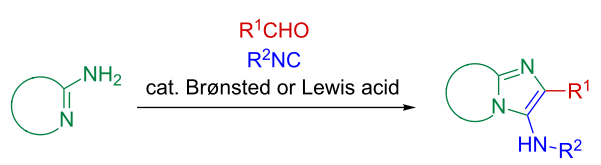
Abstract

5-Aminopyrazole-4-carbonitrile and ethyl 5-aminopyrazole-4-carboxylate, as potential trifunctional building blocks are introduced in a facile, chemo- and regioselective multicomponent assembly of imidazo[1,2-*b*]pyrazoles via the Groebke–Blackburn–Bienaymé reaction (GBB reaction). Besides the synthetic elaboration of a green-compatible isocyanide-based access in three-component mode, we describe an operationally simple, one-pot two-step GBB protocol for the rapid construction of a 46 membered imidazo[1,2-*b*]pyrazole library with yields up to 83%.

Introduction

For the relatively rapid design and construction of a diverse, large pharmacophore library, the basic concepts of diversity-oriented synthesis and isocyanide-based multicomponent reactions, such as the Ugi four-component reaction (U-4CR), can be adopted. The sequential combination of four species (amines, aldehydes, isocyanides and carboxylic acids) in a single-pot synthetic operation permits access to bisamide peptidomimetics through a highly electrophilic nitrilium intermediate [1-4]. Modification of the conventional U-4CR protocol in three-component fashion by the incorporation of bifunctional 2-amino-substituted heterocycles provides an alternative route via an intramolecular *N*-trapping procedure, leading to various *N*,*N*-heterobicyclic systems [5-12]. A number of bifunctional 2-aminoazoles, including thiazole [13,14] and 1,3,4-thiadiazole [15,16] derivatives, or 2-aminoazine-based heterocycles, such as pyridines [17-19], pyrimidines [20-24] and pyrazines [25-27], have recently been utilized as Groebke–Blackburn–Bienaymé three-component reaction (GBB-3CR) inputs (Scheme 1).

The transformations of either the 5-aminopyrazoles [28,29], or their 4-substituted ethoxycarbonyl [7,30-32] and carbonitrile



Scheme 1: The conventional GBB-3CR.

[28,33-36] analogues via the GBB-3CR have not been appreciably examined so far. In the relevant literature [7,28,29,31-33], the products have predominantly been described as 5*H*-imidazo[1,2-*b*]pyrazoles with an *endo* double bond (and not as 1*H*-imidazo[1,2-*b*]pyrazoles), but without 2D NMR-based support. However, the GBB-3CR of functionalized pyrazoles might lead to the formation of two regioisomers [24] and four different tautomeric forms (5*H*- or 1*H*-imidazo[1,2-*b*]pyrazole with an endo- or exocyclic double bond) of each regioisomer. As presented [7,28-36], the "*endo*" 1*H*- and 5*H*-imidazo[1,2-*b*]pyrazoles were synthesized by the treatment of the corresponding amino substituted pyrazoles with aldehydes and isocyanides in the presence (5–30 mol %) of Lewis or Brønsted acid at ambient temperature or under heating (50–140 °C). The main disadvantages of this protocol involve long reaction times (3–18 hours) and requisite purification protocols (column chromatography and/or recrystallisation) besides limited diversity arising from the pyrazole starting material. As far as we are aware, a one-pot two-step process involving the in situ formation of the desired amino-substituted *N*-heterocycles such as C4 functionalized 5-aminopyrazoles, followed by GBB-3CR has not been described to date.

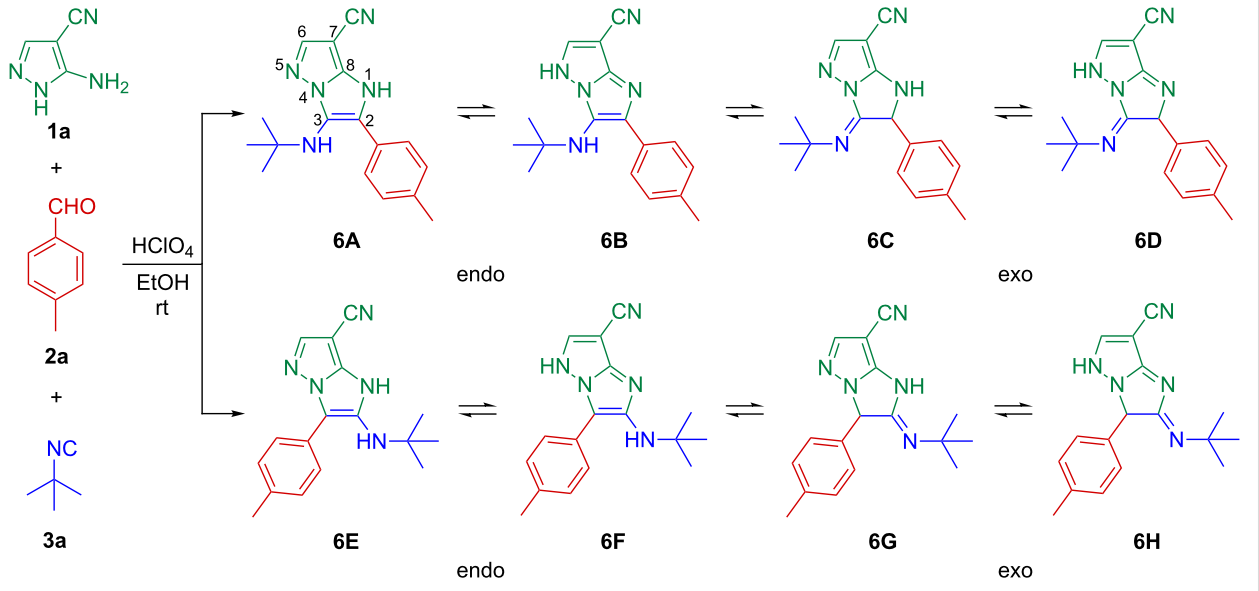
On the other hand, the imidazo[1,2-*b*]pyrazole core is definitely an attractive synthetic target, in view of its noteworthy pharmacological potential, which is strongly affected by the ring substitution pattern and the level of ring saturation. Among others, anti-inflammatory [37,38], antiviral [28,39] and antidiabetic [40] effects should be mentioned, besides the non-negligible cancer cell growth-inhibitory features of the corresponding compounds [30,34,41,42].

With respect to the current requirements of sustainable chemistry, our main aim was to design a streamlined and rapid green synthetic access route to a 1*H*-imidazo[1,2-*b*]pyrazole library in sequential one-pot protocol utilizing four components such as hydrazine hydrate, ethoxymethylene substituted malononitrile or ethyl cyanoacetate derivatives, isocyanides and aldehydes.

Results and Discussion

In the initial stage, a model GBB-3CR was performed between 5-aminopyrazole-4-carbonitrile (**1a**), *p*-tolualdehyde (**2a**) and *tert*-butyl isocyanide (**3a**) in order to elucidate the structure of the product and investigate the regioselectivity. The synthesis of 5-aminopyrazole-4-carbonitrile (**1a**) was based on a literature method [43,44].

A single product was observed in a yield of 59% during a reaction time of 15 min when a catalytic amount of $HClO_4$ (20 mol %) was used as GBB-3CR promoter [7] in EtOH. 1D- and 2D NMR techniques (^1H,^{13}C-HSQC, ^1H,^{13}C-HMBC, ^1H,^1H-COSY and ^1H,^1H-NOESY) confirmed the exclusive presence of a 1*H*-imidazo[1,2-*b*]pyrazole core with an endo-



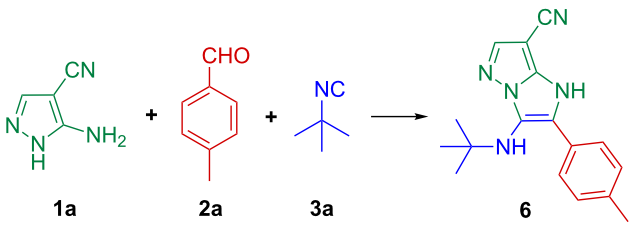
Scheme 2: Plausible products **6A–H**.

cyclic double bond (**6A**), i.e., without the other possible regioisomeric and tautomeric forms **6B**–**H** (Scheme 2, see Supporting Information File 1 for detailed data and spectra).

For optimization, the 3CR synthesis of **6** was investigated under different catalytic conditions (Table 1). No reaction occurred in the absence of either a Brønsted or a Lewis acid catalyst (Table 1, entry 1). However, the use of Lewis acids, such as indium(III) salts or TMSCl, improved the reaction rate, with yields up to 67% (Table 1, entries 2–4). The GBB-3CR catalysed by Brønsted acids, including PTSA or $HClO_4$, led to similar yields as on Lewis acid catalysis, though better results were obtained by using a catalytic amount of TFA in EtOH (Table 1, entries 5–7). From the aspect of an operationally simple green protocol, a mixture of water and EtOH as reaction medium yielded optimum results in terms of isolated yield, reaction time and mode of isolation (Table 1, entries 7–15). The one-pot 3CR of 5-aminopyrazole-4-carbonitrile (**1a**), *p*-tolualdehyde (**2a**) and *tert*-butyl isocyanide (**3a**) catalysed by TFA (20 mol %) in water/EtOH 1:1 furnished **6** isolated by simple filtration in a yield of 79% during 15 min.

These results led us to envisage a sequential one-pot access to 1*H*-imidazo[1,2-*b*]pyrazole species through the in situ microwave-assisted formation of **1a** followed by a GBB-3CR. A comparative study for the optimum synthesis of **6** revealed that the cyclocondensation of ethoxymethylene malononitrile (**4a**) with hydrazine (**5**) under microwave irradiation (80 °C, 150 W, 10 min, EtOH) proceeded with complete conversion (Scheme 3). It should be mentioned that the presence of water in this step resulted in a complex reaction mixture, moreover, the role of the reagent addition sequence was found to be crucial. The GBB reaction proceeded smoothly with acceptable efficacy during 15 min (overall yield of **6**: 65%), with the addition of water, aldehyde **2a**, a catalytic amount of TFA (20 mol %) and isocyanide **3a** to the solution of the preformed 5-aminopyrazole-4-carbonitrile (**1a**) at room temperature.

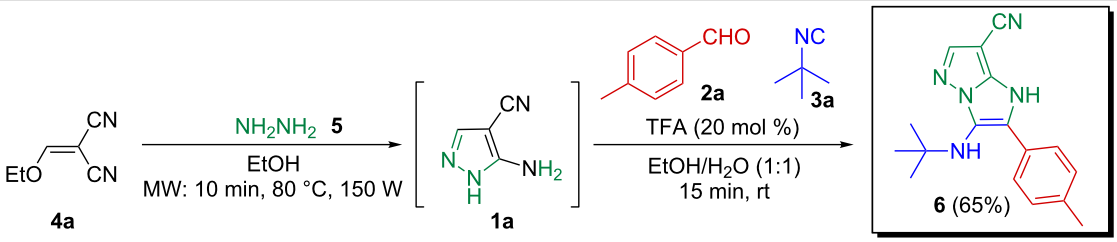
Table 1: Solvent and catalyst screen of the GBB-3CR[a].



1a **2a** **3a** **6**

Entry	Catalyst	Cat. load (mol %)	Solvent	Reaction time	Yield (%)
1	–	–	EtOH	> 72 h	0
2	$In(OTf)_3$	20	EtOH	15 min	61[b]
3	$InCl_3$	20	EtOH	15 min	67[b]
4	TMSCl	20	EtOH	15 min	64[b]
5	$TsOH·H_2O$	20	EtOH	15 min	52[b]
6	$HClO_4$	20	EtOH	15 min	59[b]
7	TFA	20	EtOH	15 min	74[b]
8	TFA	20	CH_2Cl_2	15 min	35[c]
9	TFA	20	CH_2Cl_2	20 h	59[b]
10	TFA	20	CH_2Cl_2/MeOH 1:1	15 min	68[b]
11	TFA	20	MeCN	15 min	68[b]
12	TFA	20	THF	15 min	74[b]
13	TFA	20	MeOH	15 min	71[b]
14	TFA	20	H_2O	15 min	63[c]
15	TFA	20	EtOH/H_2O 1:1	15 min	79[b]
16	TFA	1	EtOH/H_2O 1:1	36 h	46[b]
17	TFA	2	EtOH/H_2O 1:1	20 h	62[b]
18	TFA	5	EtOH/H_2O 1:1	1 h	75[b]
19	TFA	10	EtOH/H_2O 1:1	25 min	76[b]

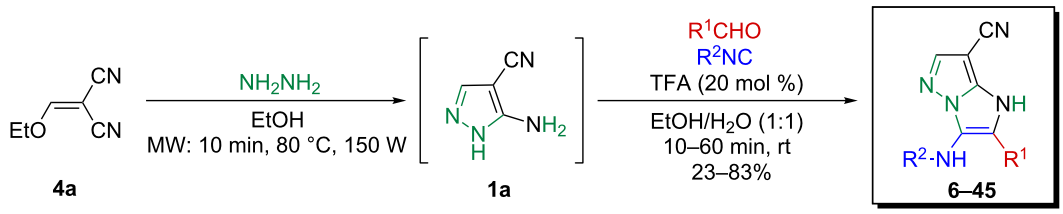
[a]Reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), **3a** (0.55 mmol), solvent (1 mL), room temperature. [b]Isolated yield after simple filtration. [c]Isolated yield after flash chromatography.



Scheme 3: Synthesis of **6** via the sequential one-pot method.

The well-established sequential one-pot protocol was then adopted to synthetize a series of 1*H*-imidazo[1,2-*b*]pyrazoles from selected aldehydes **2a–j** and isocyanide building blocks **3a–d** (Table 2). Following the microwave-assisted rapid formation of **1a**, the one-pot GBB reactions were completed during 10–60 min in yields of 23–83%. Unfortunately, limited substitution effect correlations could be established by employing aromatic aldehydes **2a–h**. The introduction of electron-donating

Table 2: Sequential one-pot GBB library generation[a].



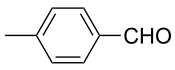
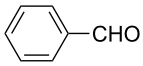
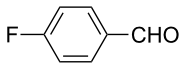
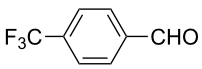
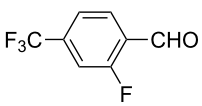
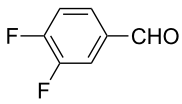
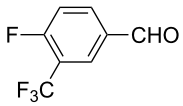
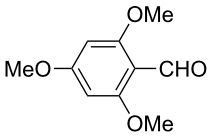
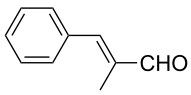
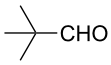
Entry	R^1CHO	R^2NC		Product	Yield (%)
1	 **2a**	*t*-BuNC	**3a**	**6**	79[b,c] (65)[c]
2		*t*-octyl-NC	**3b**	**7**	66[c]
3		$MeOOCCH_2NC$	**3c**	**8**	58[c]
4		CyNC	**3d**	**9**	75[c]
5	 **2b**	*t*-BuNC	**3a**	**10**	68[c]
6		*t*-octyl-NC	**3b**	**11**	70[c]
7		$MeOOCCH_2NC$	**3c**	**12**	70[c]
8		CyNC	**3d**	**13**	69[c]
9	 **2c**	*t*-BuNC	**3a**	**14**	67[c]
10		*t*-octyl-NC	**3b**	**15**	71[c]
11		$MeOOCCH_2NC$	**3c**	**16**	41[c]
12		CyNC	**3d**	**17**	74[c]
13	 **2d**	*t*-BuNC	**3a**	**18**	63[c]
14		*t*-octyl-NC	**3b**	**19**	59[c]
15		$MeOOCCH_2NC$	**3c**	**20**	35[c]
16		CyNC	**3d**	**21**	66[c]
17	 **2e**	*t*-BuNC	**3a**	**22**	59[c]
18		*t*-octyl-NC	**3b**	**23**	39[c]
19		$MeOOCCH_2NC$	**3c**	**24**	23[c]
20		CyNC	**3d**	**25**	46[c]
21	 **2f**	*t*-BuNC	**3a**	**26**	59[c]
22		*t*-octyl-NC	**3b**	**27**	53[c]
23		$MeOOCCH_2NC$	**3c**	**28**	28[c]
24		CyNC	**3d**	**29**	24[c]

Table 2: Sequential one-pot GBB library generation[a]. (continued)

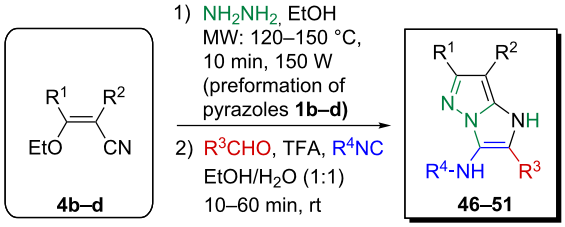
25	 **2g**	*t*-BuNC	**3a**	**30**	53[c]
26		*t*-octyl-NC	**3b**	**31**	41[c]
27		$MeOOCCH_2NC$	**3c**	**32**	33[c]
28		CyNC	**3d**	**33**	46[c]
29	 **2h**	*t*-BuNC	**3a**	**34**	70[c]
30		*t*-octyl-NC	**3b**	**35**	83[c]
31		$MeOOCCH_2NC$	**3c**	**36**	48[c]
32		CyNC	**3d**	**37**	48[c]
33	 **2i**	*t*-BuNC	**3a**	**38**	61[c]
34		*t*-octyl-NC	**3b**	**39**	67[c]
35		$MeOOCCH_2NC$	**3c**	**40**	26[c]
36		CyNC	**3d**	**41**	63[c]
37	 **2j**	*t*-BuNC	**3a**	**42**	50[d]
38		*t*-octyl-NC	**3b**	**43**	45[d]
39		$MeOOCCH_2NC$	**3c**	**44**	47[d]
40		CyNC	**3d**	**45**	40[d]

[a]Reaction conditions: **4a** (0.50 mmol), **5** (0.55 mmol), ethanol (0.5 mL), MW (10 min, 80 °C, 150 W), then water (0.5 mL), **2a–j** (0.55 mmol), TFA (0.10 mmol), **3a–d** (0.55 mmol), room temperature, 10–60 min. [b]Isolated yield from the GBB-3CR. [c]Isolated yield after simple filtration. [d]Isolated yield after flash chromatography.

substituents such as 4-Me or 2,4,6-tri-OMe (derived from aldehydes **2a** and **2h**) resulted in similar conversions as for **2b**, whereas the presence of two electron-withdrawing substituents as in **2e–g** resulted in decreased yields. α-Methylcinnamaldehyde (**2i**) as an uncommon isocyanide-based MCR component was successfully subjected to the GBB reaction, leading to the formation of the corresponding bicycles **38**–**41** in yields of 26–67%. All the reactions except those based on pivalaldehyde (**2j**) provided access to 1*H*-imidazo[1,2-*b*]pyrazoles through simple filtration. Of the aliphatic isocyanides **3a–d** applied, methyl isocyanoacetate (**3c**) often gave the lowest isolated yields, probably in consequence of self-trapping [45].

To create diversely substituted 1*H*-imidazo[1,2-*b*]pyrazoles, the sequential one-pot GBB method has been extended by means of ethyl 2-cyano-3-ethoxyacrylate (**4b**), (1-ethoxyethylidene) malononitrile (**4c**) and ethyl (*E*)-2-cyano-3-ethoxycrotonate (**4d**). Application of these starting materials in the optimized protocol with a slight modification (elevated temperature was necessary for the microwave assisted preformation of pyrazole intermediates **1b–d**) afforded highly functionalized 1*H*-imidazo[1,2-*b*]pyrazole analogues **46**–**51** in yields of 54–79% (Table 3).

Table 3: Synthesis of highly substituted 1*H*-imidazo[1,2-*b*]pyrazoles[a].



4b: R^1 = H; R^2 = COOEt; **4c**: R^1 = Me; R^2 = CN;
4d: R^1 = Me; R^2 = COOEt

Entry	R^1	R^2	R^3CHO	R^4NC	Product	Yield[b] (%)
1	H	COOEt	**2a**	**3a**	**46**	54
2	H	COOEt	**2b**	**3b**	**47**	56
3	Me	CN	**2a**	**3a**	**48**	79
4	Me	CN	**2c**	**3c**	**49**	57
5	Me	COOEt	**2a**	**3a**	**50**	74
6	Me	COOEt	**2i**	**3b**	**51**	59

[a]Reaction conditions: **4b–d** (0.50 mmol), **5** (0.55 mmol), ethanol (0.5 mL), MW (10 min; **4b**: 150 °C, **4c,d**: 120 °C; 150 W), then water (0.5 mL), **2a–c,i** (0.55 mmol), TFA (0.10 mmol), **3a–c** (0.55 mmol), room temperature, 10–60 min. [b]Isolated yield after simple filtration.

Conclusion

We have described here the development of a de novo and facile one-pot, two-step GBB method. The established protocol allowed the rapid synthesis of a 46-membered 1*H*-imidazo[1,2-*b*]pyrazole library with isolated yields up to 83%. Following the microwave-aided formation of functionalized 5-aminopyra-

zoles, the GBB-3CR transformations occurred during 10–60 min under mild conditions. This protocol offers operationally simple, green access to highly substituted 1*H*-imidazo[1,2-*b*]pyrazoles with easily variable substitution pattern and does not require complex purification techniques.

Supporting Information

Supporting Information File 1

Experimental and characterisation data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-243-S1.pdf]

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New highlights of the syntheses of pyrrolo[1,2-*a*]quinoxalin-4-ones

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Abstract

The one-pot three-component reactions of 1-substituted benzimidazoles with ethyl bromoacetate and electron-deficient alkynes, in 1,2-epoxybutane, gave a variety of pyrrolo[1,2-*a*]quinoxalin-4-ones and pyrrolo[1,2-*a*]benzimidazoles. The influence of experimental conditions on the course of reaction was investigated. A novel synthetic pathway starting from benzimidazoles unsubstituted at the five membered ring, alkyl bromoacetates and non-symmetrical electron-deficient alkynes in the molar ratio of 1:2:1, in 1,2-epoxybutane at reflux temperature, led directly to pyrrolo[1,2-*a*]quinoxalin-4-ones in fair yield by an one-pot three-component reaction.

Introduction

The pyrrolo[1,2-*a*]quinoxaline system has significant biological activities and is a subject fo constant interest. This skeleton is a constituent of several bioactive heterocyclic compounds that demonstrate interesting activity against *Mycobacterium tuberculosis* [1], anti-HIV [2], anticancer [3], and it modulates the estrogen receptor activity [4].

Synthetic methods towards pyrrolo[1,2-*a*]quinoxaline derivatives based on pyrroles [5], or quinoxalines [6] have been recently reviewed. Among other synthetic routes, the 1,3-dipolar cycloaddition of heterocyclic *N*-ylides with various activated alkynes or alkenes is an important method for constructing fused heterocyclic systems such as pyrrolo[1,2-

a]quinoxaline and pyrrolo[1,2-*a*]benzimidazole [7-13]. The development of more efficient synthetic methods towards these compounds is an active research area [14-16].

Recently, we reported on the formation of pyrrolo[1,2-*a*]benzimidazoles along with pyrrolo[1,2-*a*]quinoxalines in the one-pot three-component reaction of 1-benzylbenzimidazoles, phenacyl bromides and non-symmetrical activated alkynes in presence of propenoxide or 1,2-epoxybutane used as acid scavenger and reaction solvent [16]. These results prompted us to further investigate 1,3-cycloaddition reactions of 1-substituted 3-(alkoxycarbonylmethyl)benzimidazolium ylides with various dipolarophiles under the same reaction conditions, aiming to explore the generality of the reaction.

The previously reported data on 1,3-cycloaddition reactions of 1-substituted 3-(alkoxycarbonylmethyl)benzimidazolium ylides with various dipolarophiles are rather contradictory. Thus, 1-alkyl-3-(methoxycarbonylmethyl)benzimidazolium bromides with dimethyl acetylenedicarboxylate (DMAD) in presence of K_2CO_3 in DMF [7] or in presence of triethylamine in acetonitrile [8] give a mixture of pyrrolo[1,2-*a*]benzimidazole (2–7%) and a compound whose formation involves the loss of an alcohol molecule for which different structures have been proposed [7,8]. The correct structure of 2,3-dicarbomethoxy-5-methylpyrrolo[1,2-*a*]quinoxalin-4-one and the reaction mechanism was proposed by Meth-Cohn [9].

The reactions of 1-substituted 3-(ethoxycarbonylmethyl)benzimidazolium bromides with fluoroalkenes [10] or fluorovinyl tosylates [11] in presence of K_2CO_3 and triethylamine in DMF at 70 °C, or with activated alkenes, such as acrylates, acrylonitrile or diethyl malonate, in presence of triethylamine and an oxidant in DMF at 90 °C, led only to the normal cycloaddition products, i.e., pyrrolo[1,2-*a*]benzimidazoles [12]. When the same reactions were performed with polarized alkenes, such as 2-ethoxy acrylonitrile or 1,1-bis(methylthio)-2-nitroethylene, in presence of K_2CO_3 in chloroform at room temperature, only pyrrolo[1,2-*a*]quinoxalin-4-ones resulted in fair yields [13].

Our interest in developing simple synthetic pathways towards *N*-bridged heterocyclic compounds [17-20] prompted us to investigate the one-pot three-component reactions of various substituted benzimidazoles with alkyl bromoacetates and electron-deficient alkynes in presence of an epoxide. Herein, we report a simple one-pot three-component synthetic procedure towards pyrrolo[1,2-*a*]quinoxalin-4-ones and pyrrolo[1,2-*a*]benzimidazoles and we describe the influence of reaction conditions on the ratio of the two final reaction products. We developed also a selective one-pot three-component synthetic pathway towards pyrrolo[1,2-*a*]quinoxalin-4-one derivatives starting from benzimidazole derivatives unsubstituted at the five membered ring, alkyl bromoacetates and non-symmetrical electron-deficient alkynes in the molar ratio of 1:2:1, in 1,2-epoxybutane at reflux temperature.

Results and Discussion

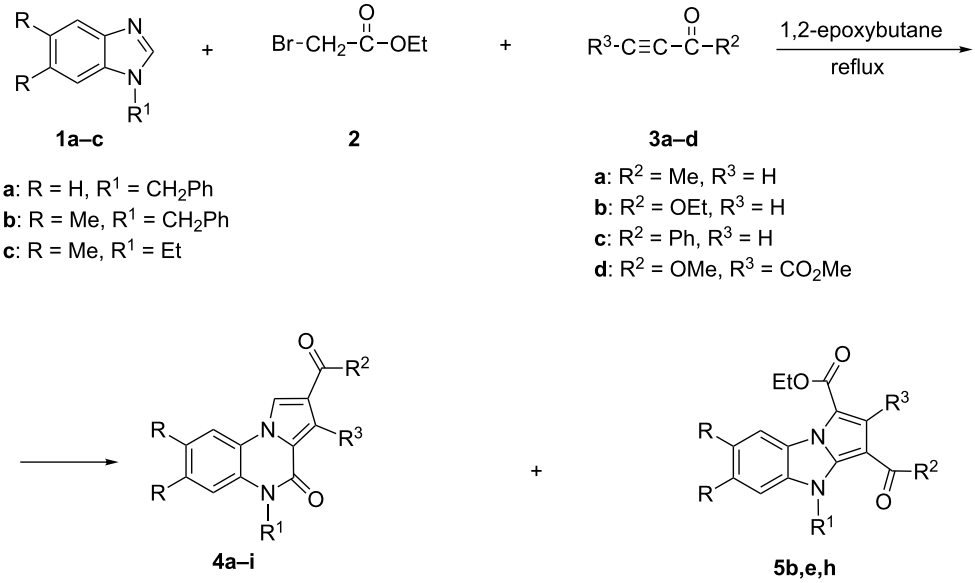
The one-pot three-component reaction of 1-substituted benzimidazoles **1a–c**, ethyl bromoacetate **2** and non-symmetrical activated alkynes **3a–c**, in almost equimolar amounts, performed in presence of 1,2-epoxybutane gave pyrrolo[1,2-*a*]quinoxaline-4-ones **4a–g** as major reaction products. Pyrrolo[1,2-*a*]benzimidazoles **5b**,**e** were isolated along with pyrrolo[1,2-*a*]quinoxaline-4-ones **4b**,**e** only in some cases (Scheme 1, Table 1). All reactions have been performed by mixing the starting components at room temperature in 1,2-epoxybutane and heating the reaction mixture for 24 hours at reflux temperature. Pyrrolo[1,2-*a*]quinoxalin-4-one derivatives **4** were isolated from the reaction mixture by crystallization. To separate pyrrolo[1,2-*a*]benzimidazole derivatives **5**, each filtrate was concentrated under vacuum and chromatographed on a SiO_2 packed column.

The HPLC analysis of crude reaction products indicated that small amounts of pyrrolo[1,2-*a*]benzimidazoles **5** were formed in all reactions, but they could not be always isolated from the reaction mixtures.

Due to the high reactivity of dimethyl acetylenedicarboxylate which can react also with the starting 1-substituted benzimidazole, the one-pot three-component synthetic procedure starting from almost equimolar amounts of 1-substituted benzimidazole **1**, ethyl bromoacetate and dimethyl acetylenedicarboxylate (**3d**) in 1,2-epoxybutane led to a complex mixture of reaction products. However, by direct reaction of 1-benzyl-3-ethoxycarbonylmethylbenzimidazolium bromide, obtained previously from 1-benzylbenzimidazole (**1a**) and ethyl bromoacetate (**2**), with dimethyl acetylenedicarboxylate (**3d**), in 1,2-epoxybutane at reflux temperature, the pyrrolo[1,2-*a*]quinoxalin-4-one (**4h**) was obtained as major reaction product along with a small amount of pyrrolo[1,2-*a*]benzimidazole (**5h**). Starting from 1-benzyl-5,6-dimethyl-3-ethoxycarbonylmethylbenzimidazolium bromide and dimethyl acetylenedicarboxylate **3d**, in the same conditions, only pyrrolo[1,2-*a*]quinoxalin-4-one **4i** was isolated from the reaction mixture (Scheme 1).

The yields and melting points of newly synthesized pyrrolo[1,2-*a*]quinoxalin-4-ones **4** and pyrrolo[1,2-*a*]bezimidazoles **5** are presented in Table 1.

The reaction pathway (Scheme 2) involves the quaternization of 1-substituted benzimidazoles **1** with ethyl bromoacetate (**2**)



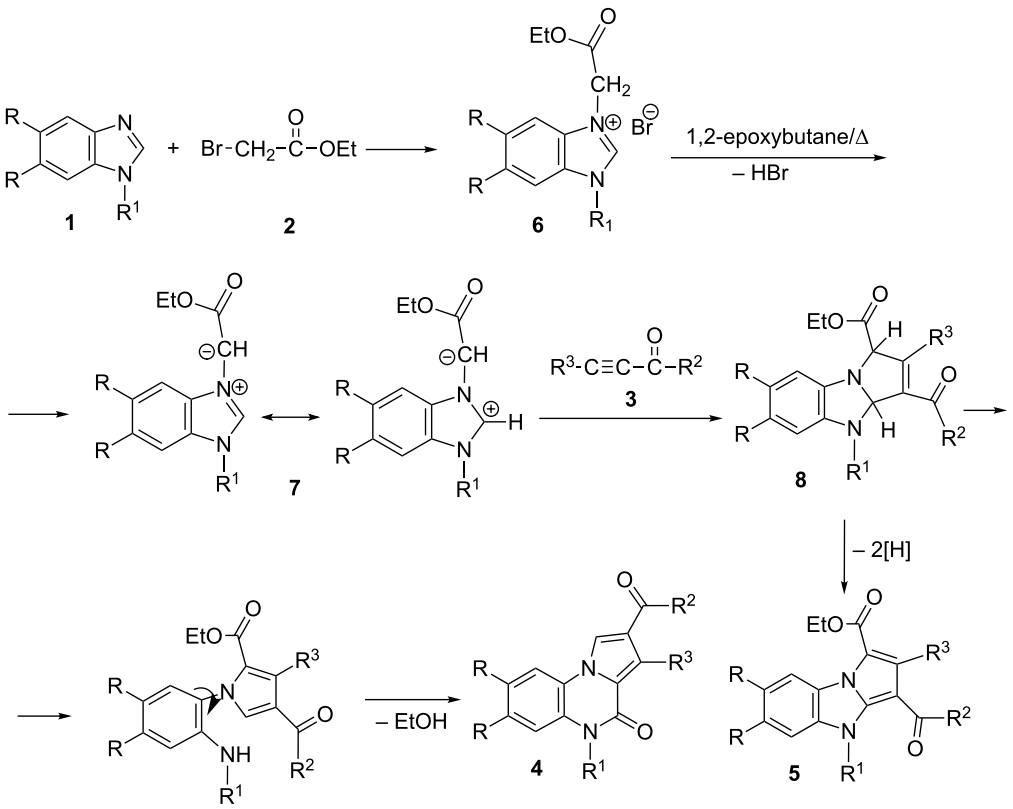
Scheme 1: Synthesis of pyrrolo[1,2-*a*]quinoxalin-4-ones **4** and pyrrolo[1,2-*a*]benzimidazoles **5**.

Table 1: Synthesized pyrrolo[1,2-*a*]quinoxalin-4-ones **4** and pyrrolo[1,2-*a*]bezimidazoles **5**.

Entry	Reaction products					
	4	mp (°C)	Yield (%)[a]	**5**	mp (°C)	Yield (%)[a]
1	**4a**	225–227	39	–	–	–
2	**4b**	178–180	42	**5b**	130–132	13
3	**4c**	220–222	57	–	–	–
4	**4d**	274–275	43	–	–	–
5	**4e**	215–217	38	**5e**	191–193	21
6	**4f**	283–285	48	–	–	–
7	**4g**	191–193	39	–	–	–
8	**4h**	259–261 258–259 [8]	42 12 [8]	**5h**	177–178	16
9	**4i**	275–276	19	–	–	–

[a]Yields for isolated and purified compounds.

leading to corresponding benzimidazolium bromides **6**. The attack of the bromine ion from the benzimidazolium bromide on the oxirane ring in 1,2-epoxybutane results in ring opening and generation of the benzimidazolium *N*-ylide **7** by the action of the alkoxide. The benzimidazolium *N*-ylide **7** reacts with the activated alkynes **3** to give the corresponding primary cycloadduct dihydropyrrolo[1,2-*a*]benzimidazoles **8**. The formation of pyrrolo[1,2-*a*]quinoxalin-4-ones **4** involves the



Scheme 2: Reaction pathway leading to the formation of pyrrolo[1,2-*a*]quinoxalin-4-ones **4** and pyrrolo[1,2-*a*]bezimidazoles **5**.

imidazole ring-opening, initiated by the deprotonation at C-1 of the primary cycloadducts **8**, followed by ring-closure involving the carbethoxy C=O group, a previously proposed rationale [9]. The formation of pyrrolo[1,2-*a*]benzimidazoles **5** involves the spontaneous in situ dehydrogenation of the primary cycloadducts **8**.

In order to explain the above mentioned results, we investigated the influence of reaction conditions on the ratio of the final reaction products **4** and **5** in 1,3-dipolar cycloaddition reactions of the 1-benzyl-3-(ethoxycarbonylmethyl)benzimidazolium bromide **6** (R = H, R^1 = benzyl) with ethyl propiolate (**3b**) and DMAD (**3d**), in different reaction conditions reported in literature (Table 2). In these experiments, all crude reaction products were treated with aqueous solution of 5% HCl and extracted with $CHCl_3$. The chloroformic extracts were dried, concentrated under vacuum, analyzed by HPLC and the peak areas of the final reaction products **4** to **5** were determined (Table 2).

The results suggest that in the presence of an organic and/or inorganic base the formation of pyrrolo[1,2-*a*]quinoxalin-4-one

Table 2: The influence of the reaction conditions on the final reaction products.

Entry	Reaction conditions	Ratio of peak areas[a]	
		4b:5b	**4h:5h**
1	1,2-epoxybutane, 24 h at reflux temperature (≈62 °C)	7.6	6.2
2	NEt_3 and TPCD in DMF, 4 h at 90 °C[b]	7.7	2.7
3	NEt_3 in acetonitrile, 4 h at reflux temperature (≈80 °C)[c]	46	54
4	K_2CO_3 in DMF, 48 h at rt[d]	27	–
5	K_2CO_3 + NEt_3 in DMF, 24 h at 70 °C[e]	91	–

[a]Calculated from HPLC chromatograms; [b]reaction conditions according to [12]; [c]according to [8]; [d]according to [7]; [e]according to [10,11].

derivatives **4** is favored, while in a neutral medium or in the presence of oxidants, such as TPCD [12], significant quantities of pyrrolo[1,2-*a*]benzimidazoles **5**, the normal 1,3-dipoar cycladdition product, are also formed. In this way, the low yields of pyrrolo[1,2-*a*]benzimidazoles **5** reported in literature [7,8] can be explained.

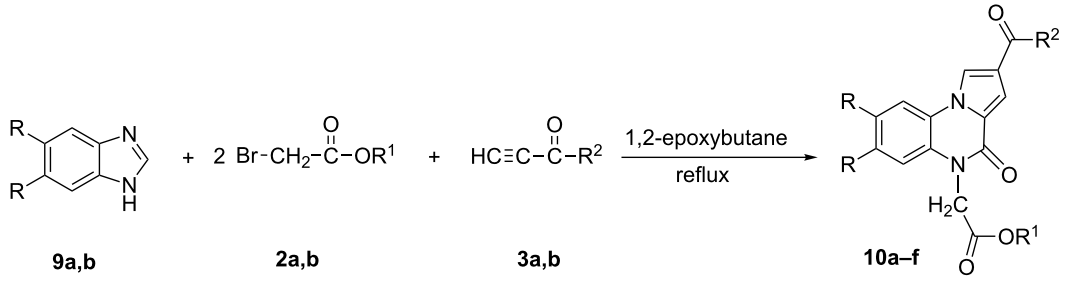
An easy access to pyrrolo[1,2-*a*]quinoxalin-4-ones **10** was provided by the one-pot three-components reaction of benzimidazoles unsubstituted at the imidazole ring **9a**,**b** with alkyl bromoacetates **2a**,**b** and non-symmetrical, electron-deficient alkynes **3a**,**b**, in the molar ratio 1:2:1, in 1,2-epoxybutane at reflux temperature. This novel synthetic procedure lead directly to pyrrolo[1,2-*a*]quinoxalin-4-ones **10a–f**, as solely reaction product, in fair yields (Scheme 3).

A range of benzimidazole, unsubstituted at the imidazole ring and bearing various substituents on the benzoanelated ring, could be used as starting compounds. The reaction could be extended for a broad range of alkyl bromoacetates and non-symmetrical electron-deficient alkynes. Mild reaction conditions are involved, implying mixing the benzimidazole derivative with an alkyl bromoacetate and a non-symmetrical activated alkyne in the molar ratio of 1:2:1 at room temperature in 1,2-epoxybutane, then heating the reaction mixture at reflux temperature for 30 hours. All final pyrrolo[1,2-*a*]quinoxalin-4-one compounds have been isolated by simple, non-chromatographic methods.

The reaction pathway involves the intermediate *N*-alkylation of the imidazole ring with one equivalent of alkyl bromoacetate yielding 1-ethoxycarbonylmethylbenzimidazole, followed by its quaternization with the second equivalent of alkyl bromoacetate leading to 1,3-di(ethoxycarbonylmethyl)benzimidazolium bromide. The final pyrrolo[1,2-*a*]quinoxalin-4-ones are obtained according to the mechanism presented in Scheme 2.

The structures of newly synthesized pyrrolo[1,2-*a*]quinoxalin-4-ones **4** and **10**, and pyrrolo[1,2-*a*]benzimidazoles **5** were assigned by elemental analysis, IR and NMR spectroscopy. The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts have been unambiguously assigned based on the following 2D NMR experiments: H,H-COSY, H,C-HSQC, H,C-HMBC, H,N-HMBC, H,H-NOESY.

In the ^{1}H NMR spectra of pyrrolo[1,2-*a*]quinoxalines and pyrrolo[1,2-*a*]benzimidazoles the protons from the phenyl ring and the annelated benzo ring are overlapping in the region of 7–8 ppm. Based on a less used undecoupled H,C-HSQC type of spectrum we assigned for the first time the individual aromatic signals, the multiplicity and the order of magnitude of the coupling constants for these classes of compounds. The full assignments are listed in the experimental section and an example is shown in Figure 1 for compound **5h**. Thus, in Figure 1, one can clearly see separated cross peaks around each ^{13}C satellite corresponding to all ^{1}H signals in the region of 7.0–7.6 ppm. The low intensity ^{13}C satellites in the ^{1}H NMR spectrum are located outside (low and high field) of the region of the main ^{1}H signal. When extracting 1D rows from the 2D H,C-undecoupled-HSQC spectrum corresponding to each ^{13}C signal, one can see traces showing individual ^{1}H signals (Figure 2). The pseudo 1D spectra from Figure 2 are traces at each ^{13}C signal around the low field ^{13}C satellite in the ^{1}H dimension. In contrast with the normal ^{1}H NMR spectrum



9a,b

a: R = H
b: R = Me

2a,b

a: R^1 = Et
b: R^1 = *t*-Bu

3a,b

a: R^2 = Me
b: R^2 = OEt

10a–f

a: R = H, R^1 = Et, R^2 = Me
b: R = H, R^1 = Et, R^2 = OEt
c: R = Me, R^1 = Et, R^2 = Me
d: R = Me, R^1 = Et, R^2 = OEt
e: R = H, R^1 = *t*-Bu, R^2 = Me
f: R = H, R^1 = *t*-Bu, R^2 = OEt

Scheme 3: Novel synthetic pathway towards pyrrolo[1,2-*a*]quinoxalin-4-ones **10**.

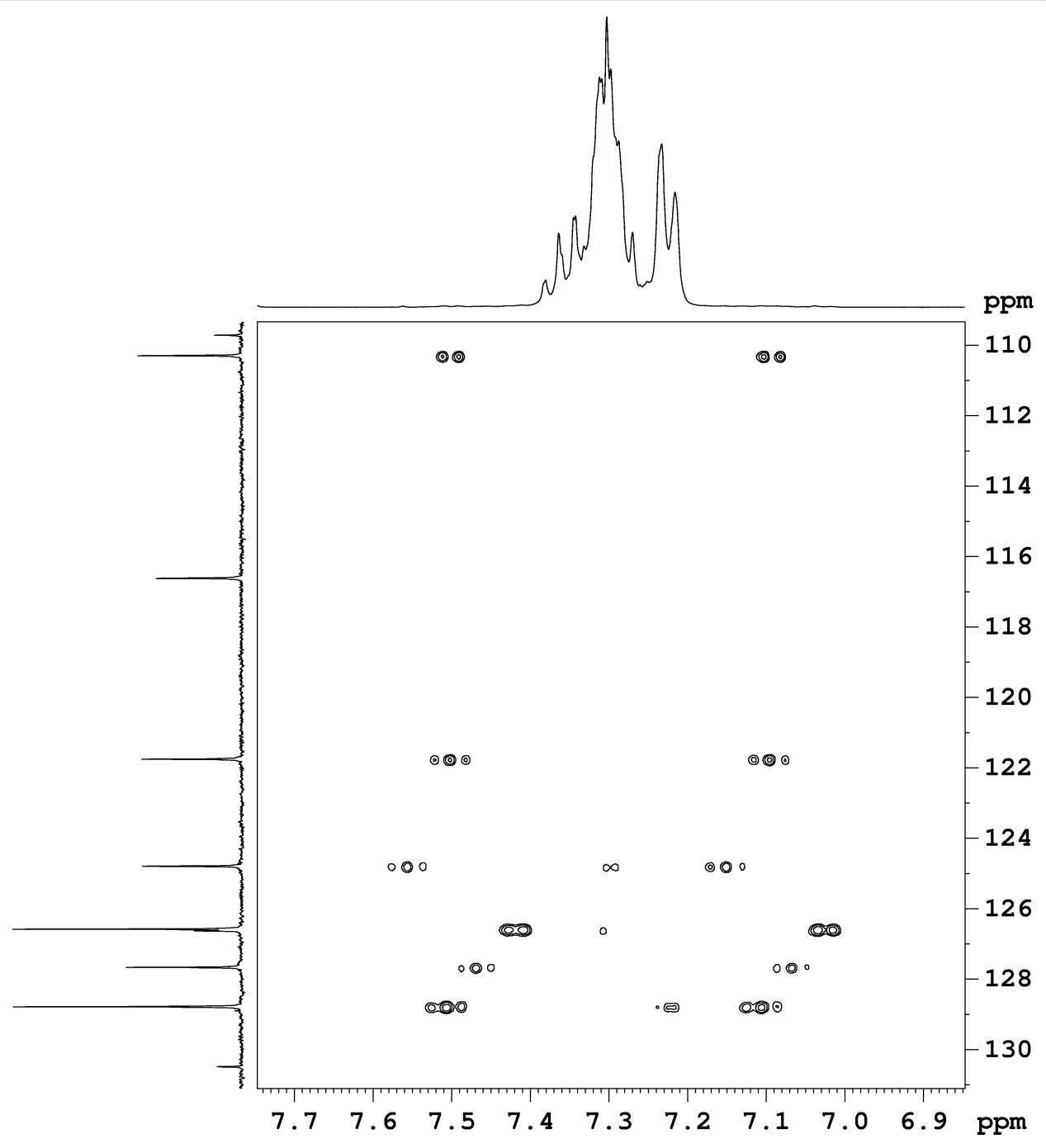


Figure 1: Undecoulpled H,C-HSQC spectrum for compound **5h**.

(Figure 2, bottom) the pseudo 1D ^{1}H spectra show individual signals allowing for the determination of chemical shifts, multiplicities, and coupling constants.

For compounds **4h**, **4i**, **5b** and **5e**, the carbomethoxy respectively carbethoxy residues were assigned based on their NOE response. Thus, for compounds **4h**,**i** the methyl protons from carbomethoxy groups situated in positions 2 and 3 were differentiated based on their NOE cross peak with the proton in position 1. For compounds **5b**,**e** the protons from carbethoxy groups situated in positions 1 and 3 were assigned based on their NOE cross peaks with the proton in position 8, an example for **5b** is shown in Figure 3.

Based on the NOE assignments of various ethyl groups, we suppose that the preferred conformation in solution for the

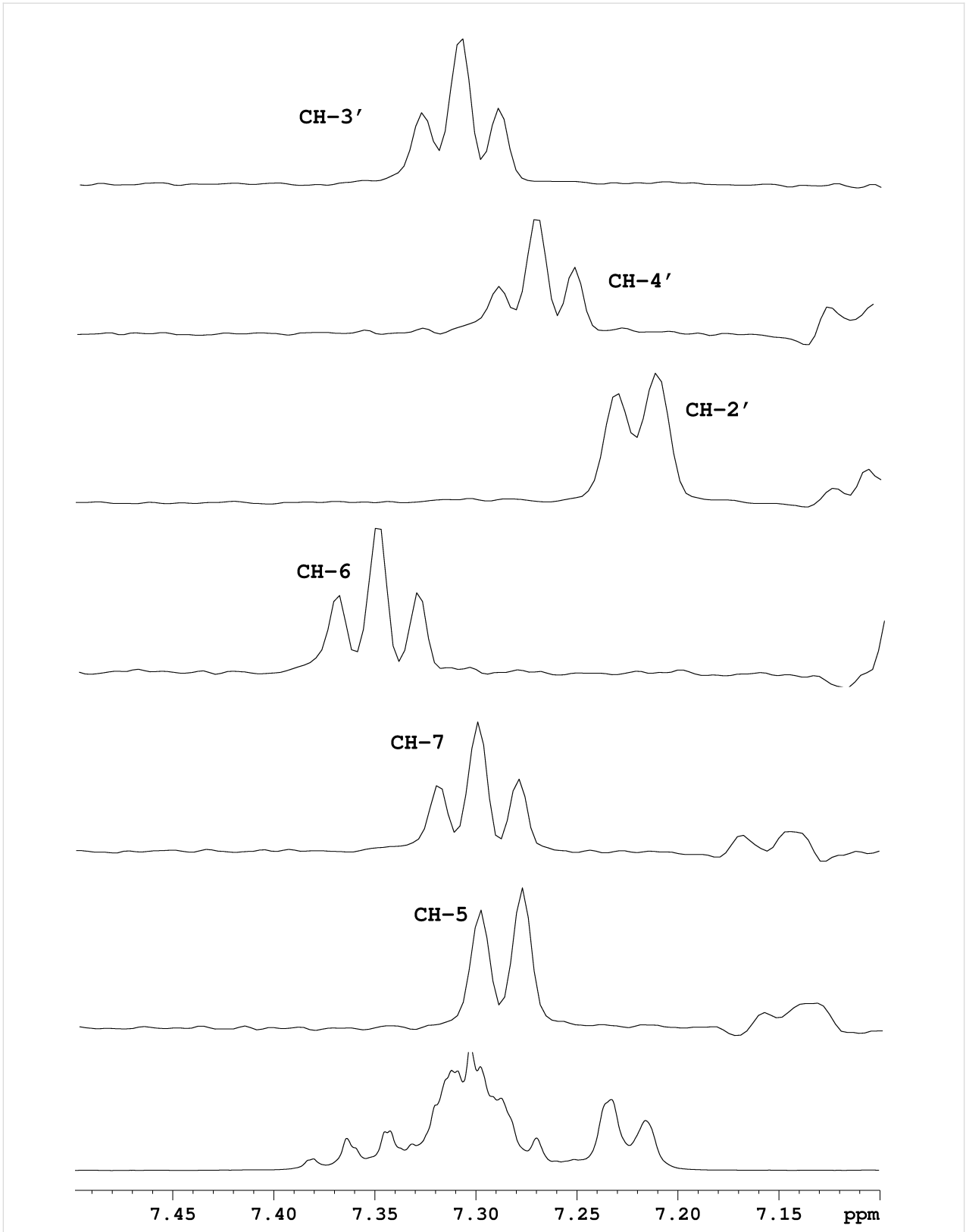


Figure 2: Individual ^{1}H signal assignments based on ^{13}C traces from H,C-undecoulpled-HSQC spectrum around the low field ^{13}C satellite, in comparison with the ^{1}H NMR spectrum (bottom) for compound **5h**.

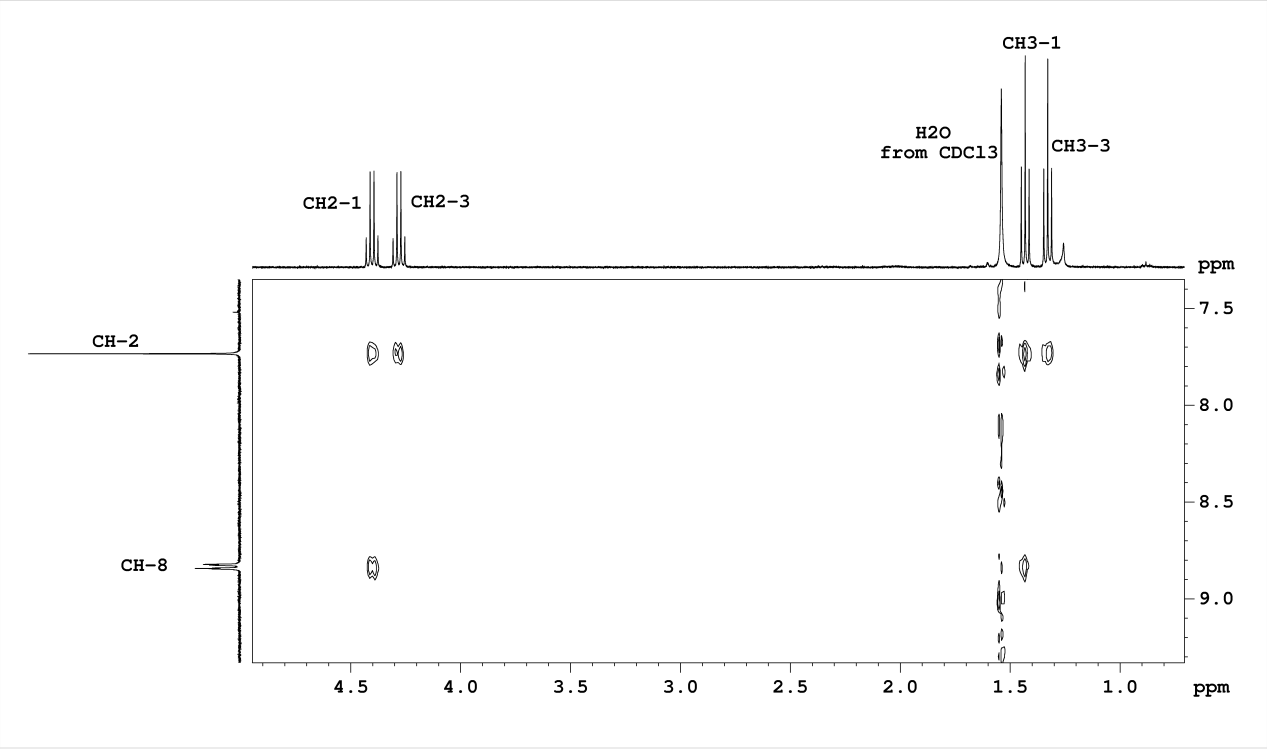


Figure 3: NOE response as cross peaks between carbethoxy group protons and protons from positions 2 and 8 of the heterocycle in a detail from the H,H-NOESY spectrum for compound **5b**.

carbethoxy group in position 1 in compounds **5b**,**e**,**h** is oriented towards the benzo-annelated nucleus, thus the aromatic ring current inducing a deshielding effect on the CH_2 and CH_3 groups. On the contrary, in compounds **10a**–**d** we assume a solution preferred orientation of the carbethoxy group in position 5-N-CH_2- of the heterocycle away from the benzo-annelated nucleus and on the same side with the carbonyl group, the latter inducing a shielding effect on the CH_3 group.

Conclusion

We have demonstrated that 1,3-dipolar cycloaddition reactions of 1-benzyl-3-(alkoxycarbonylmethyl)benzimidazolium ylides with activated alkynes led to a mixture of pyrrolo[1,2-*a*]quinoxalin-4-ones and pyrrolo[1,2-*a*]benzimidazoles. Pyrrolo[1,2-*a*]quinoxalin-4-ones are always the major reaction product and the ratio of pyrrolo[1,2-*a*]quinoxalin-4-one to pyrrolo[1,2-*a*]benzimidazole depends on reaction conditions and reactant structures.

A selective one-pot three-component synthetic protocol providing easy access to a wide range of pyrrolo[1,2-*a*]quinoxalin-4-one derivatives starts from benzimidazole unsubstituted at the imidazole ring, alkyl bromoacetates and non-symmetrical electron-deficient alkynes in the molar ratio 1:2:1, in 1,2-epoxybutane, enabling thus the expansion of studies on the biological properties of these compounds.

Experimental

General. Melting points were measured on a Boëtius hot plate microscope and are uncorrected. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The high performance liquid chromatography (HPLC) analyses were performed with an Agilent Chromatograph 1200 Series at room temperature by isocratic elution of acrylonitrile on an Agilent Zorbax SB-C18 (250 × 4.6) column with a flow rate of 1.0 mL/min. The NMR spectra have been recorded on a Bruker Avance III 400 instrument operating at 400.1, 100.6 and 40.6 MHz for ^{1}H, ^{13}C, and ^{15}N nuclei respectively. Samples were transferred in 5 mm Wilmad 507 NMR tubes and recorded with either a 5 mm multinuclear inverse detection z-gradient probe (^{1}H spectra and all H,H/H,C/H,N 2D experiments) or with a 5 mm four nuclei direct detection z-gradient probe for ^{13}C spectra. Chemical shifts are reported in δ units (ppm) and were referenced to internal TMS for ^{1}H nuclei, to the internal deuterated solvent for ^{13}C nuclei ($CDCl_3$ referenced at 77.0 ppm), and referenced to liquid ammonia (0.0 ppm) using nitromethane (380.2 ppm) as external standard for ^{15}N nuclei. Unambiguous 1D NMR signal assignments were made based on 2D NMR homo- and heteronuclearcorrelations. H,H-COSY, H,H-NOESY, H,C-HSQC and H,C-HMBC experiments were recorded using standard pulse sequences in the version with z-gradients, as delivered by Bruker with TopSpin 2.1 PL6 spectrometer control and processing software. H,C-undecoupled-

HSQC experiments have been recorded using the pulse sequence described by S. Simova [21]. The ^{15}N chemical shifts were obtained as projections from the 2D indirectly detected H,N-HMBC spectra, employing a standard pulse sequence in the version with z-gradients as delivered by Bruker (TopSpin 2.1 PL6). Elemental analyses for C, H and N were obtained using a COSTECH Instruments EAS32. Satisfactory micro-analyses for all new compounds were obtained.

Benzimidazole, 5,6-dimethylbenzimidazole, activated acetylenic esters, 3-butyn-2-one and alkyl bromoacetates were purchased from Aldrich and used without further purification. 1-Benzylbenzimidazole, 1-benzyl-5,6-dimethylbenzimidazole and 1-ethyl-5,6-dimethylbenzimidazole were obtained from corresponding benzimidazoles and benzyl chloride, respectively ethyl bromide. 1-Benzylbenzimidazolium bromides (**6**) were obtained from 1-benzylbenzimidazole, respectively 1-benzyl-5,6-dimethylbenzimidazole, and alkyl bromoacetate in acetone, according previously reported methods [8]. Tetrapyridinecobalt(II) dichromate (TPCD) was obtained according the reported method [22].

General procedure for the reaction of 1-substituted benzimidazoles (1a–c) with ethyl bromoacetate (2) and non-symmetrical alkynes (3a–c) in 1,2-epoxybutane. A mixture of 1-substituted benzimidazole **1a–c** (2 mmol), ethyl bromoacetate **2** (2 mmol) and an alkyne **3a–c** (2 mmol) in 30 mL of 1,2-epoxybutane was heated at reflux temperature (approx. 62 °C) for 24 hours. The solvent was partly removed under vacuum, 3 mL of MeOH was added under a gentle stirring, and the mixture was left 2 hours in the refrigerator. The solid formed was filtered off and recrystallized from MeOH/Et_2O giving pyrrolo[1,2-*a*]quinoxalin-4-one **4a–g**. The filtrate was concentrated under vacuum and chromatographed on a SiO_2 packed column by eluting with EtOAc:hexane (1:4 v/v) giving pyrrolo[1,2-*a*]benzimidazole **5** and an additional quantity of pyrrolo[1,2-*a*]quinoxalin-4-one **4** (the order of elution: **4**<**5**).

Ethyl 4-oxo-5-benzylpyrrolo[1,2-*a*]quinoxalin-2-carboxylate (4b). 0.29 g (42%) pale yellow crystals. FTIR (ν_{max}, cm^{-1}): 3121, 2975, 1710, 1651, 1611, 1551, 1519, 1426, 1361, 1305, 1270, 1196, 1165, 1096, 1023; ^1H NMR ($CDCl_3$) δ 1.41 (3H, t, 7.2 Hz, CH_3), 4.38 (2H, quartet, 7.2 Hz, CH_2), 5.50 (2H, bs, CH_2), 7.19–7.33 (8H, m, aromatic rings), 7.68 (1H, d, 1.6 Hz, H-3), 7.72–7.73 (1H, m, H-9), 8.24 (1H, d, 1.6 Hz, H-1). The individual chemical shifts, multiplicities and coupling constants for the 7.19–7.33 multiplet were obtained from undecoupled HSQC as follows: 7.21 (1H, m, H-8), 7.236 (1H, t, 8.1 Hz, H-7), 7.239 (1H, d, 8.2 Hz, H-6), 7.25 (1H, t, 7.4 Hz, H-4'), 7.28 (2H, d, 7.2 Hz, H-2'), 7.31 (2H, t, 7.3 Hz, H-3') ppm; ^{13}C NMR ($CDCl_3$) δ 14.38 (CH_3), 45.12 (CH_2), 60.57 (OCH_2), 113.97 (C-3), 114.99 (C-9), 116.88 (C-6), 119.42 (C-1), 120.43 (C-2), 123.27 (C-8), 123.37 (C-9a), 123.59 (C-3a), 126.58 (C-2'), 126.78 (C-7), 127.45 (C-4'), 128.87 (C-3'), 129.97 (C-5a), 136.04 (C-1'), 155.48 (C-4), 163.77 (COO); ^{15}N NMR ($CDCl_3$) δ 136.4 (N-5), 173.5 (N-10) ppm; anal. calcd for $C_{21}H_{18}N_2O_3$ (346.38): C, 72.82; H, 5.24; N, 8.09%; found: C, 72.90; H, 5.31; N, 8.01%.

Diethyl 4-benzyl-4*H*-pyrrolo[1,2-*a*]benzimidazole-1,3-dicarboxylate (5b). 0.1 g (13%) pale yellow crystals. FTIR (ν_{max}, cm^{-1}): 1700, 1685, 1580, 1514, 1479, 1453, 1400, 1303, 1290, 1233, 1181, 1136, 1106, 1070; ^1H NMR ($CDCl_3$) δ 1.37 (3H, t, 7.2 Hz, CH_3-3), 1.48 (3H, t, 7.2 Hz, CH_3-1), 4.32 (2H, quartet, 7.2 Hz, CH_2-3), 4.45 (2H, quartet, 7.2 Hz, CH_2-1), 6.13 (2H, bs, CH_2), 7.25–7.32 (8H, m, aromatic rings), 7.78 (1H, s, H-2), 8.88 (1H, d, 8.2 Hz, H-8). The individual chemical shifts, multiplicities and coupling constants for the 7.25–7.32 multiplet were obtained from undecoupled HSQC as follows: 7.240 (2H, d, 7.5 Hz, H-2'), 7.248 (1H, t, 7.3 Hz, H-4'), 7.25 (1H, d, 8.2 Hz, H-5), 7.26 (1H, t, 8 Hz, H-7), 7.29 (2H, t, 7.4 Hz, H-3'), 7.30 (1H, t, 8 Hz, H-6) ppm; ^{13}C NMR ($CDCl_3$) δ 14.47 (CH_3-3), 14.59 (CH_3-1), 48.48 (CH_2), 59.93 (CH_2-3), 60.24 (CH_2-1), 91.75 (C-3), 110.20 (C-5), 112.32 (C-1), 116.23 (C-8), 121.37 (C-7), 124.14 (C-6), 125.20 (C-2), 126.79 (C-2'), 127.07 (C-8a), 127.57 (C-4'), 128.73 (C-3'), 136.25 (C-4a), 136.91 (C-1'), 143.08 (C-3a), 160.68 (COO-1), 163.63 (COO-3) ppm; ^{15}N NMR ($CDCl_3$) δ 116.9 (N-4), 172.1 (N-9) ppm; anal. calcd. for $C_{23}H_{22}N_2O_4$ (390.43): C, 70.75; H, 5.68; N, 7.17%; found: C, 70.67; H, 5.61; N, 7.23%.

General procedure for the reaction of 1-benzylbenzimidazolium bromides (6) with DMAD (3d) in 1,2-epoxybutane. A mixture of a 1-benzylbenzimidazolium bromide **6** (2 mmol) and DMAD **3d** (2 mmol) in 30 mL of 1,2-epoxybutane was heated at reflux temperature for 24 hours. The solvent was removed under vacuum, and the residue was chromatographed on a SiO_2 packed column by eluting with EtOAc:hexane (1:4 v/v) giving pyrrolo[1,2-*a*]quinoxalin-4-ones **4h,i** and the pyrrolo[1,2-*a*]benzimidazole **5h** (the order of elution: **4**<**5**).

Dimethyl 4-oxo-5-benzylpyrrolo[1,2-*a*]quinoxalin-2,3-dicarboxylate (4h). 0.33 g (42%) white crystals. FTIR (ν_{max}, cm^{-1}): 1748, 1710, 1663, 1523, 1412, 1370, 1270, 1246, 1198, 1153, 1074; ^1H NMR ($CDCl_3$) δ 3.90 (3H, s, CH_3-2), 4.05 (3H, s, CH_3-3), 5.47 (2H, bs, CH_2), 7.22–7.33 (8H, m, aromatic rings), 7.72–7.74 (1H, m, H-9), 8.19 (1H, s, H-1). The individual chemical shifts, multiplicities and coupling constants for the 7.22–7.33 multiplet were obtained from undecoupled HSQC as follows: 7.24 (1H, t, 7.7 Hz, H-8), 7.25 (1H, t, 7.2 Hz, H-4'), 7.254 (1H, d, 8.7 Hz, H-6), 7.26 (2H, d, 7.9 Hz, H-2'), 7.28 (1H, t, 7.9 Hz, H-7), 7.31 (2H, t, 7.72 Hz, H-3'); ^{13}C NMR

($CDCl_3$) δ 45.20 (CH_2), 52.10 (CH_3-2), 53.12 (CH_3-3), 115.18 (C-9), 117.07 (C-6), 117.85 (C-2), 118.81 (C-1), 120.80 (C-3a), 121.21 (C-3), 122.66 (C-9a), 123.58 (C-8), 126.58 (C-2'), 127.46 (C-7), 127.55 (C-4'), 128.91 (C-3'), 129.92 (C-5a), 135.57 (C-1'), 154.43 (C-4), 162.84 (COO-2), 165.42 (COO-3) ppm; ^{15}N NMR ($CDCl_3$) δ 137.6 (N-5), 172.0 (N-10) ppm; anal. calcd for $C_{22}H_{18}N_2O_5$ (390.39): C, 67.68; H, 4.65; N, 7.18%; found: C, 67.75; H, 4.68; N, 7.12%.

Dimethyl 1-carbethoxy-4-benzyl-4*H*-pyrrolo[1,2-*a*]benzimidazole-2,3-dicarboxylate (5h). 0.14 g (16%) pale yellow crystals. FTIR (ν_{max}, cm^{-1}): 2997, 2951, 1745, 1710, 1687, 1663, 1572, 1522, 1456, 1408, 1369, 1269, 1216, 1177, 1140, 1066, 1074. ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, 7.2 Hz, CH_3-Et), 3.81 (3H, s, CH_3-3), 4.01 (3H, s, CH_3-2), 4.43 (2H, quartet, 7.2 Hz, CH_2-Et), 6.08 (2H, bs, CH_2), 7.22–7.38 (8H, m, aromatic rings), 8.86 (1H, d, 8.0 Hz, H-8). The individual chemical shifts, multiplicities and coupling constants for the 7.22–7.38 multiplet were obtained from undecoupled HSQC as follows: 7.22 (2H, d, 7.6 Hz, H-2'), 7.27 (1H, t, 7.5 Hz, H-4'), 7.29 (1H, d, 8.3 Hz, H-5), 7.30 (1H, t, 8.1 Hz, H-7), 7.31 (2H, t, 7.6 Hz, H-3'), 7.35 (1H, t, 8 Hz, H-6) ppm; ^{13}C NMR ($CDCl_3$) δ 14.21 (CH_3-Et), 48.51 (CH_2), 51.58 (CH_3-3), 52.58 (CH_3-2), 60.88 (CH_2-Et), 89.98 (C-3), 109.71 (C-1), 110.29 (C-5), 116.62 (C-8), 121.75 (C-7), 124.79 (C-6), 126.58 (C-2'), 126.63 (C-8a), 127.66 (C-4'), 128.78 (C-3'), 130.49 (C-2), 136.41 (C-4a), 136.57 (C-1), 141.86 (C-3a), 159.58 (COO-Et), 162.76 (COO-3), 166.10 (COO-2) ppm; ^{15}N NMR ($CDCl_3$) δ 116.1 (N-4), 168.7 (N-9) ppm; anal. calcd for $C_{24}H_{22}N_2O_6$ (434.44): C, 66.35; H, 5.10; N, 6.45%; found: C, 66.31; H, 5.14; N, 6.39%.

General synthetic procedure for pyrrolo[1,2-*a*]quinoxalin-4-ones 10a–f. A mixture of a benzimidazole **9** (2 mmol), alkyl bromoacetate **2** (4 mmol) and a non-symmetrical alkyne **3** (2 mmol) in 30 mL of 1,2-epoxybutane was heated at reflux temperature for 30 hours. The solvent was partly removed under vacuum, 3 mL of MeOH was added under a gentle stirring, and the mixture was left over night in a refrigerator. The formed solid was filtered off and recrystallized from MeOH giving pyrrolo[1,2-*a*]quinoxalin-4-one **10a–f**.

Ethyl 2-(2-acetyl-4-oxo-pyrrolo[1,2-*a*]quinoxalin-5-yl) acetate (10a). 0.235 g (38%) beige crystals, mp 193–194 °C. FTIR (ν_{max}, cm^{-1}): 3109, 2984, 1746, 1656, 1617, 1549, 1516, 1420, 1383, 1357, 1277, 1206; ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, t, 7.2 Hz, CH_3-Et), 2.56 (3H, s, CH_3), 4.25 (2H, quartet, 7.2 Hz, CH_2-Et), 5.04 (2H, s, CH_2), 7.08 (1H, d, 8.3 Hz, H-6), 7.28 (1H, t, 7.2 Hz, H-8), 7.36 (1H, t, 7.3 Hz, H-7), 7.59 (1H, d, 1.5 Hz, H-3), 7.75 (1H, d, 8.1 Hz, H-9), 8.21 (1H, d, 1.5 Hz, H-1) ppm; ^{13}C NMR ($CDCl_3$) δ 14.13 (CH_3-Et), 27.66 (CH_3), 42.83 (CH_2), 61.93 (CH_2-Et), 113.52 (C-3), 115.39 (C-9), 115.45 (C-6), 118.55 (C-1), 123.19 (C-9a), 123.50 (C-3a), 123.69 (C-8), 127.18 (C-7), 128.48 (C-2), 129.94 (C-5a), 155.07 (C-4), 167.89 (COO), 193.65 (CO)ppm; ^{15}N NMR ($CDCl_3$) δ 129.9 (N-5), 175.3 (N-10) ppm; anal. calcd for $C_{17}H_{16}N_2O_4$ (312.32): C, 65.37; H, 5.16; N, 8.97%; found: C, 65.48; H, 5.20; N, 8.88%.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, ^{1}H, ^{13}C and ^{15}N NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-248-S1.pdf]

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One-pot four-component reaction for convenient synthesis of functionalized 1-benzamidospiro[indoline-3,4'-pyridines]

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Full Research Paper

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Abstract

The one-pot four-component reaction of benzohydrazide (2-picolinohydrazide), acetylenedicarboxylate, isatins and malononitrile (ethyl cyanoacetate) with triethylamine as base catalyst afforded functionalized 1-benzamidospiro[indoline-3,4'-pyridines] in good yields. ^{1}H NMR spectra indicated that an equilibrium of *cis/trans*-conformations exist in the obtained products.

Introduction

The spirooxindole system is the core structure of many natural products and pharmaceutically important structures with notable structural complexity and biological activities of great interest [1-4]. Accordingly, many efficient and practical synthetic procedures have emerged for the synthesis of versatile spirooxindole-fused heterocycles [5-9]. In recent years, because of the emphasis on the development of green and sustainable chemistry, multicomponent reactions have been developed as efficient and potent tools for the preparation of structurally diverse molecules. Practically, multicomponent reactions based on the versatile reactivity of isatins and their 3-methylene derivatives have emerged in large numbers and become the new efficient protocols for the synthesis of various spirooxindoles [10-13].

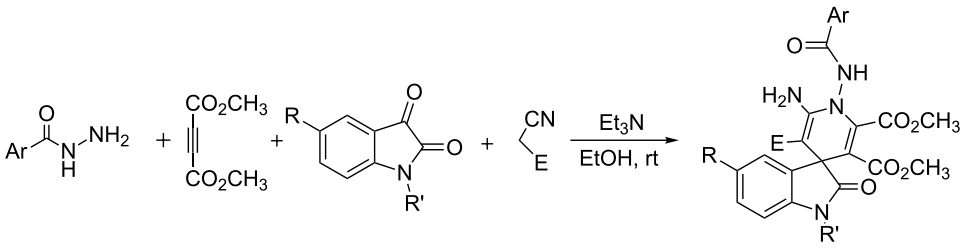
On the other hand, the chemistry of Huisgen's 1,4-dipoles, which are simply produced from the addition of nitrogen-containing nucleophiles to electron-deficient alkynes has aroused a lot of interest in organic synthesis due to its convenient formation and versatile reactivity [14,15]. The in situ formed Huisgen's 1,4-dipoles were subsequently entrapped by various electrophiles and other reagents to finish a number of carbon–carbon bond formation reactions and heterocyclic construction processes [16-18]. A literature survey indicated that the common nitrogen-containing nucleophiles for generation of Huisgen's 1,4-dipoles are aromatic heterocycles such as *N*-alkylimidazole, pyridine, quinoline, isoquinoline and primary aromatic amines. In recent years, other nitrogen-containing nucleophiles such as hydrazine and arylhydrazines are also used to generate Huisgen's 1,4-dipoles in domino reactions [19-21]. Recently, we and Perumal have demonstrated that the four-component reaction of arylamine, acetylenedicarboxylate, isatin and malononitrile can afford the spiro[indoline-3,4'-pyridine]

derivatives in satisfactory yields [22-24]. We envisioned that functionalized spiro[indoline-3,4'-pyridine] derivatives can be synthesized by employing other nitrogen-containing nucleophiles such as hydrazine and imines in the similar four-component reactions. In fact, the four-component reaction of hydrazine, acetylenedicarboxylate, isatin and malononitrile for the formation of spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles] have been developed very recently by several groups [25-27]. Against this background and in continuation of our efforts toward the development of practical multicomponent reactions based on the reactivity of isatin and its derivatives [28-34], we herein wish to report the efficient synthesis of functionalized 1-benzamidospiro[indoline-3,4'-pyridines] via one-pot four-component reactions of benzohydrazide, acetylenedicarboxylate, isatin and malononitrile.

Results and Discussion

According to the reaction conditions of the previously reported four-component reaction for the efficient synthesis of the functionalized spiro[indoline-3,4'-pyridine] derivatives [23] a mixture of benzohydrazide and dimethyl acetylenedicarboxylate in ethanol was firstly stirred at room temperature for about fifteen minutes. Then isatin and malononitrile as well as triethylamine as the base catalyst were introduced into reaction system. The subsequent reaction proceeded very smoothly at room temperature to give the 1'-benzamidospiro[indoline-3,4'-pyridines] **1a–d** in satisfactory yields (Table 1, entries 1–4). It is known that hydrazine reacts firstly with acetylenedicarboxylate to give the pyrazolone intermediate in the previously reported multicomponent reactions containing hydrazine and acetylenedicarboxylate [25-27]. Here, due to the protection of the benzoyl group, only the free amino group in benzohydrazide took part in the reaction to give the 1'-benzamido-substituted spiro[indoline-3,4'-pyridine]. It should be noted that pure products can be obtained by washing the formed precipitates from the reaction solution and no further purification process is needed. The similar reactions with ethyl cyanoacetate also produced the spiro compounds **1e–i** in 68–74% (Table 1, entries 5–9). The substituents on the isatins showed little effect on the yields. Further, 2-picolinohydrazide can also be utilized in the four-component reactions to give the corresponding 1'-picolinamidospiro[indoline-3,4'-pyridines] **1j–m** in satisfactory yields (Table 1, entries 10–13). These results indicate that this four-component reaction may have a widely variety of substrates.

Table 1: Synthesis of spiro[indoline-3,4'-pyridines] **1a–m** via four-component reaction.[a]



1a–m

Entry	Compd	Ar	R	R'	E	Yield (%, *cis/trans*)[b]
1	**1a**	C_6H_5	H	$CH_2C_6H_4$	CN	72 (4:1)
2	**1b**	C_6H_5	F	$CH_2C_6H_4$	CN	84 (6.5:1)
3	**1c**	*p*-$CH_3C_6H_4$	H	H	CN	78
4	**1d**	*p*-$CH_3C_6H_4$	F	$CH_2C_6H_4$	CN	65 (6.5:1)
5	**1e**	C_6H_5	H	H	CO_2Et	74 (5:1)
6	**1f**	C_6H_5	Cl	H	CO_2Et	70 (5:1)
7	**1g**	C_6H_5	Cl	$CH_2C_6H_4$	CO_2Et	68 (6:1)
8	**1h**	*p*-$CH_3C_6H_4$	Cl	H	CO_2Et	69 (5:1)
9	**1i**	*p*-$CH_3C_6H_4$	Cl	$CH_2C_6H_4$	CO_2Et	70 (6.5:1)
10	**1j**	2-C_5H_4N	CH_3	H	CO_2Et	80 (5:1)
11	**1k**	2-C_5H_4N	Cl	H	CO_2Et	82 (4:1)
12	**1l**	2-C_5H_4N	Cl	$CH_2C_6H_4$	CO_2Et	68 (5:1)
13	**1m**	2-C_5H_4N	CH_3	$CH_2C_6H_4$	CO_2Et	81 (3:1)

[a]Reaction conditions: arylhydrazide (1.0 mmol), acetylenedicarboxylate (1.0 mmol) in EtOH (15.0 mL), rt, 15 min; isatin (1.0 mmol), malononitrile or ethyl cyanoacetate (1.0 mmol), Et_3N (0.2 mmol), rt, 24 h; [b]Isolated yield.

The structures of the prepared spiro[indoline-3,4'-pyridines] **1a–m** were fully characterized with IR, ^{1}H, ^{13}C NMR, HRMS spectra and were further confirmed by single-crystal X-ray diffraction determination of the compound **1k** (Figure 1). The ^{1}H NMR spectra of compounds **1a–m** usually showed that two diastereoisomers with a ratio in range of 3:1 to 6.5:1 exist in the obtained products. But there is only one diastereoisomer in the product **1c** according to its ^{1}H NMR spectrum. For an example, in the ^{1}H NMR spectrum of compound **1a**, the amido group displays two singlets with a ratio of 4:1 at 11.46 and 11.38 ppm. The two singlets at 3.65 and 3.25 ppm are the signals of the two methoxy groups in the major isomer and the two singlets at 3.60 and 3.17 ppm are characteristic for the two methoxy groups in the minor isomer. From the molecular structure of spiro compound **1k** (Figure 1), it can be seen that the four carbon atoms and the nitrogen atom in the newly formed 1,4-dihydropyridyl ring exist nearly in one plane, while the C-4' atom slightly deviates in this plane (0.318(4) Å). The phenyl group of the oxindole moiety and the 1'-picolinamido group exist in the same side of the 1,4-dihydropyridyl plane. By observing the crystal structure of spiro compound **1k**, we could conclude that the 1'-picolinamido group might exist in *cis*- or *trans*-position of the phenyl group of the oxindole moiety. Thus, the *cis/trans*-conformations are in a dynamic equilibrium by inversion of the 1'-benzamido group (Scheme 1). The *cis*-conformation cannot be easily converted to the *trans*-conformation because the neighboring amino and methoxycarbonyl groups exhibit some steric hindrance for the inversion of the 1'-benzamido group. The ^{1}H NMR spectra clearly indicated the existence of *cis/trans*-conformations.

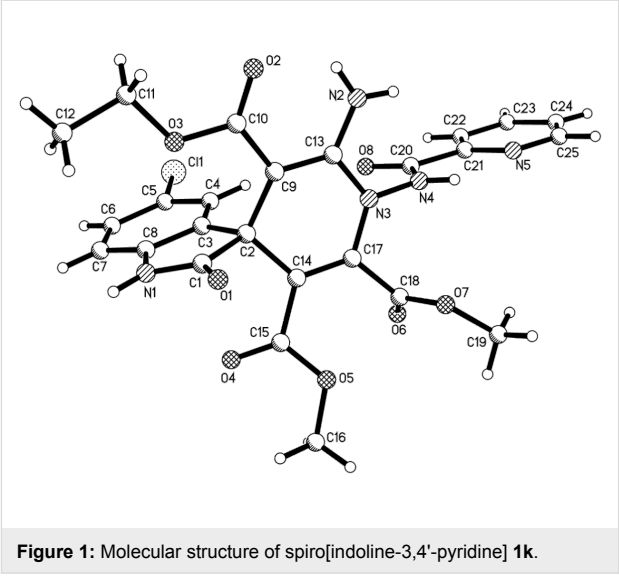
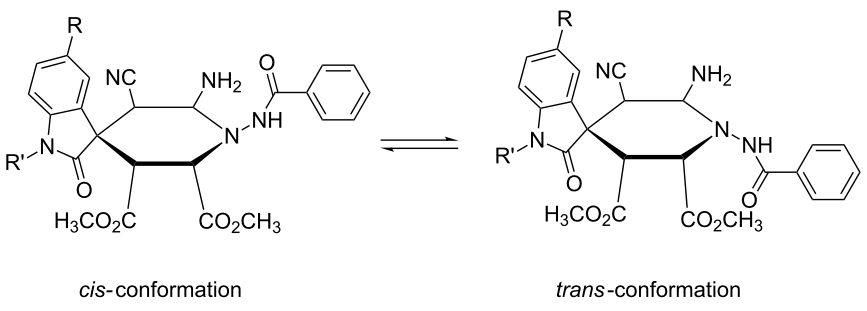


Figure 1: Molecular structure of spiro[indoline-3,4'-pyridine] **1k**.

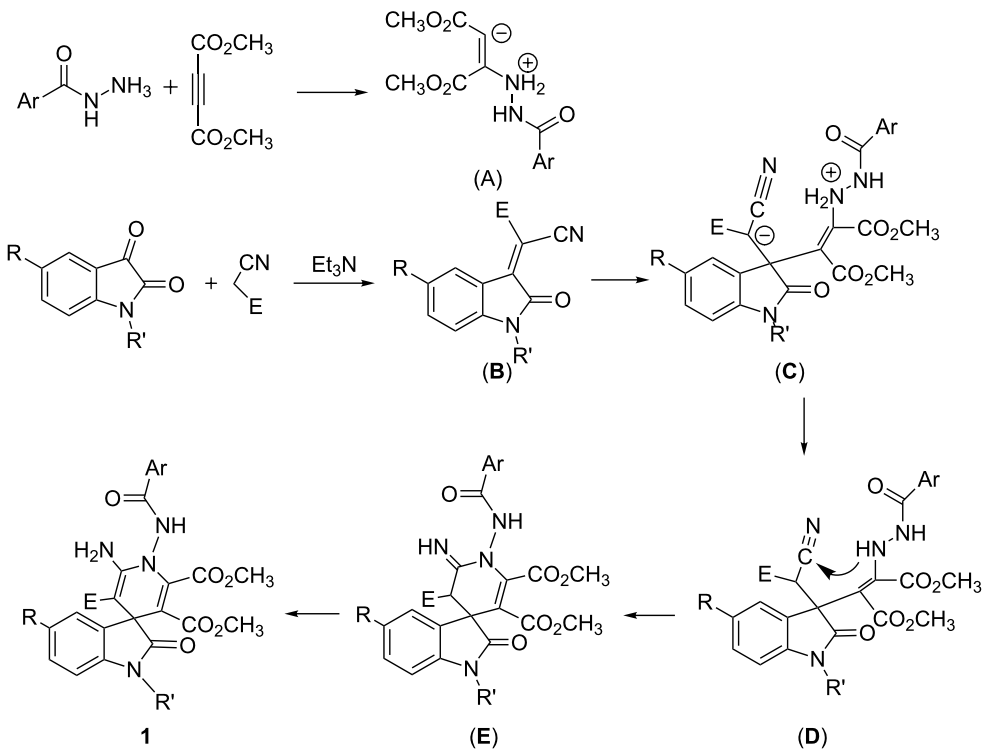
In order to explain the formation of the spiro[indoline-3,4'-pyridines], a rational reaction mechanism is briefly proposed on the basis of similar reactions of Huigen's 1,4-dipoles [22-24] (Scheme 2). Firstly, the addition of benzohydrazide to acetylenedicarboxylate results in an active zwitterionic intermediate (**A**). In the meantime, the condensation of isatin with malononitrile or ethyl cyanoacetate in the presence of triethylamine affords isatylidenemalononitrile or its derivative (**B**). Then the nucleophilic addition of the zwitterionic intermediate (**A**) to isatylidenemalononitrile (**B**) produces the adduct (**C**), which in turn transferres to intermediate (**D**) by immigration of a proton from the nitrogen atom to the carbon atom. Thirdly, the intramolecular reaction of the amino group with the cyano group gives a cyclized intermediate (**E**). Finally, the imino–enamino tautomerization results in the final spiro compound **1**. In this process, the initially formed zwitterrionic intermediate (**A**) does not cyclize to give pyrazolone intermediate as in the reaction of hydrazine with acetylenedicarboxylate. Thus, benzohydrazide shows very different reactivity to that of hydrazine in the four-component reaction.

Conclusion

In summary, we have investigated the four-component reactions of benzohydrazide, acetylenedicarboxylate, isatins and malononitrile or ethyl cyanoacetate and successfully developed



Scheme 1: The dynamic equilibrium of *cis/trans*-conformation of spiro[indoline-3,4'-pyridine].



Scheme 2: Proposed reaction mechanism for the four-component reaction.

an efficient synthetic procedure for the preparation of functionalized 1-benzamidospiro[indoline-3,4'-pyridines]. Furthermore, the reaction mechanism and the dynamic equilibrium of *cis/trans*-conformations were also briefly discussed. This reaction provided new examples for the development of potential applications of Huisgen's 1,4-dipoles in synthetic chemistry.

Experimental

Reagents and apparatus: All reactions were monitored by TLC. Melting points were taken on a hot-plate microscope apparatus. IR spectra were obtained on a Bruker Tensor 27 spectrometer (KBr disc). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV-600 spectrometer with DMSO-d_6 as solvent and TMS as internal standard (600 and 150 MHz for ^{1}H and ^{13}C NMR spectra, respectively). HPLC/MS were measured at Bruker MicroTOF spectrometer. Single-crystal structure was determined on Bruker Smart-2 CCD diffractometer.

General procedure for the synthesis of 1,4-dihydropyridines 1a–m via four-component reactions: In a round bottom flask, a solution of benzohydrazide or 2-picolinohydrazide (1.0 mmol) and dimethyl acetylenedicarboxylate (1.0 mmol) in ethanol (15.0 mL) was stirred at room temperature for about fifteen minutes. Then, isatin (1.0 mmol), malononitrile or ethyl cyanoacetate (1.0 mmol) and triethylamine (0.2 mmol) was added. The mixture was stirred at room temperature for 24 hours. The resulting precipitates were collected by filtration and washed with cold alcohol to give the pure product for analysis.

Dimethyl 2'-amino-1'-benzamido-1-benzyl-3'-cyano-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-5',6'-dicarboxylate (1a): white solid, 72%; mp 222–224 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ *cis*-isomer: 11.46 (s, 1H, NH), 7.90–7.89 (m, 2H, ArH), 7.65–7.62 (m, 2H, ArH), 7.55 (brs, 2H, ArH), 7.50 (brs, 2H, ArH), 7.34 (brs, 2H, ArH), 7.29–7.28 (m, 1H, ArH), 7.21 (brs, 1H, ArH), 7.10 (d, J = 7.2 Hz, 1H, ArH), 6.82 (d, J = 7.2 Hz, 1H, ArH), 6.72 (brs, 2H, NH_2), 4.98 (d, J = 15.0 Hz, 1H, CH_2), 4.82 (d, J = 15.0Hz, 1H, CH_2), 3.65 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3); *trans*-isomer: 11.38 (s, 1H, NH), 7.85–7.84 (m, 2H, ArH), 6.79 (brs, 2H, NH_2), 3.60 (s, 3H, OCH_3), 3.17 (s, 3H, OCH_3); *cis/trans*-isomers: 4:1; ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.3, 166.8, 163.6, 161.9, 152.1, 145.2, 141.3, 136.2, 135.2, 132.6, 131.1, 129.5, 128.6, 128.5, 128.4, 127.9, 127.6, 127.3, 124.1, 123.5, 122.8, 118.5, 108.8, 58.4, 52.9, 51.9, 49.4, 43.5; IR (KBr) υ: 3456, 2952, 2186, 1708, 1654, 1613, 1575, 1482, 1432, 1302, 1224, 1183, 1133, 1091, 1029, 936, 754, 697 cm^{-1}; HRMS (ESI) (m/z): $[M + Na]^+$ calcd. for $C_{31}H_{25}N_5NaO_6$: 586.1697; found: 586.1703.

Supporting Information

Experimental details and detailed spectroscopic data of all new compounds are available as Supporting Information. Single crystal data for compounds **1k** (CCDC 1000773) has been deposited in the Cambridge Crystallographic Data Center.

Supporting Information File 1

Experimental details and spectroscopic data of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-281-S1.pdf]

Acknowledgements

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

The unexpected influence of aryl substituents in *N*-aryl-3-oxobutanamides on the behavior of their multicomponent reactions with 5-amino-3-methylisoxazole and salicylaldehyde

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Abstract

The switchable three-component reactions of 5-amino-3-methylisoxazole, salicylaldehyde and *N*-aryl-3-oxobutanamides under different conditions were studied and discussed. The unexpected influence of the aryl substituent in *N*-aryl-3-oxobutanamides on the behavior of the reaction was discovered. The key influence of ultrasonication and Lewis acid catalysts led to an established protocol to selectively obtain two or three types of heterocyclic scaffolds depending on the substituent in the *N*-aryl moiety.

Introduction

Generally, considerable interest in heterocyclic compounds is due to their key role in biological processes in nature and biological activity. In particular, condensed heterocycles bearing a hydroxyaryl group as well as tricyclic nitrogen-containing heterocycles derived from salicylaldehyde have been reported as anticancer [1], antihypertensive agents [2], neuropeptide Y antagonists [3], and calcium channel blockers [4]. Fused azoloazines containing carboxamide substituents also exhibit a broad spectrum of biological activity [5,6], which led to choose acetoacetamides as perspective methylene-active compounds for further studies of multicomponent reactions.

The interactions of 3-oxobutanamides with aldehydes and a number of aminoazoles, namely 3-amino-1,2,4-triazoles [7-11],

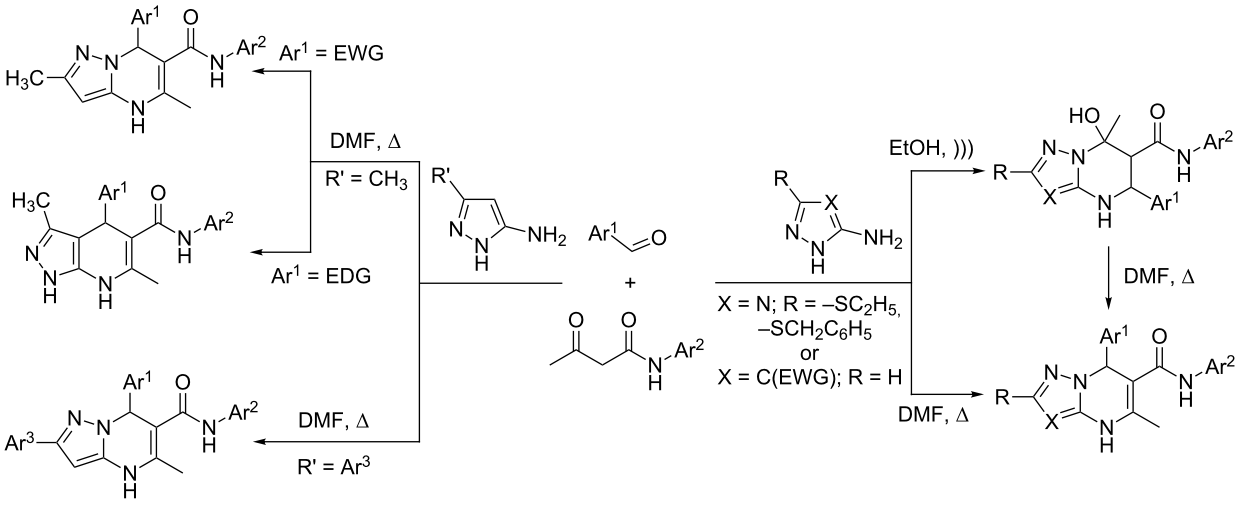
5-aminotetrazole [9], 5-aminopyrazoles [11], and 5-amino-1,2,3-triazole [12] have previously been investigated. In some cases when the reaction could proceed in two alternative pathways the conditions enabling to control the interaction direction were determined, which made it possible to obtain the desired azoloazine with high chemo- and regioselectivity [11,13-15]. In particular, three-component heterocyclizations involving 3-amino-1,2,4-triazoles or 4-substituted 5-aminopyrazoles yielded either 4,5,6,7-tetrahydroazolo[1,5-*a*]pyrimidine-6-carboxamides under ultrasonication at room temperature (kinetic control) or 4,7-dihydroazolo[1,5-*a*]pyrimidine-6-carboxamides at reflux in an applicable solvent (thermodynamic control), respectively (Scheme 1). The behavior of the reaction of 5-aminopyrazoles containing substituents in the position 3 is influenced by the structure of aminoazoles and aldehydes, giving rise either to pyrazolopyridine or pyrazolopyrimidine heterocycles. In the authors' opinion, the different outcomes in three-component reactions involving 3-methyl- or 3-aryl-substituted 5-aminopyrazoles can mainly be put down to the steric substituent effect [11].

It is noteworthy to mention that studies on multicomponent heterocyclizations involving different N-containing polynucleophiles and salicylaldehyde are of particular interest due to the bifunctional reactivity of the latter component. The presence of both electrophilic and nucleophilic reaction centers in salicylaldehyde enables condensations to proceed in various possible directions. The direction control would open pathways for selectively obtaining different classes of heterocyclic compounds [16-20]. Simultaneously, the selectivity will inevitably be dictated by the variation of the reaction conditions [17,18].

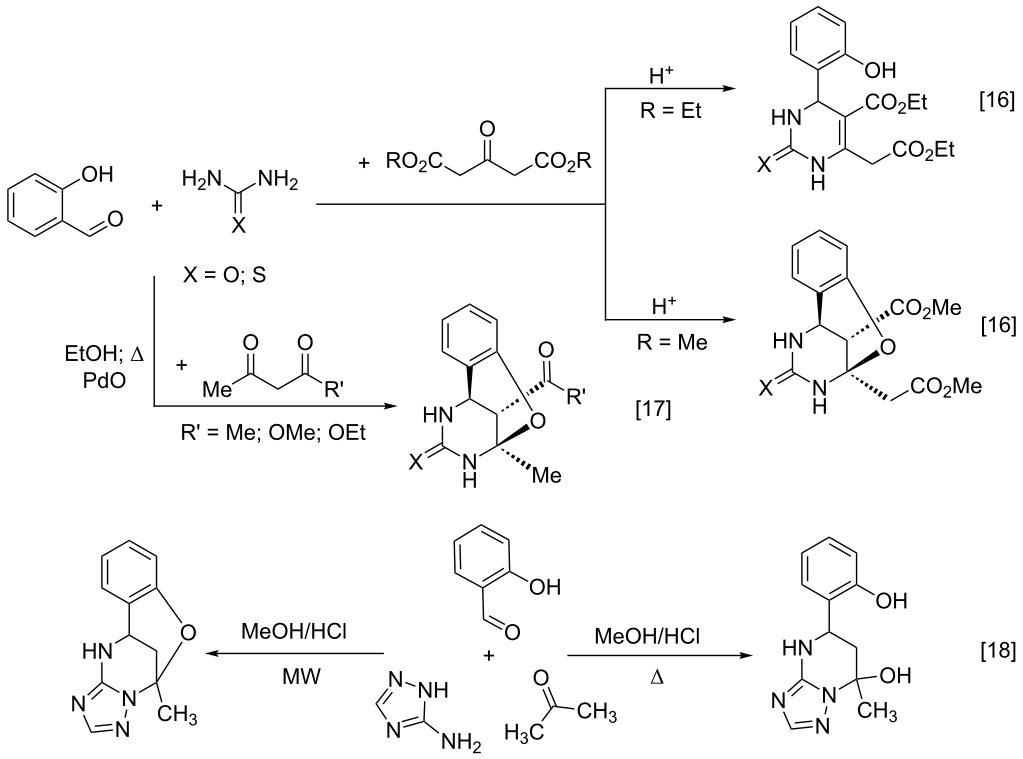
Thus, Světlik et al. studied the Biginelli-type condensation of 2-hydroxybenzaldehyde with urea (thiourea) and dialkyl acetone-1,3-dicarboxylates as active methylene components [16]. Unexpectedly, the reaction with salicylaldehyde furnished two different products depending on the ester alkyl group (Scheme 2). Obtaining of two classes of compounds was found to originate from steric influence rendered by the alkyl moiety of the ester group in the active methylene species. Inspired by Světlik's studies, Jing et al. [17] developed an efficient method for the synthesis of oxygen-bridged pyrimidine tricyclic derivatives from salicylaldehyde, various dicarbonyl compounds, and urea (thiourea) using PdO as a catalyst (Scheme 2).

Heterocyclizations involving both, salicylaldehyde and aminoazoles, are intriguing as well. Thus, for example in the course of the study on the application of 3-amino-1,2,4-triazole and salicylaldehydes in a Biginelli-like three-component condensation, two alternative outcomes were observed by Gorobets et al. [18]. When the condensation with acetone was performed in methanol with catalytic amounts of HCl under reflux conditions, a tetrahydrotriazolo[1,5-*a*]pyrimidine derivative was obtained, while under microwave irradiation the substituted oxygen-bridged triazolo[1,5-*c*][1,3,5]benzoxadiazocine was formed (Scheme 2).

Interesting results were also described by Světlik and Kettmann [19]. In the case of a three-component interaction of aminoazole, salicylaldehyde, and methyl acetoacetate in refluxing ethanol in the presence of hydrochloric acid, instead of oxygen-bridged compounds oxadiazaspiranes were isolated. On the other hand, Umarov and coworkers [20] have synthesized by



Scheme 1: Some three-component reactions involving *N*-aryl-3-oxobutanamides.



Scheme 2: Some Biginelli-type three-component condensations with salicylaldehyde.

condensation of 5-ethyl-1,3,4-thiadiazol-2-amine, salicylaldehyde, and pentane-2,4-dione in refluxing ethanol a representative of another heterocyclic class, namely thiadiazolylaminochromane.

Here we disclose our recent findings of three-component heterocyclizations involving 5-amino-3-methylisoxazole, salicylaldehyde and *N*-aryl-3-oxobutanamides that were found to differ from similar reactions of cyclic CH acids [13].

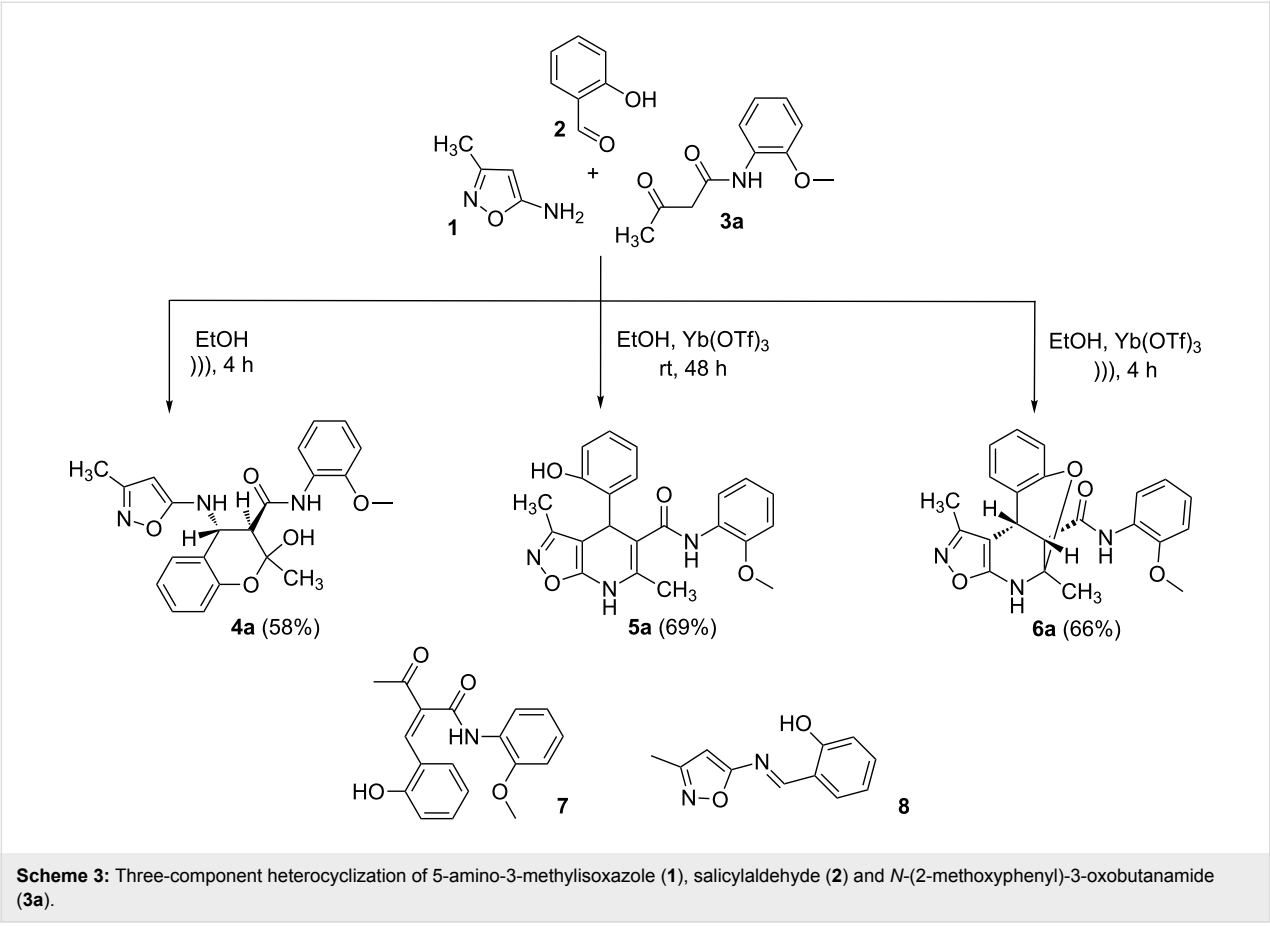
Results and Discussion

The three-component heterocyclization of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-(2-methoxyphenyl)-3-oxobutanamide (**3a**) was chosen as a model reaction which was studied by variation of the reaction conditions. First, at room temperature under mechanical stirring for 48 h the reaction proceeded to form mainly two compounds – Knoevenagel adduct **7** and Schiff base **8** (Scheme 3). Trace amounts of 2-hydroxy-*N*-(2-methoxyphenyl)-2-methyl-4-(3-methylisoxazol-5-ylamino)chroman-3-carboxamide (**4a**) were detected in the reaction mixture as well.

Furthermore, both conventional and microwave heating did not produce any positive results. Thus, refluxing of the reactants in water, ethanol, dioxane, or application of microwave irradiation at temperatures up to 140 °C only gave rise to the formation of imine **8** (Scheme 3). The reaction time in these cases reached 3 h. On the other hand, refluxing in high boiling solvents (*n*-butanol, DMF, DMSO), as well as microwave irradiation at temperatures above 140 °C, resulted in resinification of the reaction mixture. The reaction times were varied from a minute (for microwave irradiation) to 40 min (for conventional heating).

Inter alia, ultrasonic activation was applied to promote this multicomponent reaction. It was established that the three-component cyclocondensation of the starting compounds under ultrasonication at room temperature for 4 h led to the selective formation of the substituted chroman-3-carboxamide **4a** in 58% yield (Scheme 3). In contrast to the similar reaction involving derivatives of 1,3-cyclohexanedione [13], here the final product was formed with participation of the exocyclic NH_2-group of aminoisoxazole but not with its 4-CH center that may be linked via different mechanisms (see below).

Next the effect of different catalysts on the reaction was studied. It should be noted that in the case of catalytic processes both conventional and microwave heating were also inefficacious. The only noteworthy result was the detection of trace amounts of 4-(2-hydroxyphenyl)-*N*-(2-methoxyphenyl)-3,6-



Scheme 3: Three-component heterocyclization of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-(2-methoxyphenyl)-3-oxobutanamide (**3a**).

dimethyl-4,7-dihydroisoxazolo[5,4-*b*]pyridine-5-carboxamide (**5a**) (Scheme 3) in the reaction mixture when the reaction was performed in *n*-butanol under conventional heating for 25 min using ytterbium or scandium triflate as the catalysts.

Then, it was established that the three-component heterocyclization of aminoisoxazole **1**, salicylaldehyde (**2**) and acetoacetamide **3a** in the presence of 5 mol % ytterbium triflate as a catalyst in ethanol under stirring at room temperature for 48 h led to the formation of the aforementioned dihydroisoxazolopyridine **5a** in 69% yield.

To our surprise the analogous catalytic reaction in ethyl alcohol under ultrasonication at room temperature for 4 h gave exclusively *N*-(2-methoxyphenyl)-1,5-dimethyl-5,11-dihydro-4*H*-5,11-methanobenzo[*g*]isoxazolo[5,4-*d*][1,3]oxazocine-12-carboxamide (**6a**) in 66% yield (Scheme 3), while the absence of the isomeric heterocyclic compound **5a** was proven by means of TLC and NMR spectroscopy. In all cases of three-component reactions involving aminoazoles and carbonyl compounds, which were previously studied in our group [13,18,21-24], the substitution of mechanical stirring by ultrasonication did not change the structure of the final products but only affected the purity and yields of the final compounds as well as the reaction rate.

Several Lewis and Brønsted acids have been scanned as catalysts for this reaction. The results of the catalyst system selection for this reaction under stirring at room temperature are summarized in Table 1 and Table 2. Ytterbium triflate (5 mol %) was identified as the catalyst of choice.

The next step of our study was to expand the range of *N*-aryl-3-oxobutanamides. First, it is worth mentioning that the three-component cyclocondensation of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-aryl-3-oxobutanamides **3a**–**h** under ultrasonication at room temperature for 4 h without catalyst always led to the selective formation of the corresponding chroman-3-carboxamides **4a**–**h** (Table 3, entries 1, 4, 7, 10, 13, 16, 19, 22).

However, to our surprise, the ytterbium triflate-catalyzed three-component reaction of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-phenyl-3-oxobutanamide (**3b**) gave rise to the formation of 4-(2-hydroxyphenyl)-3,6-dimethyl-*N*-phenyl-4,7-dihydroisoxazolo[5,4-*b*]pyridine-5-carboxamide (**5b**) both

Table 1: Optimization of the reaction conditions for obtaining compound **5a**.

Catalyst	Catalyst amount (% of the stoichiometric)	Product yield (%)
$Sc(OTf)_3$	2	33
$Sc(OTf)_3$	5	58
$Sc(OTf)_3$	10	54
$Sc(OTf)_3$	15	47
$Yb(OTf)_3$	2	30
$Yb(OTf)_3$	**5**	**69**
$Yb(OTf)_3$	10	64
$Yb(OTf)_3$	15	52
$Al(O\text{-}iPr)_3$	10	15
$Al(O\text{-}iPr)_3$	20	18
HCl	5	no product (mixture resinification)
p-TsOH	2	no product (mixture resinification)

Table 2: Optimization of the reaction conditions for heterocycle **6a** synthesis.

Catalyst	Catalyst amount (% of the stoichiometric)	Product yield (%)
$Sc(OTf)_3$	2	27
$Sc(OTf)_3$	5	62
$Sc(OTf)_3$	10	58
$Sc(OTf)_3$	15	38
$Yb(OTf)_3$	2	35
$Yb(OTf)_3$	**5**	**66**
$Yb(OTf)_3$	10	59
$Yb(OTf)_3$	15	42
$Al(O\text{-}iPr)_3$	10	no product
$Al(O\text{-}iPr)_3$	20	15
HCl	5	no product (mixture resinification)
p-TsOH	2	no product (mixture resinification)

under stirring and under ultrasonication at room temperature (Table 3, entries 5, 6). The scope and limitations for this process was therefore studied.

It was shown that *N*-(2-ethoxyphenyl)-3-oxobutanamide (**3c**) behaved under all reaction conditions in the same way as *N*-(2-methoxyphenyl)-3-oxobutanamide (**3a**): the three-component heterocyclization in the presence of ytterbium triflate under stirring at room temperature led to the formation of dihydroisoxazolopyridine **5c** (Table 3, entry 8) whereas the analogous reaction under ultrasonication gave exclusively the benzoxazocine derivative **6c** (Table 3, entry 9).

Interestingly, such a product dichotomy in condensations under or without ultrasonication was not typical for the other studied *N*-aryl-3-oxobutanamides **3b**,**d**–**h**. By this way the 4,7-dihydroisoxazolo[5,4-*b*]pyridine-5-carboxamides **5b**,**d**,**h** were obtained if the corresponding *N*-aryl-3-oxobutanamides contained either an *ortho*-hydroxy group in the benzene ring or no *ortho*-substituent (Table 3, entries 5, 6, 11, 12, 23, 24). On the other hand, *N*-aryl-4-(2-hydroxyphenyl)-3,6-dimethylisoxazolo[5,4-*b*]pyridine-5-carboxamides **9e**–**g** were allocated if the acetoacetamide had any non oxygen-containing *ortho*-substituent on the benzene ring (Table 3, entries 14, 15, 17, 18, 20, 21). It is worth mentioning that aromatic compounds **9e**–**g** were isolated in both aerobic and anaerobic (under inert argon atmosphere) conditions.

Based on these investigations we have proposed the structure of a feasible intermediate complex in the catalytic reactions leading to compounds **6** (Figure 1). This complex presumably facilitates a subsequent nucleophilic substitution of the salicylic hydroxy group leading to the oxygen-bridged heterocycle **6**. Apparently the oxygen-containing *ortho*-substituent on the benzene ring adopts an important role in the central ion coordination.

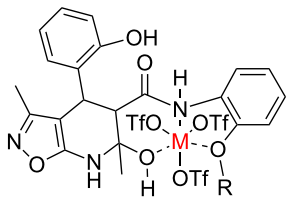
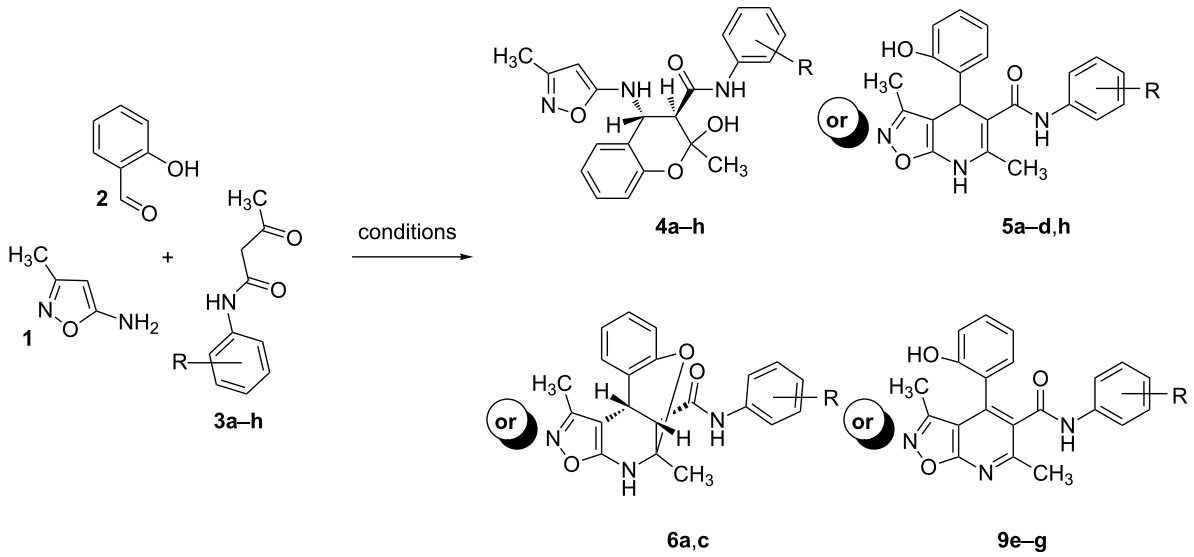


Figure 1: The possible structure of an intermediate complex in reactions forming the heterocycles **6**.

At first glance, the behavior of *N*-(2-hydroxyphenyl)-3-oxobutanamide (**3h**) in the three-component catalytic reaction with 5-amino-3-methylisoxazole (**1**) and salicylaldehyde (**2**) does not confirm this hypothesis since compound **6** was not observed in this case (Table 3, entries 23, 24). As one possible reason we assumed that the presence of an acidic phenol group – distinguishing the amide **3h** from alkoxylated amides **3a**,**c** – could be responsible for a destabilization of the aforementioned complex. Indeed, it was established that the three-component heterocyclizations of aminoisoxazole **1** with salicylaldehyde (**2**) and *N*-aryl-3-oxobutanamides **3a**,**c** supplemented with ytterbium triflate as a catalyst in the presence of an equimolar amount of phenol (as a source of phenolic acidity) led to the formation of

Table 3: Three-component heterocyclization of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-aryl-3-oxobutanamides (**3a–h**).



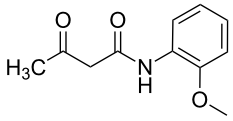
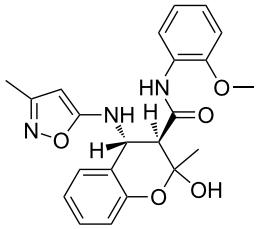
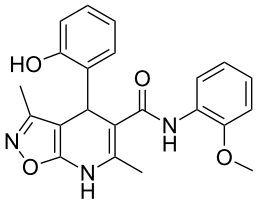
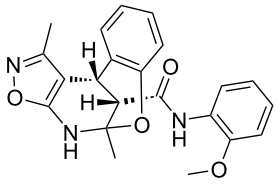
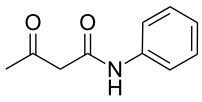
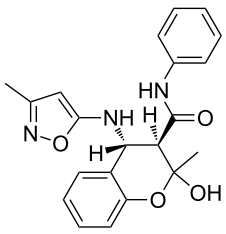
Entry	Amide	Conditions	Product	Yield, %
1	 **3a**	EtOH,))), rt, 4 h	 **4a**	58
2		EtOH, $Yb(OTf)_3$ (5 mol %), rt, 48 h	 **5a**	69
3		EtOH, $Yb(OTf)_3$ (5 mol %),))), rt, 4 h	 **6a**	66
4	 **3b**	EtOH,))), rt, 4 h	 **4b**	54

Table 3: Three-component heterocyclization of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-aryl-3-oxobutanamides (**3a**–**h**). (continued)

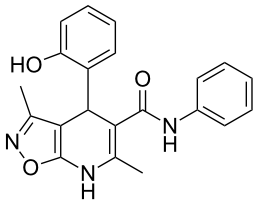
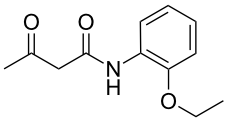
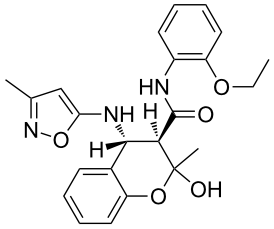
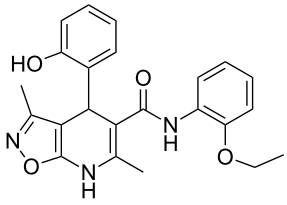
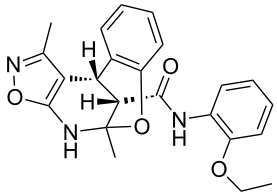
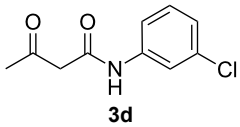
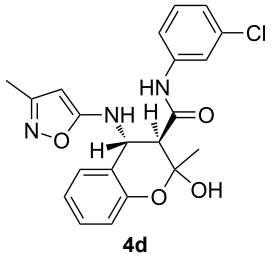
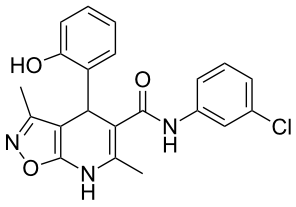
5		EtOH, $Yb(OTf)_3$ (5 mol %), rt, 48 h	 **5b**	70
6		EtOH, $Yb(OTf)_3$ (5 mol %),))), rt, 4 h		69
7	 **3c**	EtOH,))), rt, 4 h	 **4c**	51
8		EtOH, $Yb(OTf)_3$ (5 mol %), rt, 48 h	 **5c**	68
9		EtOH, $Yb(OTf)_3$ (5 mol %),))), rt, 4 h	 **6c**	64
10	 **3d**	EtOH,))), rt, 4 h	 **4d**	58
11		EtOH, $Yb(OTf)_3$ (5 mol %), rt, 48 h	 **5d**	61
12		EtOH, $Yb(OTf)_3$ (5 mol %),))), rt, 4 h		65

Table 3: Three-component heterocyclization of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-aryl-3-oxobutanamides (**3a**–**h**). (continued)

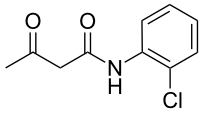
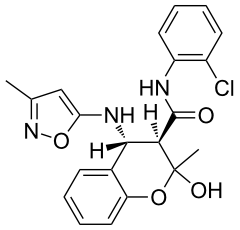
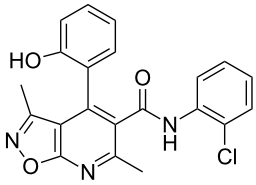
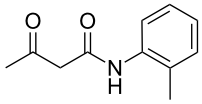
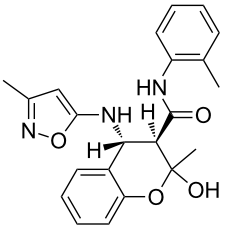
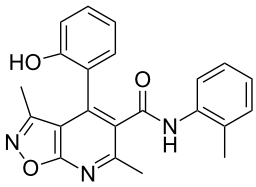
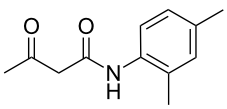
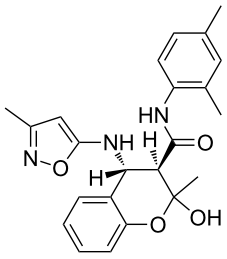
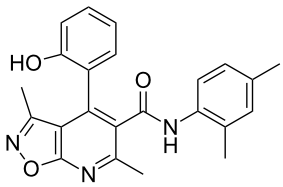
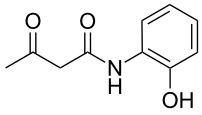
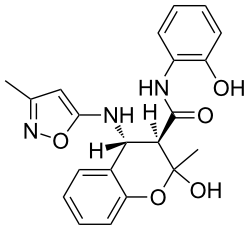
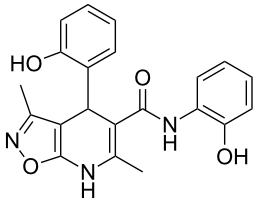
13	 **3e**	EtOH,))), rt, 4 h	 **4e**	57
14		$EtOH, Yb(OTf)_3$ (5 mol %), rt, 48 h	 **9e**	72
15		$EtOH, Yb(OTf)_3$ (5 mol %),))), rt, 4 h		81
16	 **3f**	EtOH,))), rt, 4 h	 **4f**	59
17		$EtOH, Yb(OTf)_3$ (5 mol %), rt, 48 h	 **9f**	77
18		$EtOH, Yb(OTf)_3$ (5 mol %),))), rt, 4 h		75
19	 **3g**	EtOH,))), rt, 4 h	 **4g**	63
20		$EtOH, Yb(OTf)_3$ (5 mol %), rt, 48 h	 **9g**	76
21		$EtOH, Yb(OTf)_3$ (5 mol %),))), rt, 4 h		82

Table 3: Three-component heterocyclization of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-aryl-3-oxobutanamides (**3a**–**h**). (continued)

22	 **3h**	EtOH,))), rt, 4 h	 **4h**	55
23		EtOH, $Yb(OTf)_3$ (5 mol %), rt, 48 h	 **5h**	61
24		EtOH, $Yb(OTf)_3$ (5 mol %),))), rt, 4 h		63

dihydroisoxazolopyridines **5a**,**c** rather than benzoxazocines **6a,c** thus supporting the assumptions.

A plausible mechanistic rationale is outlined in Scheme 4. It should be firstly noted that the formation of any of the compounds **4**–**6a** through the intermediate **7** (pathway A) as for cyclic 1,3-diketones [13,25] was excluded because the latter does not react with amide **3a** under any comparable conditions.

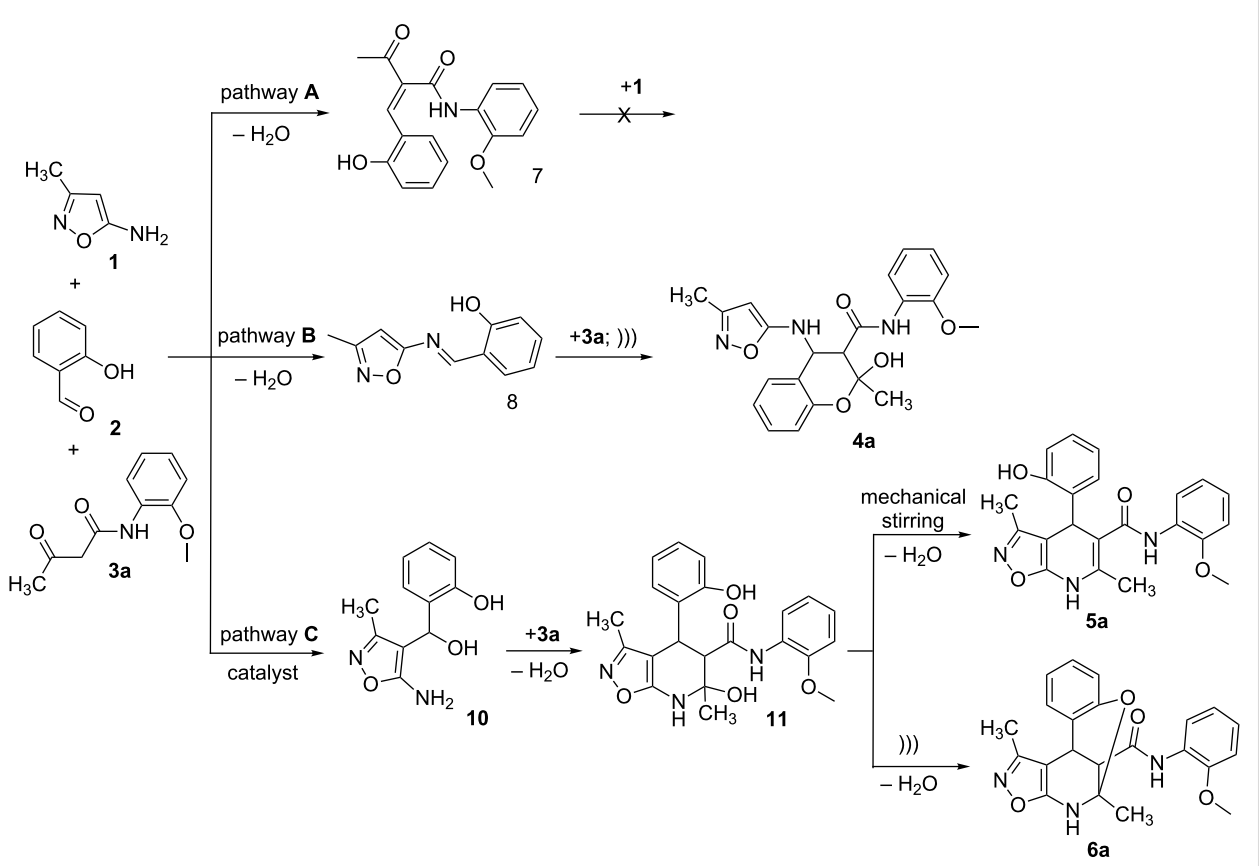
Most likely the formation of chroman-3-carboxamide **4a** proceeds through imine **8** (pathway B) since the reaction of **8** and **3a** under ultrasonication at room temperature gave the corresponding final product essentially after the same reaction time.

The Lewis acid catalyst activates the carbonyl group in salicylaldehyde (**2**), which is subsequently able to interact with the 4-CH nucleophilic center of the aminoisoxazole **1** and not only with the exocyclic NH_2 group [26]. The resulting adduct **10** (Scheme 4, pathway C) then reacts with carboxamide **3a** forming intermediate **11** which can lose a water molecule in two different ways: either by elimination occurring at room temperature leading to dihydroisoxazolo[5,4-*b*]pyridine **5a** or through nucleophilic substitution involving the phenolic hydroxy group under ultrasonic activation furnishing the oxygen-bridged compound **6a**. Most likely, here the key influence of ultrasound is the transfer of energy to the reaction mixture that is required for intramolecular cyclization that cannot be received by standard mechanical stirring.

However, it cannot be excluded that the Lewis acid catalyzed process proceeds through a primary attack of the exocyclic NH_2 group of aminoisoxazole to the activated β-carbonyl group of acetoacetamide and further reaction with the aldehyde, as it was described for analogous three-component reactions [27,28].

The structures of all synthesized compounds were unambiguously established by elemental analysis, MS, NMR spectroscopy and X-ray analysis. Thus, the ^{1}H NMR spectrum of chroman-3-carboxamide **4a** exhibits a singlet for the NH amide group at δ 9.25, a broad multiplet including peaks for the aromatic protons, a singlet for the OH group, and a doublet for the NH-isoxazole group around δ 6.70–7.84, a multiplet for the 4-CH-group at δ 4.90, a singlet for the CH-isoxazole group at δ 4.71, a doublet for the 3-CH-group at δ 2.94 as well as signals for the other terminal substituents. The relative stereochemistry of the stereogenic centers at positions 3 and 4 of compound **4a** was established by 1D and 2D NMR spectra. Thus, a ^3J coupling constant of 11.7 Hz accounts for a *trans*-orientation. The NOESY experiment showed only a quite weak interaction between these protons.

The spectral data obtained for dihydroisoxazolopyridine **5a** may correspond to at least two possible isomers **5a** and **5'a** (Figure 2). The data from COSY and NOESY experiments showed correlations between protons of NH and CH_3 groups in the dihydropyridine ring and no interactions between NH and CH groups or two CH_3 groups supporting structure **5'a** could be detected. All the data obtained from HMBC spectra also unam-



Scheme 4: Possible pathways for the three-component reaction of 5-amino-3-methylisoxazole (**1**), salicylaldehyde (**2**) and *N*-(2-methoxyphenyl)-3-oxobutanamide (**3a**).

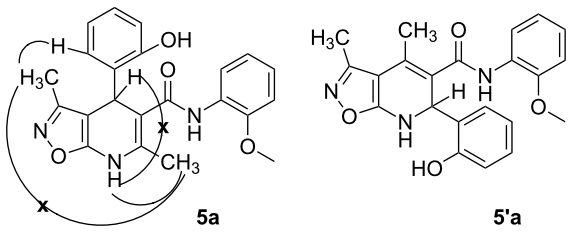


Figure 2: Alternative structures **5a** and **5'a** for dihydroisoxazolo-pyridine **5a** and selected NOESY correlations.

biguously support the connectivity of structure **5a** but not of isomer **5'a**.

The spectra observed for compound **6a** may correspond to at least three possible isomers **6a**, **6'a**, and **6''a** (Figure 3). Assignment of the structure **6a** was achieved with the help of 2D NMR experiments (Figure 4).

COSY and NOESY spectra showed correlations between the protons of the NH and CH_3 groups in the tetrahydropyridine ring which should be absent in case of structure **6''a**. Neither

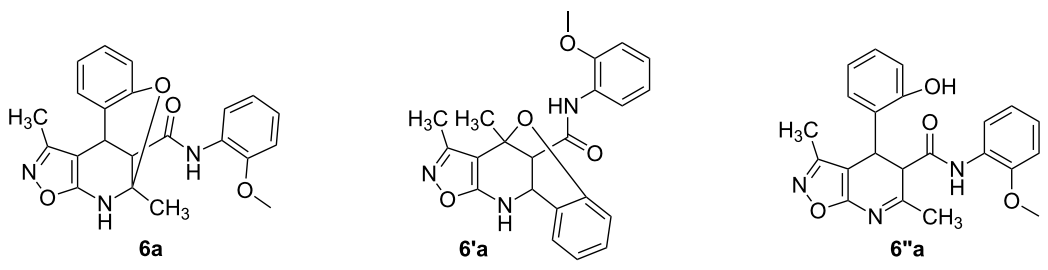


Figure 3: Alternative structures **6a**, **6'a** and **6''a** for compound **6a**.

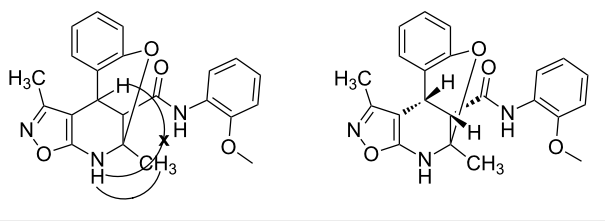


Figure 4: Selected data from NOESY experiments and relative stereochemistry of stereogenic centers at positions 4 and 12.

scalar nor dipolar coupling between NH and CH groups were detected in these experiments which would be expected for structure **6'a**. The data obtained from the HMBC spectrum also unambiguously supported the connectivity of structure **6a** and not those of structures **6'a** or **6''a**.

The relative stereochemistry of the stereogenic centers at positions 4 and 12 of compound **6a** was first established by analysis of the 1D and 2D NMR spectra. Thus, a ^3J coupling constant of 1.9 Hz corresponds with a *cis*-orientation and the NOESY experiment additionally supports the proximity of this pair of protons.

The structure of compound **6a** with relative stereochemistry of stereogenic centers was finally corroborated by an X-ray diffraction study (Figure 5). The heterocycles of the polycyclic fragment adopt a chair-like conformation (the puckering parameters [29] are: S = 0.78, Θ = 32.8°, Ψ = 1.0° and S = 0.83, Θ = 38.0°, Ψ = 1.8° for the tetrahydropyridine and dihydrooxine rings, respectively). Deviation of the C5 atom from the mean plane of the remaining atoms of the ring is 0.70 Å and −0.77 Å for these two rings.

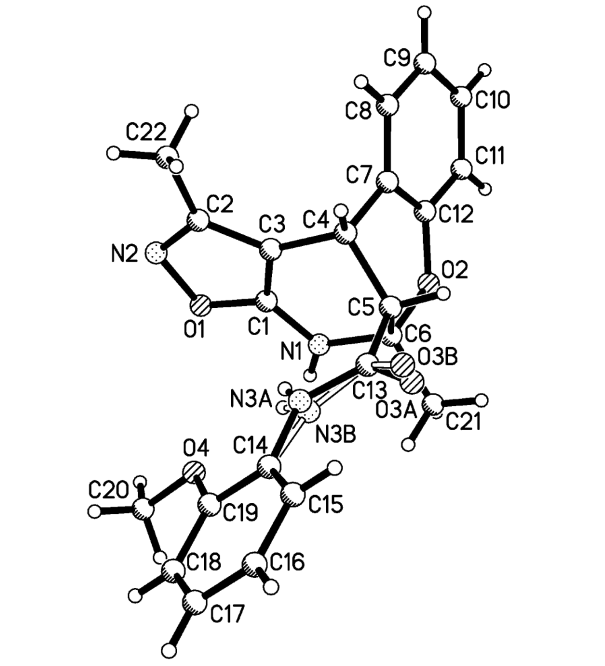


Figure 5: Molecular structure of compound **6a** according to X-ray diffraction data.

Conclusion

In summary, the three-component heterocyclizations involving 5-amino-3-methylisoxazole, salicylaldehyde and *N*-aryl-3-oxobutanamides were studied in detail. Generally the reaction may be switched between two pathways leading to the formation of 4-(isoxazol-5-ylamino)chroman-3-carboxamides (ultrasonication at room temperature without catalysts) and isoxazolo[5,4-*b*]pyrimidine-5-carboxamides (ultrasonication or mechanical stirring at room temperature with $Yb(OTf)_3$). However, an unexpected influence of the *N*-*o*-alkoxyaryl substituent in acetoacetamides on the outcome of the process under ultrasonication leading to the exclusive isolation of benzo[*g*]isoxazolo[5,4-*d*][1,3]oxazocine-12-carboxamides was additionally observed. The mechanistic rationale was developed on the basis of experiments with presumed intermediates and literature evidence.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, ^1H and ^{13}C spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-320-S1.pdf]

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Synthesis of antibacterial 1,3-diyne-linked peptoids from an Ugi-4CR/Glaser coupling approach

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Full Research Paper

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Abstract

A library of ten 1,3-diyne-linked peptoids has been synthesized through an Ugi four-component reaction (U-4CR) followed by a copper-catalysed alkyne homocoupling (Glaser reaction). The short and chemoselective reaction sequence allows generating diverse (pseudo) dimeric peptoids. A combinatorial version allows the one-pot preparation of, e.g., six-compound-libraries of homo- and heterodimers verified by ESI-MS and HPLC. In a preliminary evaluation, some compounds display moderate activity against the Gram-positive bacterium *Bacillus subtilis*.

Introduction

A re-occurring principle of nature to mediate or increase biological activity is dimerization [1]. Many protein receptors dimerize upon activation and recruit their active form by this transformation. This process is mainly initiated by dimeric natural products or symmetric bivalent ligands, which can be of peptidic origin [2,3]. As an example, Harran and co-workers synthesized a low-molecular weight C_2-symmetric 1,3-diyne-linked peptide **1** which was able to mimic the function of Smac (second mitochondria-derived activator of caspase) protein by triggering caspase 8 activation as well as apoptosis at concentrations as low as 100 pM. The higher activity of **1** in comparison to **2** (Figure 1) is possibly related to the ability of **1** to interact simultaneously with adjacent baculovirus inhibitory repeat (Bir) domains in the human X chromosome that encodes IAP (inhibitor of apoptosis) [4]. In another study Chen and co-workers found a GLP-1R antagonist only because of an unexpected dimerization [5]; and a dimer of *S*-adenosylmethionine is up to 13-fold more active than the monomer for promoting the binding of *Escherichia coli* methionine repressor to its operator DNA [6].

Peptoids are compounds which are able to mimic peptide structures [7-9]. In addition to the mimetic function, these compounds also possess an enhanced resistance to proteolytic

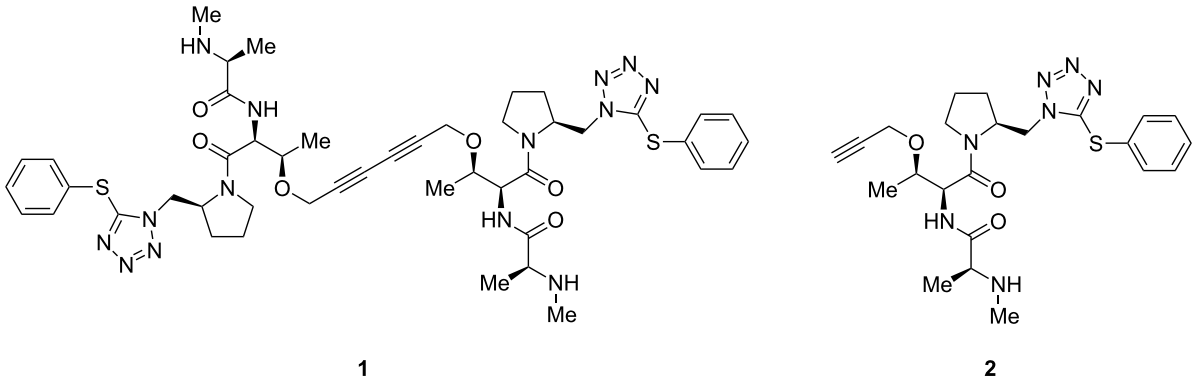


Figure 1: Apoptosis inducer C_2-symmetric 1,3-diyne-linked peptide **1** and its inactive monomer **2**.

enzymes. The fastest method for synthesizing peptoids is the Ugi four-component reaction (U-4CR) [10-12]. In combination with other protocols, this reaction has been used in the synthesis of bioactive peptides and pseudopeptides, e.g., tubulysin mimetics [13], julocrotine derivatives [14], architecturally complex peptoid macrocycles [15,16], building blocks for diversity-oriented synthesis [17], and heterocyclic compounds [18]. Complex structures as well as simple Ugi products exhibit promising biological profiles, e.g., cytotoxicity [13,19,20], fungicidal [21,22] and antibacterial properties [23-26], or inhibition of histone deacetylases [27]. The Ugi post-modification strategy has also been employed in the synthesis of heterocyclic and natural product inspired compounds [28-32]. Although several protocols of U-4CR followed by transition metal-catalysed reactions have been published so far [33], to the best of our knowledge, there are no reports about U-4CR/Glaser-type (homo) coupling combinations.

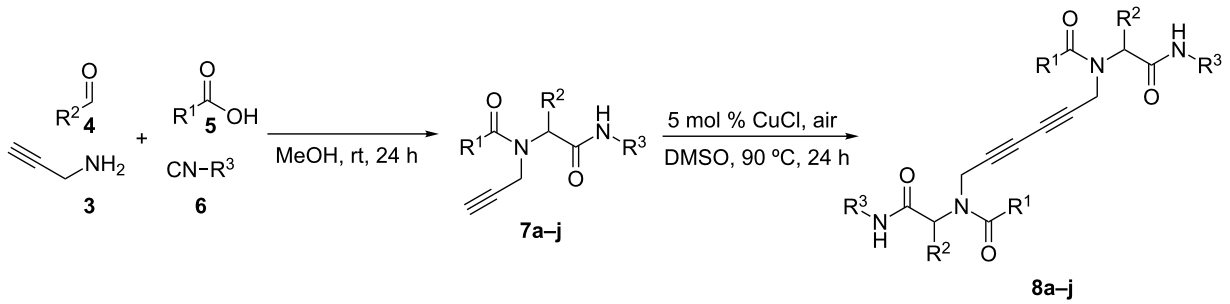
In view of an increasing interest to synthesize dimerized peptidomimetics with pharmacological properties through a step-efficient protocol that allows rapid access to highly diverse dimer libraries, we set out to develop a strategy based on an U-4CR/Glaser-type homocoupling sequence [34]. In comparison to popular cross linking reactions like, e.g., click reactions or amide bonds, the Glaser coupling allows the use of truly identical monomers. This decreases the number of steps for appropriate starting materials, and allows access to true homodimers in sensu strictu.

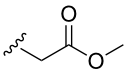
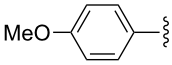
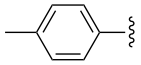
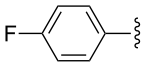
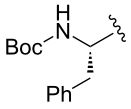
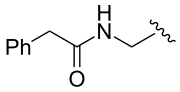
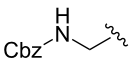
Results and Discussion

To achieve the synthesis of monomers eligible for dimerizations by Glaser coupling, equimolar amounts of propargylamine (**3**), aldehyde **4**, carboxylic acid **5**, and isocyanides **6** were reacted in methanol at room temperature over 24 h following well established Ugi protocols [12]. After flash column chromatography *N*-propargyl peptoids **7a–j** were obtained in good yields. The next step was the copper-catalysed homocoupling (Glaser reaction) of the terminal alkyne functions. Albeit several protocols are reported for this reaction, the CuCl-catalyzed method recently described by Jia and co-workers was utilised to access the C_2-symmetric 1,3-diynes because it does not require expensive catalysts, ligands, or additives (Table 1) [34]. The coupling reaction was clean without notable side product formation as confirmed by TLC analysis, and the desired peptoid dimers **8a–j** could be obtained in high to quantitative yields. Aromatic as well as aliphatic carboxylic acids and aldehydes have been successfully employed in both multicomponent and coupling reactions. When performing the reaction with methyl isocyanoacetate (Table 1, entry 2) the desired products could be obtained in good yields with the ester group remaining untouched. It is important to note that different protecting groups can be used: Boc-, PhAc- and Cbz-protected peptoid derivatives (Table 1, entries 8–10) reacted to the corresponding dimers **7h–j** without complications. The structure of the compounds **7a–j**, as well as **8a–j**, have been confirmed by ^{1}H, ^{13}C NMR spectra, and HRMS. In addition, HPLC analyses revealed that an adjacent stereocenter (Table 1, entry 8, **7h**/**8h**) does not racemize under the reaction conditions of both the MCR and the Glaser coupling.

Due to the high selectivity and high conversions found in the Glaser coupling step, our attention turned toward the development of a combinatorial version of the copper-catalysed homodimerization. In this strategy two or more alkyne peptoids should couple simultaneously in the same reaction vessel in order to generate small libraries of dimers. In contrast to parallel synthesis, the combinatorial approach easily generates non-symmetric dimers **9**, **10** and **11**. Thus, the peptoids **7f**, **7h** and **7j** were pooled to a Glaser reaction as depicted in Scheme 1.

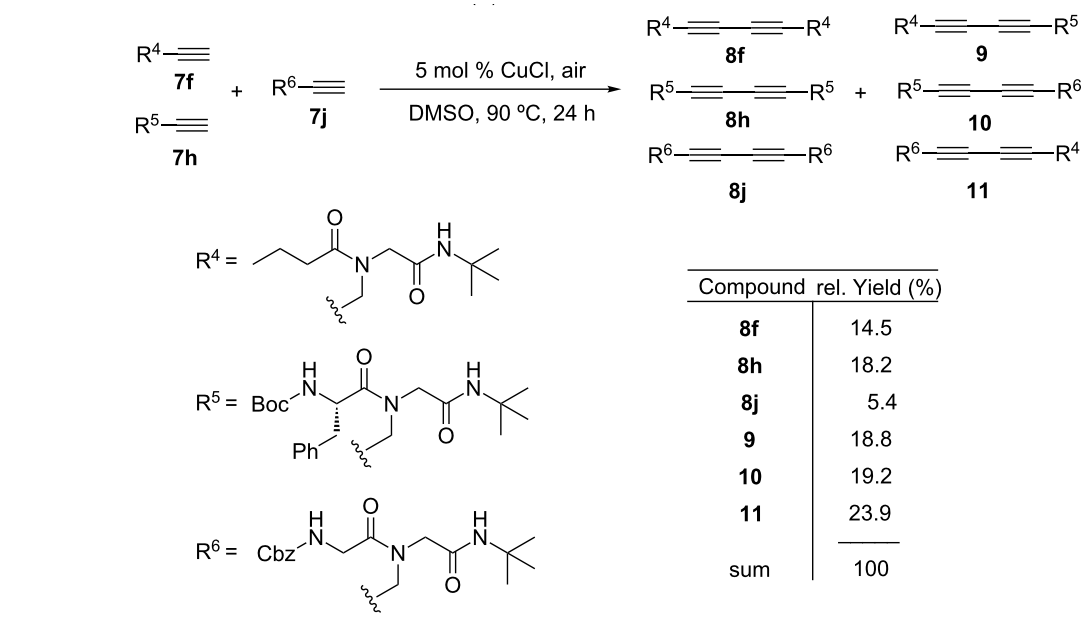
Table 1: Synthesis of compounds **7a–j** and **8a–j**.



Entry	R^1	R^2	R^3	Monomer **7** yield (%)	Dimer **8** yield (%)
1	CH_3			**7a** 97	**8a** 88
2	CH_3			**7b** 95	**8b** 80
3	CH_3			**7c** 99	**8c** 99
4	Ph			**7d** 70	**8d** 91
5	*n*-C_3H_7			**7e** 91	**8e** 99
6	*n*-C_3H_7	H		**7f** 70	**8f** 99
7				**7g** 98	**8g** 97
8		H		**7h** 82	**8h** 99
9				**7i** 82	**8i** 96
10		H		**7j** 80	**8j** 99

The ESI-MS spectrum of the crude library confirmed the presence of all expected Glaser-coupled products **8f**, **8h**, **8j**, **9**, **10** and **11**. The HPLC–MS analysis of the composition resulted in six peaks with different retention times and intensities identified via MS as the six desired components of the library. Figure 2 illustrates the expanded region of the ESI-MS spectrum (positive mode) and the HPLC chromatogram with the respective assignments of the obtained peaks. The analysis of the obtained spectra revealed that the non-symmetric dimers **9**, **10** and **11** are formed preferentially. The abundance differences observed are mostly lower than 2-fold, in one case up to ca. 4-fold. This is still acceptable for our initial bioactivity assays, as most screening setups cover several orders of magnitude of concentration anyhow. Therefore no further attempt to optimize for an equal product distribution was deemed necessary.

To gain insight into the antibiotic potential of the products, single compound dimers **8a–j** were subjected to a preliminary evaluation against *Bacillus subtilis* (Figure 3) [35,36]. The



Compound	rel. Yield (%)
8f	14.5
8h	18.2
8j	5.4
9	18.8
10	19.2
11	23.9
sum	100

Scheme 1: Combinatorial Glaser coupling involving acetylenes **7f**, **7j** and **7h**.

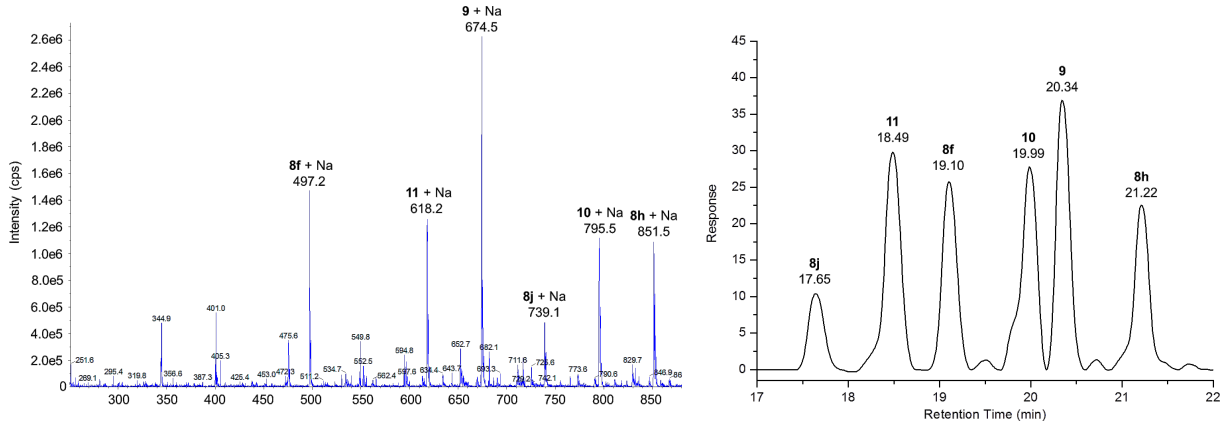


Figure 2: Expanded region of the ESI-MS spectrum (positive mode) and the HPLC chromatogram of the crude mixed library of 1,3-diyne peptoids (**8f**, **8h**, **8j**, **9**, **10** and **11**) produced by a combinatorial Glaser coupling of three different monomers (see Scheme 1).

active compounds inhibited bacterial growth in a range from 29% to 44% at 1 μM concentration, while erythromycin as the standard led to a growth inhibition of 71% under the same assay conditions. The most active compounds were **8b**, **8d** and **8h** which displayed inhibition rates (%) of 44.0 ± 26.7, 44.0 ± 21.8 and 43.9 ± 23.0. Interestingly, compounds **8c** and **8f** showed almost no effect on bacterial growth, i.e., 1.3 ± 5.1% and 2.3 ± 13.5%, respectively, i.e., the diyne core fulfils its function as linker and spacer without itself negatively (or positively) influencing the specific activity of the active ligand moieties.

Conclusion

In summary, a reliable sequential U-4CR/Glaser coupling approach towards the synthesis of 1,3-diyne-linked peptoids was developed. The strategy resulted in a library consisting of ten homodimers in good yields. The post-MCR copper-catalysed homocoupling reaction has also been performed in a combinatorial fashion combining three monomers. This procedure resulted in a mixed library containing six 1,3-diyne-linked symmetric and non-symmetric peptoids as confirmed by ESI-MS and HPLC experiments. Some of the synthesized compounds **8a–j**

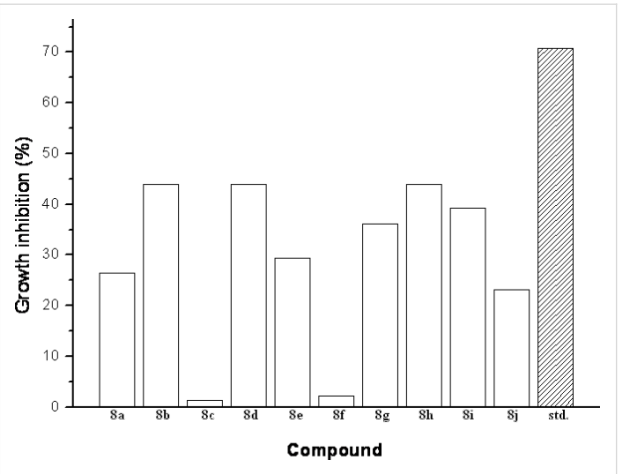


Figure 3: Growth inhibition of *Bacillus subtilis* by compounds **8a–j** at 1 μM (15 h), and standard erythromycin at 1 μM (15 h).

displayed growth inhibitory activity against *Bacillus subtilis* in a preliminary assay.

Supporting Information

Supporting Information File 1

Complete experimental procedures, characterization and figures of ^{1}H and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-4-S1.pdf]

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