Chinese Chemical Letters 34 (2023) 107778

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Benzisoxazole core and benzoxazolopyrrolidine *via* HDDA-derived benzyne with PTIO/DMPO

Yu Lei, Wenjing Zhu, Yajuan Zhang, Qiong Hu, Jie Dong, Yimin Hu*

Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, State Laboratory Cultivation Base, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, China

ARTICLE INFO

Article history:
Received 16 May 2022
Revised 19 August 2022
Accepted 23 August 2022
Available online 25 August 2022

Keywords:
Benzisoxazole
HDDA reaction
Benzyne
Nitrone
Heterocycle

ABSTRACT

A novel method for HDDA-derived benzyne trapped by nitrone was developed. This research described a simple and efficient pathway for the synthesis of benzisoxazoles from arynes and PTIO (2-phenyl-4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyl), C–C and C–O bonds were formed in a single step without catalyst under mild conditions. The unexpected cleavage of C–N bond contributed to the formation of isoxazole ring, as indicated by DFT studies. Furthermore, we obtained the structure of benzoxazolopyrrolidine when the trapping agent is DMPO (5,5-dimethyl-1-pyrroline *N*-oxide).

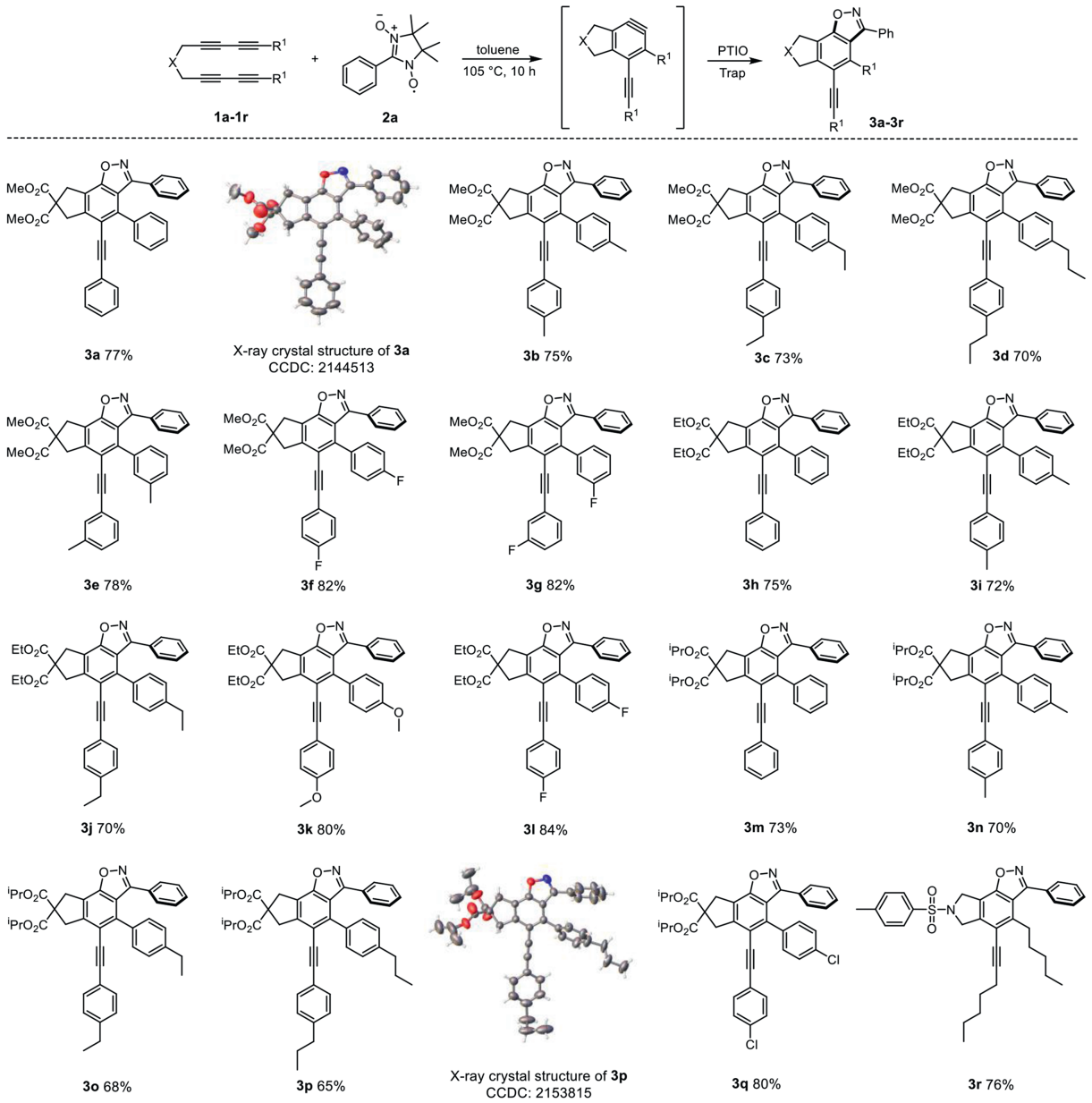
Functionalized isoxazoles have a broad spectrum of biological and pharmacological properties [1–5] and are thus an important component of natural products and small-molecule drugs [6–10], such as paliperidone, risperidone, iloperidone, which are drugs for treating psychosis; zoliflodacin, an antibacterial agent; and zonisamide is anticonvulsant (Fig. 1a). These drugs are benzisoxazoles. To date, chemists have conducted extensive research for the synthesis of benzisoxazoles. These processes involve two main strategies: metal-catalyzed intramolecular or intermolecular cyclization reaction [11–15] and intra- or intermolecular cyclization under alkaline or acidic conditions [16–20]. The medical value of bioactive molecules containing benzisoxazole structure is very extensive, which is the focus of scientists' research, these reported novel and efficient methods have made great contributions, however a strategy for synthesizing benzisoxazole under mild conditions without metal remains significant.

The hexadehydro-Diels–Alder reaction (HDDA), proposed by Hoye, has created a new field of benzyne chemistry [21–24]. Compared with the principle of D–A reaction, in HDDA reaction, diyne and diynophile portions are connected by a tether, a benzyne intermediate is formed through a thermodynamic intramolecular cycloaddition process induced by triyne or tetrayne precursors [25–28]. A benzyne intermediate can be obtained by heating without any reagent and then traped by much more active substances to form a series of polyfunctionalized aromatic compounds [29–33]. Here we report a novel method for synthesizing a series of heterocycles from HDDA reaction/Kobayashi method-derived benzynes and nitrones (Fig. 1b). The formation of the benzisoxazole skeleton relies upon the trapping of the benzyne intermediate by a molecule containing an O–N–C tether [16,19], and effective attack site is equally important. PTIO (2-phenyl-4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyl) [34,35] may be a suitable trapping agent owing to unstable valence state and nitrone [36–38] property.

To our delight, the strategy is effective and feasible indeed, as confirmed by experimental results. Under the optimal reaction conditions, 1.0 equiv. of tetrayne precursor and 1.1 equiv. of PTIO were dissolved in toluene, reacted at 105 °C for 10 h through magnetic stirring. Eighteen functionalized benzisoxazole derivatives (Scheme 1) were obtained in good yield (65%-84%), which indicated that different functional groups of C-tetrayne reacted well with PTIO. In fact, the yield of this reaction was affected by the substituent R^1 of tetrayne precursor more. Experimental results indicated that the yield of the synthesized product is higher in the presence of the electron-withdrawing group (*para*-F, *meta*-F and *para*-Cl) on the benzene ring than the electron-donating group [39], such as compounds **3f**, **3g**, **3l** and **3q**. We speculate that the electron-withdrawing group polarizes the triple bond of benzyne to increase the reactivity of cycloaddition process [40], and the preferred attack site is the more accessible aryne carbon due to effect of steric hindrance [41]. Then we tried to use *N*-tetrayne-derived benzyne instead of C-tetrayne, fortunately target product **3r** was obtained. Moreover, the structure of compounds

* Corresponding author.
E-mail addresses: yiminhu@ahnu.edu.cn, yiminhu@aliyun.com (Y. Hu).

https://doi.org/10.1016/j.cclet.2022.107778
1001-8417/



Scheme 1. Preparation of benzisoxazoles *via* HDDA reaction. Reaction conditions: tetraynes **1a**-**1r** (1.0 mmol), PTIO **2a** (1.1 equiv.), toluene (3 mL), stirred at 105 °C for 10 h. Isolated yield.

3a (CCDC: 2144513) and **3p** (CCDC: 2153815) were unambiguously confirmed by X-ray diffraction techniques (CCDC contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre).

Then we verified the general applicability of benzyne by using Kobayashi aryne precursors [42,43]. Fortunately, through the brief screening of reaction parameters, molar ratio, fluoride source, solvent, time and temperature, we obtained a series of target products and established the optimal condition: Kobayashi method-derived benzyne precursor (1.0 equiv.), PTIO (1.1 equiv.), 18-crown-6 ether (2.0 equiv.) and CsF (2.0 equiv.) as the fluoride source, dissolved in acetonitrile and react at 70 °C for 12 h. Aryne precursors containing electron-withdrawing group and electron-donating group participated in this reaction successfully. The isolated yield of this reaction was in the range of 61%-78% (Scheme 2), of which the lowest yield was compound **5f** likely because the instability of the highly reactive 4,5-dimethoxybenzyne intermediate. Besides, a mixture of regioisomers **5b/5b'** at a ratio of 1.7:1 was obtained by using unsymmetrical 4-methylbenzyne, the regioisomer ratios were determined by ^{1}H NMR analysis because individual isomer was unable to separate. Experimental results indicated that the benzynes derived from the classical method can also participate in this reaction well to generate a series of benzisoxazoles. The structure of **5d** (CCDC: 2168299) was confirmed by X-ray diffraction techniques.

Unexpected scission of chemical bonds of PTIO contributed to the success of this reaction, likely because the instability of nitroxyl radical from PTIO. To verify this idea, we attempted to use another nitrone DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) as trapping agent, reacted with different tetraynes (Scheme 3). 1.0 equiv. of tetrayne precursor and 1.1 equiv. of DMPO were dissolved in toluene, reacted at 100 °C for 8 h through magnetic stirring. In this reaction DMPO reacted with tetraynes to obtain 6 benzoxazolopyrrolidine [44–46] derivatives at good yield (71%-81%) under optimal reaction conditions, and both C-tetrayne and *N*-tetrayne

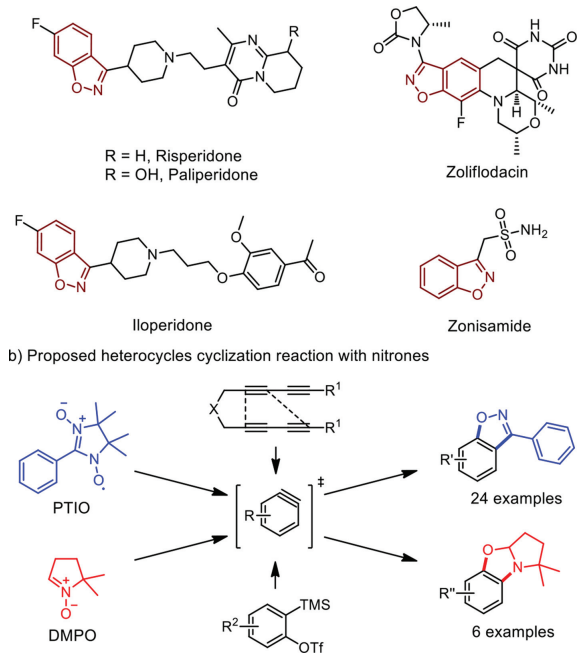
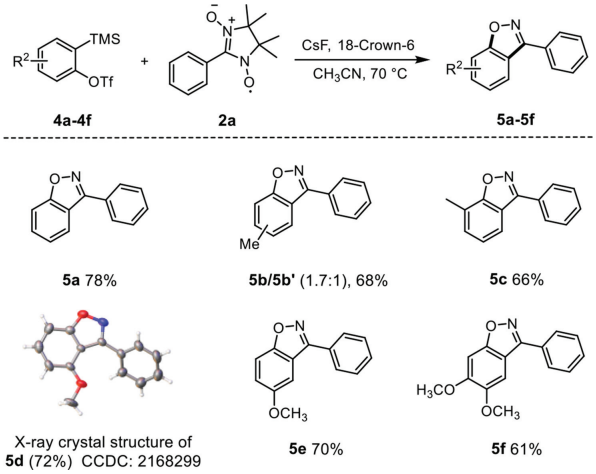


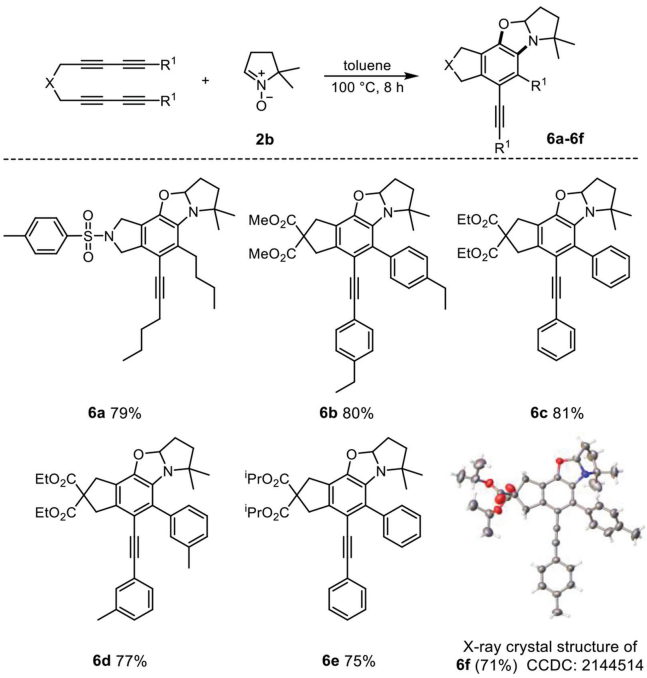
Fig. 1. Selected biologically active scaffolds containing benzisoxazole and our work.

substrates worked well. With DMPO, the experimental results were completely different from PTIO, which likely because under the elevated temperature of this reaction mixture, the DMPO was in thermal equilibrium with its valence bond isomer, the oxaziridine, that engaged with the benzyne faster than the nitrone isomer [47]. Further work on the expansion of this research is still in progress. Moreover, the structure of compound **6f** (CCDC: 2144514) was unambiguously confirmed by X-ray diffraction techniques.

A reasonable mechanism was provided based on the experimental evidence, and density functional theory calculations at the B3LYP-D3(BJ)/6-311+G(2d,p) level of theory were performed to relative free-energy profiles for the reaction of tetraynes and PTIO (Fig. 2). We used tetrayne **1a**-derived benzyne as the starting point and set the relative free-energy of **IN1** to 0. First, **1a** was engaged in thermodynamic cycloisomerization to produce the highly reactive benzyne intermediate **IN1** to form intermediate **IN2** by reaction with PTIO **2a** through a 1,3-dipolar cyclization process



Scheme 2. Preparation of benzisoxazoles *via* Kobayashi method. Reaction conditions: Kobayashi method-derived benzyne precursors **4a**-**4f** (1.0 mmol), PTIO **2a** (1.1 equiv.), 18-crown-6 ether (2.0 equiv.), CsF (2.0 equiv.), CH_3CN (5 mL), stirred at 70 °C for 12 h. Isolated yield.



Scheme 3. Preparation of benzoxazolopyrrolidines *via* HDDA reaction. Reaction conditions: tetraynes (1.0 mmol), DMPO **2b** (1.1 equiv.), toluene (3 mL), stirred at 100 °C for 8 h. Isolated yield.

[48–52]. Then, the opening process of PTIO five-membered ring was initiated by oxygen free radical, which conducted consecutive twice β-fragmentations to form isoxazole ring through **TS1**. The energy barrier of **TS1** was computed to be 36.86 kcal/mol, which is the most critical transition state from all of these processes. Finally, the benzisoxazole derivative **3a** was obtained, and an unstable nitroxide compound was formed through the homolytic cleavage of C–N bonds concurrently. Theoretically, the energy barrier of each step was feasible at 105 °C.

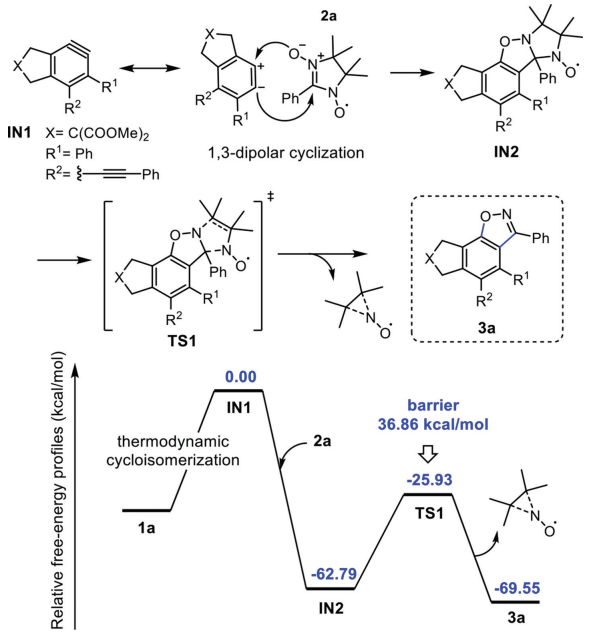


Fig. 2. Proposed mechanism and relative free-energy profiles for the reaction of benzyne derived from tetrayne **1a** and PTIO **2a**.

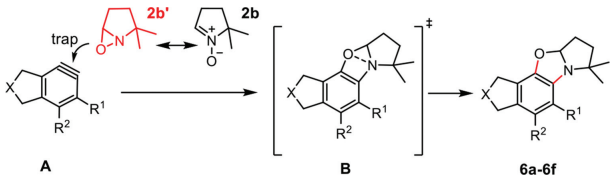


Fig. 3. Proposed mechanism for the reaction of benzyne derived from tetraynes and DMPO **2b**.

Then, a plausible mechanism for the reaction *via* arynes and DMPO was provided (Fig. 3). DMPO **2b** was in thermal equilibrium with its valence bond isomer **2b'** under the elevated temperature of this reaction mixture [47]. HDDA-derived benzyne intermediate **INA** was trapped by **2b'** to form product *via* a four-membered ring-containing transition state **TSB** underwent [2 + 2] cycloaddition process. Finally, five-membered heterocyclic ring was formed to generate the benzoxazolopyrrolidine derivatives **6a-6f**.

In summary, we have proposed a feasible and efficient method for synthesizing benzisoxazoles from HDDA reaction/Kobayashi method-derived benzynes and PTIO, and this strategy was found effective under mild conditions without metal catalyst, density functional theory calculations confirmed that unexpected cleavage of C−N bonds contributed to the formation of isoxazole ring. Besides, we obtained an unanticipated gain by using another nitrone DMPO, this reaction underwent a [2 + 2] cycloaddition process, leading to the formation of benzoxazolopyrrolidine. The transformation by using benzyne and nitrone promote the development of HDDA reaction and this strategy may be a novel method for synthesizing benzenoid bioactive heterocycles under mild conditions. Our group will continue to make exploitation in this field.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We greatly acknowledge the National Natural Science Foundation of China (No. 22071001), The Research Culture Funds of Anhui Normal University, and Department of Human Resources of Anhui Province for financial support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107778.

References

[1] Y. Chen, Y. Lan, X.D. Cao, et al., Med. Chem. Commun. 6 (2015) 831–838.
[2] M.A. Barmade, P.R. Murumkar, M.K. Sharma, M.R. Yadav, Curr. Top. Med. Chem. 16 (2016) 2863–2883.
[3] A. Sysak, B. Obmińska-Mrukowicz, Eur. J. Med. Chem. 137 (2017) 292–309.
[4] M.D. Delost, D.T. Smith, B.J. Anderson, J.T. Njardarson, J. Med. Chem. 61 (2018) 10996–11020.
[5] G.C. Arya, K. Kaur, V. Jaitak, Eur. J. Med. Chem. 221 (2021) 113511.
[6] X.Y. Guo, G. Liu, Chin. Chem. Lett. 24 (2013) 295–298.
[7] R. Di Santo, Nat. Prod. Rep. 27 (2010) 1084–1098.
[8] R. Suhas, S. Chandrashekar, D.C. Gowda, Eur. J. Med. Chem. 46 (2011) 704–711.
[9] C. Kesornpun, T. Aree, C. Mahidol, S. Ruchirawat, P. Kittakoopet, Angew. Chem. Int. Ed. 55 (2016) 3997–4001.
[10] X.D. Cao, Y. Chen, Y.F. Zhang, et al., Eur. J. Med. Chem. 124 (2016) 713–728.
[11] F. Himo, T. Lovell, R. Hilgraf, et al., J. Am. Chem. Soc. 127 (2005) 210–216.
[12] P. De, K.Pandurangan Nonappa, U. Maitra, S. Waileset, Org. Lett. 9 (2007) 2767–2770.
[13] S. Udd, R. Jokela, R. Franzén, J. Tois, Tetrahedron Lett. 51 (2010) 1030–1033.
[14] P.P. Duan, Y.F. Yang, R. Ben, et al., Chem. Sci. 5 (2014) 1574–1578.
[15] G.F. Chen, H. Liu, S.J. Li, et al., Org. Lett. 19 (2017) 1792–1795.
[16] C. Spiteri, P. Sharma, F.Z. Zhang, et al., Chem. Commun. 46 (2010) 1272–1274.
[17] C.Y. Chen, T. Andreani, H.M. Li, Org. Lett. 13 (2011) 6300–6303.
[18] W.J. Ang, C.Y. Chu, T.C. Chou, L.C. Lo, Y. Lam, Green Chem. 15 (2013) 780–785.
[19] A.V. Dubrovskiy, P. Jain, F. Shi, et al., ACS Comb. Sci. 15 (2013) 193–201.
[20] G. Shan, G.Y. Huang, Y. Rao, H. Zhang, Chin. Chem. Lett. 26 (2015) 1236–1240.
[21] T.R. Hoye, B. Baire, D.W. Niu, P.H. Willoughby, B.P. Woods, Nature 490 (2012) 208–212.
[22] C. Holden, M.F. Greaney, Angew. Chem. Int. Ed. 53 (2014) 5746–5749.
[23] O.J. Diamond, T.B. Marder, Org. Chem. Front. 4 (2017) 891–910.
[24] L.L. Fluegel, T.R. Hoye, Chem. Rev. 121 (2021) 2413–2444.
[25] B.P. Woods, B. Baire, T.R. Hoye, Org. Lett. 16 (2014) 4578–4581.
[26] Q.L. Nguyen, B. Baire, T.R. Hoye, Tetrahedron Lett. 56 (2015) 3265–3267.
[27] D.J. Marell, L.R. Furan, B.P. Woods, et al., J. Org. Chem. 80 (2015) 11744–11754.
[28] T. Wang, D.W. Niu, T.R. Hoye, J. Am. Chem. Soc. 138 (2016) 7832–7835.
[29] B.H. Liu, C.Y. Mao, Q. Hu, L.L. Yao, Y.M. Hu, Org. Chem. Front. 6 (2019) 2788–2791.
[30] B.H. Liu, Q. Hu, F.H. Yang, X.J. Zheng, Y.M. Hu, Chin. Chem. Lett. 31 (2020) 1305–1308.
[31] L.L. Yao, Q. Hu, Y. Lei, L. Bao, Y.M. Hu, Org. Chem. Front. 7 (2020) 3633–3637.
[32] L.L. Yao, B. Fang, Q. Hu, et al., Chem. Commun. 56 (2020) 15185–15188.
[33] X.J. Zheng, B.H. Liu, F.H. Yang, et al., Org. Lett. 22 (2020) 956–959.
[34] X.C. Li, J. Agric. Food Chem. 65 (2017) 6288–6297.
[35] I. Nakanishi, Y. Shoji, K. Ohkubo, et al., Chem. Commun. 56 (2020) 11505–11507.
[36] Y. Fu, H.Y. Zhang, Y.H. Liu, et al., Chin. Chem. Lett. 21 (2010) 1075–1078.
[37] Q.K. Wu, Y.X. Li, Y.M. Jia, C.Y. Yu, Chin. Chem. Lett. 28 (2017) 909–912.
[38] S.I. Murahashi, Y. Imada, Chem. Rev. 119 (2019) 4684–4716.
[39] L.L. Yao, Q. Hu, L. Bao, W.J. Zhu, Y.M. Hu, Org. Lett. 23 (2021) 4971–4975.
[40] J.M. Medina, J.L. Mackey, N.K. Garg, K.N. Houk, J. Am. Chem. Soc. 136 (2014) 15798–15805.
[41] S.M. Bronner, J.L. Mackey, K.N. Houk, N.K. Garg, J. Am. Chem. Soc. 134 (2012) 13966–13969.
[42] Y. Himeshima, T. Sonoda, H. Kobayashi, Chem. Lett. 12 (1983) 1211–1214.
[43] J.R. Shi, L.G. Li, Y. Li, Chem. Rev. 121 (2021) 3892–4044.
[44] K.J. Falci, R.W. Franck, G.P. Smith, J. Org. Chem. 42 (1977) 3317–3319.
[45] Y.G. Chen, M.G. Steinmetz, Org. Lett. 7 (2005) 3729–3732.
[46] I. Kumar, RSC Adv. 4 (2014) 16397–16408.
[47] N. Coşkun, M. Ay, Heterocycles 48 (1998) 537–544.
[48] T. Matsumoto, T. Sohma, S. Hatazaki, K. Suzuki, Synlett 11 (1993) 843–846.
[49] A.M.A. Hameed, Chin. Chem. Lett. 23 (2012) 411–414.
[50] J.S. Barber, E.D. Styduhar, H.V. Pham, et al., J. Am. Chem. Soc. 138 (2016) 2512–2515.
[51] Z.H. Wang, H.H. Zhang, P.F. Xu, Y.C. Luo, Chem. Commun. 54 (2018) 10128–10131.
[52] Z.N. Zhao, Z. Ou, S.J. Kalita, et al., Chin. Chem. Lett. 33 (2022) 3012–3016.