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Metal-free intramolecular N-S bond formation to access benzisothiazol-3-ones

Ke Yang,*[a,b] Hao Zhang,[a] Ben Niu,[b] Tiandi Tang,[a] and Haibo Ge*[b]

Abstract: The highly efficient synthesis of benzoisothiazol-3-ones from thiobenzamides has been described with good functional group compatibility and excellent yields. This work represents the first example of selectfluor-promoted N−S bond formation processes. This method provides a facile approach to access various important bioactive benzoisothiazol-3-ones.

Introduction

Benzoisothiazol-3-ones are ubiquitous structural units in medical and agricultural compounds with a broad range of biological activities including antivirus, anti-bacterial, anti-psychotic, antithrombotic, and analgesic activities (Figure 1).[1] Substantial efforts have been devoted to develop efficient methodologies to construct such skeletons.[2,3] Among them, the metal-free synthetic approach has gained considerable interest due to the green and sustainable properties. However, current metal-free processes often require the use of toxic and/or corrosive thionyl chloride,[3a-d] chlorine gas,[3e-f] trimethyl chlorosilane,[3g] or strong acids.[3h-k] Furthermore, their applications are also severely limited due to the narrow substrate scope.[3] Therefore, the development of facile and efficient methods to construct benzoisothiazol-3-ones would be of prime synthetic value.

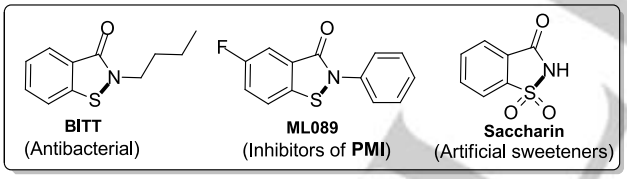
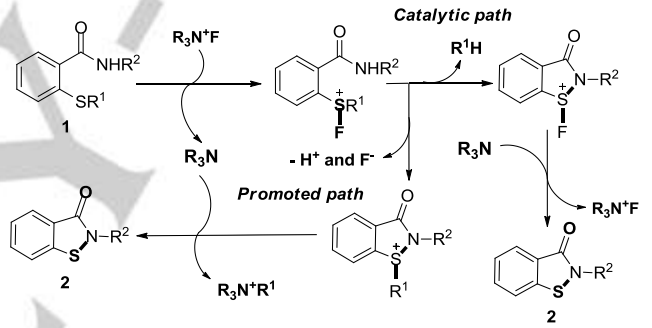


Figure 1. The selected biologically active compounds containing benzoisothiazol-3-one skeletons.

Recently, electrophilic fluorinating reagents with the general structure of $R_2N{-}F$ or $R_3N^+{-}F$ have gained much attention due to their applications in fluorination reactions.[4] However, the use of these reagents for other transformations is relatively underexplored.[4f, 5] Inspired by the reaction of α-fluorination of thioethers,[6] we conceived that the F^+ reagents could be used as catalysts or mediators to react with thiobenzamides **1**, forming the corresponding cyclic fluorosulfonium salts, and then produce the desired products **2** (Scheme 1). This might offer a novel and mild method to access benzoisothiazol-3-ones. Herein, we disclose our results on the synthesis of benzoisothiazol-3-ones via a sequential N−S bond formation and C−S bond cleavage process. It should be mentioned that studies on exploiting F^+ reagents for such transformations have not been reported so far.



Scheme 1. The strategy to directly access benzoisothiazol-3-ones with F^+ reagents.

Results and Discussion

To probe chemical selectivity of this reaction, we have chosen the alkynyl substituted starting material, 2-(methylthio)-*N*-(prop-2-yn-1-yl)benzamide **1a** as the substrate which could be easily prepared through the condensation reaction of commercially available 2-(methylthio)benzoic acid and prop-2-yn-1-amine. We commenced our investigation on intramolecular cyclization of **1a** in the presence of selectfluor. It was found that the desired product 2-(prop-2-yn-1-yl)benzo[*d*]isothiazol-3(2*H*)-one **2a** could be detected in 54% yield by employing 1.0 equivalent of selectfluor in MeCN at 40 °C (Table 1, entry 3). To our delight, the yield was improved to 92% by simply increasing the reaction temperature to 80 °C (Table 1, entry 9). It was also noticed that other electrophilic fluorinating reagents such as *N*-fluorobenzenesulfonimide (NFSI) and 1-fluoro-2,4,6-trimethylpyridinium triflate (NFPT) could promote the process, albeit with lower yields (Table 1, entries 10-11). Next, various substituents including H, Et, Bn and Ph on the sulfur atom were examined, and either lower yield or no desired product was observed, indicating that methyl group is the optimal substituent (Scheme 2).

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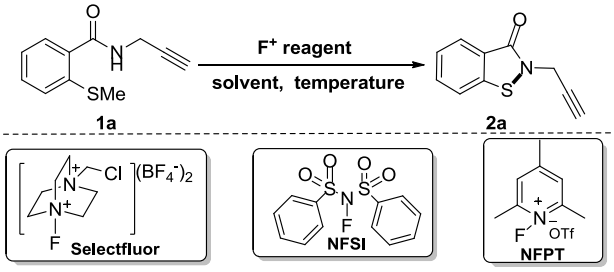
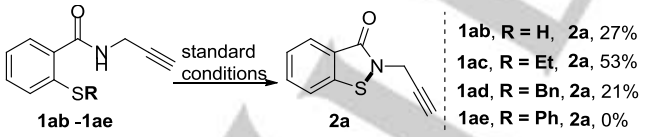
Table 1. Optimization of Reaction Conditions[a].



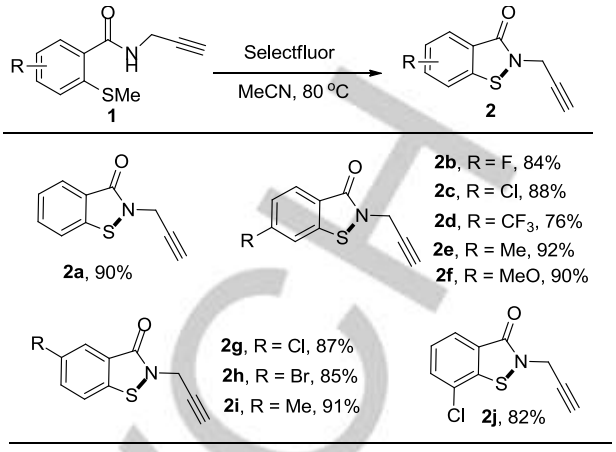
Entry	F^+ reagent (mol%)	Solvent	Temperature (^oC)	Yield (%)[b]
1	Selectfluor (20)	MeCN	40	10
2	Selectfluor (50)	MeCN	40	23
3	Selectfluor (100)	MeCN	40	54
4	Selectfluor (150)	MeCN	40	42
5	Selectfluor (100)	Aetone	40	20
6	Selectfluor (100)	MeOH	40	trace
7	Selectfluor (100)	DMF	40	50
8	Selectfluor (100)	MeCN	60	75
9	Selectfluor (100)	MeCN	80	92(90)[c]
10	NFSI (100)	MeCN	80	31
11	NFPT (100)	MeCN	80	36

[a] Conditions: **1a** (0.2 mmol), electrophilic fluorinating reagent, 2.0 mL of solvent, 12 h. [b] Yields are based on **1a**, determined by crude ^{1}H NMR using dibromomethane as the internal standard. [c] Isolated yield.

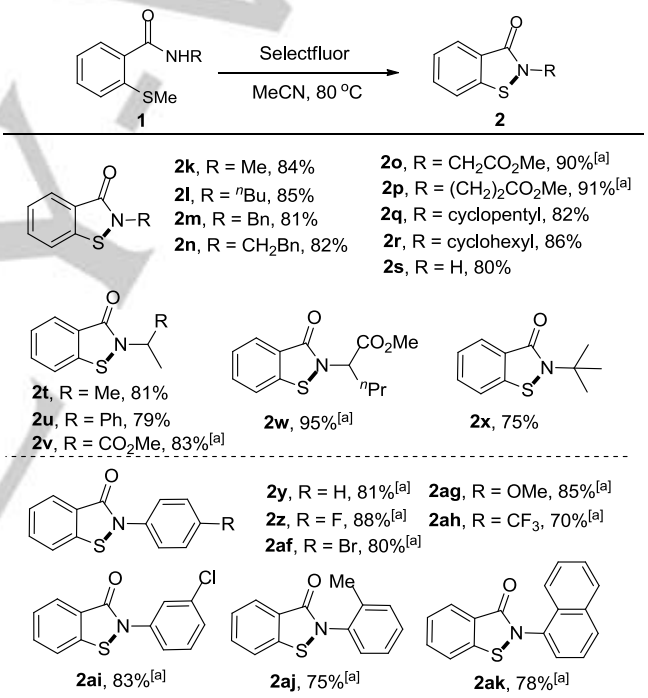


Scheme 2. The investigation of substituents on the sulfur atom.

With the optimized conditions in hand, the substrate scope study of *N*-substituted 2-methylthiobenzamides was carried out (Scheme 3). Various aryl-substituted 2-(methylthio)-*N*-(prop-2-yn-1-yl)benzamides including an electron-withdrawing groups (F, Cl, Br or CF_3) and electron-donating group (Me or MeO), were examined, and the desired products (**2a**-**j**) were isolated in good to excellent yields. It is noteworthy to mention that the well-tolerated halogens enable the further manipulations of the initial products.



Scheme 3. Scope of aryl-substituted methylthiobenzamide. Conditions: **1** (0.2 mmol), selectfluor (0.2 mmol), MeCN (2.0 mL), 80 °C, 12 h, isolated yield.



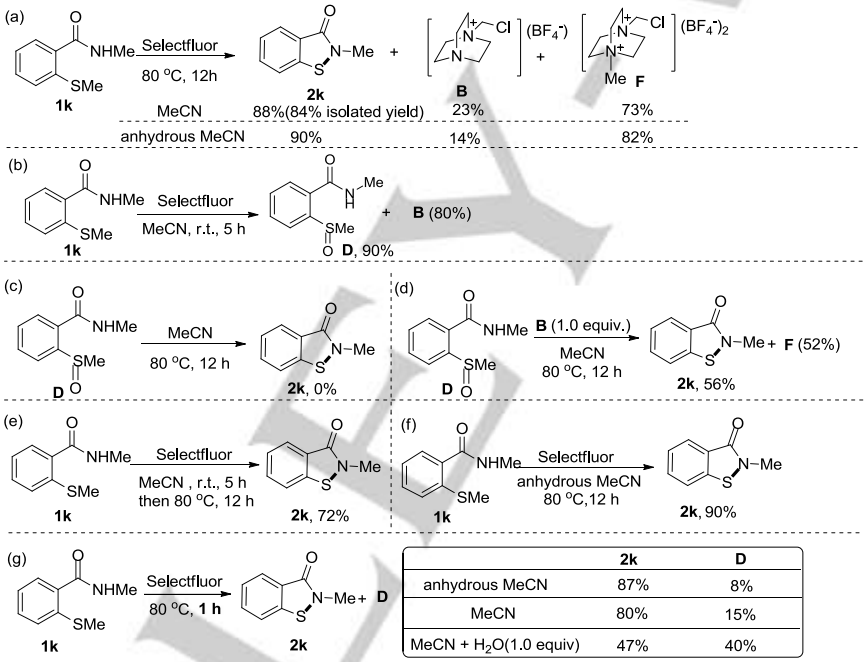
Scheme 4. Scope of *N*-substituted methylthiobenzamide. Conditions: **1** (0.2 mmol), selectfluor (0.2 mmol), MeCN (2.0 mL), 80 °C, 12 h, isolated yield. [a] 100 °C.

Next, we explored the substrate scope of *N*-substituted 2-methylthiobenzamides under the standard conditions (Scheme 4). Various linear alkyl-substituted substrates provided the corresponding products (**2k**-**p**) in excellent yields. As expected, both cyclic alkyl-substituted substrates **1q** and **1r** generated the corresponding products in good yields. Moreover, different branched alkyl-substituted substrates also provided the corresponding products (**2s**-**w**) in good yields. Additionally, 2-methylthiobenzamide **1s** was first tested, and to our delight, the desired product benzo[*d*]isothiazol-3(2*H*)-one **2s** could be smoothly obtained in a moderate yield. It is noteworthy that the bulky *t*-butyl group afforded the desired product **2w** in 75% isolated yield. Finally, *N*-aryl-substituted 2-

methylthiobenzamides were also investigated in this system. As expected, substrates with either an electron-withdrawing or electron-donating group at the *para*-, *meta*- or *ortho*-position of the aromatic ring were compatible under the modified reaction conditions (**2y-z** and **2af-ak**).

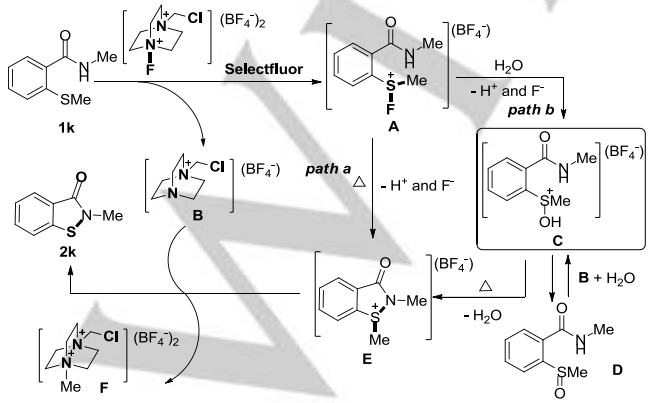
To shed light on the reaction mechanism, a series of control experiments were performed. The ^{1}H NMR experiment indicated that the selectfluor was almost completely converted to the salts **B** and **F** under the standard conditions (Scheme 5a). Additionally, reaction of **1k** with selectfluor produced sulfoxide **D** with 90% NMR yield at room temperature in 5 h (Scheme 3b). It was then found that no desired product **2k** could be obtained if the salt **B** was absent, indicating that the salt **B** plays an important role in this intramolecular cyclization reaction (Scheme 5c and 5d). Furthermore, the desired product **2k** could be obtained in 72% NMR yield while the reaction mixture was kept at room temperature for 5 h, and then heated to 80 °C for another 12 h (Scheme 5e). These results suggest that the sulfoxide intermediate may be involved in this process. Moreover, reaction of **1k** with selectfluor in anhydrous MeCN gave the desired product **2k** in high yield, indicating a different reaction pathway (Scheme 5f and 5g).

On the basis of the above results and previous reports,[3, 6-7] a plausible reaction mechanism has been proposed (Scheme 6). It is believed that the transient fluorosulfonium salt **A** is formed in the presence of selectfluor. Then, the cyclic sulfonium salt **E** can be generated through the direct cyclization of this salt (path a). On the other hand, the cyclic sulfonium salt **E** can also be produced through dehydration of intermediate **C** obtained from nucleophilic substitution of intermediate **A** (path b). In the presence of salt **B**, nucleophilic displacement of the methyl group on the sulfonium salt **E** ultimately gives the desired product **2k** and salt **F**. It should be mentioned that a radical cyclization process cannot be excluded. The starting material **1k** might be oxidized to the corresponding amidyl radical which is further transformed into the desired product **2k** through the an addition to the sulfur atom and subsequent demethylation.[8-9]

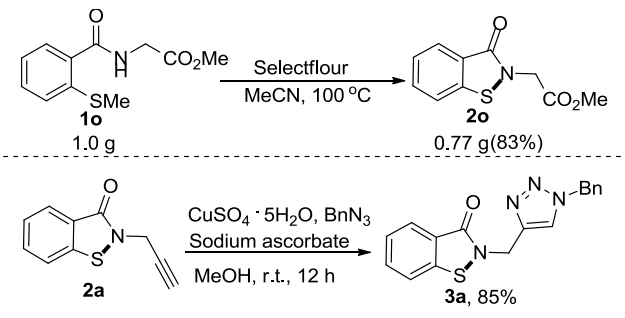


	2k	D
anhydrous MeCN	87%	8%
MeCN	80%	15%
MeCN + H_2O(1.0 equiv)	47%	40%

Scheme 5. The control experiments.



Scheme 6. The plausible reaction mechanism.



Scheme 7. The gram-scale synthesis of drug precursor **2o** and the synthesis of caspase-3 inhibitor **3a**

Finally, to demonstrate the synthetic utility of this method, a gram scale reaction was carried out (Scheme 7). When methyl 2-(2-(methylthio)benzamido)acetate **1o** was treated with 1.0 equivalent of selectfluor in MeCN (10 mL) at 100 °C, drug precursor **2o**[2c] was obtained in 83% yield. Furthermore, the caspase-3 inhibitor **3a**[1g] could also be readily prepared by using 2-(prop-2-yn-1-yl)benzo[d]isothiazol-3(2*H*)-one **2a** and BnN_3 as the starting materials in the presence of catalytic amount of $CuSO_4 \cdot 5H_2O$.

Conclusions

In summary, we have developed an efficient selectfluor-promoted synthesis of benzoisothiazol-3-one derivatives through a sequential N−S bond formation and C−S bond cleavage process. This transformation is the first example of selectfluor-mediated N−S bond formation processes. Moreover, this reaction tolerates various functional groups with excellent yields. In combination, this novel method provides an important complementary approach to access various bioactive benzoisothiazol-3-one derivatives.

Experimental Section

A 10 mL Schlenk tube was charged with 2-methylthiobenzamide (**1**, 0.2 mmol), selectfluor (0.2 mmol, 70.9 mg) and MeCN (2.0 mL). The tube was sealed and the reaction was then stirred vigorously at 80 ˚C for 12h. After cooling to room temperature, the reaction mixture was then concentrated in vacuo. The residue was purified by flash chromatography on silica gel to yield the desired product **2**.

Acknowledgements

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Keywords: Cleavage reactions • Cyclization • Metal-free • Selectfluor • Sulfur heterocycles

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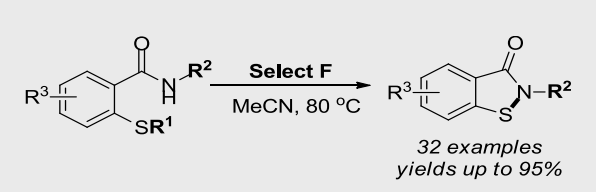

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Synthetic methodology

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