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Radical difluoromethylthiolation of aromatics enabled by visible light†

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Direct introduction of a difluoromethylthio group (–SCF_2H) to arenes represents an efficient route to access a valuable catalogue of organofluorines; however, to realize this transformation under metal-free and mild conditions still remains challenging and rarely reported. Herein, a metal-catalyst-free and redox-neutral innate difluoromethylthiolation method with a shelf-stable and readily available reagent, $PhSO_2SCF_2H$, under visible light irradiation is described. This light-mediated protocol successfully converts a broad spectrum of arenes and heteroarenes to difluoromethylthioethers in the absence of noble metals and stoichiometric amounts of additives.

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The difluoromethylthio group, as a member of the fluoroalkyl family, has been receiving growing attention from both academia and industry.[1] This is not only because it incorporates two instrumental elements, sulfur and fluorine, into one functionality, but also due to its unique properties (Fig. 1b): (1) –SCF_2H is intermediately lipophilic (Hansch lipophilicity parameter, $\pi_R = 0.68$ for –SCF_2H, 0.56 for –CH_3 and 1.44 for –SCF_3),[2] providing flexibility to medicinal chemists in the rational design of drug candidates; (2) –SCF_2H features a slightly acidic proton, rendering it a weak hydrogen bond donor ($pK_a = 35.2$; hydrogen bond acidity parameter $A = 0.098$) to tune the molecule's binding ability;[1b,3] (3) the electron-withdrawing nature of –SCF_2H could promote the metabolic stability of target compounds; and (4) difluoromethylsulfides can participate in some late-stage modification events, which could diversify this functionality and may regulate the bio-activity of host molecules. Pyriprole, patented in 2008 as a novel pest control agent, showed advantageous performance (Fig. 1a).[4] Its invention detailed that the C-4 position bearing –SCF_2H was identified as the most preferable structure. Furthermore, the important role of –SCF_2H in pharmaceuticals and agrochemicals is evidenced by its frequent enrolment in other bioactive compounds, *e.g.*, herbicide SSH-108,[5] nifedipine analogue,[6] and thymol analogue[7] (Fig. 1a).

Despite the intriguing pharmaceutical potential exhibited by difluoromethylthioethers, their widespread application remains limited possibly owing to a lack of efficient preparative methods.[8] Classical and commonly used approaches to synthesize difluoromethylthioethers employ the nucleophilic attack of an appropriate thiolate (RS^-) to some "CF_2" species,[9] typically a difluoromethyl carbene (:CF_2),[10] (Scheme 1a, left). A complementary but less common approach to assemble –SCF_2H is difluoromethylation of disulfides using nucleophilic difluoromethyl sources (*e.g.*, activated $TMSCF_2H$).[11] A major step forward to expand the substrate scope was made by the Gooßen group who described a stepwise synthetic route involving preformed thiocyanates and the subsequent copper-mediated Langlois type nucleophilic substitution by $TMSCF_2H$ (Scheme 1a, right).[3a,12] Nevertheless, these indirect methods still suffer from a limited substrate scope. In addition, they usually necessitate strong bases, harsh thermal conditions and environmentally unfriendly reagents to generate reactive thiolates and "CF_2" species.

To address these issues, a key contribution was made by Shen and his co-workers who delineated the first nucleophilic difluoromethylthiolating reagent **1**, [(SIPr)Ag(SCF_2H)] (Scheme 1b).[13] In the presence of transition metals (M = Pd, Cu), this complex could couple with diverse aryl and heteroaryl halides,

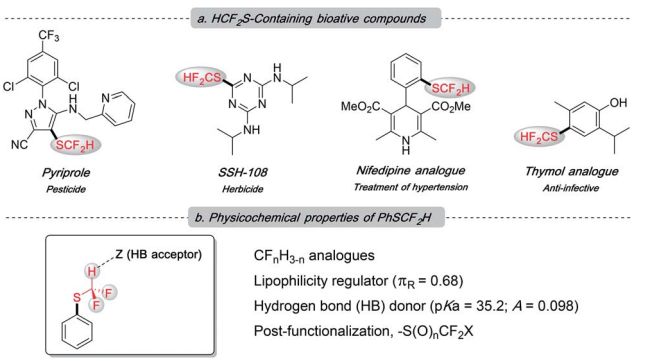

Fig. 1 (a) Frequent appearance of the –SCF_2H residue in bioactive molecules; (b) overview of the uniqueness of –SCF_2H.

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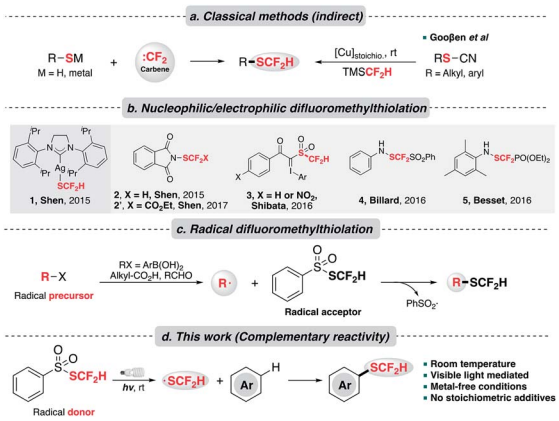
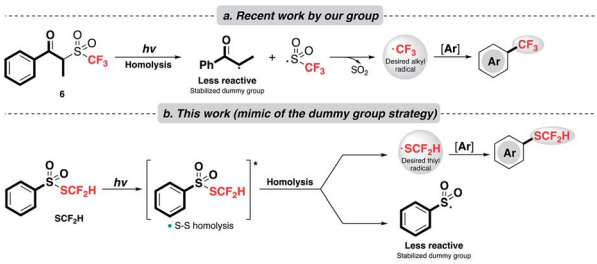


Scheme 1 Different recipes to install $-SCF_2H$ on arenes. (a) Classical methods to prepare difluoromethylthioethers; (b) direct difluoromethylthiolating reagents (**1**: nucleophilic; **2**–**5**: electrophilic); (c) radical difluoromethylthiolation wherein $PhSO_2SCF_2H$ acts as a radical acceptor; (d) this work: catalyst-free and redox-neutral innate difluoromethylthiolation with $PhSO_2SCF_2H$ as the radical source under visible light.



Scheme 2 (a) Controlled radical generation *via* the "dummy fragment" concept; (b) this work: catalyst-free and redox-neutral innate difluoromethylthiolation enabled by light.

triflates and diazonium compounds to prepare difluoromethylthioethers. Complementarily, the same group debuted an electrophilic difluoromethylthiolating reagent **2**,[14] which could undergo a Friedel–Craft type C_{sp^2}–H difluoromethylthiolation on various N-heteroarenes. Shortly after, Shibata *et al.* uncovered a hypervalent difluoromethanesulfonyliodonium ylide reagent **3**, which efficiently difluoromethylthiolated N-heterocycles under copper catalysis.[15] Moreover, the Billard,[16] Besset[17] and Shen[18] groups independently synthesized three electrophilic $-SCF_2FG$ group transfer reagents (FG = $PhSO_2$, $PO(OEt)_2$ and CO_2Et respectively), although a separate reductive workup was necessary to give difluoromethylthioethers. Inspired by these elegant examples, other difluoromethylthiolating systems were unveiled.[7,19]

Alternatively, difluoromethylthiolation could be operated in a radical pathway. *S*-(Difluoromethyl)benzenesulfonothioate, $PhSO_2SCF_2H$, invented in 2016 by Shen *et al.*, was revealed as an effective difluoromethylthiolating reagent (Scheme 1c).[20] Mechanistically, it was proposed to execute as a radical acceptor and combine with the alkyl or aryl radicals generated from the Ag/persulfate-involved oxidation event. This reactivity was further elaborated in two recent studies on the ring-opening difluoromethylthiolation of cycloalkanols[21] and the preparation of difluoromethylthioesters by using aldehydes as acyl radical precursors.[22]

Promising though these strategies are, the main drawbacks lie in their requirement of relatively high thermal energy (ranging from 50 to 120 °C), or involvement of precious metal catalysts and stoichiometric amounts of additives. In the case of $-SCF_2FG$ group transfer, additional steps were required to furnish the final thioether products. Clearly, a more sustainable synthetic protocol that features mild conditions and step economy is highly desired.

In 2017, our group disclosed a radical trifluoromethylation reaction on arenes with a novel sulfone reagent **6** (Scheme 2a).[23] With light irradiation, **6** engenders two twin radicals *via* Norrish type I cleavage as the sulfinyl radical fragments further to produce the CF_3 radical and implements trifluoromethylation. The success of this chemistry lies in the judicious design of the reagent structure. In the so-called "dummy group" strategy, the undesirable radical produced by homolysis of **6** is diminished in reactivity by the "captodative effect"[24] as well as sterics.

Inspired by this work, we would like to apply a similar strategy and achieve a rarely known direct radical difluoromethylthiolation (Scheme 2b). A key component of this project is to explore and identify a suitable SCF_2H radical precursor. After a careful examination of the literature, we consider that the thiosulfonate reagent, $PhSO_2SCF_2H$, might be applicable, although it was documented to be a radical acceptor as its principle utility.[20,22] We proposed that the homolytic fragmentation of $PhSO_2SCF_2H$ with a suitable light source is feasible due to the well-studied propensity of homolysis of the S–S bond[25] and the stabilization of the resulting sulfonyl radical exerted by the resonance effect of the phenyl group.[26] The stabilization of the dummy radical is beneficial in two ways: (1) it facilitates homolytic bond scission and allows the accumulation of SCF_2H radicals; (2) it is expected to cause less competition toward the targeted reaction pathway. Radical addition of the desired SCF_2H radical will furnish the target product.

As a part of our interest in photo-induced fluorine chemistry, we wish to document a photo-induced metal-free aromatic difluoromethylthiolation protocol with $PhSO_2SCF_2H$, wherein $PhSO_2SCF_2H$ was utilized as a difluoromethylthiyl radical source. To the best of our knowledge, direct aromatic difluoromethylthiolation realized by radical attack of SCF_2H radical on arenes remained unexplored.

To commence the study, *N*-methylindole **1a** was chosen as a model substrate and treated with difluoromethylthiolating sources in CH_3CN under an inert atmosphere based on some literature parallels on difluoromethylthiolation (see ESI† for full details). Although no desired product was detected when using $BnSCF_2H$, the reaction with $PhSO_2SCF_2H$ proceeded as expected and upon 16 hours of UV irradiation, 20% yield of the desired product was obtained (Table 1, entries 1 and 2). Using compact fluorescence lamps (CFL) as a light source gave 64% yield of the target compound (entry 3). Fortunately, prolonging the reaction time enabled the consumption of unreacted substrates and increased the yield to 80% (entry 4). The

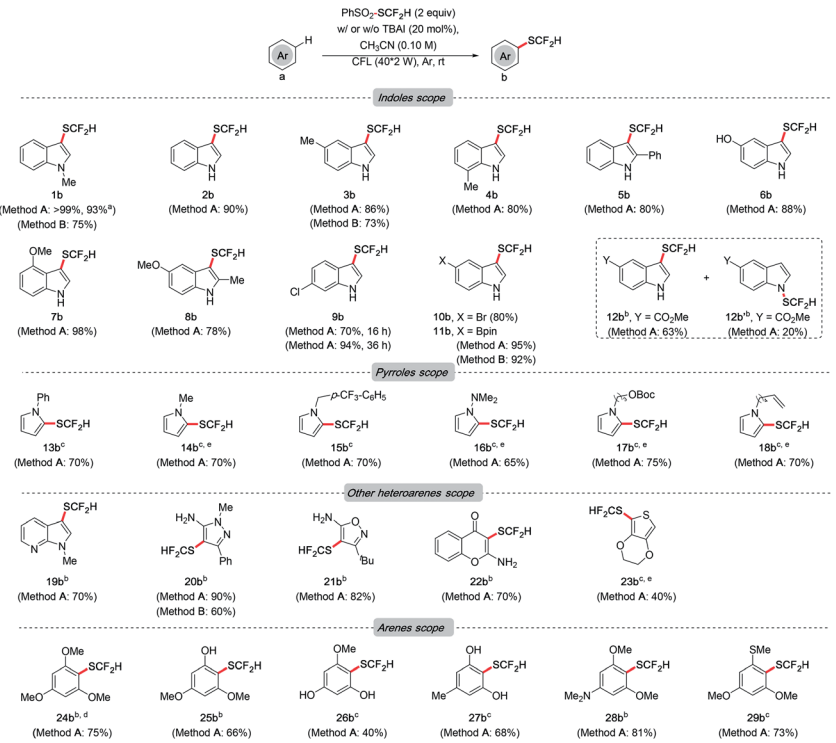
Table 1 Selected results of evaluation under various conditions[a]

entry[a]	1a : [SCF$_2$H]	additive(equiv)	time	yield[b]
1[c,d]	1 : 2	-	16 h	NR
2[d]	1 : 2	-	16 h	20%
3	1 : 2	-	16 h	64%
4	1 : 2	-	48 h	80%
5[e]	1 : 2	-	16 h	NR
6	1 : 2	NaI (5 mol%)	16 h	80%
7	1 : 2	KI (5 mol%)	16 h	80%
8	1 : 2	TBAI (5 mol%)	16 h	86%
9	1 : 2	TBAI (20 mol%)	16 h	99%
10	1 : 1	TBAI (20 mol%)	16 h	65%
11	2 : 1	TBAI (20 mol%)	16 h	80%

[a] Abbreviations: CFL, compact fluorescent lamp; rt, room temperature; TBAI, tetrabutylammonium iodide; NR, no reaction. [b] All reactions were conducted with 0.10 mmol **1a**, 0.20 mmol $PhSO_2SCF_2H$, 0.020 mmol TBAI in 1.0 mL CH_3CN under argon with irradiation of two 40 W CFL unless otherwise noted. [c] The yield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [d] $BnSCF_2H$ as the difluoromethylthiolating source. [e] Six 254 nm 2.5 W UV lamps (photo-box). [f] In the dark.

essential role played by light was illustrated by the control experiment as the dark condition disabled the reaction completely (entry 5 and see ESI† for details on control experiments). Recent work by our group revealed the unique properties of NaI, *e.g.*, high reducing ability along with low nucleophilicity,[27] which were helpful in radical generation. Therefore, we expected the SCF_2H radical generation would be accelerated by a complementary reductive pathway. Gratifyingly, catalytic incubation of iodide gave similarly good yield in a shortened reaction time (entries 6–8). Among the tested iodides, tetrabutylammonium iodide (TBAI) offered the highest yield (entry 8). Further increment of TBAI loading could promote the reaction to be quantitative (entry 9). Conforming to other electrophilic difluoromethylthiolation studies, **1a** as a limiting reagent would be more profitable as an excess of difluoromethylthiolating reagent is crucial to maintain a decent level of active difluoromethylthiolating species (entries 10 and 11).

With the optimal conditions identified, the generality of this method was examined (Scheme 3). Initially, the functional group tolerance of different indoles was investigated. In general, indoles bearing substituents with different electronic and steric properties at various sites are compatible with the optimal conditions. Reaction rates of substrates with electron-donating groups were higher than those with electron-withdrawing groups. Satisfactorily, quantitative yield was obtained for non-substituted indole (**2b**). Product formation was not



Scheme 3 Scope of arenes. Method A: arene (0.10 mmol), $PhSO_2SCF_2H$ (0.20 mmol), TBAI (0.020 mmol) in 1.0 mL CH_3CN under argon for CFL irradiation at rt for 16 h. Method B: arene (0.10 mmol), $PhSO_2SCF_2H$ (0.20 mmol) in 1.0 mL CH_3CN under argon for CFL irradiation at rt for 48 h. The yields in the parentheses refer to the isolated ones unless otherwise specified. Volatility resulted in the low isolated yield of **17b** and **18b**. [a]Reaction performed on the 0.40 mmol scale. [b]The reactions were performed for 24 h. [c]The reactions were performed for 48 h. [d]4 equiv. $PhSO_2SCF_2H$ were used. [e]Yields are quantified by GC-MS due to the volatility of target compounds.

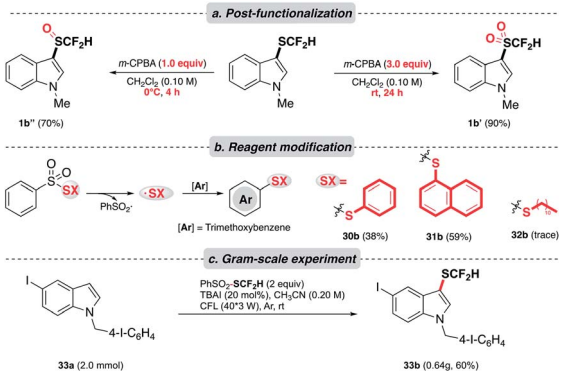
affected by the methyl group at the C-5 or C-7 position (**3b** and **4b**). Even in the presence of a phenyl group at the C-2 position, a decent yield can also be achieved (**5b**). Notably, the reaction proceeded smoothly in indole tethering a phenolic proton (**6b**). Methoxylated indoles could result in 98% and 78% of desired products respectively (**7b** and **8b**). Indole derivatives bearing the chloro, bromo and boryl groups resulted in good to excellent yields of products, which allow further cross coupling to achieve more complex settings (**9b** to **11b**). Unexpectedly, regiomers were isolated for substrates with an ester group (**12b** and **12b′**). Then we moved the focus to a class of closely related N-heterocycles, pyrroles. Pyrroles with phenyl, methyl, benzyl, dimethylamino and carbonato groups all gave around 70% of target difluoromethylthioethers (**13b** to **17b**). Of note is the substrate bearing a double bond, which is known to be reactive toward $PhSO_2SCF_2H$. Gratifyingly, the C_{sp^2}–H difluoromethylthiolation product was selectively obtained (**18b**).

Other heteroarenes, *e.g.*, azaindole, pyrazole, isoxazole, and chromone, which are pharmaceutically important scaffolds, were also effective (**19b** to **22b**). Notably, this protocol was viable for thiophene, which was generally unreactive in other difluoromethylthiolating recipes (**23b**).[10m,20] Finally, the versatility of this method on some arenes was explored. 1,3,5-Trimethoxybenzene was difluoromethylthiolated successfully (**24b**). As this method was proved adaptable to phenolic protons, installing –SCF_2H on phenol (**25b**) and resorcinol derivatives (**26b** and **27b**) was efficient. Aniline and sulfide underwent difluoromethylthiolation smoothly as well, resulting in good yields (**28b** and **29b**).

Generally, high regioselectivity was observed for this difluoromethylthiolation reaction, which was a combined effect of electronics and sterics. In most cases, the site of the highest electron density was difluoromethylthiolated, *e.g.*, C-2 in indoles and C-1 in pyrroles. When multiple sites of similar electron richness were available, the reaction occurred at the sterically less hindered C_{sp^2}–H (**25b** and **29b**). Although an excess amount of $PhSO_2SCF_2H$ was used, the difunctionalization product was rarely detected during our scope exploration (see ESI† for details of mono-/difunctionalization and regioselectivity issues).

Knowing that the difluoromethylsulfoxides and difluoromethylsulfones[28] are valuable entities in medicinal chemistry, we were encouraged to alter the oxidation state of sulfur in –SCF_2H. As expected, the oxidation of difluoromethylthioethers could be accomplished in a controlled manner under different oxidizing conditions (Scheme 4a). Besides, the versatility of this photochemical strategy was extended to produce other synthetically useful thiyl radicals. Under the optimal conditions, phenylthioether (**30b**) and naphthylthioether (**31b**) were furnished smoothly. However, alkylthiolation (**32b**) was undermined by the homocoupling event of alkylthiyl radicals. Moreover, **33a** was subjected to a gram-scale experiment to demonstrate the practicality of this method (Scheme 4c). We were pleased to see that the reaction proceeded smoothly and a good yield of the desired product was obtained (**33b**).

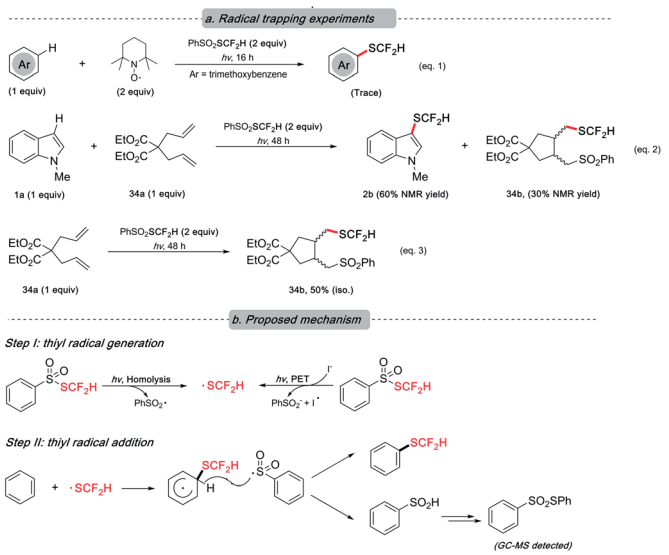
Although the underlying mechanism remained obscure at this stage, our preliminary study hints at the radical nature of



Scheme 4 Application. (a) Controlled oxidation of thioethers to corresponding sulfoxides and sulfones; (b) modified reagents to afford arylthiolation products; (c) scaled-up experiments.

this reaction as designed. The presence of various radical quenchers significantly impacted the desired reactivity (Scheme 5, eqn (1) and (2)). When diallylmalonate (**34a**) was employed as the radical clock-type trapper, a cyclization adduct (**34b**) with $PhSO_2SCF_2H$ was observed irrespective of the presence of **1a** (eqn (2) and (3)). This result, to a degree, supports our postulation of the radical mechanism.

Based on the previous literature[20,22a] and the above-mentioned experiments (see ESI† for details that rationalized the intermediacy of the proposed radical and the by-product formation), we envisioned that a radical-involved mechanism was operative. Under light irradiation, a difluoromethylthiyl radical resulted from either the homolysis of $PhSO_2SCF_2H$ or the photo-induced electron transfer (PET) event between $PhSO_2SCF_2H$ and iodide. Subsequently, the action of SCF_2H radical on arenes was followed by hydrogen atom abstraction by phenylsulfonium (radical) to furnish the target compound. The resulting phenylsulfinic acid was unstable and further transformed into thiosulfonate.[29]



Scheme 5 Mechanistic study. (a) Termination of the desired reactivity in the presence of radical trappers; (b) plausible mechanism.

Conclusions

In summary, we have developed a metal-catalyst-free aromatic difluoromethylthiolation reaction at room temperature enabled by visible light. This operationally simple strategy features the synthesis of a series of difluoromethylthioethers under mild conditions, which are a class of compounds with high medicinal value.[1,2,3b] These difluoromethylthioethers could be readily diversified into corresponding sulfones and sulfoxides. Moreover, this "dummy group" strategy holds great potential for achieving other types of radical thiolations by simply switching the functionalities tethered on thiosulfonate reagents. Details of mechanistic insight remain to be explored and we are dedicated to introducing fluorine-containing functional groups on arenes with similar strategies.

Conflicts of interest

There are no conflicts to declare.

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