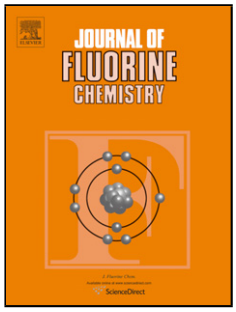

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Silver-Catalyzed Fluoroalkylation of Thiols Using Fluoroalkanesulfinates

Jing-jing Ma,[+a] Qi-ran Liu, [+a] Guo-ping Lu and Wen-bin Yi [*a]

[a] *Chemical Engineering College, Nanjing University of Science & Technology, 200 Xiaolingwei, Nanjing 210094, P. R. China*
[+] *These authors contributed equally to this paper*.

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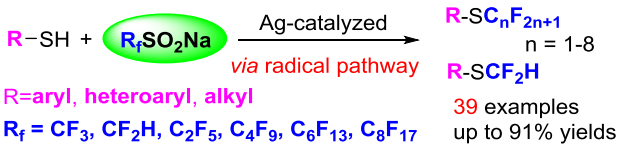
* Corresponding author. e-mail: yiwb@njust.edu.cn

ABSTRACT



A practical sliver-catalyzed fluoroalkylation of aryl-, heteroaryl- and alkylthiols has been developed. The reaction has a good functional-group tolerance and excellent selectivity. A variety of stable and solid fluoroalkanesulfinates including di- and perfluoroalkanesulfinates can be employed. This methodology provides a straightforward and streamlined access to perfluoroalkylthiolated organic molecules.

Keywords: Silver-catalyzed, fluoroalkylation, fluoroalkanesulfinates, thiols

1. Introduction

Remarkable progress witnessed in recent organofluorine chemistry is obviously related to a rapid expansion on the discovery of potential biological and therapeutic molecules containing fluoroalkylthio moieties (Fig. 1) [1]. Notably, the most prominent among those fluoroalkylthiolated compounds is the trifluoromethylthio group (SCF_3). It plays a pivotal role thanks to its high lipophilicity and strong electron-withdrawing characters [2]. In this blossoming field, much attention has been paid on di- and perfluoroalkylthio residues (SCF_2H and SR_f) owing to their intrinsic properties. For instance, the introduction of SCF_2H onto drug molecules often changes the desirable physical and biological properties [3]. Compounds containing SR_f have been involved in the manufacturing processes of blockbuster drugs and effective agrochemicals [4].

Thus, efficient methodologies for the synthesis of the fluoroalkylthio motifs are of high demand.

Halogen-fluorine exchange of polyhalogenomethyl thioethers is a classical method for the formation of S-CF_3 bond [5]. Besides this method, two foremost synthetic strategies for the incorporation of SCF_3 have fascinated synthetic chemists: the direct trifluoromethylthiolation and the trifluoromethylation of sulfur-containing compounds [6]. The direct method often utilize shelfstable reagents, which suffers from some drawbacks such as regioselectivity issues, limitations of reactivity, the use of excess metal, necessity of directing groups and the use of unstable reagents [7]. Another one is the trifluoromethylation of various sulfur sources [8]. Several elegant transformations involved the electrophilic [9] and nucleophilic trifluoromethylation [10] have been developed. The trifluoromethylation reagents employed in these studies are often electrophilic CF_3 sources such as expensive Umemoto reagents [9b] and Togni reagent [9c]. Some reports used the nucleophilic CF_3 source $TMSCF_3$ (Ruppert's reagent) [10b-10d], which often require an activating agent and thus pose constrains in the functional-group compatibility. Apart from these two approaches, the formation of S-CF_3 bonds with simple thiols *via* radical pathway was an attractive protocol. In the initial time, several reports employ volatile or unstable reagents under harsh reaction conditions [11]. To solve this problem, Langlois *et al*. synthesized a manipulative and stable CF_3 reagent sodium trifluoromethanesulfinate (CF_3SO_2Na), twhich could transfer the CF_3 group to CF_3• species [12]. Followed by this, they found that *tert*-butyl hydroperoxide (TBHP) was a good partner and combined CF_3SO_2Na with disulfides. However, narrow substrate scope, low utilization of disulfides and over-oxidized products limited its application [13].

As part of our ongoing program toward the trifluoromethylation with iodine pentoxide [14], we paid our attention to transition metal catalysts. Indeed, Ag/$K_2S_2O_8$ reaction system has been studied exhaustively for the generation of free radicals [15]. Inspired by this, we were engaged in combining thiols with CF_3SO_2Na in the presence of silver catalysts. Furthermore, other fluoroalkylsulfinates ($(R_fSO_2)_nM$) have been successfully prepared and few has been explored for the formation of S-CF_2H and S-R_f bonds [16]. Higher acidity of CF_2H and long perfluoroalkylative chain repercussion boycotted the formation of corresponding radicals, thus selective functionalization under mild conditions represents a significant challenge and goal in modern organofluorine chemistry. Herein, we report a silver-catalyzed trifluoromethylation of aryl-, heteroaryl- and alkylthiols. This method allows smooth transformation to various SCF_3 in aqueous medium, avoids excessive oxidization of thiols and products, uses relatively low loading of silver nitrate [17]. Moreover, we extended the scope of di- and perfluoroalkylthiolation employing the corresponding fluoroalkylated reagents.

2. Results and discussion

Initially, we investigated the trifluoromethylation of 4-methylbenzenethiol (**1b**) in the presence of 2.0 equiv. of $K_2S_2O_8$ and 20 mol% $AgNO_3$ in MeCN, and obtained 19% yield of expected product **3b** (Table 1, entry 1). Gratifyingly, other solvents were tested and CH_3CN/H_2O seemed best (entries 1-4). With regard to the influence of the amount of $AgNO_3$, as well as the amount of CF_3SO_2Na, the yield increased to 54% (entries 5-8). Furthermore, the yield was up to 63% when this reaction was carried out under argon atmosphere (entry 9). Almost no difference was found as used other peroxide salt ($Na_2S_2O_8$), which proved that $S_2O_8^{2-}$ played a crucial role in this reaction (entry 10). It was worth mentioning that no or low yields were detected in the absence of $K_2S_2O_8$ or $AgNO_3$ (entries 11-13). It was noted that TBHP was employed as initiator and 4-chlorothiophenol as substrate to avoid oxidation in this process, giving low yield with relatively poor selectivity (entry 14).

With the optimal reaction conditions in hand, we explored the scope of thiols (Table 2). Firstly, the reaction proceeded smoothly with aromatic rings bearing Me (**3b**), *t*Bu (**3c**), OMe, (**3d**), halogens (**3e**-**3g**), hydroxyl (**3h**) and nitro (**3j**) showcasing the functional group

tolerance of the process. It should be noted that MeCN was used as solvent to avoid the hydrolysis of **3k**, which led to the decreased yield. Importantly, the substitution pattern on the aromatic ring does not have an influence on the result since *meta*- or *orth*-substituted thiols with different functional groups (**3k-3m**) were obtained in moderate to good yields. In addition, benzeneselenol was feasible in this process and obtained **3n** in 74% yield. It was worth mentioning that the thiols with heteroaryl ring (thiazole, pyrimidine), were viable substrates in the current reaction, giving the corresponding products (**3o**-**3q**) in good to high yields. Furthermore, alkylthiol also smoothly generated the desired product (**3r**). To illustrate, several compounds (**3a**, **3e**, **3k**, **3l**, **3p**) were detected by GC yields with impurities in NMR spectrums due to high volatility.

Besides, the intrinsic ability of SCF_2H makes it one of the appealing points in synthetic chemistry [18]. In this context, we have been interested in extending our strategy to the formation of S-CF_2H bonds with difluoromethanesulfinates (HCF_2SO_2Na) (Table 3). Several thiols bearing methoxyl (**4a**), *tert*-butyl (**4b**), halos (**4c**-**4d**), hydroxyl (**4e**) and amides (**4g**) functional groups, have been successfully acquired the desired products in moderate to good yields. Importantly, heteroaromatic difluoromethyl thioethers (**4h**-**4i**) were respectively obtained in 61% and 78% yields.

Perfluoroalkylthio groups are versatile class of compounds and suitable for large-scale synthesis. We then focus on perfluoroalkylation of thiols with homologous reagents (Table 4). These reagents were prepared as the literatures [15a,19]. Both aromatic and heteroaromatic thiols could smoothly transform to the desired products (**5a**-**5h**). Moreover, alkylthiols were feasible, giving ideal outcomes **5i-5l** to 71%-87% yields.

To better understand the mechanism of this reaction, radical trapping experiments were carried out (Scheme 1). No desired product was detected in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (3.0 equiv.) and 1,1-diphenylethylene (3.0 equiv.), which points toward a radical reaction process.

A postulated mechanism was described in Scheme 2. Initially, Ag^+ is oxidized by the persulfate anion ($S_2O_8^{2-}$) to generate Ag^{2+} cation and sulfate radical anion. Then, Ag^{2+} cation obtains a single electron from R_fSO_2Na to produce R_fSO_2 radicals [16h]. Removal of sulfur dioxide provides the corresponding R_f radicals. Disulfides were detected at the initial time and gradually reduced in the trifluoromethylative process. Hence, there are two plausible paths during the reaction. Path a: assisted by sulfate radical anion abstracted the hydrogen from thiols, R_f radicals smoothly combined with sulfurs to obtain the desired products. Path b: reaction conditions promoted the formation of disulfides, then connected with R_f radicals for the final compounds.

3. Conclusions

In conclusion, we developed a silver-catalyzed selectively trifluoromethylation of various aryl-, heteroaryl- and alkylthiols by using $K_2S_2O_8$ as oxidant and CF_3SO_2Na as trifluoromethylated reagent. Good yields, excellent functional group tolerance, as well as high selectivity made this trifluoromethylative manner useful and practical for the formation of SCF_3-containing compounds. Furthermore, this method has been extended for di- and perfluoroalkylation of thiols with corresponding R_fSO_2Na.

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Supplementary Material

Supplementary data associated with this article can be found in the online version.

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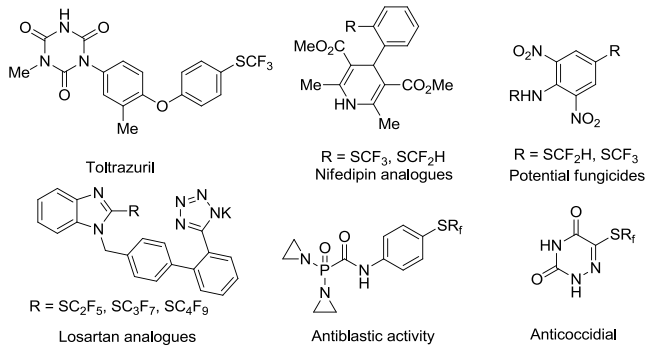
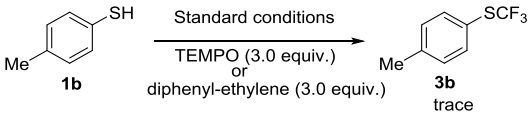
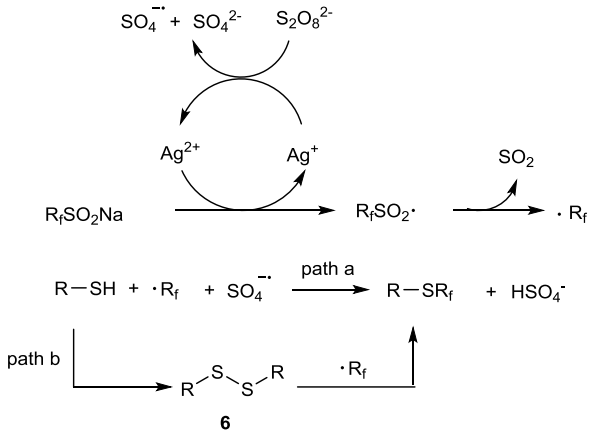


Fig. 1. The variety of the pharmacological activity of fluoroalkylthiol substituted compounds.



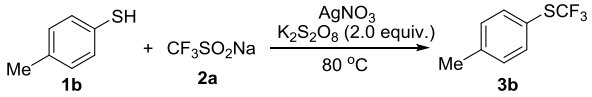
Scheme 1. Trapping experiments.



Scheme 2. Proposed reaction mechanism.

Table 1

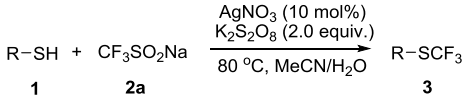
Optimization of the reaction conditions.[a]



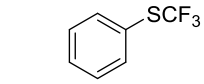
Entry	Cat (mol%)	**2a** (equiv.)	Solvent[b]	**3b**[c]
1	20	2.0	MeCN	19%
2	20	2.0	DMSO	11%
3	20	2.0	DMF	trace
4	20	2.0	MeCN/H_2O	42%
5	10	2.0	MeCN/H_2O	54%
6	30	2.0	MeCN/H_2O	45%
7	10	1.5	MeCN/H_2O	48%
8	10	2.5	MeCN/H_2O	51%
9[d]	10	2.0	MeCN/H_2O	63%
10[de]	10	2.0	MeCN/H_2O	62%
11[f]	10	2.0	MeCN/H_2O	/
12[f]	/	2.0	MeCN/H_2O	/
13	/	2.0	MeCN/H_2O	35%
14[g]	/	2.0	MeCN/H_2O	14%

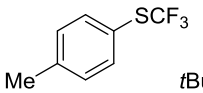
[a] Unless otherwise stated, all reactions were carried out with **1b** (0.2 mmol), $AgNO_3$ as catalyst, $K_2S_2O_8$ (2.0 equiv.) at 80 °C for 24 h.
[b] MeCN/H_2O (1:1, 0.8 mL).
[c] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as the internal standard..
[d] Under argon atmosphere.
[e] 2.0 equiv. $Na_2S_2O_8$ was used to replace $K_2S_2O_8$.
[f] Without $K_2S_2O_8$.
[g] TBHP (3equiv.) replaced $AgNO_3/K_2S_2O_8$ and to avoid oxidation using 4-chlorothiophenol as substrate.

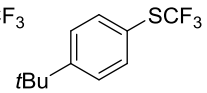
Table 2
Scope of the trifluoromethylation.[a]

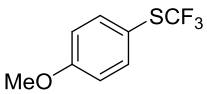


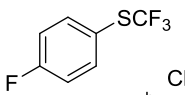
1 2a 3

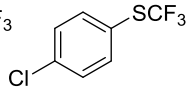

3a, 65%[b]

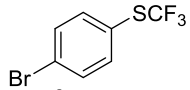

3b, 60%

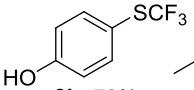

3c, 73%

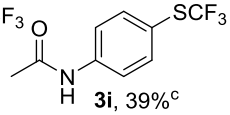

3d 81%

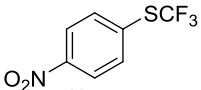

3e, 59% (81%)[b]

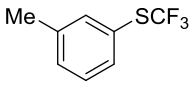

3f, 69%

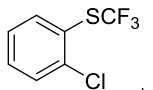

3g, 71%

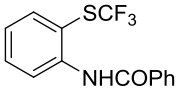

3h, 72%

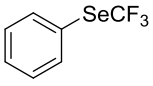

3i, 39%[c]

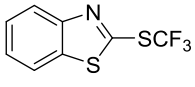

3j, 41%

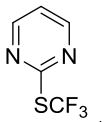

3k, 51%[b]

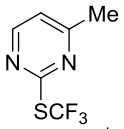

3l, 45% (77%)[b]

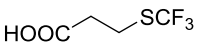

3m, 82%


3n, 74%[b]


3o, 76%

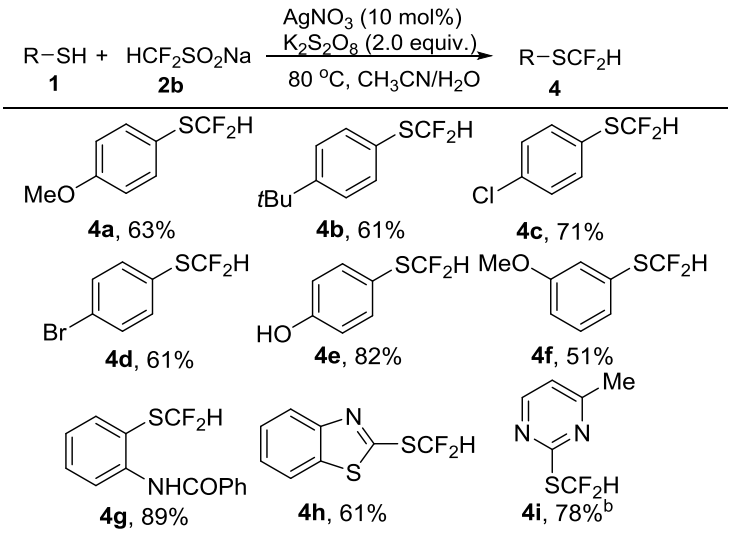

3p, 89%[b]


3q, 88%[d]


3r, 91%

[a] Reaction condition: **1** (0.2 mmol), CF_3SO_2Na (2.0 equiv.), $AgNO_3$ (0.1 equiv.) and $K_2S_2O_8$ (2.0 equiv.) in 0.8 mL CH_3CN/H_2O (1:1), 80 ℃ for 24 h, argon atmosphere, isolated yield.
[b] GC yield (due to high volatility).
[c] 0.8 mL MeCN was used as solvent.
[d] Using 4-methyl-2-pyrimidinethiol hydrochloride as substrate.

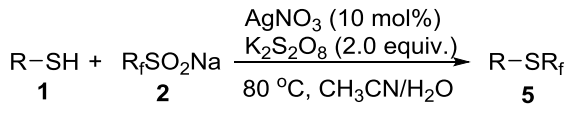
Table 3
Scope of the difluoromethylation.[a]



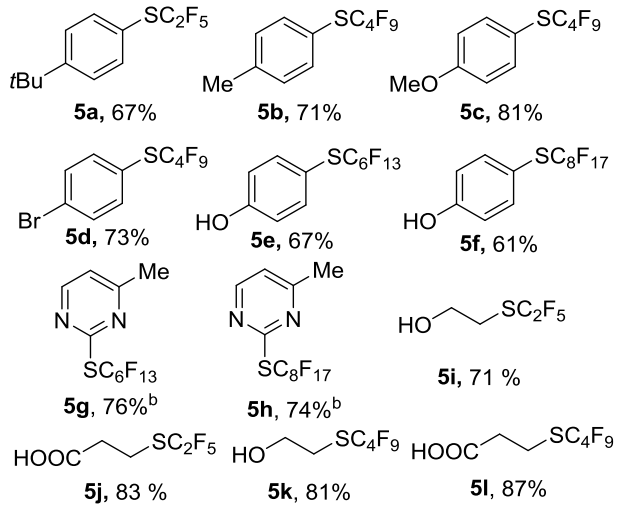
[a] Reaction condition: **1** (0.2 mmol), HCF_2SO_2Na (2.0 equiv.), $AgNO_3$ (0.1 equiv.) and $K_2S_2O_8$ (2.0 equiv.) in 0.8 mL CH_3CN/H_2O (1:1), 80 ℃ for 24 h, argon atmosphere, isolated yield.
[b] Using 4-methyl-2-pyrimidinethiol hydrochloride as substrate.

Table 4

Scope of perfluoroalkylation.[a]



1 **2** **5**



5a, 67% **5b,** 71% **5c,** 81%

5d, 73% **5e,** 67% **5f,** 61%

5g, 76%[b] **5h**, 74%[b] **5i,** 71 %

5j, 83 % **5k**, 81% **5l**, 87%

[a] Reaction condition: 1 (0.2 mmol), R_fSO_2Na (2.0 equiv.), $AgNO_3$ (0.1 equiv.) and $K_2S_2O_8$ (2.0 equiv.) in 0.8 mL CH_3CN/H_2O (1:1), 80 ℃ for 24 h, argon atmosphere, isolated yield.

[b] Using 4-methyl-2-pyrimidinethiol hydrochloride as substrate.