Organic & Biomolecular Chemistry

PAPER

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Cite this: *Org. Biomol. Chem.*, 2018, **16**, 8565

# Visible light-promoted difluoromethylthiolation of aryldiazonium salts†

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Received 29th September 2018,
Accepted 19th October 2018

DOI: 10.1039/c8ob02431f

rsc.li/obc

Difluoromethylthiolation of aryldiazonium salts under photocatalytic conditions with a shelf-stable, easily prepared and inexpensive reagent, $PhSO_2SCF_2H$ was described. A variety of difluoromethylthioethers were obtained utilizing aryldiazonium salts containing different functional groups. Aryldiazonium salts with a heteroarene moiety were tolerated. Fluorescence quenching experiments indicated that both oxidative and reductive quenching cycles occurred during this process.

## Introduction

Due to the unique properties of a fluorine atom, organofluorine compounds have found widespread applications in different areas, especially in the field of pharmaceuticals and agrochemicals.[1] Consequently, in the past two decades, great effort has been devoted to developing efficient methods for the introduction of fluorine and fluorine-containing groups into molecules. The difluoromethylthio group (–$SCF_2H$) represents as one of the underdeveloped fluoroalkyl groups with great potential. First, the lipophilicity of the difluoromethylthio group ranges between $CF_3$ and $SCF_3$,[2] thus providing the medicinal chemists flexibility in fine-tuning the pharmacokinetic properties of a drug molecule. Secondary, the hydrogen of the difluoromethylthio group is slightly acidic, which allows these lipophilic compounds to bind with other molecules through weak hydrogen bonds.[3] Not surprisingly, in the past five years, several difluoromethylthiolating reagents have been invented, and accordingly, a few difluoromethylthiolating methods have been developed to incorporate the difluoromethylthio group into molecules under mild conditions.[4] Among them, $PhSO_2SCF_2H$ (Shen's reagent)[5] which is shelf-stable and easily available, was known to be a radical acceptor that reacted smoothly with aryl or alkyl radicals generated from alkyl boronic acids or carboxylic acids. In addition, in 2018, Shen and co-workers reported a radical ring-opening difluoromethylthiolation of cycloalkanols initiated by $AgNO_3/K_2S_2O_8$, which can easily gain access to a family of β-difluoromethylthiolated ketones.[6] Furthermore, it was also reported that acyl radicals could react with $PhSO_2SCF_2H$ to obtain difluoromethylthioesters.[7] Very recently, Li and coworkers reported that under the irradiation of visible light, $PhSO_2SCF_2H$ underwent a hemolytic S–S bond cleavage to generate difluoromethylthio radicals, which could be trapped by electron-rich arenes to give difluoromethylthiolated arenes under mild conditions.[8]

Aryldiazonium salts are easily available and widely applied common organic reagents that are able be converted into a variety of different functional groups through the well-known Sandmeyer reactions.[9] Specifically, transition metal-mediated fluoroalkylation of aryldiazonium salts has become an important route for the preparation of organofluorine compounds.[10] The difluoromethylthiolation of aryldiazonium salts was reported by Shen *et al.* by using a difluoromethylthio-substituted silver complex [(SIPr)Ag($SCF_2H$)].[11] Yet, the preparation of the reagent was tedious and required the use of a drybox.

It was reported that under the irradiation of visible light, aryldiazonium salts could be easily activated through a SET process to generate an aryl radical, which allows for further functional group transformation. We thus wondered whether the aryl radical generated from aryldiazonium salts under these conditions could be trapped by $PhSO_2SCF_2H$. Herein, we reported the realization of such a difluoromethylthiolation reaction by reactions of a variety of aryldiazonium salts with $PhSO_2SCF_2H$ under visible light irradiation and a photocatalyst (Scheme 1).

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**Privious work**

$Ar—N_2BF_4 + [(SIPr)Ag(SCF_2H)] \xrightarrow{[Cu(CH_3CN)_4]PF_6/bpy} Ar—SCF_2H$

**This work**

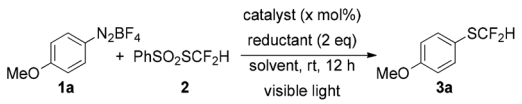
$Ar—N_2BF_4 + PhSO_2SCF_2H \xrightarrow{[Ru],\ visible\ light} Ar—SCF_2H$

**Scheme 1** Difluoromethylthiolation of aryldiazonium salts.

## Results and discussion

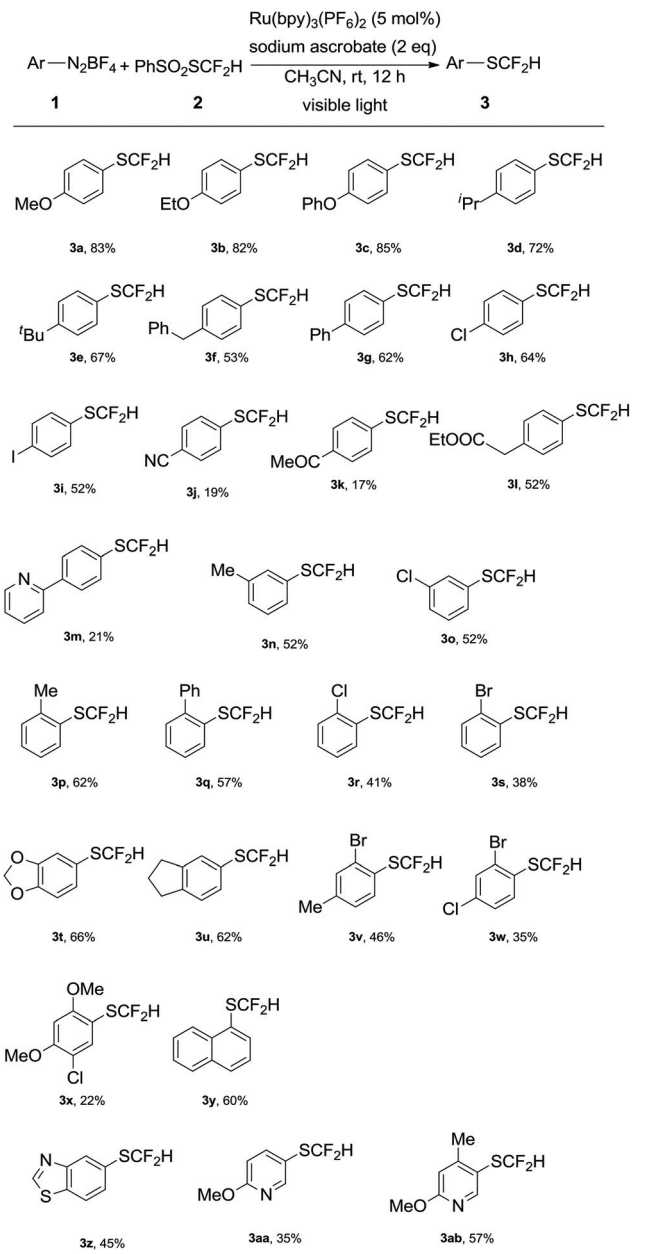
We initiated our study by choosing the reaction of 4-methoxyl benzenediazonium tetrafluoroborate (**1a**) and $PhSO_2SCF_2H$ (**2**) in $CH_3CN$ as a model reaction to optimize the conditions. To our delight, when $Ru(bpy)_3(PF_6)_2$ was used as a photocatalyst in the presence of DIPEA, the formation of the desired difluoromethylthiolated product **3a** was observed in 55% yield, as determined by $^{19}F$ NMR spectroscopy (Table 1, entry 1). Next, different reductants were examined and it was found that sodium ascorbate as the reductant gave the highest yield (Table 1, entries 2–5). We further studied the effect of different photocatalysts. Among many photocatalysts including $Ru(bpy)_3Cl_2{\cdot}H_2O$, $[Ir(ppy)_2(dtbbpy)](PF_6)$ and $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$, $Ru(bpy)_3(PF_6)_2$ was the most efficient catalyst (Table 1, entries 6–8). Switching the solvent from $CH_3CN$ to other commonly used solvents under visible light-catalyzed conditions such as $CH_2Cl_2$, DMF or DMSO, the yields decreased significantly (Table 1, entries 9–11). Further studies demonstrated that the loading of the catalyst could be decreased to 1.0 mol% without diminishing the yield of the product (Table 1, entries 5, 12 and 13). Control experiments showed that the desired product was formed in 25% yield after 12 h in the dark at ambient temperature, demonstrating the necessity of visible light in promoting the formation of the aryl radical (Table 1, entry 14). Reactions could also occur without a photocatalyst. However, only 46% yield was given (Table 1, entry 15). The result confirmed that both light and the photocatalyst promote this difluoromethylthiolation process (Scheme 2).

**Table 1** Optimization of the conditions for the visible-light photoredox reaction of aryldiazonium salt **1a** with $PhSO_2SCF_2H$ **2** [a]




| Entry | Catalyst | Reductant | Solvent | $x$ | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Ru(bpy)_3(PF_6)_2$ | DIPEA | $CH_3CN$ | 5 | 55 |
| 2 | $Ru(bpy)_3(PF_6)_2$ | $Et_3N$ | $CH_3CN$ | 5 | 65 |
| 3 | $Ru(bpy)_3(PF_6)_2$ | TMEDA | $CH_3CN$ | 5 | 54 |
| 4 | $Ru(bpy)_3(PF_6)_2$ | $PPh_3$ | $CH_3CN$ | 5 | 34 |
| 5 | $Ru(bpy)_3(PF_6)_2$ | Sodium ascorbate | $CH_3CN$ | 5 | 95 |
| 6 | $Ru(bpy)_3Cl_2{\cdot}6H_2O$ | Sodium ascorbate | $CH_3CN$ | 5 | 87 |
| 7 | $[Ir(ppy)_2(dtbbpy)](PF_6)$ | Sodium ascorbate | $CH_3CN$ | 5 | 93 |
| 8 | $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ | Sodium ascorbate | $CH_3CN$ | 5 | 64 |
| 9 | $Ru(bpy)_3(PF6)_2$ | Sodium ascorbate | DCM | 5 | 48 |
| 10 | $Ru(bpy)_3(PF6)_2$ | Sodium ascorbate | DMF | 5 | 9 |
| 11 | $Ru(bpy)_3(PF_6)_2$ | Sodium ascorbate | DMSO | 5 | Trace |
| 12 | $Ru(bpy)_3(PF_6)_2$ | Sodium ascorbate | $CH_3CN$ | 3 | 87 |
| 13 | $Ru(bpy)_3(PF_6)_2$ | Sodium ascorbate | $CH_3CN$ | 1 | 84 |
| 14[c] | $Ru(bpy)_3(PF_6)_2$ | Sodium ascorbate | $CH_3CN$ | 5 | 25 |
| 15[d] | — | Sodium ascorbate | $CH_3CN$ | 5 | 46 |

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), catalyst and reductant (0.4 mmol) in solvent (2.0 mL) for 12 h at room temperature under a $N_2$ atmosphere. [b] Yields were determined by $^{19}F$ NMR spectroscopy. [c] The reaction system was stirred in the dark for 12 h at room temperature. [d] Reaction without a photocatalyst.




**Scheme 2** Investigation of the substrate scope of the visible light promoted difluoromethylthiolation of aryldiazonium salts. Yields of the isolated products are given. Reaction conditions: **1** (0.75 mmol), 2 (0.5 mmol), $Ru(bpy)_3(PF_6)_2$ (0.025 mmol), and sodium ascorbate (1 mmol) in $CH_3CN$ (5 mL) for 12 h at room temperature under a $N_2$ atmosphere.

With the optimal conditions in hand, the substrate scope was next investigated. In general, aryldiazonium salts with both electron-donating and electron-withdrawing groups could be subjected to this visible light promoted process, affording the corresponding products in moderate to good yields. Substrates with electron-rich groups (MeO, EtO, PhO) in the *p*-position gave products in high yields (**3a–3c**). Various other substituents could also be tolerated, such as alkyl (**3d–3f**), phenyl (**3g**), chlorine (**3h**), iodine (**3i**), cyano (**3j**), ketone (**3k**), ester (**3l**) and heteroaryl (**3m**). However, substrates with electron-withdrawing groups gave low yields (**3j**, **3k**, and **3m**). When substituents were present on the *o*- and *m*-positions, the desired products were generated in moderate yields (38–62%) (**3n–3s**). Disubstituted and trisubstituted aryldiazonium salts also reacted smoothly under the standard conditions, giving the difluoromethylthiolation products (**3t–3x**) in 22–66% yields. Likewise, a naphthyldiazonium salt reacted with **2** in 60% yield (**3y**). Difluoromethylthiolation of heteroaryl diazonium salts could be realized in moderate yields (**3z**, **3aa**, and **3ab**).

To explore the mechanism of this reaction, fluorescence quenching experiments were carried out. It was shown that there were two possible pathways in this process. The addition

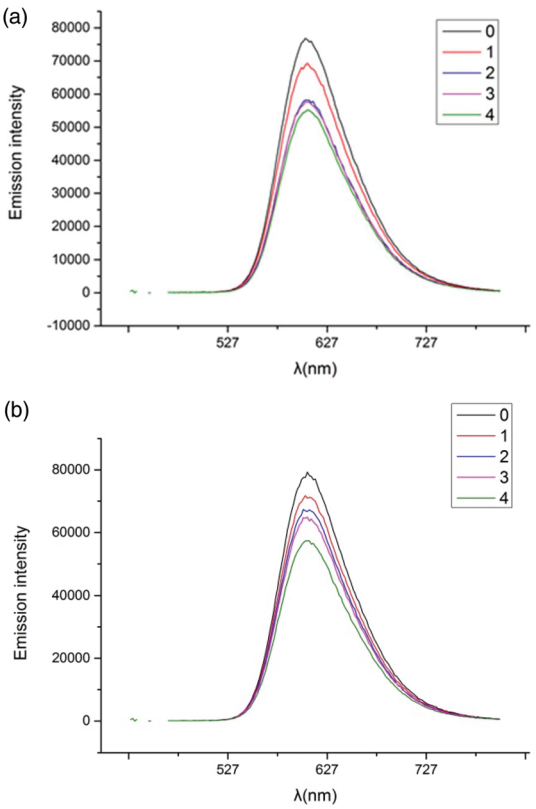
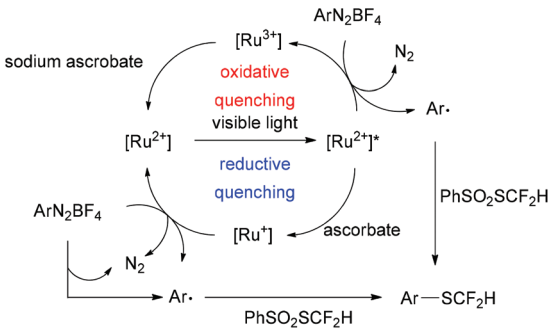



**Fig. 1** Fluorescence quenching experiment using (a) aryl diazonium salts **1a** as quenchers and (b) sodium ascorbate as quenchers (0: emission intensity of a 0.0001 M solution of $Ru(bpy)_3(PF_6)_2$ in $CH_3CN$. 1: Addition of 0.25 eq. of quenchers. 2: Addition of 0.5 eq. of quenchers. 3: Addition of 0.75 eq. of quenchers. 4: Addition of 1 eq. of quenchers).




**Scheme 3** Proposed mechanism for visible light-promoted difluoromethylthiolation of aryldiazonium salts.

of either aryl diazonium salts or sodium ascorbate could quench the excited state of the photocatalyst (Fig. 1).

Thus, an oxidative quenching pathway and a reductive quenching pathway both contributed to this photocatalytic reaction (Scheme 3). Firstly, $[Ru(bpy)_3^{2+}]$ was excited to $[Ru(bpy)_3^{2+}]^*$. Then, in the oxidative quenching cycle, diazonium salts oxidized this excited state to $[Ru(bpy)_3^{3+}]$ and aryl radicals were generated. The oxidative $[Ru(bpy)_3^{3+}]$ was reduced by sodium ascorbate to give $[Ru(bpy)_3^{2+}]$. In the reductive quenching cycle, the excited state of the Ru complex was reduced by sodium ascorbate, and a reductive-sate $[Ru(bpy)_3^{+}]$ was afforded. Aryl radicals were generated through a SET process from the reductive $[Ru(bpy)_3^{+}]$ to aryldiazonium salts and $Ru(bpy)_3^{2+}$ was regenerated. Simultaneously, the diazonium salts could decompose to release the aryl radicals under visible light. In the last step, $PhSO_2SCF_2H$ was trapped by the aryl radicals and gave the difluoromethylthioethers.

## Experimental

### General procedure for the visible light promoted difluoromethylthiolation of aryldiazonium salts

$ArN_2BF_4$ (0.75 mmol, 1.5 eq.), $Ru(bpy)_3(PF_6)_2$ (0.025 mmol, 5 mol%), sodium ascorbate (1 mmol, 2.0 eq.), $PhSO_2SCF_2H$ (0.5 mmol, 1.0 eq.) and anhydrous $CH_3CN$ (5 mL) were added to a flame-dried reaction tube under a nitrogen atmosphere. The mixture was subjected to visible light irradiation with a 12 W white CFL for 12 h at room temperature. Then 100 mL $Et_2O$ was added and the mixture was washed with brine (20 mL × 3). After drying with $Na_2SO_4$, the solvent was evaporated, and the residue was subjected to flash column chromatography to give the desired products.

## Conclusions

In summary, a visible light catalyzed difluoromethylthiolation of aryldiazonium salts with $PhSO_2SCF_2H$ was reported. Various substituents were tolerated under these mild conditions. As aryldiazonium salts could be easily prepared from arylamines,

which exist widely in naturally occurring compounds and pharmaceuticals, the process provides a versatile route to difluoromethylthioethers derived from arylamines and indicates their potential use in pharmaceuticals and agrochemicals.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support from the Shandong Provincial Natural Science Foundation (ZR2016BQ31, ZR2016HM44, and ZR2016JL009), the Shandong Key Research Program (2017GSF218061), the Major Program of Shandong Province Natural Science Foundation (ZR2017ZC0529) of China and the University of Jinan is gratefully acknowledged.

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