

The unique reactivity of 5,6-unsubstituted 1,4-dihydropyridine in the Huisgen 1,4-dipolar cycloaddition and formal [2 + 2] cycloaddition

Xiu-Yu Chen, Hui Zheng, Ying Han*, Jing Sun and Chao-Guo Yan*

Full Research Paper

Open Access

Address:
College of Chemistry & Chemical Engineering, Yangzhou University,
Jiangsu, Yangzhou 225002, China

Email:
Ying Han* - hanying@yzu.edu.cn;
Chao-Guo Yan* - cgyan@yzu.edu.cn

* Corresponding author

Keywords:
1,4-dihydropyridine; electron-withdrawing alkyne; formal [2 + 2]
cycloaddition; Huisgen's 1,4-dipole; isoquinoline;
isoquinolino[1,2-*f*][1,6]naphthyridine

Beilstein J. Org. Chem. **2023**, *19*, 982–990.
<https://doi.org/10.3762/bjoc.19.73>

Received: 03 May 2023
Accepted: 21 June 2023
Published: 29 June 2023

Associate Editor: I. Baxendale



© 2023 Chen et al.; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

The three-component reaction of isoquinolines, dialkyl acetylenedicarboxylates, and 5,6-unsubstituted 1,4-dihydropyridines in acetonitrile at room temperature afforded functionalized isoquinolino[1,2-*f*][1,6]naphthyridines in good yields and with high diastereoselectivity. More importantly, the formal [2 + 2] cycloaddition reaction of dialkyl acetylenedicarboxylates and 5,6-unsubstituted 1,4-dihydropyridines in refluxing acetonitrile gave unique 2-azabicyclo[4.2.0]octa-3,7-dienes as major products and 1,3a,4,6a-tetrahydrocyclopenta[*b*]pyrroles as minor products via further rearrangement.

Introduction

Among various well-known cycloaddition reactions such as the 1,3-dipolar cycloaddition reaction, Diels–Alder reaction, and the Povarov reaction, the cycloaddition reaction of Huisgen 1,4-dipoles with activated alkenes received increasing attention [1–3]. The well-known Huisgen 1,4-dipoles have a special kind of zwitterionic intermediates and are usually prepared by a nucleophilic addition of pyridine, quinoline, isoquinoline and other aza-arenes to electron-deficient alkynes [4–8]. The reactive Huisgen 1,4-dipoles have been widely employed as one of

the most valuable synthons to construct diverse carbocyclic and heterocyclic systems as well as many open-chain compounds [9–15]. In recent years, in situ generated Huisgen 1,4-dipoles were also widely employed to design highly efficient multicomponent and domino reactions [16–25]. Recently, much attention has been devoted to the development of new domino reactions containing reactive Huisgen 1,4-dipoles as key components for the assembly of many biologically important nitrogen-containing six-membered heterocyclic compounds [26–30].

The 5,6-unsubstituted 1,4-dihydropyridines can be easily prepared from the three-component reaction of an arylamine, cinnamaldehyde, and methyl acetoacetate [31–34]. The unsubstituted C=C double bond in 5,6-unsubstituted 1,4-dihydropyridines exhibits high reactivity and could act as activated alkene to take part in various cycloaddition reactions [35–40]. For example, Lavilla and co-workers developed a $\text{Sc}(\text{OTf})_3$ -catalyzed three-component reaction of 5,6-unsubstituted 1,4-dihydropyridines, arylamines and ethyl glyoxylate for the preparation of various pyrido-fused tetrahydroquinolines (reaction 1 in Scheme 1) [41,42]. Menéndez and co-workers reported a $\text{Yb}(\text{OTf})_3$ -mediated Povarov reaction of imines and *N*-alkyl-1,4-dihydropyridines for the synthesis of hexahydrobenzo[*h*][1,6]naphthyridines (reaction 2 in Scheme 1) [43]. Khan and co-workers employed a one-pot Povarov reaction of 3-aminocoumarins, aldehydes, and 5,6-unsubstituted 1,4-dihydropyridine derivatives for the construction of exo-hexahydrochromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate derivatives (reaction 3 in Scheme 1) [44]. In these reactions, the 5,6-unsubstituted 1,4-dihydropyridines usually behaved as an activated electron-rich dienophile. Inspired by these elegant synthe-

tic methodologies and in continuation of our aim to develop well-known Huisgen 1,4-dipoles for the construction of diverse nitrogen-containing heterocyclic compounds [45–64], herein, we wish to report the use of 5,6-unsubstituted 1,4-dihydropyridines as electron-deficient alkenes in the Huisgen 1,4-dipolar cycloaddition and as electron-rich alkenes in formal [2 + 2] cycloadditions for the efficient synthesis of isoquinolino[1,2-*f*][1,6]naphthyridine and 2-azabicyclo[4.2.0]octa-3,7-diene derivatives.

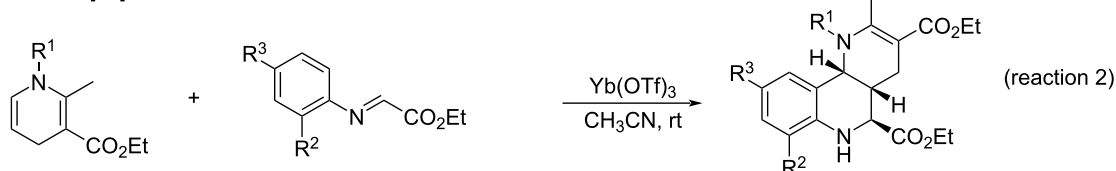
Results and Discussion

Initially, the reaction conditions were briefly examined by using isoquinoline (**1**), dimethyl acetylenedicarboxylate (DMAD, **2**) and 5,6-unsubstituted 1,4-dihydropyridine **3** as standard reaction (Table 1). The three-component reaction was carried out in common solvents such as ethanol, methanol, dichloromethane, and chloroform at room temperature for two hours. The expected isoquinolino[1,2-*f*][1,6]naphthyridine derivative **4a** was successfully obtained in 35%, 40% 70% and 65% yields, respectively (Table 1, entries 1–4). The reaction in acetonitrile afforded the product **4a** in 75% yield (Table 1, entry 5). When

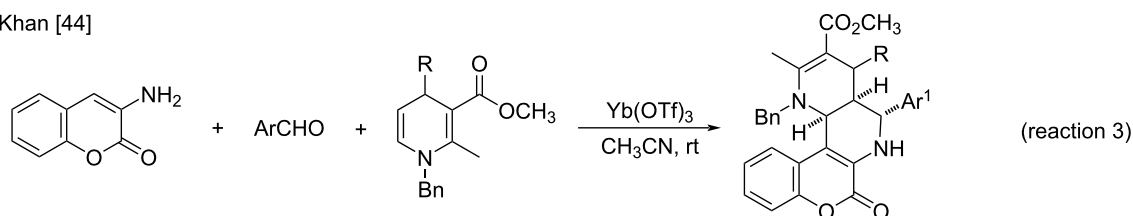
Lavilla [41]



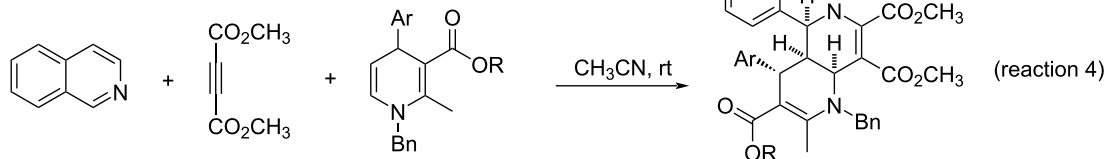
Menéndez [43]



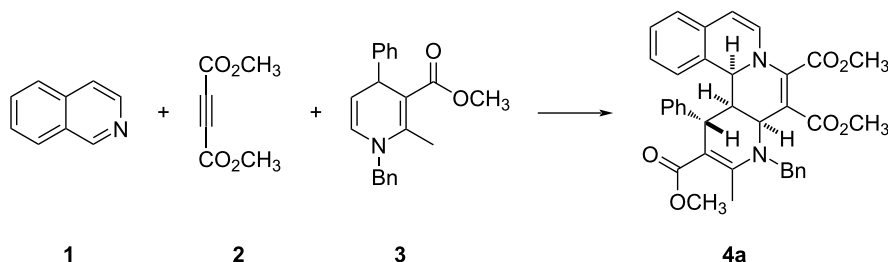
Khan [44]



this work



Scheme 1: Various cycloaddition reactions of 5,6-unsymmetric 1,4-dihydropyridines.

Table 1: Optimizing the reaction conditions.^a

Entry	Solvent	Temp. [°C]	Time [h]	Yield [%] ^b
1	EtOH	rt	2	35
2	MeOH	rt	2	40
3	CH ₂ Cl ₂	rt	2	70
4	CHCl ₃	rt	2	65
5	MeCN	rt	2	75
6	MeCN	rt	12	72
7	MeCN	50	2	68
8	MeCN	80	2	55

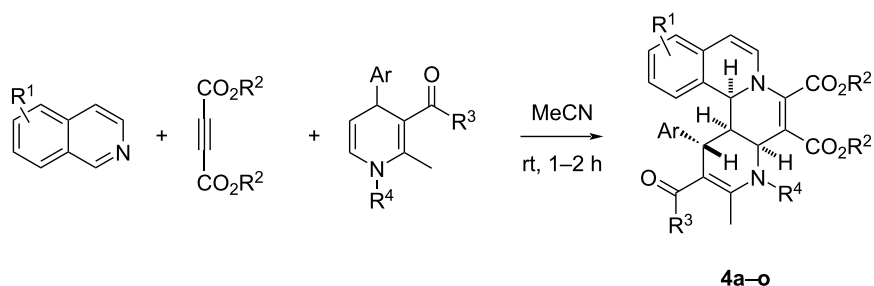
^aReaction conditions: isoquinoline (0.5 mmol), DMAD (0.6 mmol), 5,6-unsubstituted 1,4-dihydropyridine (0.5 mmol), solvent (5.0 mL). ^bIsolated yields.

the reaction time was extended to 12 h at room temperature, the yield of product **4a** did not increase (Table 1, entry 6). When the reaction was carried out in acetonitrile at elevated temperatures, the yield of product **4a** decreased to 68% and 55% (Table 1, entries 7 and 8). Therefore, the optimal reaction conditions for this three-component reaction were simply carrying out the reaction in acetonitrile at room temperature for two hours.

Under the optimal reaction conditions, various substrates were employed in the reaction for developing the scope of the reaction and the results are summarized in Table 2. It can be seen that all reactions gave the desired isoquinolino[1,2-*f*][1,6]naphthyridine derivatives **4a–o** in good to excellent yields. Isoquinoline itself and its 4-, 5-, and 6-bromo-substituted derivatives were successfully used in the reaction. Dimethyl or diethyl acetylenedicarboxylates gave the products in comparable yields in the reaction. The 5,6-unsubstituted 1,4-dihydropyridines with an *N*-benzyl group usually gave the products in good yields (Table 2, entries 1–12). It should be pointed out that 6-unsubstituted 1,4-dihydropyridines with an *N*-(3,4-(CH₃O)₂C₆H₃CH₂CH₂) group also afforded the desired product **4h** in 88% yield (Table 2, entry 8). Even 5,6-unsubstituted 1,4-dihydropyridines with an *N*-*n*-Bu group also gave the products **4m** and **4n** in satisfactory yields. At last, 5,6-unsubstituted 1,4-dihydropyridines derived from the condensation of acetylacetone also afforded the expected product **4o** in 65% yield.

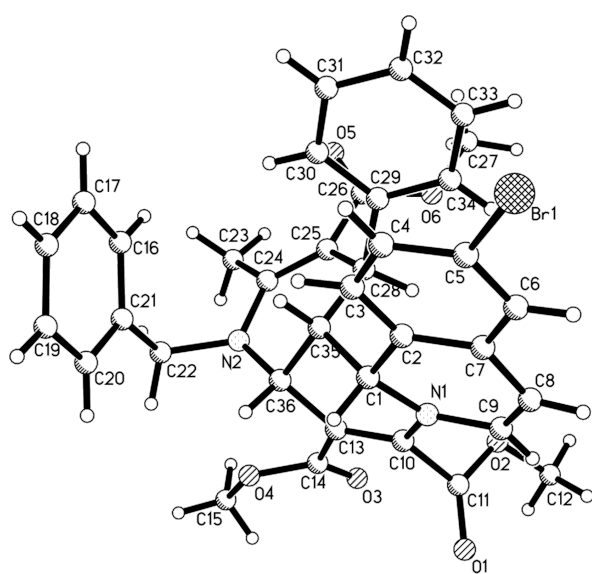
The chemical structures of the obtained isoquinoline[2,1-*h*][1,7]naphthyridines **4a–o** were fully characterized by various spectroscopy methods and further confirmed by determination of the single crystal structure of compound **4k** (Figure 1, CCDC 2059918). Though there are four chiral centers in the product structure of the isoquinolino[1,2-*f*][1,6]naphthyridine, the ¹H NMR spectra of the products all showed that only one diastereomer was produced in the reaction, which showed that this reaction has a high diastereoselectivity. From Figure 1, it can be seen that the three protons and the phenyl group have *cis*-configuration in the hexahydro-1,6-naphthyridyl ring.

During the investigation of the above three-component reaction, we found that the three-component reaction of isoquinoline, dimethyl acetylenedicarboxylate and 5,6-unsubstituted 1,4-dihydropyridines with *N*-Ar groups did not give the above isoquinolino[1,2-*f*][1,6]naphthyridines, but the unique 2-azabicyclo[4.2.0]octa-3,7-diene-7,8-dicarboxylates were isolated in moderate yields. These products were obviously produced from the formal [2 + 2] cycloaddition between dimethyl acetylenedicarboxylate and the 5,6-unsubstituted 1,4-dihydropyridine. Therefore, the reactions of dimethyl acetylenedicarboxylate and 5,6-unsubstituted 1,4-dihydropyridines were carefully explored. After adjusting the reaction conditions, we were pleased to find that 2-azabicyclo[4.2.0]octa-3,7-dienes **5a–o** could be successfully obtained in moderate to good yields by carrying out the reaction of dimethyl acetylenedicarboxylate and 5,6-unsubsti-

Table 2: Synthesis of isoquinolino[1,2-*f*][1,6]naphthyridines **4a–o**.^a

Entry	Compd	R ¹	R ²	Ar	R ³	R ⁴	Yield [%] ^b
1	4a	H	CH ₃	C ₆ H ₅	OCH ₃	Bn	75
2	4b	H	CH ₃	C ₆ H ₅	OC ₂ H ₅	Bn	65
3	4c	H	CH ₃	<i>p</i> -FC ₆ H ₄	OCH ₃	Bn	58
4	4d	H	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	OCH ₃	Bn	88
5	4e	H	C ₂ H ₅	C ₆ H ₅	OCH ₃	Bn	80
6	4f	H	C ₂ H ₅	C ₆ H ₅	OC ₂ H ₅	Bn	82
7	4g	H	CH ₃	C ₆ H ₅	OCH ₃	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	84
8	4h	H	CH ₃	C ₆ H ₅	OCH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃ (CH ₂) ₂	88
9	4i	4-Br	CH ₃	C ₆ H ₅	OCH ₃	Bn	78
10	4j	5-Br	CH ₃	C ₆ H ₅	OCH ₃	Bn	67
11	4k	6-Br	CH ₃	C ₆ H ₅	OCH ₃	Bn	65
12	4l	4-Br	CH ₃	C ₆ H ₅	OC ₂ H ₅	Bn	74
13	4m	H	CH ₃	C ₆ H ₅	OCH ₃	<i>n</i> -Bu	77
14	4n	5-Br	CH ₃	C ₆ H ₅	OCH ₃	<i>n</i> -Bu	78
15	4o	H	CH ₃	C ₆ H ₅	CH ₃	Bn	65

^aReaction conditions: isoquinoline (0.5 mmol), dialkyl acetylenedicarboxylate (0.6 mmol), 5,6-unsubstituted 1,4-dihydropyridine (0.5 mmol), CH₃CN (5.0 mL), rt, 2 h. ^bIsolated yields.

**Figure 1:** Single crystal structure of the compound **4k**.

tuted 1,4-dihydropyridines in refluxing acetonitrile for three hours (Table 3). As can be seen, unsymmetric 1,4-dihydropyridines with *N*-Bn and *N*-4-(CH₃OC₆H₄CH₂) groups can be successfully employed in the reaction (Table 3, entries 1–10). Additionally, 5,6-unsubstituted 1,4-dihydropyridines with various *N*-Ar groups also gave the expected products **5k–o** in good yields. Sometimes, as unexpected byproducts, 1,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrole derivatives **6e**, **6f**, **6i**, **6k**, **6l**, and **6m** were isolated in 23–39% yield from the reaction mixture. In other cases, the corresponding 1,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrole derivatives could not be isolated due to too low yields. By analyzing the chemical structures of the 1,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrole derivatives **6**, it was found that the 1,4-dihydropyridinyl ring of the substrate was converted to a fused pyrrole ring, which might be a result from a rearrangement process of the formed 2-azabicyclo[4.2.0]octa-3,7-diene-7,8-dicarboxylates **5a–o** at elevated temperature. The chemical structures of both bicyclic compounds **5a–o** and **6a–o** were fully characterized by various spectroscopy methods. The single crystal structures of compounds **5a** (Figure 2) and **6f**

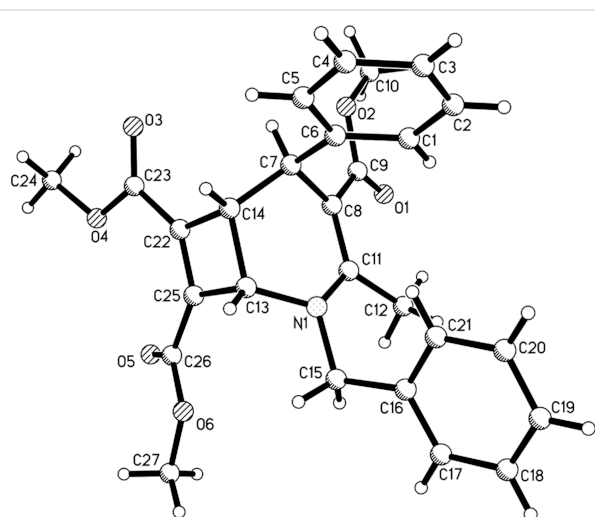
Table 3: Synthesis of the bicyclic compounds **5a–o** and **6a–o**.^a

Entry	R ¹	Ar	R ²	Compd	Yield (%) ^b	Compd	Yield (%) ^b
1	CH ₃	C ₆ H ₅	Bn	5a	89%	6a	—
2	CH ₂ CH ₃	C ₆ H ₅	Bn	5b	70%	6b	—
3	CH ₃	<i>o</i> -CH ₃ OC ₆ H ₄	Bn	5c	80%	6c	—
4	CH ₂ CH ₃	<i>o</i> -CH ₃ OC ₆ H ₄	Bn	5d	65%	6d	—
5	CH ₂ CH ₃	<i>p</i> -NO ₂ C ₆ H ₄	Bn	5e	36%	6e	35%
6	CH ₃	C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	5f	40%	6f	23%
7	CH ₃	<i>o</i> -CH ₃ OC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	5g	57%	6g	—
8	CH ₂ CH ₃	<i>o</i> -CH ₃ OC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	5h	62%	6h	—
9	CH ₂ CH ₃	<i>p</i> -NO ₂ C ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	5i	41%	6i	39%
10	CH ₃	<i>p</i> -NO ₂ C ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	5j	64%	6j	—
11	CH ₃	C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄	5k	35%	6k	36%
12	CH ₂ CH ₃	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	5l	31%	6l	33%
13	CH ₃	C ₆ H ₅	<i>p</i> -BrC ₆ H ₄	5m	33%	6m	35%
14	CH ₃	C ₆ H ₅	<i>m</i> -ClC ₆ H ₄	5n	55%	6n	—
15	CH ₃	<i>o</i> -CH ₃ OC ₆ H ₄	<i>o</i> -CH ₃ C ₆ H ₄	5o	64%	6o	—

^aReaction conditions: dialkyl acetylenedicarboxylate (0.9 mmol), 5,6-unsubstituted 1,4-dihydropyridine (0.3 mmol), CH₃CN (5.0 mL), reflux, 3 h.
^bIsolated yields.

(Figure 3) were successfully determined by X-ray diffraction analysis. From Figure 2 (compound **5a**), it can be seen that the cyclobutenyl ring and the 1,4-dihydropyridyl ring exist on the fused position. The two protons at the bridged position and the phenyl group are *cis*-configured. From Figure 3 (compound **6f**), it can be seen that the fused pyrrole ring and the cyclopentyl ring are butterfly shaped. The unusual feature is that the C=C double bond is not located between the two carbon atoms substituted with the methoxycarbonyl groups, but between the methylene carbon atom and one carbon atom connected with an electron-withdrawing methoxycarbonyl group. The aryl group and the neighbouring methoxycarbonyl group are *cis*-configured.

For explaining the formation of the various cyclic compounds, a plausible reaction mechanism was proposed on the base of the previously reported works [41–44] and the present experiments (Scheme 2). Initially, the nucleophilic addition of isoquinoline to dimethyl acetylenedicarboxylate gives the well-known Huisgen 1,4-dipole **A**. Secondly, Michael addition of the 1,4-dipole **A** to 5,6-unsubstituted 1,4-dihydropyridine gives the adduct intermediate **B**. At last, the intramolecular coupling of the negative and the positive charges in intermediate **B** directly

**Figure 2:** Single crystal structure of compound **5a**.

affords isoquinolino[1,2-*f*][1,6]naphthyridines **4**. Because all reactions in this process are retro-equilibrium reactions, the most thermodynamically stable diastereomer is preferentially produced in the reaction. In the absence of isoquinoline, the 5,6-unsubstituted 1,4-dihydropyridine acts as an active enamine,

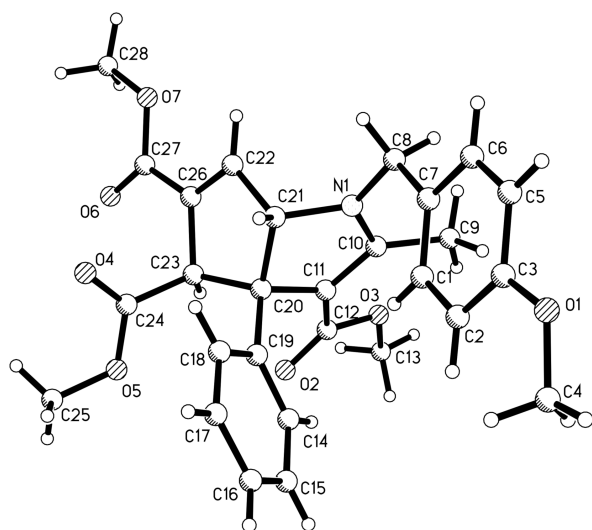


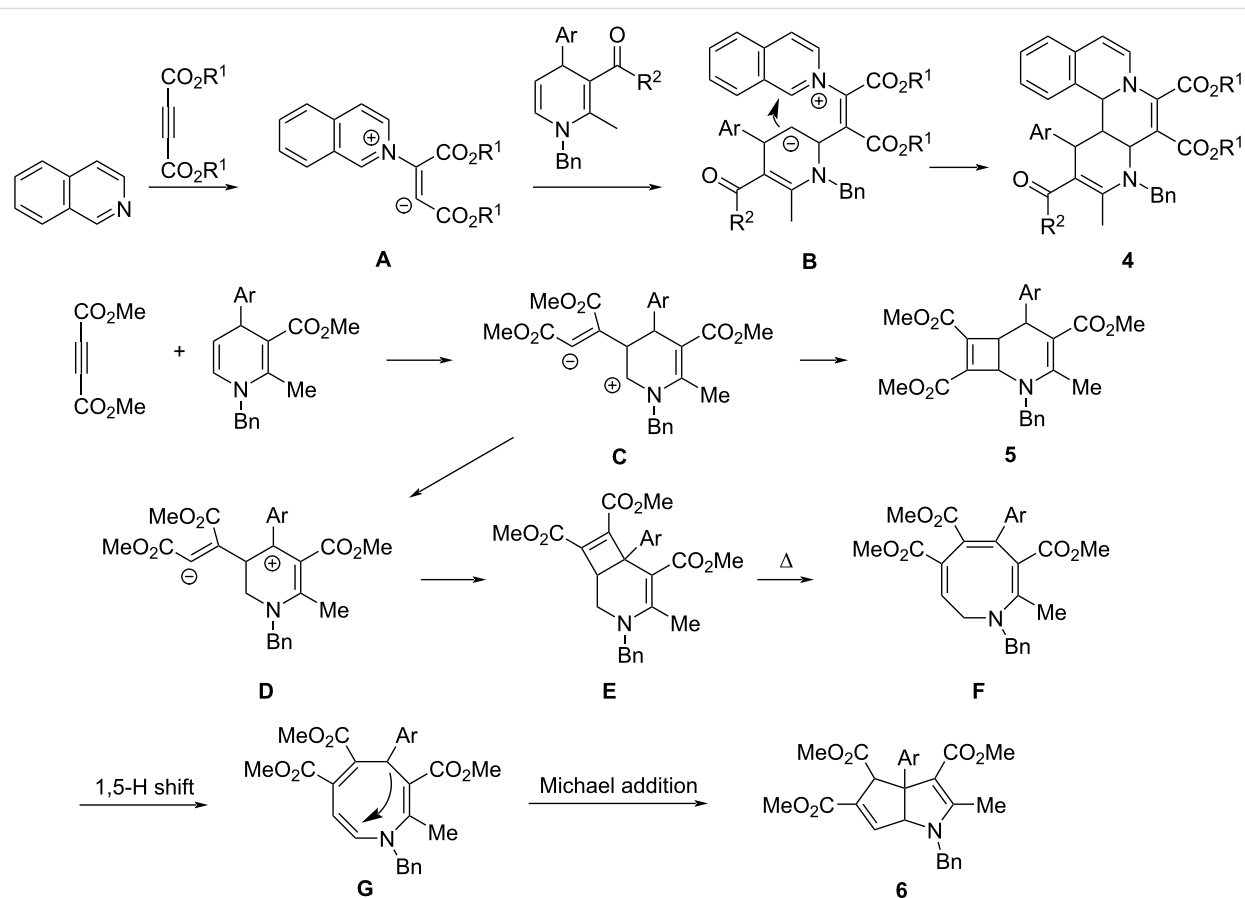
Figure 3: Single crystal structure of compound **6f**.

which adds to dimethyl acetylenedicarboxylate to give the adduct **C**. Then, the direct coupling of the positive charge and the negative charge affords the 2-azabicyclo[4.2.0]octa-3,7-

diene **5**. On the other hand, a carbenium ion **D** can be formed by migration of a hydrogen atom in intermediate **C**, which in turn converts into a fused bicyclic intermediate **E** by a charge coupling process. At elevated temperature, the ring-opening of the unstable cyclobutenyl ring gives a 1,2-dihydroazocine intermediate **F**, which is transformed into a 1,4-dihydroazocine intermediate **G** by a 1,5-H shift process. At last, the tetrahydrocyclopenta[*b*]pyrrole **6** is formed by an intramolecular Michael addition process.

Conclusion

In summary, we have investigated the three-component reaction of isoquinoline, dialkyl acetylenedicarboxylate and 5,6-unsubstituted 1,4-dihydropyridines. This reaction successfully provided an efficient protocol for the synthesis of functionalized isoquinolino[1,2-*f*][1,6]naphthyridines in good yields and with high diastereoselectivity. We also found that the unique 2-azabicyclo[4.2.0]octa-3,7-diene and 1,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrole derivatives can be conveniently produced by the cycloaddition reaction of dialkyl acetylenedicarboxylates and 5,6-unsubstituted 1,4-dihydropyridines. The advantages of the reaction include the use of readily available starting materi-



Scheme 2: Plausible reaction mechanism for the various products **4**, **5**, and **6**.

als, simple reaction conditions, without using any catalyst, high molecular diversity and atomic economy. Therefore, this reaction not only successfully developed unprecedented synthetic reactivity of the electron-deficient alkynes, but also provides efficient synthetic methodologies for complex nitrogen-containing heterocycles. The potential application of this reaction in organic synthesis and medicinal chemistry might be significant.

Experimental

General procedure for the three-component reaction of isoquinoline, dialkyl acetylenedicarboxylate and 5,6-unsubstituted 1,4-dihydropyridine

A mixture of isoquinoline (0.5 mmol), dialkyl acetylenedicarboxylate (0.6 mmol), 5,6-unsubstituted 1,4-dihydropyridine (0.5 mmol) in acetonitrile (5.0 mL) was stirred at room temperature for two hours. After removing the solvent by rotatory evaporation at reduced pressure, the residue was subjected to column chromatography with petroleum ether and ethyl acetate (v/v = 5:1) as eluent to give the pure product for analysis.

Trimethyl 4-benzyl-3-methyl-1-phenyl-4,4a,13b,13c-tetrahydro-1H-isoquinolino[1,2-f][1,6]naphthyridine-2,5,6-tricarboxylate (4a): orange solid, 75%; mp 174–175 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.48–7.42 (m, 4H, ArH), 7.39–7.35 (m, 1H, ArH), 6.80 (t, J = 7.6 Hz, 1H, ArH), 6.75–6.71 (m, 4H, ArH), 6.63 (d, J = 6.4 Hz, 2H, ArH), 6.39 (t, J = 7.6 Hz, 1H, ArH), 6.22 (d, J = 8.0 Hz, 1H, ArH), 5.91 (d, J = 8.0 Hz, 1H, CH), 5.43 (d, J = 8.0 Hz, 1H, CH), 5.25 (s, 1H, CH), 5.04 (d, J = 15.6 Hz, 1H, CH_2), 4.60 (d, J = 6.0 Hz, 1H, CH), 4.45 (d, J = 15.6 Hz, 1H, CH_2), 4.17 (d, J = 8.8 Hz, 1H, CH), 3.93 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 2.60 (t, J = 7.6 Hz, 1H, CH), 2.44 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 168.7, 166.2, 164.9, 150.2, 146.1, 145.7, 138.7, 129.3, 128.8, 128.1, 128.0, 127.8, 127.5, 127.3, 127.0, 126.3, 126.1, 125.1, 124.7, 124.6, 106.3, 104.6, 102.8, 61.3, 57.6, 56.0, 53.0, 51.6, 50.0, 44.8, 39.5, 17.9 ppm. IR (KBr) ν : 3732, 3023, 2952, 2843, 1967, 1737, 1678, 1556, 1372, 1147, 1097, 1010, 957, 866, 759 cm^{-1} ; HRESIMS (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{36}\text{H}_{34}\text{NaN}_2\text{O}_6$, 613.2315; found, 613.2309.

General procedure for the reaction of dialkyl acetylenedicarboxylate and 5,6-unsubstituted 1,4-dihydropyridine

A mixture of dialkyl acetylenedicarboxylate (0.9 mmol), 5,6-unsubstituted 1,4-dihydropyridine (0.3 mmol) in acetonitrile (5.0 mL) was heated a reflux for three hours. After removing the solvent by rotatory evaporation at reduced pressure, the residue was subjected to column chromatography with petro-

leum ether and ethyl acetate (v/v = 6:1) as eluent to give the pure product for analysis.

7,8-Diethyl 4-methyl 2-benzyl-3-methyl-5-(4-nitrophenyl)-2-azabicyclo[4.2.0]octa-3,7-diene-4,7,8-tricarboxylate (5e): yellow solid, 36%; mp 161–163 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.07–8.05 (m, 2H, ArH), 7.37–7.34 (m, 2H, ArH), 7.33–7.29 (m, 3H, ArH), 7.13–7.10 (m, 2H, ArH) 4.86 (d, J = 15.2 Hz, 1H, CH_2), 4.59 (s, 1H, CH), 4.48 (d, J = 15.2 Hz, 1H, CH_2), 4.37–4.34 (m, 1H, CH), 4.34–4.31 (m, 2H, CH_2), 4.31–4.26 (m, 2H, CH_2), 3.71 (d, J = 4.4 Hz, 1H, CH), 3.63 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3), 1.40–1.37 (m, 3H, CH_3), 1.37–1.33 (m, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 169.3, 160.9, 160.7, 156.2, 152.0, 146.4, 144.5, 137.2, 136.1, 128.7, 128.5, 128.1, 127.9, 123.4, 101.1, 61.5, 61.4, 56.6, 53.8, 51.8, 51.0, 38.9, 17.3, 14.1, 14.1 ppm; IR (KBr) ν : 3746, 2983, 2945, 1729, 1651, 1557, 1434, 1347, 1251, 1129, 1088, 841, 732, 709 cm^{-1} ; HRESIMS (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_8$, 535.2075; found, 535.2076.

4,5-Diethyl 3-methyl 1-benzyl-2-methyl-3a-(4-nitrophenyl)-1,3a,4,6a-tetrahydrocyclopenta[b]pyrrole-3,4,5-tricarboxylate (6e): yellow solid, 35%; mp 153–155 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, J = 8.8 Hz, ArH), 7.45–7.37 (m, 5H, ArH), 7.30–7.27 (m, 2H, ArH), 6.70 (s, 1H, CH_2), 5.07–5.05 (m, 1H, CH), 5.00–4.98 (m, 1H, CH), 4.76 (d, J = 15.2 Hz, 1H, CH_2), 4.37 (d, J = 15.6 Hz, 1H, CH_2), 4.29–4.21 (m, 1H, CH_2), 4.21–4.14 (m, 1H, CH_2), 3.91–3.82 (m, 1H, CH_2), 3.82–3.72 (m, 1H, CH_2), 3.69 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3), 1.29 (t, J = 7.2 Hz, CH_3), 0.99 (t, J = 7.2 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.2, 166.1, 163.5, 158.0, 149.9, 146.3, 137.8, 137.4, 135.9, 129.2, 128.5, 128.0, 127.2, 123.0, 101.9, 75.5, 62.9, 61.1, 61.0, 58.3, 50.3, 49.2, 14.1, 13.8, 13.4 ppm; IR (KBr) ν : 3069, 2981, 1736, 1660, 1552, 1514, 1344, 1222, 1121, 1040, 914, 854, 769, 704 cm^{-1} ; HRESIMS (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{30}\text{NaN}_2\text{O}_8$, 557.1894; found, 557.1891.

Supporting Information

The crystallographic data of compounds **4k** (CCDC 2260340), **5a** (CCDC 2260341), and **5f** (CCDC 2260342) have been deposited at the Cambridge Crystallographic Data Center (<https://www.ccdc.cam.ac.uk>).

Supporting Information File 1

Characterization data and ^1H NMR, ^{13}C NMR, HRMS spectra of the synthesized compounds.

[\[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-73-S1.pdf\]](https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-73-S1.pdf)

Funding

This work was financially supported by the National Natural Science Foundation of China (Nos. 21572196, 21871227).

References

- Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094–1106. doi:10.1002/cber.19671000406
- Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907. doi:10.1021/ar020258p
- Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520–530. doi:10.1021/ar0502026
- Kielland, N.; Lavilla, R. *Top. Heterocycl. Chem.* **2010**, *25*, 127–168. doi:10.1007/7081_2010_42
- Shaabani, A.; Maleki, A.; Rezayan, A. H.; Sarvary, A. *Mol. Diversity* **2011**, *15*, 41–68. doi:10.1007/s11030-010-9258-1
- Nair, V.; Deepthi, A.; Ashok, D.; Raveendran, A. E.; Paul, R. R. *Tetrahedron* **2014**, *70*, 3085–3105. doi:10.1016/j.tet.2014.03.014
- Sharma, U. K.; Ranjan, P.; Van der Eycken, E. V.; You, S.-L. *Chem. Soc. Rev.* **2020**, *49*, 8721–8748. doi:10.1039/d0cs00128g
- Piltan, M.; Yavari, I.; Moradi, L. *Chin. Chem. Lett.* **2013**, *24*, 979–983. doi:10.1016/j.ccl.2013.06.023
- Sun, J.; Hu, H.; Wang, F.; Wu, H.; Liu, Y. *RSC Adv.* **2014**, *4*, 36498–36501. doi:10.1039/c4ra06048b
- Xing, Y.; Zhang, M.; Ciccarelli, S.; Lee, J.; Catano, B. *Eur. J. Org. Chem.* **2017**, 781–785. doi:10.1002/ejoc.201601416
- Ghafoori, S. S.; Afshari, M. A.; Saeedi, N.; Djahaniani, H.; Mohtat, B. *Asian J. Chem.* **2013**, *25*, 4111–4112. doi:10.14233/ajchem.2013.13772
- Sun, J.; Wang, F.; Hu, H.; Wang, X.; Wu, H.; Liu, Y. *J. Org. Chem.* **2014**, *79*, 3992–3998. doi:10.1021/jo500456d
- Yang, H.-B.; Guan, X.-Y.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2012**, 2792–2800. doi:10.1002/ejoc.201200185
- Wang, G.-W.; Li, J.-X. *Org. Biomol. Chem.* **2006**, *4*, 4063–4064. doi:10.1039/b612641c
- Douglas, T.; Pordea, A.; Dowden, J. *Org. Lett.* **2017**, *19*, 6396–6399. doi:10.1021/acs.orglett.7b03252
- Dong, S.; Huang, J.; Sha, H.; Qiu, L.; Hu, W.; Xu, X. *Org. Biomol. Chem.* **2020**, *18*, 1926–1932. doi:10.1039/d0ob00222d
- Cheng, B.; Li, Y.; Wang, T.; Zhang, X.; Li, H.; He, Y.; Li, Y.; Zhai, H. *J. Org. Chem.* **2020**, *85*, 6794–6802. doi:10.1021/acs.joc.0c00374
- Heo, N.; Jung, I.; Kim, D. K.; Han, S. H.; Lee, K.; Lee, P. H. *Org. Lett.* **2020**, *22*, 6562–6567. doi:10.1021/acs.orglett.0c02333
- Cheng, B.; Zhang, X.; Li, H.; He, Y.; Li, Y.; Sun, H.; Wang, T.; Zhai, H. *Adv. Synth. Catal.* **2020**, *362*, 4668–4672. doi:10.1002/adsc.202000655
- Duan, S.; Chen, C.; Chen, Y.; Jie, Y.; Luo, H.; Xu, Z.-F.; Cheng, B.; Li, C.-Y. *Org. Chem. Front.* **2021**, *8*, 6962–6967. doi:10.1039/d1qo01237a
- Yavari, I.; Hojati, M.; Azad, L.; Halvaghar, M. *Synlett* **2018**, *29*, 1024–1027. doi:10.1055/s-0037-1609302
- Cao, H.; Cheng, Q.; Studer, A. *Science* **2022**, *378*, 779–785. doi:10.1126/science.ade6029
- Sun, S.; Wei, Y.; Xu, J. *Org. Lett.* **2022**, *24*, 6024–6030. doi:10.1021/acs.orglett.2c02321
- Galeev, A. R.; Moroz, A. A.; Dmitriev, M. V.; Maslivets, A. N. *RSC Adv.* **2022**, *12*, 578–587. doi:10.1039/d1ra08384h
- Li, T.-T.; You, Y.; Sun, T.-J.; Zhang, Y.-P.; Zhao, J.-Q.; Wang, Z.-H.; Yuan, W.-C. *Org. Lett.* **2022**, *24*, 5120–5125. doi:10.1021/acs.orglett.2c01959
- He, B.; Huang, J.; Zhang, J.; Liu, X.; Wang, D.; Sung, H. H. Y.; Liu, Y.; Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Sci. China: Chem.* **2022**, *65*, 789–795. doi:10.1007/s11426-021-1225-4
- Wei, Y.; Sun, S.; Xu, J. *Tetrahedron Lett.* **2023**, *120*, 154444. doi:10.1016/j.tetlet.2023.154444
- He, B.; Huang, J.; Zhang, J.; Sung, H. H. Y.; Lam, J. W. Y.; Zhang, Z.; Yan, S.; Wang, D.; Zhang, J.; Tang, B. Z. *Angew. Chem., Int. Ed.* **2022**, *61*, e202117709. doi:10.1002/anie.202117709
- Yao, Y.; Lin, B.; Wu, M.; Zhang, Y.; Huang, Y.; Han, X.; Weng, Z. *Org. Biomol. Chem.* **2022**, *20*, 8761–8765. doi:10.1039/d2ob01749k
- Sun, S.; Zhang, M.; Xu, J. *Org. Chem. Front.* **2022**, *9*, 3335–3341. doi:10.1039/d2qo00556e
- Kumar, A.; Maurya, R. A. *Tetrahedron* **2008**, *64*, 3477–3482. doi:10.1016/j.tet.2008.02.022
- Yang, S.-H.; Zhao, F.-Y.; Lü, H.-Y.; Deng, J.; Zhang, Z.-H. *J. Heterocycl. Chem.* **2012**, *49*, 1126–1129. doi:10.1002/jhet.953
- Ramesh, D.; Rajaram, S.; Narasimulu, M.; Reddy, T. S.; Mahesh, K. C.; Manasa, G.; Venkateswarlu, Y. *Chin. J. Chem.* **2011**, *29*, 2471–2475. doi:10.1002/cjoc.201100032
- Kumar, A.; Maurya, R. A.; Sharma, S.; Kumar, M.; Bhatia, G. *Eur. J. Med. Chem.* **2010**, *45*, 501–509. doi:10.1016/j.ejmech.2009.10.036
- Lavilla, R.; Carranco, I.; Díaz, J. L.; Bernabeu, M. C.; de la Rosa, G. *Mol. Diversity* **2003**, *6*, 171–175. doi:10.1023/b:modi.0000006756.83821.80
- Di Pietro, O.; Viayna, E.; Vicente-García, E.; Bartolini, M.; Ramón, R.; Juárez-Jiménez, J.; Clos, M. V.; Pérez, B.; Andrisano, V.; Luque, F. J.; Lavilla, R.; Muñoz-Torrero, D. *Eur. J. Med. Chem.* **2014**, *73*, 141–152. doi:10.1016/j.ejmech.2013.12.008
- Vicente-García, E.; Catti, F.; Ramón, R.; Lavilla, R. *Org. Lett.* **2010**, *12*, 860–863. doi:10.1021/ol902913j
- Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458–2462. doi:10.1002/anie.200705300
- Vohra, R. K.; Bruneau, C.; Renaud, J.-L. *Adv. Synth. Catal.* **2006**, *348*, 2571–2574. doi:10.1002/adsc.200600343
- Basu, S.; Chatterjee, S.; Ray, S.; Maity, S.; Ghosh, P.; Bhaumik, A.; Mukhopadhyay, C. *Beilstein J. Org. Chem.* **2022**, *18*, 133–142. doi:10.3762/bjoc.18.14
- Lavilla, R.; Bernabeu, M. C.; Carranco, I.; Díaz, J. L. *Org. Lett.* **2003**, *5*, 717–720. doi:10.1021/ol027545d
- Carranco, I.; Díaz, J. L.; Jiménez, O.; Vendrell, M.; Albericio, F.; Royo, M.; Lavilla, R. *J. Comb. Chem.* **2005**, *7*, 33–41. doi:10.1021/cc049877a
- Maiti, S.; Sridharan, V.; Menéndez, J. C. *J. Comb. Chem.* **2010**, *12*, 713–722. doi:10.1021/cc100084b
- Islam, K.; Das, D. K.; Akram, E.; Khan, A. T. *Synthesis* **2015**, *47*, 2745–2755. doi:10.1055/s-0034-1380431
- Sun, J.; Sun, Y.; Gong, H.; Xie, Y.-J.; Yan, C.-G. *Org. Lett.* **2012**, *14*, 5172–5175. doi:10.1021/ol302530m
- Sun, J.; Gong, H.; Sun, Y.; Yan, C.-G. *Mol. Diversity* **2013**, *17*, 627–639. doi:10.1007/s11030-013-9459-5
- Sun, J.; Gong, H.; Yan, C.-G. *Tetrahedron* **2013**, *69*, 10235–10244. doi:10.1016/j.tet.2013.10.044
- Sun, J.; Zhu, D.; Gong, H.; Yan, C.-G. *Tetrahedron* **2013**, *69*, 10565–10572. doi:10.1016/j.tet.2013.10.040

49. Gong, H.; Sun, J.; Yan, C.-G. *Tetrahedron* **2014**, *70*, 6641–6650. doi:10.1016/j.tet.2014.06.097
50. Yang, F.; Zhang, L.-J.; Yan, C.-G. *RSC Adv.* **2014**, *4*, 64466–64475. doi:10.1039/c4ra12278j
51. Sun, J.; Sun, Y.; Gong, H.; Yan, C.-G. *J. Heterocycl. Chem.* **2015**, *52*, 1278–1285. doi:10.1002/jhet.2140
52. Zhu, D.; Sun, J.; Yan, C.-G. *Synthesis* **2015**, *47*, 193–198. doi:10.1055/s-0034-1379234
53. Sun, J.; Gong, H.; Yan, C. *Chin. J. Chem.* **2015**, *33*, 1049–1056. doi:10.1002/cjoc.201500332
54. Yang, F.; Sun, J.; Yan, C. *Chin. J. Chem.* **2015**, *33*, 1371–1379. doi:10.1002/cjoc.201500664
55. Zhang, Y.-Y.; Han, Y.; Sun, J.; Yan, C.-G. *ChemistrySelect* **2017**, *2*, 7382–7386. doi:10.1002/slct.201701348
56. Fang, H.-L.; Sun, J.; Yan, C.-G. *ChemistrySelect* **2021**, *6*, 10537–10541. doi:10.1002/slct.202102255
57. Xu, F.-S.; Yan, C.; Sun, J.; Yan, C.-G. *New J. Chem.* **2021**, *45*, 19666–19670. doi:10.1039/d1nj03772b
58. Zheng, H.; Han, Y.; Sun, J.; Yan, C.-G. *Chin. Chem. Lett.* **2021**, *32*, 1683–1686. doi:10.1016/j.cclet.2020.12.024
59. Liu, D.; Sun, J.; Xie, J.; Shi, H.; Yan, C.-G. *J. Org. Chem.* **2021**, *86*, 1827–1842. doi:10.1021/acs.joc.0c02645
60. Han, Y.; Zheng, H.; Zhang, Y.-Y.; Yan, C.-G. *Chin. Chem. Lett.* **2020**, *31*, 1337–1341. doi:10.1016/j.cclet.2019.10.042
61. Zheng, H.; Han, Y.; Sun, J.; Yan, C.-G. *Beilstein J. Org. Chem.* **2022**, *18*, 669–679. doi:10.3762/bjoc.18.68
62. Zheng, H.; Han, Y.; Sun, J.; Yan, C.-G. *Beilstein J. Org. Chem.* **2022**, *18*, 991–998. doi:10.3762/bjoc.18.99
63. Liu, X.; Sun, J.; Yan, C.-G. *New J. Chem.* **2022**, *46*, 11877–11882. doi:10.1039/d2nj01135b
64. Zhan, S.-C.; Fang, R.-J.; Sun, J.; Yan, C.-G. *Beilstein J. Org. Chem.* **2022**, *18*, 796–808. doi:10.3762/bjoc.18.80

License and Terms

This is an open access article licensed under the terms of the Beilstein-Institut Open Access License Agreement (<https://www.beilstein-journals.org/bjoc/terms>), which is identical to the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0>). The reuse of material under this license requires that the author(s), source and license are credited. Third-party material in this article could be subject to other licenses (typically indicated in the credit line), and in this case, users are required to obtain permission from the license holder to reuse the material.

The definitive version of this article is the electronic one which can be found at:
<https://doi.org/10.3762/bjoc.19.73>