Chinese Chemical Letters 34 (2023) 107599

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Photocatalyst-free visible-light-mediated three-component reaction of α-diazoesters, cyclic ethers and NaSCN to access organic thiocyanates

Zhiwei Wang[a,1], Na Meng[a,1], Yufen Lv[a], Wei Wei[a,b,*], Huilan Yue[b,*], Guofu Zhong[a,*]

[a] School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, China
[b] Qinghai Provincial Key Laboratory of Tibetan Medicine Research and CAS Key Laboratory of Tibetan Medicine Research, Northwest Institute of Plateau Biology, Xining 810008, China

ARTICLE INFO

Article history:
Received 18 April 2022
Revised 2 June 2022
Accepted 8 June 2022
Available online 13 June 2022

Keywords:
Photocatalyst-free
Visible-light
Three-component reaction
Organic thiocyanates

ABSTRACT

A facile and environmentally friendly visible-light-induced three-component reaction of α-diazoesters, cyclic ethers and NaSCN to construct organic thiocyanates has been developed at room temperature. This reaction could occur under photocatalyst- and additive-free conditions to afford a number of organic thiocyanates with moderate to good yield and favorable functional group tolerance.

As highly valuable functionalities, thiocyanates are widely existed in the core structural motifs of a wide range of natural products and biologically active molecules, such as Psammaplin B, 9-thiocyanato pupukeanane, and fasicularin (Fig. 1) [1–5]. More importantly, organic thiocyanates are also key intermediates in organic synthesis since they can be readily transformed to a variety of sulfur-containing derivatives including thiocarbamates [6,7], thioethers [8,9], thionitriles [10], and sulfur heterocycles, *etc.* [11–13].

Owing to their importance in pharmaceuticals and synthetic chemistry, numerous synthetic strategies have been exploited for the synthesis of organic thiocyanates. Generally, organic thiocyanates are prepared by the nucleophilic substitutions of alkyl halides with thiocyanide, trimethylsilyl isothiocyanate or acyl isothiocyanates [14–18]. In recent years, some alternative synthetic methods have been developed for the synthesis of organic thiocyanates through the thiocyanation of enaminones [19,20], alkylboronic acids [21], epoxides [22], alkenes [23–25], ketones [26–28], and arenes [29,30] using a variety of thiocyanating reagents under different reaction conditions. Nevertheless, most of the above-mentioned reactions involve the use of transition metals, strong oxidants, corrosive halogen reagents, or strong acids, which have negative environmental impacts. Thus, the development of a mild, facile and environmentally benign thiocyanation procedure from easily available substrates is highly desirable.

As abundant and clean energy source, visible light has been extensively utilized for promoting various synthetic transformations under mild and environmentally friendly conditions [11,31–47]. α-Diazoesters are easily prepared, handled and colored compounds, which are increasingly used in photoinduced reactions to construct a number of valuable organic compounds *via* free carbene intermediates at room temperature [48,57]. With our continuous interests in photochemical reactions [58–60] and synthesis of organosulfur compounds [61–63], herein, we wish to report a new and photocatalyst-free strategy for the assembly of organic thiocyanates *via* three-component reaction of α-diazoesters, cyclic ethers and NaSCN (Scheme 1). This methodology provides a mild and efficient approach to access a series of diverse organic thiocyanates without requiring the use of any metal reagent, oxidant, and additive.

Initially, 1-methyl phenyldiazoacetate and KSCN were chosen as the model substrates to screen the reaction conditions by the irradiation of 3 W blue LED lamps at room temperature. The three-component product **4a** was isolated in 27% yield when the reaction was carried out in THF by using of Eosin B (2 mol%) as the photocatalyst (Table 1, entry 1). Then, other photocatalysts such as Rose Bengal, Eosin Y, 4CzIPN and Acridine Red were examined, and the result showed the yield of product **4a** was not obviously increased (Table 1, entries 2–5). To our delight, the reaction efficiency was greatly improved when reaction was conducted in the absence of photocatalyst (Table 1, entry 6). Encouraged by this result, other

* Corresponding authors.
E-mail addresses: weiweiqfnu@163.com (W. Wei), hlyue@nwipb.cas.cn (H. Yue), guofuzhong@eias.ac.cn (G. Zhong).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cclet.2022.06.022
1001-8417/

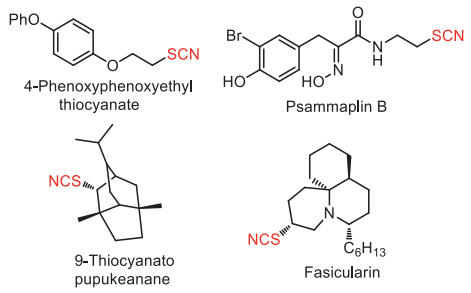
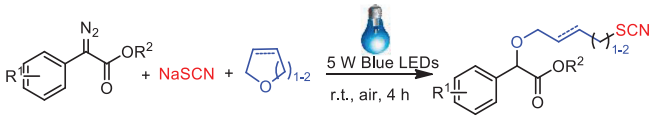
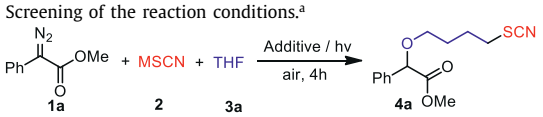


Fig. 1. Biologically active molecules.



Scheme 1. Visible-light-induced three-component reaction of α-diazoesters, cyclic ethers and NaSCN to synthesize organic thiocyanates.

Table 1
Screening of the reaction conditions.[a]



Entry	Additive	MSCN	Solvent	Yield (%)
1	Eosin B (2 mol%)	KSCN	THF	27
2	Rose Bengal (2 mol%)	KSCN	THF	21
3	Eosin Y (2 mol%)	KSCN	THF	15
4	4CzIPN (2 mol%)	KSCN	THF	19
5	Acridine Red (2 mol%)	KSCN	THF	33
6	–	KSCN	THF	56
7	–	NH_4SCN	THF	67
8	–	NaSCN	THF	75
9	Cs_2CO_3 (1 equiv.)	NaSCN	THF	20
10	DABCO (1 equiv.)	NaSCN	THF	14
11	–	NaSCN	THF	35[b]
12	–	NaSCN	THF	30[c]
13	–	NaSCN	THF	69[d]
14	–	NaSCN	THF	70[e]
15	–	NaSCN	THF	78[f]
16	–	NaSCN	THF	0[g]
17	–	NaSCN	THF	57[h]
18	–	NaSCN	DCE/THF (1:1)	24
19	–	NaSCN	CH_2Cl_2/THF (1:1)	23
20	–	NaSCN	CH_3CN/THF (1:1)	5
21	–	NaSCN	DMF/THF (1:1)	10
22	–	NaSCN	toluene/THF (1:1)	7
23	–	NaSCN	DCE/THF (1:2)	47
24	–	NaSCN	DCE/THF (1:4)	61

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), additive, solvent (2 mL), 3 W blue LED lamps, r.t., 4 h. Isolated yields based on **1a**.
[b] 3 W green LEDs.
[c] 3 W white LEDs.
[d] 32 W blue LEDs.
[e] 10 W blue LEDs.
[f] 5 W blue LEDs.
[g] Without light irradiation.
[h] Under N_2.

thiocyanating reagents such as NH_4SCN and NaSCN were further investigated, and result demonstrated that the use of NaSCN could increase the yield of product **4a** to 75% (Table 1, entry 8). The addition of base such as Cs_2CO_3 or DABCO did not improve the reaction efficiency (Table 1, entries 9 and 10). Next, the low yield was detected when other light sources such as green LEDs and white LEDs were employed in this reaction (Table 1, entries 11 and 12). The highest yield (78%) was obtained when reaction was performed under the irradiation of 5 W blue LED lamps (Table 1, entry 15). No transformation was observed without light-irradiation (Table 1, entry 16). Furthermore, the desired product **5a** was obtained in 57% yield when the model reaction was conducted under nitrogen atmosphere (Table 1, entry 17). Finally, the screening of a number of mixed solvents found that the mixture of other organic solvents with THF gave the relatively low reaction efficiency (Table 1, entries 18-24).

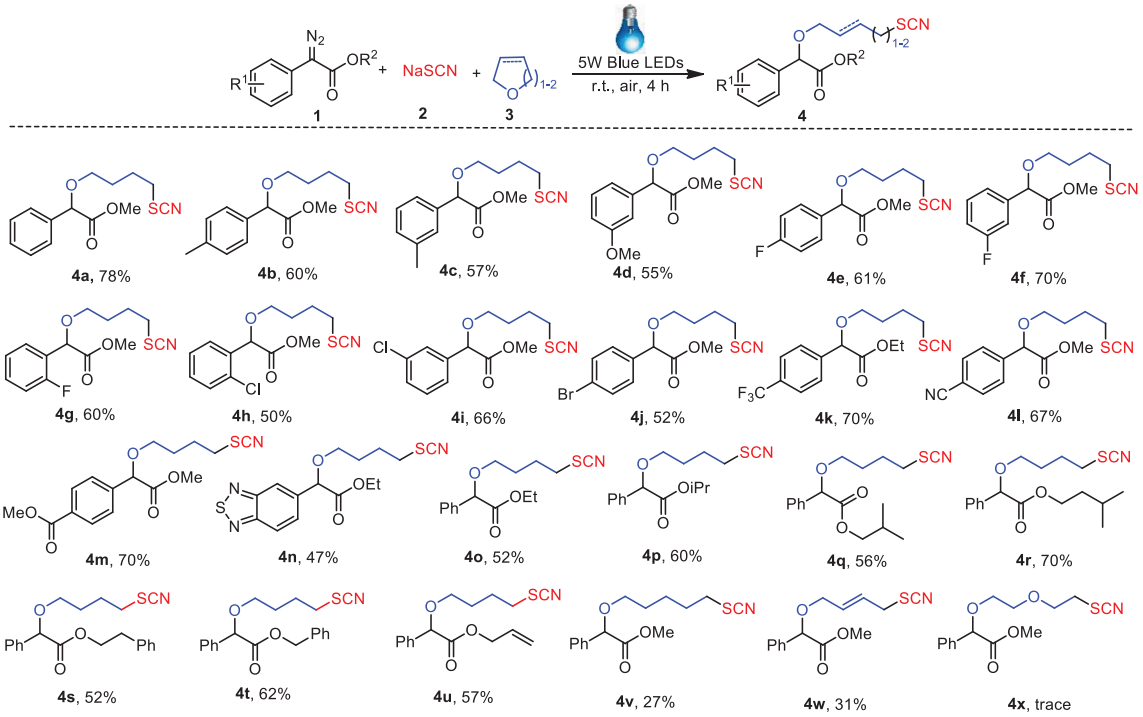
With the above optimal conditions in hand, we further examined the scope of this visible-light mediated three-component reaction of α-diazoesters, NaSCN, and cyclic ethers. As shown in Scheme 2, in general, the reaction of α-diazoesters with various electron-donating and electron-withdrawing substituents on the phenyl ring were efficiently converted into the corresponding products **4b**-**4m** in moderate to good yields. Notably, some functional groups such as -Cl, -F, -Br, $-CF_3$, -C(O)OMe and -CN groups could be well accommodated in the present procedure, which could be further utilized for subsequent modification. Furthermore, the reaction could also be extended to heteroarylcycle α-diazoester, and the desired product **4n** could be obtained in 47% yield. Moreover, a series of substituents at ester group of α-diazoester were also examined. It was found that alkyl groups such as ethyl, isopropyl, isobutyl, 2-phenylethyl, benzyl, isopentyl, and allyl groups were all compatible with this process to give the corresponding products **4o**-**4u** in 52%-70% yields. Unfortunately, the reaction was not expanded to other diazo compounds such as 2-diazo-1-phenylbutane-1,3-dione. Finally, other cyclic ethers were also evaluated under the standard conditions. In addition to THF, cyclic ethers including tetrahydropyran and 2,5-dihydrofuran were also suitable substrates, providing the corresponding products **4v** and **4w** in 27% and 31% yields. Nevertheless, only a trace amount of product **4x** was detected when 1,4-dioxane was employed in the present reaction system, which might be caused by the weaker nucleophilicity of 1,4-dioxane. Moreover, when acyclic ethers such as *n*-butyl ether and diethyl ether were investigated in this system, none of the desired products were detected.

Some control experiments were further carried out to understand the possible reaction mechanism (Scheme 3). Firstly, deuterium experiment with D_2O was conducted in anhydrous THF to investigate the hydrogen source of α-carbon hydrogen at ester (Scheme 3a), and the deuteration phenomenon was observed by ^1H NMR (see Supporting information). The result suggested that proton at α-position of ester derived from water in solvent. Furthermore, when radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added in this system, the model reaction was not suppressed and the product **4a** was still obtained in 70% yield (Scheme 3b). This result indicated that this three-component reaction might not involve a radical process. Moreover, the result of On/Off light-illumination experiments showed that the continuous visible-light irradiation was important for promoting this three-component reaction (Fig. 2).

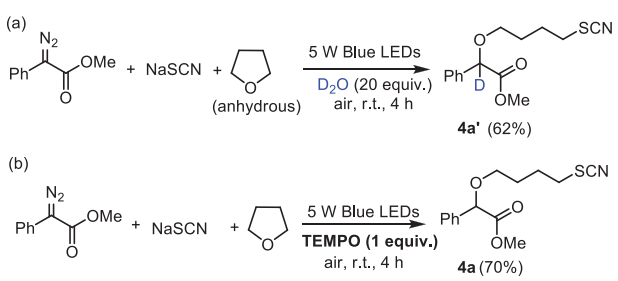
To demonstrate the synthetic utility of this method, the model product **4a** was treated with $Ph_2P(O)H$ in the presence of DBU, and an enzymatically stable phosphate analogue, phosphonothioate A was obtained in 60% yield (Scheme 4).

On the basis of the above results and previous reports [48–56], a plausible mechanism was proposed as demonstrated in Scheme 5. Firstly, an excited state **1a*** was generated from α-diazoester **1a** under the irradiation of blue light. Subsequently, the carbene intermediate **5a** was formed through the decomposition of an excited state **1a***. Then, the interaction of THF with carbene intermediate **5a** would lead to the formation of oxonium ylide intermediate **6a**, which was attacked by NaSCN **2a** to afford carbon anion intermediate **7a**. Finally, the product **4a** was produced from carbon anion intermediate **7a** by hydrogen abstraction from water in solvent.

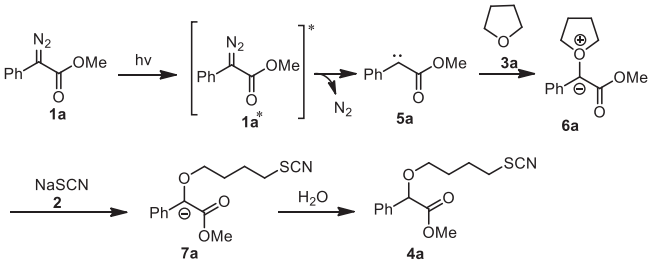
In summary, we have presented a facile and environmentally friendly visible-light-induced method for the assembly of organic



Scheme 2. Substrate scope. Reaction condition: α-diazoester **1** (0.2 mmol), NaSCN **2** (0.4 mmol), cyclic ethers **3** (2 mL), 5 W blue LED lamps, r.t., air, 4 h. Isolated yields based on **1**.



Scheme 3. Control experiments.



Scheme 5. Possible reaction pathway.

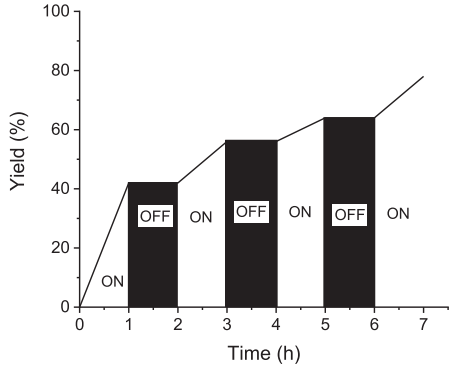


Fig. 2. On/off experiments.

Scheme 4. Synthetic transformation.

thiocyanates from α-diazoesters, cyclic ethers and NaSCN. This three-component reaction could undergo smoothly under mild conditions to afford a series of structurally diverse organic thiocyanates in moderate to good yields. The methodology features short reaction time, green energy source, good functional group tolerance, and photocatalyst-free conditions. Further investigation on the reaction mechanism and the synthetic application is ongoing in our group.

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

This work was supported by the program of Science and Technology International Cooperation Project of Qinghai Province (No. 2022-HZ-813), the Youth Innovation and Technology Project of High School in Shandong Province (No. 2019KJC021), the Natural Science Foundation of Shandong Province (No. ZR2021MB065), and the National Natural Science Foundation of China (No. 31900298).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.06.022.

References

[1] S. Dutta, H. Abe, S. Aoyagi, C. Kibayashi, K.S. Gates, J. Am. Chem. Soc. 127 (2005) 15004–15005.
[2] M. Burow, A. Bergner, J. Gershenzon, U. Wittstock, Plant Mol. Biol. 63 (2006) 49–61.
[3] Y. Yasman, R.A. Edrada, V. Wray, P. Proksch, J. Nat. Prod. 66 (2003) 1512–1523.
[4] J.R. Falck, S.H. Gao, R.N. Prasad, S.R. Koduru, Bioorg. Med. Chem. Lett. 18 (2008) 1768–1771.
[5] E. Elhalem, B.N. Bailey, R. Docampoet, et al., J. Med. Chem. 45 (2002) 3984–3999.
[6] Y.G. Kim, H.N. Lim, K.J. Lee, J. Heterocycl. Chem. 46 (2009) 23–27.
[7] J.R. Falck, S. Gao, R.N. Prasad, S.R. Koduru, Bioorg. Med. Chem. Lett. 18 (2008) 1768–1771.
[8] L. Melzig, C.B. Rauhut, N. Naredi-Rainer, P. Knochel, Chem. Eur. J. 17 (2011) 5362–5372.
[9] B. Bayarmagnai, C. Matheis, K. Jouvin, L.J. Goossen, Angew. Chem. Int. Ed. 54 (2015) 5753–5756.
[10] Y.T. Lee, S.Y. Choi, Y.K. Chung, Tetrahedron Lett. 48 (2007) 5673–5677.
[11] W.B. He, L.Q. Gao, X.J. Chen, et al., Chin. Chem. Lett. 31 (2020) 1895–1898.
[12] Y. Guo, Y. Liu, J.P. Wan, Chin. Chem. Lett. 33 (2022) 855–858.
[13] F.R. Bisogno, A. Cuetos, I. Lavandera, V. Gotor, Green Chem. 11 (2009) 452–454.
[14] D.J. Bound, B.K. Bettadaiah, P. Srinivas, Synth. Commun. 43 (2013) 1138–1144.
[15] A.R. Kiasat, Z. Nasrollah, S. Soheil, Chin. J. Chem. 30 (2012) 699–702.
[16] C.C. Palsuledesai, S. Murru, S.K. Sahoo, B.K. Petel, Org. Lett. 11 (2009) 3382–3385.
[17] A.R. Kiasat, R. Badri, S. Sayyahi, Chin. Chem. Lett. 19 (2008) 1301–1304.
[18] M. Gorjizadeh, S. Sayyahi, Chin. Chem. Lett. 22 (2011) 659–662.
[19] Y. Gao, Y. Liu, J.P. Wan, J. Org. Chem. 84 (2019) 2243–2251.
[20] Z. Fu, Y. Gao, H. Yin, F.X. Chen, J. Org. Chem. 86 (2021) 17418–17427.
[21] M. Dyga, D. Hayrapetyan, R.K. Rit, L.J. Gooßen, Adv. Synth. Catal. 361 (2019) 3548–3553.
[22] A.R. Kiasat, R. Mirzajani, H. Shalbaf, T. Tabatabaei, Chin. Chem. Lett. 20 (2009) 1025–1029.
[23] L.H. Lu, Z. Wang, W. Xia, et al., Chin. Chem. Lett. 30 (2019) 1237–1240.
[24] A.H. Ye, Y. Zhang, Y.Y. Xie, et al., J. Org. Chem. 85 (2020) 2814–2822.
[25] A.H. Ye, Y. Zhang, Y.Y. Xie, et al., Org. Lett. 21 (2019) 5106–5110.
[26] J. Yadav, B. Reddy, U. Reddy, D. Chary, Synthesis 8 (2008) 1283–1287.
[27] S. Liang, C.C. Zeng, H.Y. Tian, et al., Adv. Synth. Catal. 360 (2018) 1444–1452.
[28] D. Wu, J. Qiu, P.G. Karmaker, H. Yin, F.X. Chen, J. Org. Chem. 83 (2018) 1576–1583.
[29] Q.Q. Min, J.W. Yang, M.J. Pang, G.Z. Ao, F. Liu, Org. Chem. Front. 8 (2021) 249–253.
[30] D. Wu, Y. Duan, K. Liang, H. Yin, F.X. Che, Chem. Commun. 57 (2021) 9938–9941.
[31] J.R. Chen, X.Q. Hu, L.Q. Lu, W.J. Xiao, Chem. Soc. Rev. 45 (2016) 2044–2056.
[32] Z.J. Shen, H.N. Shi, W.J. Hao, S.J. Tu, B. Jiang, Chem. Commun. 54 (2018) 11542–11545.
[33] Y. Chen, L.Q. Lu, D.G. Yu, C.J. Zhu, W.J. Xiao, Sci. China Chem. 63 (2020) 1652–1658.
[34] P. Bao, F. Liu, Y. Lv, et al., Org. Chem. Front. 7 (2020) 492–498.
[35] S. He, X. Chen, F. Zeng, et al., Chin. Chem. Lett. 31 (2020) 1863–1867.
[36] Z. Gan, G. Li, X. Yang, et al., Sci. China Chem. 63 (2020) 1652–1658.
[37] L.Y. Xie, T.G. Fang, J.X. Tan, et al., Green Chem. 21 (2019) 3858–3863.
[38] D.Q. Dong, L.X. Li, G.H. Li, et al., Chin. J. Catal. 40 (2019) 1494–1498.
[39] S.Q. He, X.L. Chen, F.L. Zeng, et al., Chin. Chem. Lett. 31 (2020) 1863–1867.
[40] D. Yang, Q. Yan, E. Zhu, J. Lv, W.M. He, Chin. Chem. Lett. 33 (2022) 1798–1816.
[41] Q.Q. Ge, J.S. Qian, J. Xuan, J. Org. Chem. 84 (2019) 8691–8701.
[42] D. Chen, Y. Sun, D. Dong, Q. Han, Z. Wang, Chin. J. Org. Chem. 40 (2020) 4267–4273.
[43] S. Peng, Y. Lin, W. He, Chin. J. Org. Chem. 40 (2020) 541–542.
[44] Y. Ma, F. Gao, W. Xiao, et al., Chin. Chem. Lett. 33 (2022) 4395–4399.
[45] Q.W. Gui, F. Teng, Z.C. Li, et al., Chin. Chem. Lett. 32 (2021) 1907–1910.
[46] J. Jiang, F. Xiao, W.M. He, L. Wang, Chin. Chem. Lett. 32 (2021) 1637–1644.
[47] Q. Yu, Y. Zhang, J.P. Wan, Green Chem. 21 (2019) 3436–3441.
[48] Z. Yang, M.L. Stivanin, I.D. Jurberg, R.M. Koenigs, Chem. Soc. Rev. 49 (2020) 6833–6847.
[49] B.G. Cai, J. Xuan, Chin. J. Org. Chem. 41 (2021) 4565–4574.
[50] F. He, C. Pei, R.M. Koenigs, Chem. Commun. 56 (2020) 599–602.
[51] R. Cheng, C. Qi, L. Wang, et al., Green Chem. 22 (2020) 4890–4895.
[52] L. Qian, B.G. Cai, L. Li, J. Xuan, Org. Lett. 23 (2021) 6951–6955.
[53] B.G. Cai, Q. Li, Q. Zhang, L. Li, J. Xuan, Org. Chem. Front. 8 (2021) 5982–5987.
[54] Y.N. Wang, X. Wang, S.J. Li, Y. Lan, Org. Chem. Front. 9 (2022) 1247–1253.
[55] M.L. Stivanin, R.D.C. Gallo, J.P.M. Spadeto, et al., Org. Chem. Front. 9 (2022) 1321–1326.
[56] B.G. Cai, L. Li, G.Y. Xu, W.J. Xiao, J. Xuan, Photochem. Photobiol. Sci. 20 (2021) 823–829.
[57] B. Zhao, L. Yang, K. Cheng, L. Zhou, J.P. Wan, Chin. J. Org. Chem. 41 (2021) 4732–4737.
[58] R. Liu, Q. Liu, H. Meng, et al., Org. Chem. Front. 8 (2021) 1970–1975.
[59] N. Meng, Y. Lv, Q. Liu, et al., Chin. Chem. Lett. 32 (2021) 258–262.
[60] Z. Wang, Q. Liu, R. Liu, et al., Chin. Chem. Lett. 33 (2022) 1479–1482.
[61] Q. Liu, L. Wang, H. Yue, et al., Green Chem. 21 (2019) 1609–1613.
[62] Q. Liu, Y. Lv, R. Liu, et al., Chin. Chem. Lett. 32 (2021) 136–139.
[63] Y. Lv, H. Cui, N. Meng, et al., Chin. Chem. Lett. 33 (2022) 979–114.