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One-pot Ugi-azide and Heck reactions for the synthesis of heterocyclic systems containing tetrazole and 1,2,3,4-tetrahydroisoquinoline

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Full Research Paper

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Abstract

A new method for the synthesis of heterocyclic systems containing tetrazole and tetrahydroisoquinoline is developed via the performance of one-pot Ugi-azide and Heck cyclization reactions. The integration of the multicomponent and post-condensation reactions in one-pot maximizes the pot-, atom-, and step-economy (PASE).

Introduction

Tetrazole is a privileged heterocycle existing in a range of biological and medicinally interesting compounds [1,2] with antifungal [3,4], antibacterial [5], anticancer [6,7], antiparasitic [8], and antihypertensive properties [9] including FDA approved drugs such as valsartan and cefmetazole [10,11] (Figure 1). The tetrazole ring can also be found in functional materials for photography, imaging, and military applications [12-17]. The hydroisoquinoline core, such as 1,2,3,4-tetrahydroisoquinoline and pyrazino[2,1-*a*]isoquinolinone, is also a privileged heterocycle which can be found in natural products and synthetic compounds with antitumor, anti-HIV, antibiotic, antifungal, antivirus, and anti-inflammatory activities [18-21]. The antischistosomal drug praziquantel (PZQ), a tetrahydroisoquinoline derivative, is a commercialized drug for the treatment of schis-

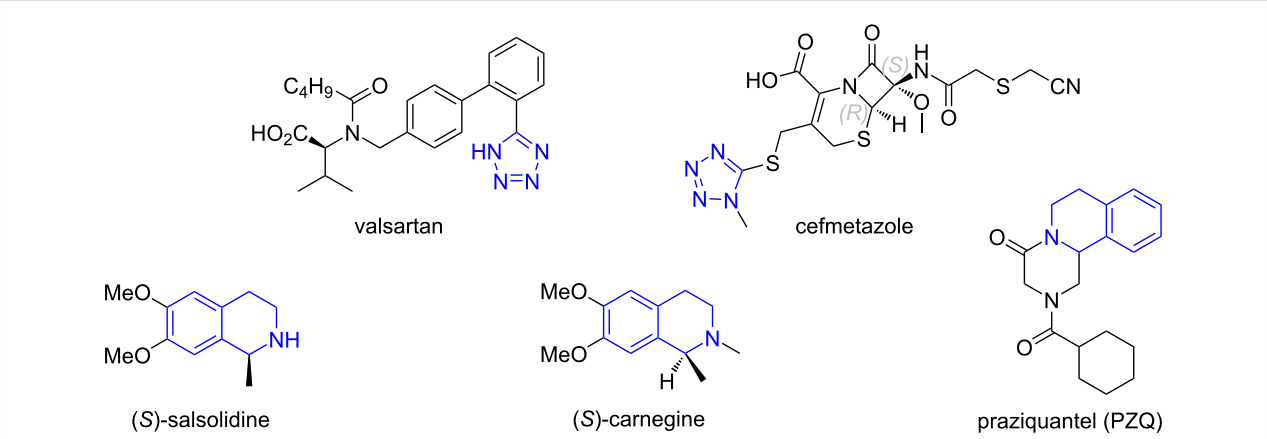


Figure 1: Representative bioactive tetrazole- and tetrahydroisoquinoline-containing compounds.

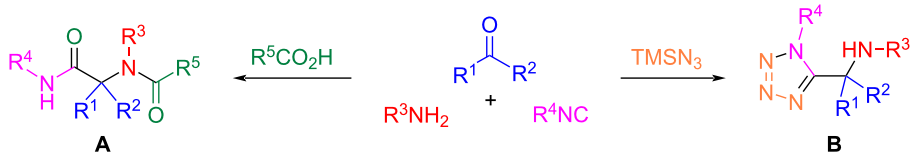
tosomiasis [22-25]. The combination of the privileged heterocycles tetrazole and tetrahydroisoquinoline in one molecule generates new molecules which could have biological activities.

A standard Ugi four-component reaction (Ugi-4CR) of an aldehyde, amine, isocyanide, and a carboxylic acid produces highly diverse peptidic structures **A** with up to four points of substitution (Scheme 1) [26,27]. By replacing the carboxylic acid with a nucleophilic azide reagent XN_3 (generally $TMSN_3$), the Ugi-azide four-component reaction (UA-4CR) of an aldehyde, amine, isocyanide, and azide gives 1,5-disubstituted 1*H*-tetrazoles (1,5-DS-1*H*-Ts) **B**. The performance of post-condensation reactions of UA-4CR adducts has resulted in various 1,5-DS-1*H*-Ts containing heterocyclic compounds [28-32], such as bis-heterocyclic lactam-tetrazoles [33,34], 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines [35], ketopiperazinetetrazoles [36], imidazotetrazolodiazepinones [37], tetracyclic tetrazolylpyridoimidazoquinolines [38], bis-heterocyclic 1,5-disubstituted tetrazoleindolizines [39] and (*E*)-12-tetrazolyl-5*H*-quinazolino[3,2-*a*]quinazolines [40]. Among them, the Hulme group reported a UA-4CR/post-condensation sequence to give fused imidazotetrazolodiazepinones (Scheme 2A) [37]. The Gámez-Montaño group introduced a one-pot synthesis of Ugi-azide/*N*-acylation/Diels–Alder/dehydration reactions for isoindolin-1-one and 1,5-DS-T in a linked manner (Scheme 2B) [41]. The Ding group developed sequential Ugi-azide/Ag-catalyzed oxidative cycloisomerization reactions for the synthesis of 2-tetrazolyl-substituted 3-acylpyrroles (Scheme 2C) [42]. The Ding group also reported sequential Ugi-azide/Staudinger/aza-Wittig/addition/Ag-catalyzed cyclization reactions for obtaining 12-tetrazolyl-substituted (*E*)-5*H*-quinazolino[3,2-*a*]quinazolines (Scheme 2D) [40].

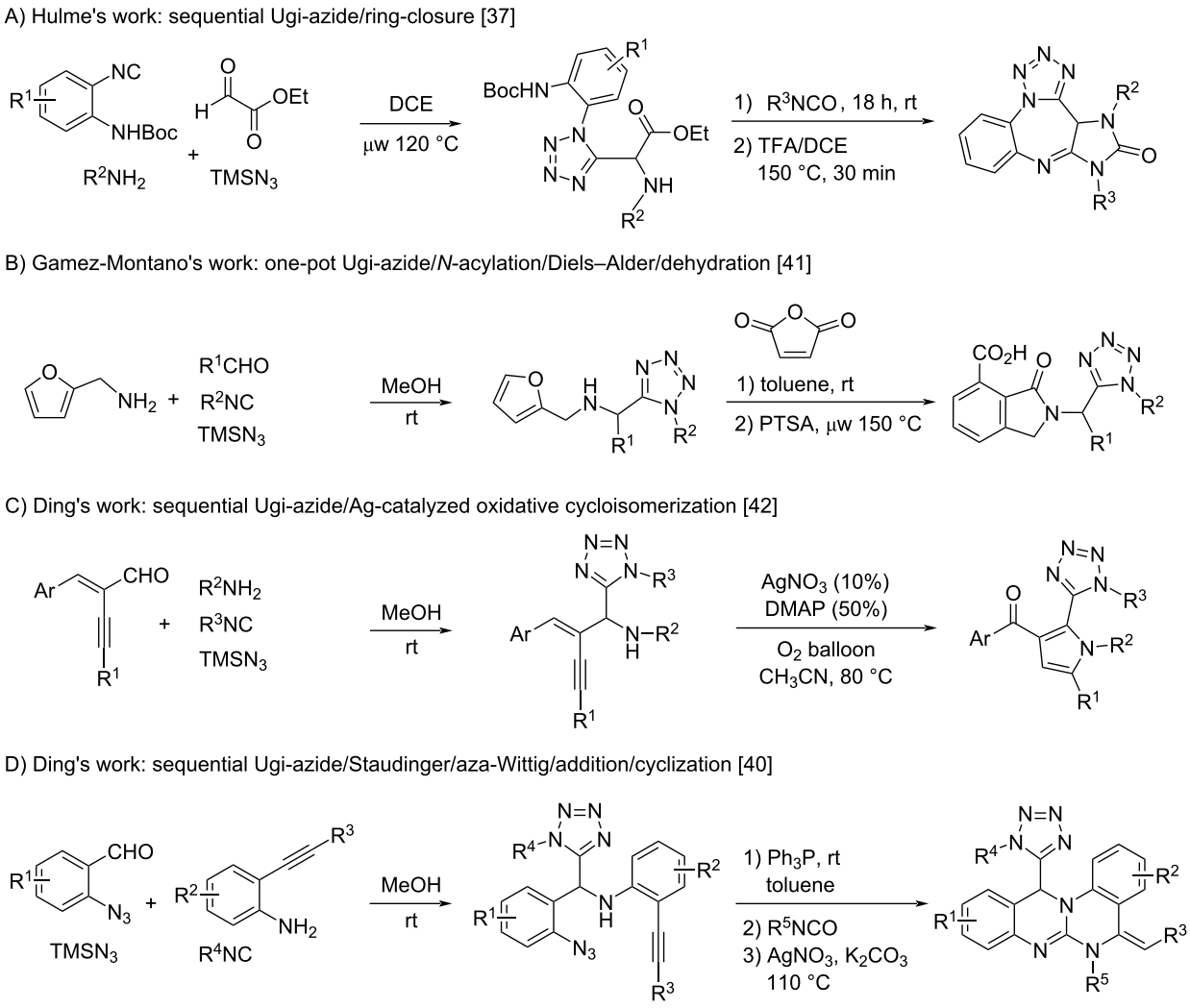
There are numbers of Ugi and subsequential Heck (or reductive Heck) reactions that have been developed for the synthesis of poly-heterocyclic compounds [43-51]. Reported in this paper is a one-pot Ugi-azide reaction followed by an intramolecular Heck reaction for the synthesis of tetrazolyl-1,2,3,4-tetrahydroisoquinoline scaffolds **6** and **8** (Scheme 3). The first step is the Ugi-azide reaction of a 2-bromobenzoaldehyde **1**, allylamine hydrochloride (**2**), azidotrimethylsilane ($TMSN_3$, **3**), and an isocyanide **4** affording tetrazoles **5**. If ethyl isocyanoacetate is used as the isocyanide source, the Ugi-azide reaction gives rise to ring-fused tetrazolo[1,5-*a*]pyrazin-6(5*H*)-one adducts **5**. The subsequent Pd-catalyzed intramolecular Heck reaction of compounds **5** or **7** then affords 1,2,3,4-tetrohydroisoquinolines **6** and **8**, respectively.

Results and Discussion

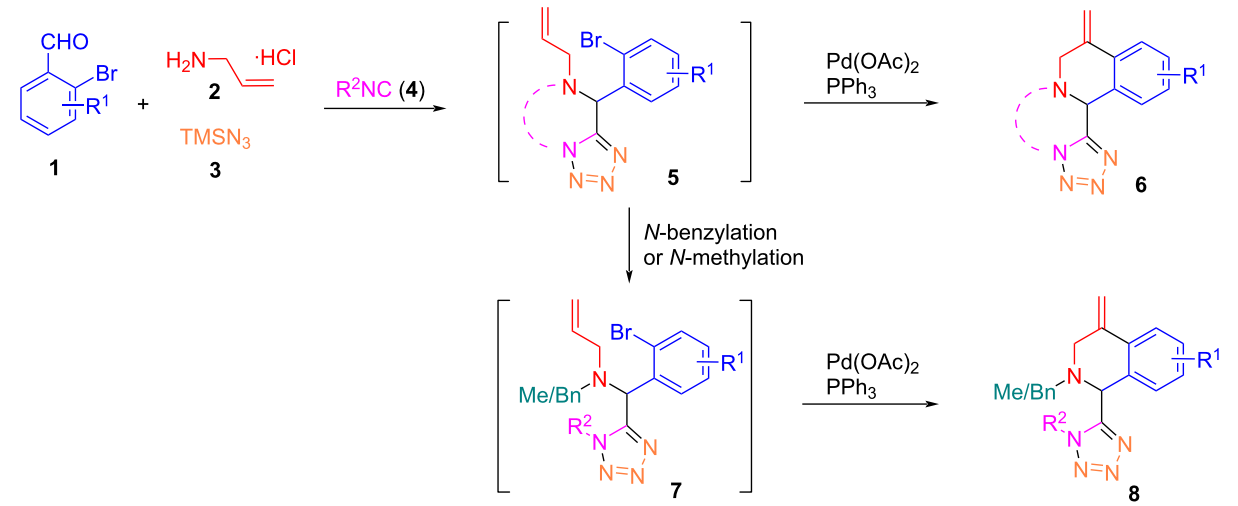
Following the reported procedures [41], the Ugi-azide reaction of 2-bromobenzaldehyde (**1a**, 1 mmol), allylamine hydrochloride (**2**, 1 mmol), trimethylsilyl azide (**3**, 1 mmol) and *tert*-



Scheme 1: The Ugi and Ugi-azide reactions.



Scheme 2: Ugi-azide and post-condensation reactions for the synthesis of various heterocyclic scaffolds.

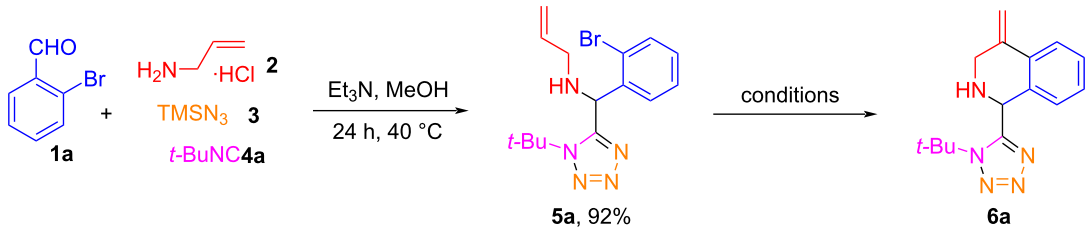


Scheme 3: One-pot synthesis of tetrazolyl-1,2,3,4-tetrahydroisoquinoline.

butyl isocyanide (**4a**, 1 mmol) in MeOH at 40 °C for 24 h afforded 1,5-DS-1*H*-T **5a** in 92% yield after chromatography purification. Our effort was then focused on the optimization of the intramolecular Heck reaction of **5a** for making 1,2,3,4-tetrahydroisoquinoline **6a**. A systematic evaluation of different catalysts and ligands, solvents, bases, as well as reaction temperatures and times was conducted (Table 1). The Heck reaction of **5a** was first examined by using 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 2 equiv of Et_3N in CH_3CN or DMF at 105 °C for 24 h under N_2 atmosphere. However, the reactions failed under these conditions (Table 1, entries 1 and 2). When K_2CO_3 was used as a base to replace Et_3N, the reactions in either CH_3CN or DMF for 3 h both gave cyclized product **6a** in 70% yield (Table 1, entries 3 and 4). An increase of the reaction time to 12 h did not improve the yield (Table 1, entry 5). The reaction was further evaluated in the absence of ligand which afforded the product in 35% yield (Table 1, entry 6). Screening of ligands, e.g., PCy_3 and $P(o\text{-tol})_3$ reduced the yield of the desired product **6a** (Table 1, entries 7 and 8). Lowering the amount of $Pd(OAc)_2$ or changing the reaction temperatures resulted low yields of **6a** (Table 1, entries 9–11). Similar results were observed from the reactions using other bases, such as K_3PO_4, NaOAc, and Cs_2CO_3 (Table 1, entries 12–14). Investigating other Pd catalysts, suche as $PdCl_2$ and $Pd(dba)_2$ also gave low yields (Table 1, entries 15 and 16). Since CH_3CN is a more favorable solvent than DMF in green chemistry consideration [52,53], the optimal reaction conditions for the Heck reaction were to use 1 mmol of **5a** with 10 mol % $Pd(OAc)_2$ and 20 mol % PPh_3, 2 equiv of K_2CO_3 in 3 mL CH_3CN at 105 °C for 3 h under N_2 atmosphere which afforded product **6a** in 70% yield (Table 1, entry 3).

The combination of an initial multicomponent reaction with post-condensation reactions in one-pot is a good strategy to develop high pot, atom and step economy (PASE) syntheses [54-58]. We then made the effort to integrate the Ugi and Heck

Table 1: Conditions for one-pot Ugi-azide and Heck reactions.[a]



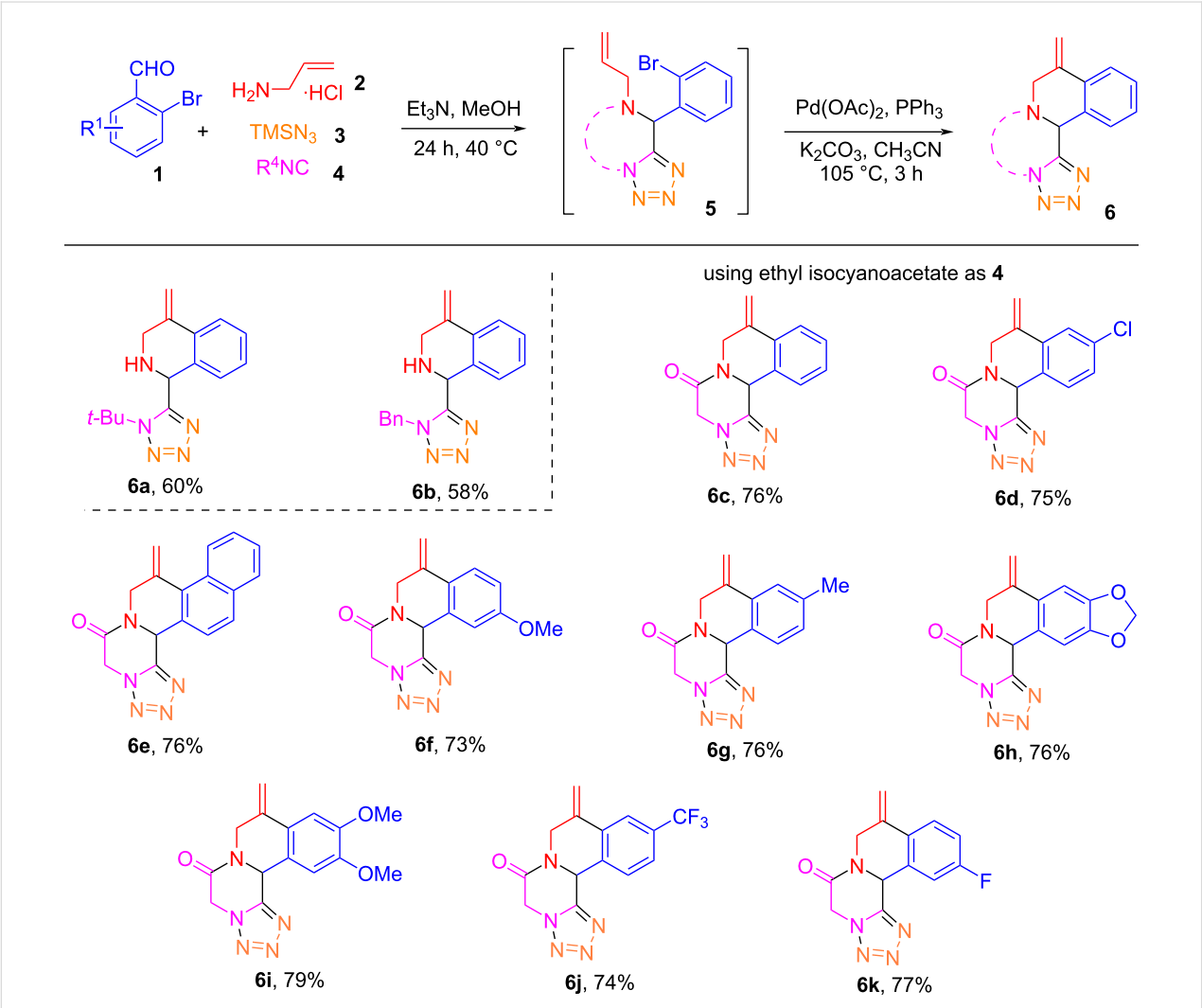
Entry	Catalyst	Ligand	Solvent	Base	Temp (°C)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	MeCN	Et_3N	105	24	–
2	$Pd(OAc)_2$	PPh_3	DMF	Et_3N	105	24	–
3	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	105	3	70
4	$Pd(OAc)_2$	PPh_3	DMF	K_2CO_3	105	3	70
5	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	105	12	65
6	$Pd(OAc)_2$	–	MeCN	K_2CO_3	105	6	35
7	$Pd(OAc)_2$	PCy_3	MeCN	K_2CO_3	105	6	46
8	$Pd(OAc)_2$	$P(o\text{-tol})_3$	MeCN	K_2CO_3	105	6	56
9[c]	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	105	3	58
10	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	70	8	60
11	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	120	3	62
12	$Pd(OAc)_2$	PPh_3	MeCN	K_3PO_4	105	3	39
13	$Pd(OAc)_2$	PPh_3	MeCN	NaOAc	105	3	62
14	$Pd(OAc)_2$	PPh_3	MeCN	Cs_2CO_3	105	3	56
15	$PdCl_2$	PPh_3	MeCN	K_2CO_3	105	5	53
16	$Pd(dba)_2$	PPh_3	MeCN	K_2CO_3	105	6	61
17[d]	**$Pd(OAc)_2$**	**PPh_3**	**MeCN**	**K_2CO_3**	**105**	**3**	**60**

[a]Reaction conditions: Ugi-azide step, 2-bromobenzaldehyde (**1a**, 1 mmol), allylamine hydrochloride (**2**, 1 mmol), trimethylsilyl azide (**3**, 1 mmol) and *tert*-butyl isocyanide (**4a**, 1 mmol), Et_3N (1.2 mmol) in 5 mL MeOH, 40 °C for 24 h. Heck reaction step, catalyst (10 mol %), ligand (20 mol %), solvent (3 mL), base (2 equiv), nitrogen atmosphere. [b]Isolated yield. [c]$Pd(OAc)_2$ 5 mol %, PPh_3 10 mol %. [d]Reaction was carried out in one-pot, starting compound is **1a** (1 mmol), first Ugi-azide reaction followed by the Heck reaction.

reactions in one-pot for making tetrazolyl-1,2,3,4-tetrahydroisoquinolines **6**. Thus, a mixture of 2-bromobenzaldehyde (**1a**, 1 mmol), allylamine hydrochloride (**2**, 1 mmol), trimethylsilyl azide (**3**, 1 mmol), and *tert*-butyl isocyanide (**4a**, 1 mmol) was stirred in MeOH at 40 °C for 24 h, and after the reaction was completed, the solvent was evaporated under vacuum to give crude Ugi adduct **5a** which was used for the intramolecular Heck reaction without further purification. Thus, to the solution of crude **5a** dissolved in MeCN (3 mL) were added 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, and 2 equiv of K_2CO_3 and the mixture stirred for 3 h at 105 °C under N_2 atmosphere to give the desired product **6a** in 60% isolated yield (entry 17 in Table 1).

With the optimized one-pot reactions in hands, we next evaluated the substrate scope by synthesizing 11 derivatives (Scheme 4) using nine benzaldehydes **1**, two isonitriles or ethyl isocyanoacetate **4**, allylamine hydrochloride (**2**), and trimethylsilyl azide (**3**) for the initial Ugi-azide reaction. Among them, products **6a** and **6b** from the reaction of isonitriles were synthesized in moderate yields (58–60%). For the Ugi reaction involving isocyanoacetate, lactamination occurred spontaneously to provide the ring-fused tetrazolo[1,5-*a*]pyrazin-6(5*H*)-one adducts **5** which after intramolecular Heck reaction gave functionalized tetracyclic tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-ones **6c**–**k** in 73–79% yields. The presence of electron-donating or electron-withdrawing groups on the aromatic ring did not show significant effects on the Heck reaction.

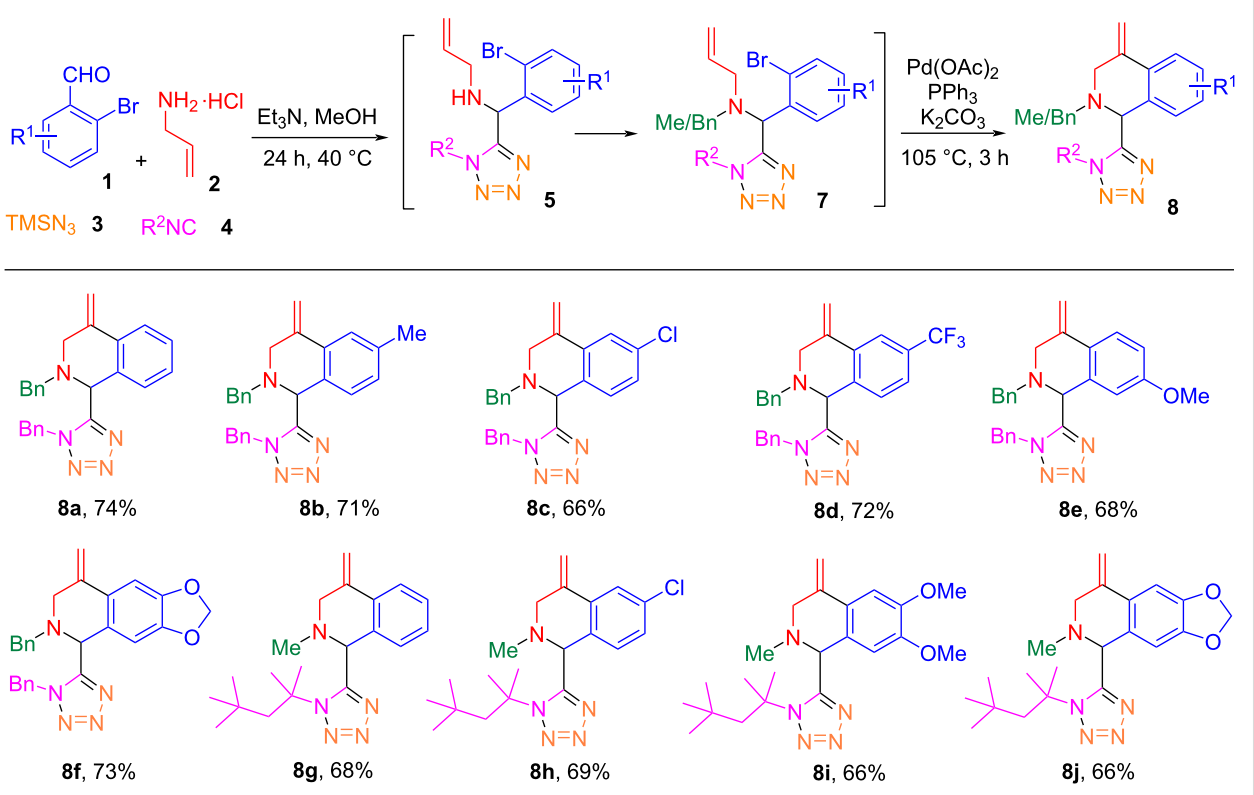
Products **6c**–**k** were obtained in higher yields than products **6a**,**b**. We believe that the secondary amine in the Ugi reaction products **5** could affect the yield of the Heck reaction. To address the issue, compounds **5** were *N*-alkylated to afford intermediates **7** which were used in the subsequent Heck reac-



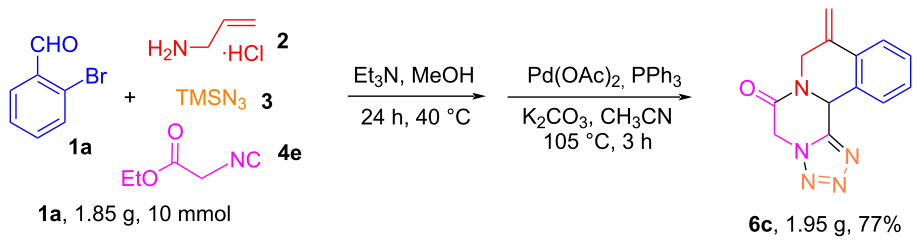
Scheme 4: One-pot synthesis of tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-ones **6**.

tion step. Thus, an alternative one-pot Ugi-azide/*N*-alkylation/Heck reaction procedure was developed (Scheme 5). A mixture of 2-bromobenzaldehyde (**1a**, 1 mmol), allylamine hydrochloride (**2**, 1 mmol), trimethylsilyl azide (**3**, 1 mmol) and benzyl isocyanide (1 mmol) in MeOH was reacted at 40 °C for 24 h. After evaporating the solvent, 3 mL CH_3CN were added to the crude 1,5-DS-1*H*-T **5a** followed by the addition of 1 equiv of benzyl bromide and 2 equiv of K_2CO_3 for the alkylation reaction at 80 °C for 3 h to give *N*-benzylated compound **7a**. Finally, 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 2 equiv of K_2CO_3 were added to the reaction mixture for the Heck reaction at 105 °C for 3 h under N_2 atmosphere to afford tetrazolyl-1,2,3,4-tetrahydroisoquinoline **8a** in 74% isolated yield which is higher than the one-pot Ugi/Hecke reaction to give product **6b** (58%). Under the alternative one-pot reaction conditions involving an *N*-alkylation step, the substrate scope was explored by the preparation of 10 derivatives **8a–j** (Scheme 5) using seven benzaldehydes **1**, two isonitriles **4**, and allylamine hydrochloride (**2**) with trimethylsilyl azide (**3**) for the Ugi-azide reaction. The *N*-alkylations were conducted using benzyl bromide and iodomethane, respectively. The final products **8b–j** were obtained in 66–74% yields.

To evaluate the scalability of the two-step one-pot reaction protocol, we performed the synthesis of tetracyclic tetrazolopyrazino[2,1-*a*]isoquinolin-6(5*H*)-one **6c** in gram quantity from 10 mmol of **1a** which led to the formation of product **6c** in a satisfactory yield 77% (Scheme 6).



Scheme 5: One-pot synthesis for tetrazolyl-1,2,3,4-tetrahydroisoquinolines **8**.



Scheme 6: Gram-scale two-step one-pot synthesis of **6c**.

The products **6** and **8** were characterized by ^{1}H and ^{13}C NMR, and HRMS analysis. In addition, single crystals of compound **6d** and **8c** were obtained for X-ray analysis to confirm the structures (Figure 2).

Conclusion

In conclusion, we have developed a one-pot synthesis with two or three steps for making tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-ones. The initial Ugi-azide four-component reaction constructs the tetrazole motif while the subsequent intramolecular Heck reaction assembles the tetrahydroisoquinoline. The one-pot reaction avoids the intermediate purification which has favorable PASE in the synthesis of heterocyclic compounds.

Experimental

General procedure for the synthesis of Ugi-azide adduct 5a

A solution of 2-bromobenzaldehyde **1** (1 mmol, 1 equiv), allylamine hydrochloride (**2**, 1 mmol, 1 equiv), trimethylsilyl azide (**3**, 1 mmol, 1 equiv) and *tert*-butyl isocyanide **4a** (1 mmol, 1 equiv) in MeOH (5 mL) with Et_3N (1.5 mmol) was heated at 40 °C for 24 h in a sealed vial. Upon completion of the reaction, the reaction mixture was filtered and evaporated under vacuum to give crude products **5a**. Further purification was conducted by flash chromatography with 1:6 petroleum ether/EtOAc to afford **5a** in 92% yields. The adduct was confirmed by NMR.

General procedure for the Heck reaction; synthesis of product 6a

A mixture of Ugi-azide adduct **5a** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), PPh_3 (0.2 mmol), K_2CO_3 (2 mmol) or NaOAc (2 mmol) in MeCN (3 mL) was stirred at 105 °C for 3 h under nitrogen atmosphere. After aqueous work-up, the crude product was purified by flash chromatography with 1:4 ethyl acetate/petroleum ether to afford product **6a**.

General procedure for the one-pot synthesis of tetrazole-containing 1,2,3,4-tetrahydroisoquinolines 6

A mixture of 2-bromobenzaldehyde **1** (1 mmol), allylamine hydrochloride (**2**, 1 mmol), trimethylsilyl azide (**3**, 1 mmol) and isocyanide **4** (1 mmol) in MeOH was stirred at 40 °C for 24 h. After the reaction was complete, the solvent was evaporated under vacuum to give the crude Ugi adduct **5**, which was used in the Heck reaction without further purification. To a solution of the crude intermediate **5** in MeCN (3 mL) was added 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 2 equiv of K_2CO_3 and the mixture stirred for 3 h at 105 °C under N_2 atmosphere. After aqueous work-up, the crude product was purified by flash chromatography with 1:3 ethyl acetate/petroleum ether to afford products **6**.

General procedure for the one-pot synthesis of tetrazolyl-1,2,3,4-tetrahydroisoquinolines 8

A mixture of 2-bromobenzaldehyde **1** (1 mmol), allylamine hydrochloride (**2**, 1 mmol), trimethylsilyl azide (**3**, 1 mmol) and isocyanide **4** (1 mmol) in MeOH was reacted at 40 °C for 24 h. After evaporating the solvent, 3 mL CH_3CN were added to the crude 1,5-DS-1*H*-T **5** followed by the addition of 1 equiv of benzyl bromide or iodomethane and 2 equiv of K_2CO_3 for the alkylation reaction at 80 °C for 3 h to give *N*-alkylated compounds **7**. Finally, 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, 2 equiv of K_2CO_3 were added to the reaction mixture for the Heck reaction at 105 °C for 3 h under N_2 atmosphere. After aqueous work-up, the crude products were purified by flash

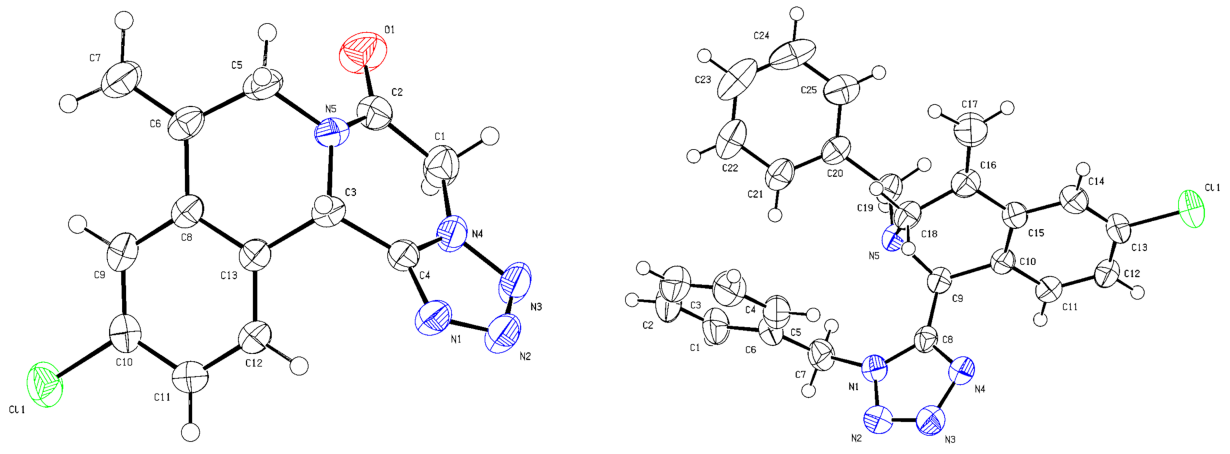


Figure 2: ORTEP diagrams of compound **6d** (left) [CCDC: 2164364] and **8c** (right) [CCDC: 2321622].

chromatography with 1:4 ethyl acetate/petroleum ether to afford products **8**.

Supporting Information

Supporting Information File 1

General reaction procedures, compound characterization data, and copies of NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-81-S1.pdf]

Supporting Information File 2

Crystallographic information file for compound **6d**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-81-S2.cif]

Supporting Information File 3

Crystallographic information file for compound **8c**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-81-S3.cif]

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Author Contributions

Jiawei Niu: investigation; methodology. Yuhui Wang: investigation; methodology. Shenghu Yan: investigation; methodology. Yue Zhang: investigation; methodology. Xiaoming Ma: conceptualization; data curation; supervision; validation; writing – original draft. Qiang Zhang: data curation; supervision; validation. Wei Zhang: conceptualization; supervision; writing – review & editing.

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information to this article. Data generated and analyzed during this study is openly available in CCDC. The data of CCDC-2164364 can be obtained free of charge at doi: https://doi.org/10.5517/ccdc.csd.cc2bn66f; the data of CCDC- 2321622: can be obtained free of charge at doi: https://doi.org/10.5517/ccdc.csd.cc2hxv1b.

Preprint

A non-peer-reviewed version of this article has been previously published as a preprint: https://doi.org/10.3762/bxiv.2024.2.v1

References

1. Neochoritis, C. G.; Zhao, T.; Dömling, A. *Chem. Rev.* **2019,** *119,* 1970–2042. doi:10.1021/acs.chemrev.8b00564
2. Ostrovskii, V. A.; Popova, E. A.; Trifonov, R. E. Tetrazoles. In *Comprehensive Heterocyclic Chemistry IV;* StC. Black, D.; Cossy, J.; Stevens, C. V., Eds.; Elsevier: Amsterdam, Netherlands, 2022; Vol. 6, pp 182–232. doi:10.1016/b978-0-12-818655-8.00131-1
3. Vandecruys, P.; Baldewijns, S.; Sillen, M.; Van Genechten, W.; Van Dijck, P. *Expert Rev. Anti-Infect. Ther.* **2023,** *21,* 799–812. doi:10.1080/14787210.2023.2233696
4. Staniszewska, M.; Zdrojewski, T.; Gizińska, M.; Rogalska, M.; Kuryk, Ł.; Kowalkowska, A.; Łukowska-Chojnacka, E. *Eur. J. Med. Chem.* **2022,** *230,* 114060. doi:10.1016/j.ejmech.2021.114060
5. Kritchenkov, A. S.; Lipkan, N. A.; Kurliuk, A. V.; Shakola, T. V.; Egorov, A. R.; Volkova, O. V.; Meledina, T. V.; Suchkova, E. P.; Zabodalova, L. A.; Dysin, A. P. *Pharm. Chem. J.* **2020,** *54,* 138–141. doi:10.1007/s11094-020-02180-4
6. Cortes-García, C. J.; Islas-Jácome, A.; Rentería-Gómez, A.; Gámez-Montaño, R. *Monatsh. Chem.* **2016,** *147,* 1277–1290. doi:10.1007/s00706-016-1686-x
7. Vanam, N. R.; Anireddy, J. S. *Chem. Data Collect.* **2023,** *48,* 101092. doi:10.1016/j.cdc.2023.101092
8. Cano, P. A.; Islas-Jácome, A.; González-Marrero, J.; Yépez-Mulia, L.; Calzada, F.; Gámez-Montaño, R. *Bioorg. Med. Chem.* **2014,** *22,* 1370–1376. doi:10.1016/j.bmc.2013.12.069
9. Toplak Časar, R.; Časar, Z. *Bioorg. Med. Chem.* **2018,** *26,* 4348–4359. doi:10.1016/j.bmc.2018.06.036
10. Prieto, C.; Evtoski, Z.; Pardo-Figuerez, M.; Hrakovsky, J.; Lagaron, J. M. *Mol. Pharmaceutics* **2021,** *18,* 2947–2958. doi:10.1021/acs.molpharmaceut.1c00098
11. Li, L.-H.; Yen, M.-Y.; Ho, C.-C.; Wu, P.; Wang, C.-C.; Maurya, P. K.; Chen, P.-S.; Chen, W.; Hsieh, W.-Y.; Chen, H.-W. *PLoS One* **2013,** *8,* e64794. doi:10.1371/journal.pone.0064794
12. Wei, C.-X.; Bian, M.; Gong, G.-H. *Molecules* **2015,** *20,* 5528–5553. doi:10.3390/molecules20045528
13. Frija, L. M. T.; Ismael, A.; Cristiano, M. L. S. *Molecules* **2010,** *15,* 3757–3774. doi:10.3390/molecules15053757
14. Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2007,** *43,* 1–9. doi:10.1007/s10593-007-0001-5
15. Lv, F.; Liu, Y.; Zou, J.; Zhang, D.; Yao, Z. *Dyes Pigm.* **2006,** *68,* 211–216. doi:10.1016/j.dyepig.2004.07.017
16. Song, W.; Wang, Y.; Qu, J.; Madden, M. M.; Lin, Q. *Angew. Chem., Int. Ed.* **2008,** *47,* 2832–2835. doi:10.1002/anie.200705805
17. Shmatova, O. I.; Nenajdenko, V. G. *J. Org. Chem.* **2013,** *78,* 9214–9222. doi:10.1021/jo401428q
18. Shang, X.-F.; Yang, C.-J.; Morris-Natschke, S. L.; Li, J.-C.; Yin, X.-D.; Liu, Y.-Q.; Guo, X.; Peng, J.-W.; Goto, M.; Zhang, J.-Y.; Lee, K.-H. *Med. Res. Rev.* **2020,** *40,* 2212–2289. doi:10.1002/med.21703
19. Li, D.-D.; Yu, P.; Xiao, W.; Wang, Z.-Z.; Zhao, L.-G. *Curr. Top. Med. Chem.* **2020,** *20,* 2634–2647. doi:10.2174/1568026620666200908165913
20. Qing, Z.-X.; Yang, P.; Tang, Q.; Cheng, P.; Liu, X.-B.; Zheng, Y.-J.; Liu, Y.-S.; Zeng, J.-G. *Curr. Org. Chem.* **2017,** *21,* 1920–1934. doi:10.2174/1385272821666170207114214
21. Maiti, M.; Kumar, G. S. *J. Nucleic Acids* **2010,** *2010,* 593408. doi:10.4061/2010/593408

22. Wang, Z.-x.; Chen, J.-l.; Qiao, C. *Chem. Biol. Drug Des.* **2013,** *82,* 216–225. doi:10.1111/cbdd.12153
23. Liu, H.; William, S.; Herdtweck, E.; Botros, S.; Dömling, A. *Chem. Biol. Drug Des.* **2012,** *79,* 470–477. doi:10.1111/j.1747-0285.2011.01288.x
24. Dömling, A.; Khoury, K. *ChemMedChem* **2010,** *5,* 1420–1434. doi:10.1002/cmdc.201000202
25. Waechtler, A.; Cezanne, B.; Maillard, D.; Sun, R.; Wang, S.; Wang, J.; Harder, A. *ChemMedChem* **2023,** *18,* e202300154. doi:10.1002/cmdc.202300154
26. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000,** *39,* 3168–3210. doi:10.1002/1521-3773(20000915)39:18<3168::aid-anie3168>3.0.co;2-u
27. Hooshmand, S. E.; Zhang, W. *Molecules* **2023,** *28,* 1642. doi:10.3390/molecules28041642
28. Maleki, A.; Sarvary, A. *RSC Adv.* **2015,** *5,* 60938–60955. doi:10.1039/c5ra11531k
29. Mohammadkhani, L.; Heravi, M. M. *Mol. Diversity* **2020,** *24,* 841–853. doi:10.1007/s11030-019-09972-1
30. Barreto, A. d. F. S.; Santos, V. A. d.; Andrade, C. K. Z. *Beilstein J. Org. Chem.* **2017,** *13,* 2596–2602. doi:10.3762/bjoc.13.256
31. Foley, C.; Shaw, A.; Hulme, C. *Org. Lett.* **2018,** *20,* 1275–1278. doi:10.1021/acs.orglett.7b03977
32. Wang, Y.; Patil, P.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Dömling, A. *Org. Lett.* **2019,** *21,* 3533–3537. doi:10.1021/acs.orglett.9b00778
33. Gunawan, S.; Petit, J.; Hulme, C. *ACS Comb. Sci.* **2012,** *14,* 160–163. doi:10.1021/co200209a
34. Gunawan, S.; Hulme, C. *Org. Biomol. Chem.* **2013,** *11,* 6036. doi:10.1039/c3ob40900g
35. Cárdenas-Galindo, L. E.; Islas-Jácome, A.; Alvarez-Rodríguez, N. V.; El Kaim, L.; Gámez-Montaño, R. *Synthesis* **2014,** *46,* 49–56. doi:10.1055/s-0033-1340051
36. Zarganes-Tzitzikas, T.; Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. *Eur. J. Org. Chem.* **2015,** 51–55. doi:10.1002/ejoc.201403401
37. Medda, F.; Martinez-Ariza, G.; Hulme, C. *Tetrahedron Lett.* **2015,** *56,* 5295–5298. doi:10.1016/j.tetlet.2015.07.083
38. Saha, D.; Kharbanda, A.; Essien, N.; Zhang, L.; Cooper, R.; Basak, D.; Kendrick, S.; Frett, B.; Li, H.-y. *Org. Chem. Front.* **2019,** *6,* 2234–2239. doi:10.1039/c9qo00389d
39. Niño-Pantoja, I.; Gallardo-Alfonzo, A.; Solis-Santos, M.; Ordoñez, M.; Contreras-Celedón, C.; Islas-Jácome, A.; Chacón-García, L.; Cortés-García, C. J. *Eur. J. Org. Chem.* **2022,** e202200230. doi:10.1002/ejoc.202200230
40. Yang, M.-L.; Zhao, L.; Chen, H.-R.; Ding, M.-W. *J. Org. Chem.* **2023,** *88,* 1898–1906. doi:10.1021/acs.joc.2c02621
41. Rentería-Gómez, A.; Islas-Jácome, A.; Cruz-Jiménez, A. E.; Manzano-Velázquez, J. C.; Rojas-Lima, S.; Jiménez-Halla, J. O. C.; Gámez-Montaño, R. *ACS Omega* **2016,** *1,* 943–951. doi:10.1021/acsomega.6b00281
42. Kong, H.-H.; Pan, H.-L.; Ding, M.-W. *J. Org. Chem.* **2018,** *83,* 12921–12930. doi:10.1021/acs.joc.8b01984
43. Amador-Sánchez, Y. A.; Hernández-Vázquez, E.; González-Mojica, N.; Ramírez-Apan, M. T.; Miranda, L. D. *Tetrahedron* **2020,** *76,* 131383. doi:10.1016/j.tet.2020.131383
44. Janatian Ghazvini, H.; Müller, T. J. J.; Rominger, F.; Balalaie, S. *J. Org. Chem.* **2019,** *84,* 10740–10748. doi:10.1021/acs.joc.9b01269
45. García-González, M. C.; Hernández-Vázquez, E.; Vengochea-Gómez, F. A.; Miranda, L. D. *Tetrahedron Lett.* **2018,** *59,* 848–852. doi:10.1016/j.tetlet.2018.01.058
46. Balalaie, S.; Ramezani Kejani, R.; Ghabraie, E.; Darvish, F.; Rominger, F.; Hamdan, F.; Bijanzadeh, H. R. *J. Org. Chem.* **2017,** *82,* 12141–12152. doi:10.1021/acs.joc.7b01855
47. Hernández-Vázquez, E.; Miranda, L. D. *Org. Biomol. Chem.* **2016,** *14,* 4875–4884. doi:10.1039/c6ob00431h
48. Vachhani, D. D.; Butani, H. H.; Sharma, N.; Bhoya, U. C.; Shah, A. K.; Van der Eycken, E. V. *Chem. Commun.* **2015,** *51,* 14862–14865. doi:10.1039/c5cc05193b
49. Moni, L.; Denißen, M.; Valentini, G.; Müller, T. J. J.; Riva, R. *Chem. – Eur. J.* **2015,** *21,* 753–762. doi:10.1002/chem.201404209
50. Rasouli, M. A.; Miri, S.; Rashidi Ranjbar, P. *J. Heterocycl. Chem.* **2015,** *52,* 1864–1870. doi:10.1002/jhet.2270
51. Peshkov, A. A.; Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Tetrahedron* **2015,** *71,* 3863–3871. doi:10.1016/j.tet.2015.04.022
52. Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008,** *10,* 31–36. doi:10.1039/b711717e
53. Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. *Green Chem.* **2016,** *18,* 288–296. doi:10.1039/c5gc01008j
54. Zhang, W.; Yi, W.-B. *Pot, Atom, and Step Economy (PASE) Synthesis; SpringerBriefs in Molecular Science*; Springer International Publishing: Cham, Switzerland, 2019. doi:10.1007/978-3-030-22596-4
55. Ma, X.; Zhang, W. *iScience* **2022,** *25,* 105005. doi:10.1016/j.isci.2022.105005
56. Hayashi, Y. *Chem. Sci.* **2016,** *7,* 866–880. doi:10.1039/c5sc02913a
57. Hayashi, Y. *Acc. Chem. Res.* **2021,** *54,* 1385–1398. doi:10.1021/acs.accounts.0c00803
58. Biesen, L.; Müller, T. J. J. *Adv. Synth. Catal.* **2021,** *363,* 980–1006. doi:10.1002/adsc.202001219

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