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Communication

Metal-free direct C(sp^3)–H functionalization of 2-alkylthiobenzoic acid to access 1,3-benzooxathiin-4-one

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ABSTRACT

Metal-free direct α-C(sp^3)–H intramolecular cyclization of 2-alkylthiobenzoic acid in the presence of Selectfluor is described. This novel strategy provides a facile and efficient method to access important 1,3-benzooxathiin-4-one derivatives with good functional groups tolerance and yields.

1,3-Benzooxathiin-4-ones have received much attention due to their vital use in a large number of insecticidal and fungicidal agents, crop protection agents, and food additives (Fig. 1) [1–3]. Previous methods for the synthesis of 1,3-benzooxathiin-4-ones mainly rely on the cross-coupling of thiophenol derivatives with alkynes [4–7] and alkenes [8,9], or the Pummerer reaction of sulfoxide derivatives [10,11]. However, these methods always suffer from some drawbacks, including the use of odour smelling thiophenols, the requirement of pre-functionalization of thioethers or limited substrate scope.

Recently, direct C–H bond functionalization has been regarded as one of the most effective and direct methods for the construction of C–C or C–heteroatom bond [12–24]. Within this reaction class, transition-metal mediated C(sp^3)–H bond functionalization of thioether derivatives has been developed to synthesize 1,3-benzooxathiin-4-ones. The Porcel group reported the allylic C–H bond intramolecular cyclization of 2-(allylthio) benzoic acid mediated by the excess amounts of AgOAc (Scheme 1a) [25]. Moreover, our group also demonstrated the Ag_2O-promoted intramolecular C(sp^3)–H bond functionalization of 2-methylthiobenzamide and sequential acidolysis to access 4*H*-benzo[*d*][1,3]oxathiin-4-one (Scheme 1b) [26]. However, the current methods often need expensive silver salts and with the limited substrate scope. Therefore, development of a metal-free and highly efficient method *via* a direct C(sp^3)–H functionalization for the synthesis of 1,3-benzooxathiin-4-ones would be of great significance.

Selectfluor, as a remarkable electrophilic fluorinating reagent, has been widely used in the fluorination process in recent years due to its low toxicity, high thermal stability, good solubility and stability in polar solvents [27–30]. Besides, it can also be employed as a radical initiator, fluorine cation initiator and transition metal oxidant to achieve "fluorine-free" reactions [31–44]. In the continuing efforts for developing novel metal-free strategies in the direct C(sp^3)–H functionalization, herein we disclose the Selectfluor-mediated cyclization of 2-alkylthiobenzoic acid to access 1,3-benzooxathiin-4-one *via* a direct sp^3 α-C–H functionalization reaction (Scheme 1c).

Our investigation began with the direct C(sp^3)–H intramolecular cyclization of 2-(ethylthio)benzoic acid **1a** in the presence of Selectfluor in DCE at 80 °C, the desired product **2a** was isolated in 53% yield (Table 1, entry 1). To our delight, the subsequent examination of different reaction solvents indicated that MeCN was the optimal solvent, affording the desired product **2a** in 82% isolated yield (Table 1, entries 2–7). Next, the additive agent screening showed that none of the other additives provided better results than Selectfluor (Table 1, entries 8–14). It was then noticed that the yield of **2a** could not be improved any more by increasing or decreasing the amounts of Selectfluor and the reaction temperature (Table 1, entries 15–18). Finally, the desired product **2a** could not be detected in the absence of Selectfluor (Table 1, entry 19).

With the optimized reaction conditions in hand, the substrate scope study on the sulfur atom substituents of 2-alkylthiobenzoic

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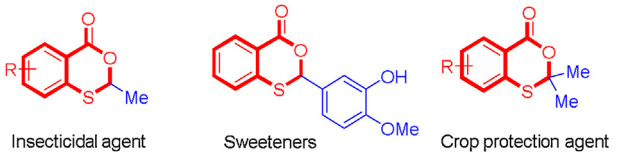
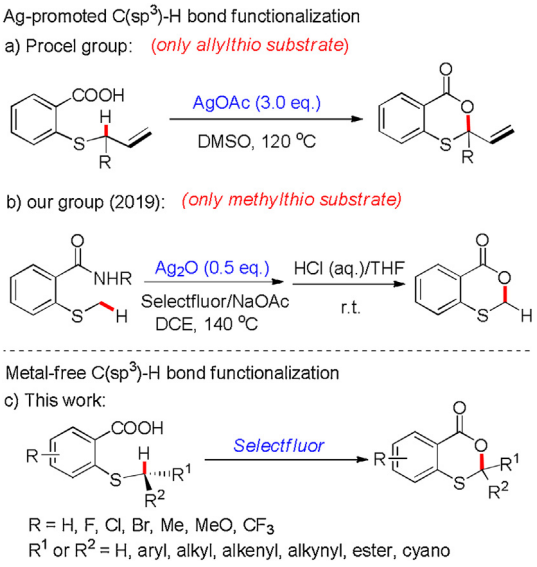


Fig. 1. Selected important 1,3-benzooxathiin-4-one derivatives.



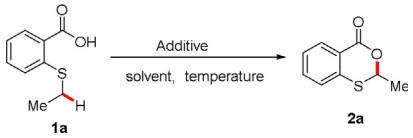
Scheme 1. Direct C(sp^3–H bond functionalization for the construction of 1,3-benzooxathiin-4-one derivatives.

acid was carried out in Scheme 2. As expected, the substrates bearing different linear and branched alkyl substituents on the sulfur atom, including methyl, ethyl, *n*-propyl, *n*-butyl, *n*-hexyl, *i*-propyl and *i*-butyl, were transformed to the desired products **2a-g** in good yields. Moreover, the substrates with a benzyl or phenethyl group also gave the desired products **2h-i** in excellent yield. In addition, both cyano- and ester-substituted substrate were well-tolerated to afford the desired products **2j** and **2k** in 81% and 63% yield. It was noteworthy that the highly reactive allyl and propargyl substrates could also provide the desired products **2l-m** in good yield.

Next, the substrate scope of substituents on the aromatic ring was also tested (Scheme 3). Both electron withdrawing and electron-donating groups on the phenyl ring were compatible under the current reaction system, affording the desired products **2n-u** in good yields. Notably, a variety of functional groups such as methyl, methoxy and halogen groups were well-suited for this reaction, allowing for further transformations of the initial products. However, the pyridine-containing substrate **1v** failed to access the desired product **2v**.

To provide some insights into the reaction mechanism, a series of control experiments were carried out (Scheme 4). Firstly, radical trapping experiments were performed, and the results showed that the addition of TEMPO inhibited this process, suggesting that a single electron transfer (SET) may be involved in the reaction (Scheme 4a). Furthermore, the reaction of sulfoxide **3** with Selectfluor failed to produce the desired product **2b**, indicating that the sulfoxide intermediate may not be involved in this reaction (Scheme 4b). Next, the H/D exchange could not be detected when this reaction was performed with an isotopically labelled substrate [D]-**1b** (Scheme 4c). The KIE experiment between **1b** and [D]-**1b** showed that the second-order of kinetic

Table 1
Optimization of reaction conditions.[a]



Entry	Additive (equiv.)	Solvent	Temp (°C)	Yield (%)[b]
1	Selectfluor (1.5)	DCE	80	53
2	Selectfluor (1.5)	MeCN	80	82
3	Selectfluor (1.5)	MeOH	80	0
4	Selectfluor (1.5)	Acetone	80	39
5	Selectfluor (1.5)	1,4-Dioxane	80	0
6	Selectfluor (1.5)	THF	80	0
7	Selectfluor (1.5)	DMSO	80	0
8	Selectfluor-II (1.5)	MeCN	80	56
9	NFSI (1.5)	MeCN	80	54
10	NFPT (1.5)	MeCN	80	66
11	$K_2S_2O_8$ (1.5)	MeCN	80	10
12	TBHP (1.5)	MeCN	80	28
13	AIBN (1.5)	MeCN	80	0
14	$PhI(OAc)_2$ (1.5)	MeCN	80	67
15	Selectfluor (1.5)	MeCN	60	75
16	Selectfluor (1.5)	MeCN	100	70
17	Selectfluor (1.0)	MeCN	80	63
18	Selectfluor (2.0)	MeCN	80	27
19	—	MeCN	80	0

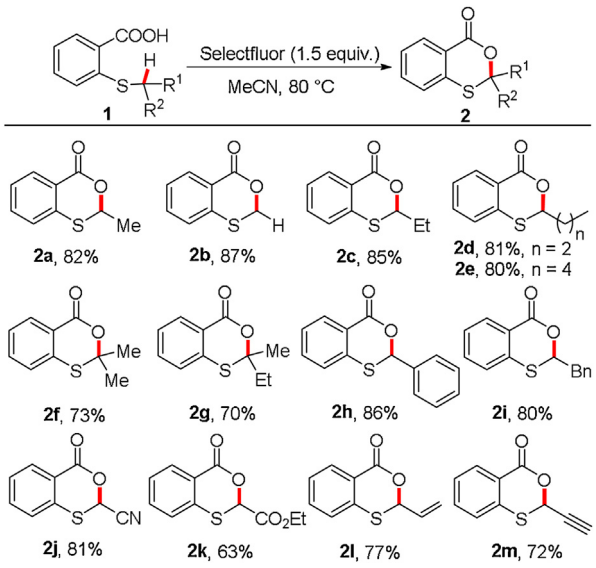
Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate), Selectfluor-II = 1-fluoro-4-methyl-1,4-diazoniabicyclo-[2.2.2]octane-bis (tetrafluoroborate), NFSI = *N*-fluorobenzenesulfonimide, NFPT = 1-fluoropyridinium triflate, TBHP = *tert*-butyl hydroperoxide, AIBN = azodiisobutyronitrile.

[a] Conditions: **1a** (0.2 mmol), additive (0.2∼0.4 mmol), solvent (2.0 mL), temperature, 12 h.

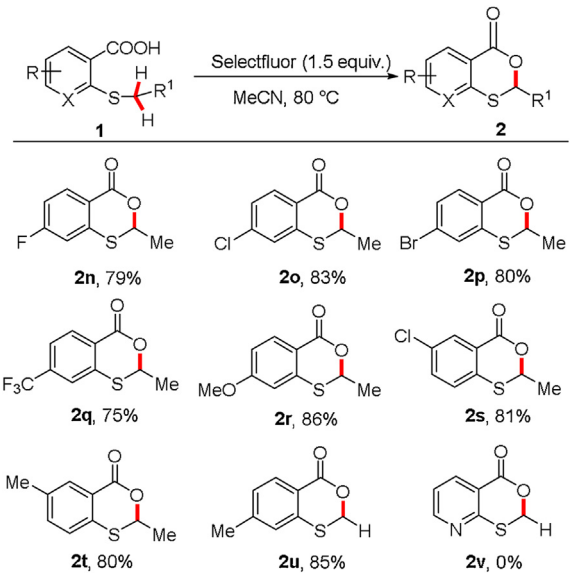
[b] Isolated yield.

isotope effect was observed and the cleavage of the C(sp^3)–H bond may not be involved in a rate-determining step (Scheme 4d).

On the basis of previous literatures [26,45–54] and our control experiments, a plausible mechanism has been depicted in Scheme 5. The initial oxidation of 2-methylthiobenzoic acid **1b** by Selectfluor affords the radical **A** and radical cation **B** [45–48]. Then the carbon-centered radical **C** can be formed through a 1,6-H



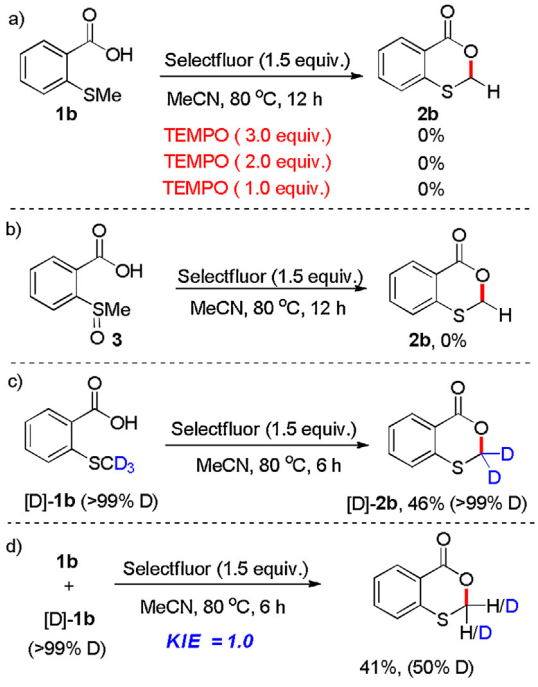
Scheme 2. Substrate scope of substituents on the sulfur atom. Reaction conditions: **1** (0.2 mmol), Selectfluor (0.3 mmol), MeCN (2.0 mL), 80 °C, 12 h. Isolated yield.



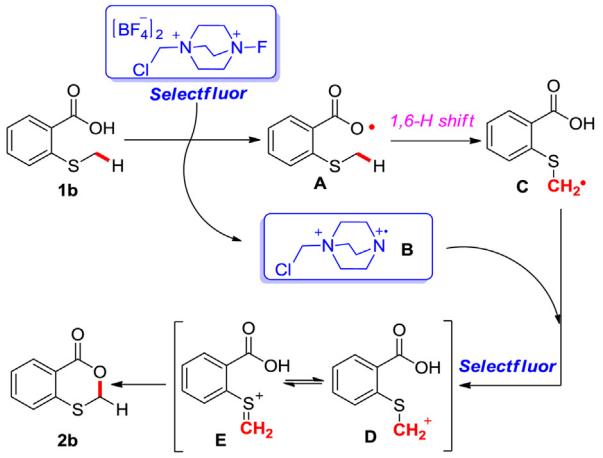
Scheme 3. Substrate scope of substituents on the aromatic ring. Reaction conditions: **1** (0.2 mmol), Selectfluor (0.3 mmol), MeCN (2.0 mL), 80 °C, 12 h. Isolated yield.

radical shift process [49,50]. Subsequently, the radical **C** is oxidized to the corresponding carbocation **D** and its isomer **E** in the presence of radical cation **B** and Selectfluor [51,52]. Finally, an intramolecular cyclization of intermediate **E** and the sequential deprotonation provide the desired product **2b**. However, a plausible pathway involving α-C–H fluorination and sequential intramolecular cyclization cannot be excluded at the present stage [53,46–54].

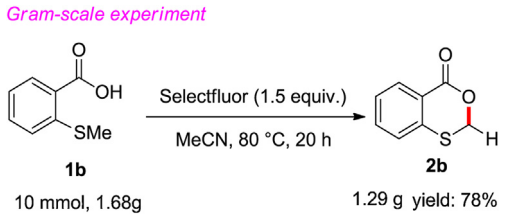
In order to illustrate the synthetic utility of this novel method, a gram-scale reaction for the synthesis of benzooxathiin-4-one **2b** was carried out (Scheme 6). When 2-(methylthio)benzoic acid **1b** (1.68 g, 10 mmol) was treated with 1.5 equiv. of Selectfluor in MeCN



Scheme 4. Mechanistic studies.



Scheme 5. The proposed mechanism.



Scheme 6. A gram-scale reaction for the synthesis of benzooxathiin-4-one **2b.**

(30 mL) at 80 °C, the desired product **2b** was obtained in 78% isolated yield.

In summary, an efficient and direct cyclization of 2-alkylthiobenzoic acid *via* a Selectfluor-promoted α-C(sp^3)–H functionalization has been developed. This process may involve a radical pathway in the presence of Selectfluor. Moreover, this metal-free strategy also provides an important complementary method to access various 1,3-benzooxathiin-4-one derivatives.

Declaration of competing interest

The authors report no declarations of interest.

Acknowledgments

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References

[1] J. Rheinheimer, U.J. Vogelbacher, E. Baumann, et al., US Patent 5569640, 1996.
[2] M. Yamato, K. Hashigaki, Chem. Senses Flavour 4 (1979) 35–47.
[3] A. Senning, S.O. Lawesson, Acta Chem. Scand. 16 (1962) 1175–1182.
[4] T. Sonehara, S. Murakami, S. Yamazaki, et al., Org. Lett. 19 (2017) 4299–4302.
[5] H.H. Wang, T. Shi, W.W. Gao, et al., Org. Biomol. Chem. 15 (2017) 8013–8017.
[6] Y. Nishina, J. Miyata, Synthesis 44 (2012) 2607–2613.
[7] N.G. Kundu, B. Nandi, Synlett (2001) 415–417.
[8] X. Chaminade, L. Coulombel, S. Olivero, et al., Eur. J. Org. Chem. 2006 (2006) 3554–3593.
[9] D.T. Mowry, W.H. Yanko, E.L. Ringwald, J. Am. Chem. Soc. 69 (1947) 2358–2361.
[10] S. Ito, Y. Kubota, M. Asami, Chem. Lett. 45 (2016) 16–18.
[11] M. Yamanaka, S. Shimada, W. Ando, et al., Phosphorus Sulfur Silicon Relat. Elem. 190 (2015) 1307–1308.
[12] Q. Shao, K. Wu, Z. Zhuang, et al., Acc. Chem. Res. 53 (2020) 833–851.
[13] X.M. Xu, D.M. Chen, Z.L. Wang, Chin. Chem. Lett. 31 (2020) 49–57.
[14] K. Yang, M. Song, H. Liu, et al., Chem. Sci. (2020), doi:http://dx.doi.org/10.1039/d0sc03052j.
[15] W.B. He, L.Q. Gao, X.J. Chen, et al., Chin. Chem. Lett. 31 (2020) 1895–1898.

[16] B. Niu, K. Yang, B. Lawrence, et al., ChemSusChem 12 (2019) 2955–2969.
[17] K. Yang, M. Song, Z. Ma, et al., Org. Chem. Front. 6 (2019) 3996–3999.
[18] Z. Shen, C. Pi, X. Cui, et al., Chin. Chem. Lett. 30 (2019) 1374–1378.
[19] Q. Zhao, X.S. Ji, Y.Y. Gao, et al., Org. Lett. 20 (2018) 3596–3600.
[20] X.T. Zhu, T.S. Zhang, Q. Zhao, et al., Chem. Asian J. 13 (2018) 1157–1164.
[21] K. Yang, D. Li, L. Zhang, et al., RSC Adv. 51 (2018) 13671–13674.
[22] Y. Yang, J. Lan, J. You, Chem. Rev. 117 (2017) 8787–8863.
[23] M.M. Chen, L.Y. Shao, L.J. Lun, Chin. Chem. Lett. 30 (2019) 702–706.
[24] Z.K. Chen, B.J. Wang, J.T. Zhang, et al., Org. Chem. Front. 2 (2015) 1107–1297.
[25] U.A. Carrillo-Arcos, J. Rojas-Ocampo, S. Porcel, Dalton Trans. 45 (2016) 479–483.
[26] K. Yang, B. Niu, Z. Ma, et al., J. Org. Chem. 84 (2019) 14045–14052.
[27] P.A. Champagne, J. Desroches, J.D. Hamel, et al., Chem. Rev. 115 (2015) 9073–9174.
[28] M.G. Campbell, T. Ritter, Chem. Rev. 115 (2015) 612–633.
[29] J. Xu, Z. Kuang, Q. Song, Chin. Chem. Lett. 29 (2018) 963–966.
[30] M.R.P. Heravi, Chin. Chem. Lett. 21 (2010) 1399–1402.
[31] K. Yang, M. Song, A. Ali, et al., Chem. Asian J. 15 (2020) 729–741.
[32] F.J.A. Troyano, K. Merkens, A. Gomez-Suarez, Asian J. Org. Chem. 9 (2020) 992–1007.
[33] S. Stavber, Molecules 16 (2011) 6432–6464.
[34] H. Mei, J. Liu, R. Pajkert, et al., Org. Biomol. Chem. 18 (2020) 3761–3766.
[35] L. Niu, J. Liu, X.A. Liang, et al., Nature Commun. 10 (2019) 467–473.
[36] Y. Kong, W. Xu, X. Liu, Chin. Chem. Lett. (2020), doi:http://dx.doi.org/10.1016/j.cclet.2020.05.022.
[37] Z. Cao, Q. Zhu, Y.W. Lin, et al., Chin. Chem. Lett. 30 (2019) 2132–2138.
[38] H. Zhao, J. Jin, Org. Lett. 21 (2019) 6179–6184.
[39] G. He, Y. Li, Z. Yu, et al., Org. Chem. Front. 6 (2019) 3644–3648.
[40] B. Sun, W.P. Mai, L.R. Yang, et al., Chin. Chem. Lett. 26 (2015) 977–979.
[41] K. Yang, Y. Li, Z. Ma, et al., Eur. J. Org. Chem. 2019 (2019) 5812–5814.
[42] K. Yang, H. Zhang, B. Niu, et al., Eur. J. Org. Chem. 2018 (2018) 5520–5523.
[43] L.Y. Xie, S. Peng, F. Liu, et al., Adv. Synth. Catal. 360 (2018) 4259–4264.
[44] L.Y. Xie, J. Qu, S. Peng, et al., Green Chem. 20 (2018) 760–764.
[45] Y. Chen, H. Qi, N. Chen, et al., J. Org. Chem. 84 (2019) 9044–9050.
[46] X. Zhang, Y. Liao, R. Qian, et al., Org. Lett. 7 (2005) 3877–3880.
[47] B. Sun, S. Yin, X. Zhuang, et al., Org. Biomol. Chem. 16 (2018) 6017–6024.
[48] Y.H. Lv, K. Sun, W.Y. Pu, et al., RSC Adv. 6 (2016) 93486–93490.
[49] D. Shi, H.T. Qin, C. Zhu, et al., Eur. J. Org. Chem. 2015 (2015) 5084–5088.
[50] S. Chiba, H. Chen, Org. Biomol. Chem. 12 (2014) 4051–4060.
[51] Z. Li, H. Li, X. Guo, et al., Org. Lett. 10 (2008) 803–805.
[52] L. Wang, M. Zhang, Y. Zhang, et al., Chin. Chem. Lett. 31 (2020) 67–70.
[53] S.C. Annedi, K. Majumder, L. Wei, et al., Bioorg. Med. Chem. 13 (2005) 2943–2958.
[54] S.C. Annedi, W. Li, S. Samson, et al., J. Org. Chem. 68 (2003) 1043–1049.