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Sodium Sulfite-Involved Photocatalytic Radical Cascade Cyclization of 2-Isocyanoaryl Thioethers: Access to 2-CF_2/CF_3-Containing Benzothiazoles

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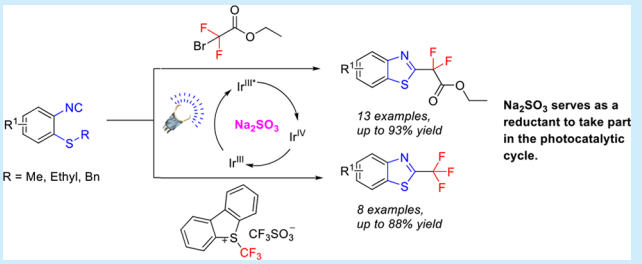
Supporting Information

ABSTRACT: A visible-light-induced radical cascade cyclization of 2-isocyanoaryl thioethers for the synthesis of 2-CF_2/CF_3-containing benzothiazoles has been developed. Sodium sulfite can participate in the photocatalytic cycle as a reductant that efficiently transforms Ir^{4+} into Ir^{3+} to promote the fluoroalkylation under mild reaction conditions.



Fluorine-containing molecules are biologically significant structures that are widely found in numerous pharmaceuticals, materials, and agrochemicals.[1] Moreover, the incorporation of fluorine into medicinal agents can modify their features in terms of metabolic stability, lipophilicity, and bioavailability. Therefore, developing novel and efficient methods for the introduction of fluorine or fluorinated moieties into organic molecules has vital significance. In the past few years, visible-light photoredox catalysis has emerged as a powerful tool to achieve the fluoromethylation of organic compounds through a radical process. In 2011, Stephenson's group[2] reported a visible-light-catalyzed difluoroalkylation of alkenes with $BrCF_2CO_2Et$. In the same year, MacMillan's group[3] realized the trifluoromethylation of arenes and heteroarenes by means of photoredox catalysis with CF_3SO_2Cl. Later, Akita,[4] Zhu,[5] Yu,[6] and other groups[7] developed fluoromethylation of alkenes, isocyanides, and heteroarenes to construct fluorinated polycyclic compounds.

Because 2-CF_2/CF_3-containing benzothiazoles are a special class of benzothiazole heterocycles that exist in several biologically active molecules (Figure 1),[8] notable progress has been achieved in the construction of benzothiazoles.[9] However, the direct synthesis of 2-CF_2/CF_3-containing benzothiazoles is still sporadically reported, including condensation of *o*-aminothiophenols with trifluoroacetic acid or difluoroacetic acid (Scheme 1a),[10] palladium-catalyzed cyclization of thiobenzamides via C−H functionalization,[11] and oxidative cyclization of thiobenzamides with CAN[12] (Scheme 1b). Recently, Song developed an elegant method for the direct synthesis of 2-fluorinated benzothiazole via copper-catalyzed coupling of $BrCF_2CO_2Et$ and 2-isocyanoaryl thioethers starting from 2-aminothioanisole and difluorocarbene (Scheme 1c).[13] However, these methods still required stoichiometric oxidants or had to be conducted under high temperature. Herein, we disclose a visible-light-induced radical cascade cyclization of $BrCF_2CO_2Et$ and 2-isocyanoaryl thioethers for the construction of 2-fluorinated benzothiazoles, which proceeds under mild conditions with good to excellent yields and high efficiency.

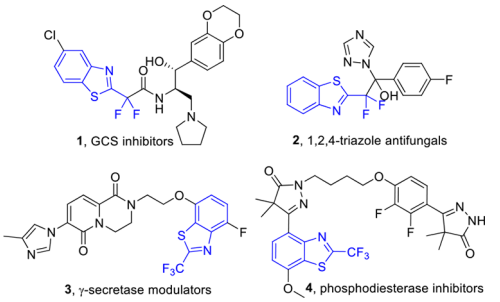


Figure 1. Representative biologically active molecules with 2-CF_2/CF_3-containing benzothiazole motifs.

We initiated our investigation by using (2-isocyanophenyl)(methyl)sulfane **1a** and ethyl 2-bromo-2,2-difluoroacetate **2a** as the model substrates to screen the radical cascade cyclization reaction conditions, and the results are summarized in Table 1. The preliminary experiment was done in an acetonitrile solution of **1a** and 2.0 equiv of **2a** in the presence of 1 mol % of photocatalyst *fac*-Ir(ppy)$_3$ with irradiation from a 7 W blue LED at room temperature under N_2 atmosphere for 4 h. To our delight, the target product **3aa** was obtained in 55% yield, along

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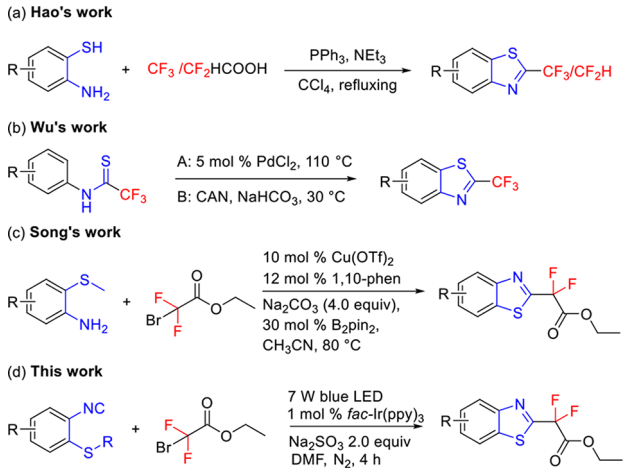
Org. Lett. XXXX, XXX, XXX−XXX

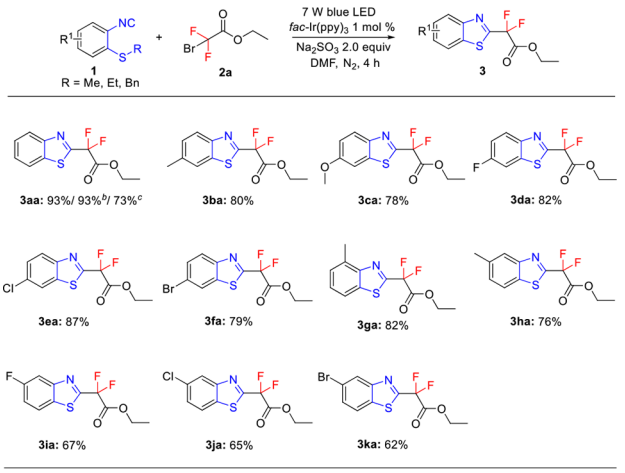
Scheme 1. Synthesis of 2-CF_2/CF_3-Containing Benzothiazoles



with one byproduct, 2-methylbenzo[*d*]thiazole **4aa** (Table 1, entry 1). No products were obtained when other commonly used photocatalysts were subjected to this reaction (Table 1, entries 2−5), which suggested that the generation of the CF_2COOEt radical species needs a more reductive photocatalyst (*fac*-Ir(ppy)$_3$, $E_{1/2}^{IV/*III} = -1.73$ vs SCE).[14] Then, we tried different solvents (DMSO, DMF, DCE, MeOH, and 1,4-dioxane), and the results showed that the solvent has little influence on this reaction (Table 1, entries 6−10). Next, we screened the base to improve the yields of the products. Inorganic base (K_2CO_3) resulted in moderate yield; however, organic bases led to even lower yields (Table 1, entries 11 and 12). Furthermore, the fact that we found that the light-brown reaction solution can make starch/KI test paper blue, indicating that there must be some oxidizing substances in the solution, we tried to add some reductive base to the reaction. The isolated yield was remarkably increased to 73% when Na_2SO_3 was used as the reductive base (Table 1, entry 13). By increasing the amount of Na_2SO_3 to 2.0 equiv, a significant increase of yield (93%) was obtained with trace of **4aa** (Table 1, entry 14). Finally, the control experiments demonstrated that both visible light and photosensitizer were indispensable in this reaction (Table 1, entries 15 and 16).

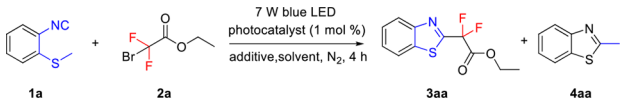
To evaluate the utility of this difluoroalkylation method, a variety of 2-isocyanoaryl thioethers were employed to react with **2a** under the optimized reaction conditions. As shown in Scheme 2, a series of substituted 2-isocyanoaryl thioethers underwent the transformation smoothly to give the corresponding products in good to excellent yields. N-para-substituted 2-

Scheme 2. Substrates Scope of 2-Bromo-2,2-difluoroacetate and Isocyanides[a]



[a]Conditions: **1** (0.3 mmol), **2a** (121.8 mg, 0.6 mmol), Na_2SO_3 (75.6 mg, 0.6 mmol), *fac*-Ir(ppy)$_3$ (4.2 mg, 1 mol %), DMF (2 mL), irradiation with a 7 W blue LED under N_2 atmosphere at rt for 4 h, R = Me. [b]R = Et. [c]R = Bn, and the reaction time was extended to 7 h.

Table 1. Optimization of Reaction Conditions[a]



entry	photocatalyst	solvent	additive (equiv)	**3aa**[b] yield (%)	**4aa**[b] yield (%)
1	*fac*-Ir(ppy)$_3$	CH_3CN		55	29
2	Ir[(ppy)$_2$dtb-bpy]PF_6	CH_3CN		0	0
3	Ru(bpy)$_3$$Cl_2$·6$H_2O$	CH_3CN		0	0
4	eosin Y	CH_3CN		0	0
5	Mes-Acr$^+$$ClO_4^-$	CH_3CN		0	0
6	*fac*-Ir(ppy)$_3$	DMSO		49	31
7	*fac*-Ir(ppy)$_3$	DMF		52	25
8	*fac*-Ir(ppy)$_3$	DCE		32	42
9	*fac*-Ir(ppy)$_3$	MeOH		52	38
10	*fac*-Ir(ppy)$_3$	1,4-dioxane		51	42
11	*fac*-Ir(ppy)$_3$	DMF	K_2CO_3 (1)	52	35
12	*fac*-Ir(ppy)$_3$	DMF	NEt_3 (1)	38	46
13	*fac*-Ir(ppy)$_3$	DMF	Na_2SO_3 (1)	73	23
14	*fac*-Ir(ppy)$_3$	DMF	Na_2SO_3 (2)	93	trace
15[c]	*fac*-Ir(ppy)$_3$	DMF	Na_2SO_3 (2)	0	0
16		DMF	Na_2SO_3 (2)	0	0

[a]Conditions: **1a** (44.8 mg, 0.3 mmol), **2a** (121.8 mg, 0.6 mmol), photocatalyst (1 mol %), solvent (2.0 mL), irradiation with a 7 W blue LED at room temperature under N_2 atmosphere for 4 h. [b]Isolated yield. [c]Reaction was carried out in the dark.

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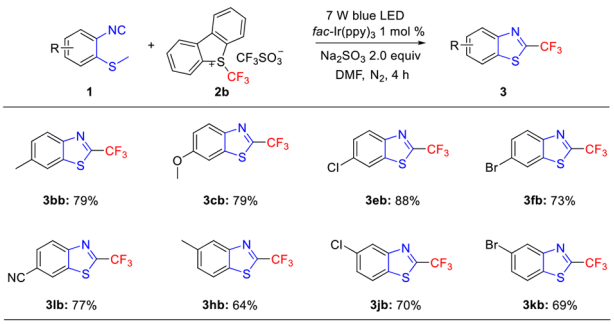
Org. Lett. XXXX, XXX, XXX−XXX

isocyanoaryl thioethers with an electron-donating or weak electron-withdrawing group afforded **3ba**–**3fa** in 80–90% yields. Interestingly, fluoro, chloro, and bromo groups on the phenyl ring were well tolerated, enabling their potential applications in further transformation (Scheme 2). 6-Methyl-substituted 2-isocyanoaryl thioethers also worked well in this reaction, and the desired product **3ga** was obtained in 82% yield (Scheme 2). In addition, moderate yields were obtained when 4-substituted 2-isocyanoaryl thioethers were used as substrates (Scheme 2, **3ha**–**3ka**). Notably, when ethyl(2-isocyanophenyl)-sulfane and benzyl(2-isocyanophenyl)sulfane were subjected to this reaction, **3aa** was obtained successfully in 93% and 73% yield, respectively. The bulky benzyl residue had a negative effect on this transformation, and the reaction time needed to be extended to 7 h when benzyl(2-isocyanophenyl)sulfane was empoyed as the substrate. A gram-scale reaction with **1a** and **2a** was carried out under standard conditions to give the target product **3aa** in 65% yield.

2-Bromo-2,2-difluoroacetate **2a** and 5-(trifluoromethyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethanesulfonate **2b** could deliver the 2-CF_3-substituted benzothiazoles. As listed in Scheme 3, the result was similar to that of the

Scheme 3. Substrates Scope of 5-(Trifluoromethyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium Trifluoromethanesulfonate and Isocyanides[a]

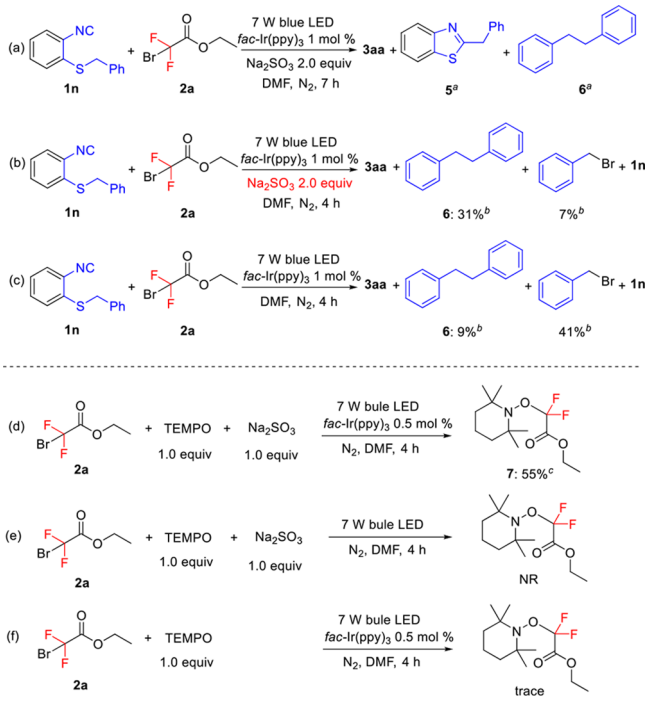


[a]Conditions: **1** (0.3 mmol), **2b** (241.4 mg, 0.6 mmol), Na_2SO_3 (75.6 mg, 0.6 mmol), *fac*-Ir(ppy)$_3$ (4.2 mg, 1 mol %), DMF (2 mL), irradiation with a 7 W blue LED under nitrogen atmosphere at rt for 4 h.

difluoroalkylation process. 5-Substituted 2-isocyanoaryl thioethers were more efficient substrates than 4-substituted 2-isocyanoaryl thioethers to give the desired products (Scheme 3, **3bb**, **3cb**, **3eb**, **3fb**, and **3lb** vs **3hb**, **3jb**, and **3kb**), and the reaction was insensitive to the electronic effects of substituents.

To gain further insight into the product-forming profile, a series of verification experiments were performed, as shown in Scheme 4. First, when benzyl(2-isocyanophenyl)sulfane **1n** was subjected to the reaction, the cross-coupled product of 1,2-diphenylethane **6** was detected by GC-MS, which implied the presence of a benzyl radical and the radical process of the reaction. To further prove the existence of 1,2-diphenylethane and determine its yield, the reaction system was monitored by gas chromatography. After irradiation for 4 h, 31% of 1,2-diphenylethane was detected along with 7% benzyl bromide and partially unreacted **1n** (Scheme 4b). Notably, when the reaction was carried out without Na_2SO_3, the yield of 1,2-diphenylethane dropped to 9% and the yield of benzyl bromide increased to 41% (Scheme 4c). We turned our attention to investigate the role of Na_2SO_3 in this transformation. In 2005, Fábián disclosed a

Scheme 4. Control Experiments



[a]Detected by GC-MS. [b]GC yields using 1,4-dimethoxybenzene as an internal standard. [c]Isolated yields.

photoinitiated and cerium(III)-catalyzed aqueous reaction between sulfite ion and oxygen, in which SO_3^{2-} and Ce^{4+} could react to produce a sulfite ion radical ($SO_3^{-\bullet}$) and Ce^{3+} through a single electron transfer (SET) process.[15] Therefore, we conjectured that Na_2SO_3 could also react with Ir^{4+} to produce a sulfite ion radical and Ir^{3+}, which helped finish the catalytic cycle and sped up the production of the CF_2COOEt radical, thereby improving the yields of the fluoroalkylation products. Meanwhile, the SET between benzyl radical and Ir^{4+} was prevented and, therefore, improved the yield of 1,2-diphenylethane **6**. To test our hypothesis, we carried out a photoreaction between **2a** and Na_2SO_3 under the standard conditions with the radical scavenger TEMPO to capture the produced CF_2COOEt radical, and the ethyl 2,2-difluoro-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate **7** was isolated in 55% yield as expected (Scheme 4d). Control experiments (Scheme 4e,f) confirmed the necessity of *fac*-Ir(ppy)$_3$ and Na_2SO_3 and further supported our conjecture. Finally, the experiments with on/off light suggested that the chain propagation is not a main mechanistic pathway (see Supporting Information).

According to the above experiments and relevant literature,[9e,16] a plausible mechanism is proposed in Scheme 5. Initially, irradiation of *fac*-Ir(ppy)$_3$ with visible light leads to the formation of an excited state *fac*-Ir*(ppy)$_3$ species, which undergoes an SET process with **2a** to generate the CF_2COOEt radical species **A** and Ir^{4+}. Subsequently, addition of **A** to isonitrile **1n** generates the imidoyl radical intermediate **B**, which further undergoes an intramolecular attack by the benzylthio moiety to produce the desired product **3aa** along with the release of a benzyl radical. Meanwhile, Ir^{4+} is reduced to Ir^{3+} by Na_2SO_3 to complete the catalytic cycle. The benzyl radical is also able to be oxidized to a benzyl cation by Ir^{4+} and finally encounters a Br^- to form benzyl bromide or directly dimerizes to produce 1,2-

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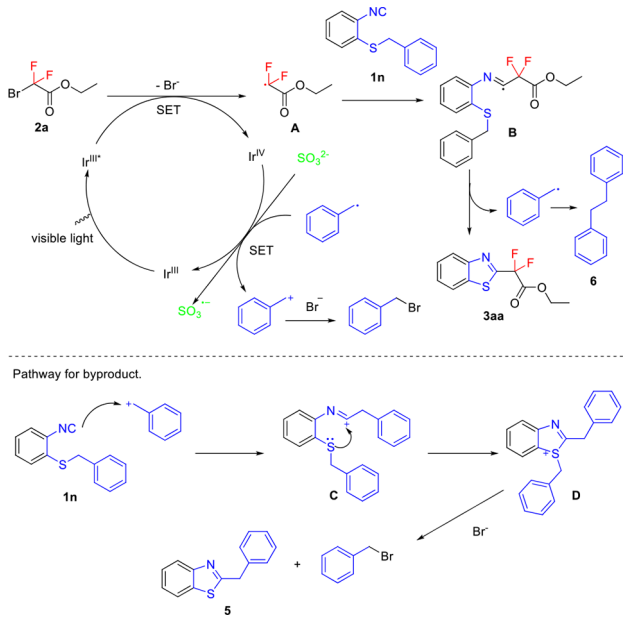
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Proposed Mechanism



diphenylethane **6**. The generation mechanism of byproduct was also proposed. If no Na_2SO_3 is added to the reaction, the benzyl radical will probably be oxidized to a benzyl cation. The benzyl cation can be attacked by **1n** to produce the cation intermediate **C**, and subsequent intramolecular nucleophilic attack generates the cation intermediate **D**. Finally, the nucleophilic attack by Br^- produces benzyl bromide and byproduct **5**.

In summary, we have successfully constructed 2-CF_2/CF_3-containing benzothiazoles through a visible-light-induced radical cascade cyclization process. In contrast with the traditional use of tertiary amine as reductant to achieve SET processes in photocatalytic reactions,[11] we use the inorganic salt sodium sulfite as a reductant to play the same role and improve the efficiency of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03710.

Preparation of substrates, general procedure, characterization data, ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX