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Difluoromethylthiolation of Phenols and Related Compounds with a $HF_2CSO_2Na/Ph_2PCl/Me_3SiCl$ System

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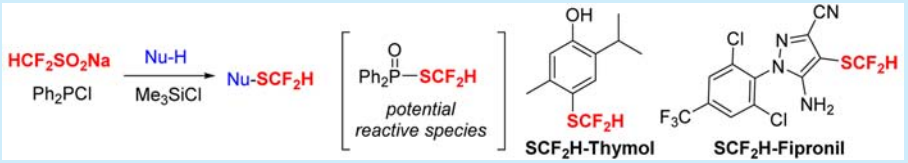
Supporting Information



ABSTRACT: A novel $HF_2CSO_2Na/Ph_2PCl/Me_3SiCl$ system is disclosed for the late-stage direct difluoromethylthiolation of C_{sp2} and C_{sp3} nucleophiles. Difluoromethylthiolation of phenols and naphthols proceeded nicely under this system to regioselectively provide corresponding SCF_2H compounds in good yields. Other substrates such as indoles, pyrroles, pyrazoles, enamines, ketones, and β-keto esters were also transformed to corresponding SCF_2H products in good yields. The late-stage direct difluoromethylthiolation of a number of natural products and pharmaceutically attractive molecules was also achieved.

Fluorine and sulfur have become crucial elements in the fields of agrochemicals, pharmaceuticals, and material sciences.[1] In the last two decades, the trifluoromethylthio (SCF_3) group has gained special attention as a potential functional group to improve and/or alter the physical and biological properties of original compounds.[2] Thus, numerous methods for the direct introduction of the SCF_3 group into target compounds have been actively developed worldwide.[3−6] In this context, we are interested in the difluoromethylthio (SCF_2H) group.[7−10] The SCF_2H group is generally considered as a weak lipophilic hydrogen-bonding donor and has and may have more advantages than the SCF_3 group leading to the design of novel drug candidates.[11] The traditional strategy for the synthesis of SCF_2H compounds focuses on the difluoromethylation of thiols or disulfides, while only a handful of studies have focused on the direct introduction of the SCF_2H unit, i.e., difluoromethylthiolation.[12] The first direct electrophilic difluoromethylthiolation reagent, *N*-difluoromethylthiophthalimide (**1**), was developed by Shen and co-workers in 2015.[12a] We also reported difluoromethanesulfonyl hypervalent iodonium ylides **2** for electrophilic difluoromethylthiolation (Figure 1a).[12b] Both reagents **1** and **2** are shelf-stable and have substrate generality, but they require multiple steps for their preparation. Moreover, they are not applicable for the difluoromethylthiolation of phenols and naphthols, which are the ubiquitous structural units of biologically active molecules and natural products. In this context, we became interested in the use of HF_2CSO_2Na as a direct electrophilic difluoromethylthiolation reagent via in situ rearrangement and reduction.[6,12b] The HF_2CSO_2Na is reported by Hu and co-workers to be an efficient CF_2H radical precursor under silver catalysis with SO_2 extrusion.[13] Herein, we disclose the first direct difluoromethylthiolation of phenols and naphthols using a novel $HF_2CSO_2Na/Ph_2PCl/Me_3SiCl$ system. The reaction proceeds very nicely for a wide range of phenols and naphthols in good to high yields in the presence of trimethylsilyl

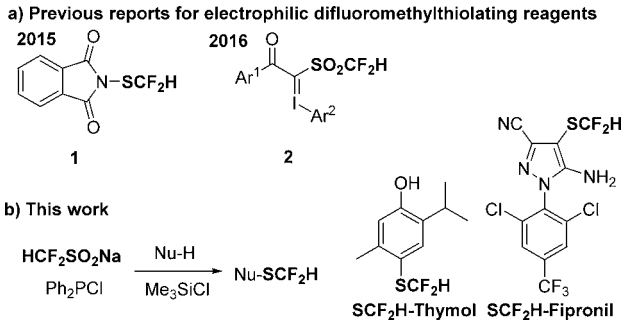


Figure 1. (a) Electrophilic difluoromethylthiolating reagents. (b) Novel $HF_2CSO_2Na/Ph_2PCl/Me_3SiCl$ system for electrophilic difluoromethylthiolation.

chloride (Me_3SiCl). The reaction is carried out under mild, base-free, and metal-free conditions. The method is applicable for the electrophilic difluoromethylthiolation of several kinds of C_{sp2} and C_{sp3} nucleophiles including anisoles, anilines, pyrroles, indoles, coumarins, enamines, ketones, and β-keto esters. A pharmaceutically important natural product, thymol, and a pesticide, fipronil, were directly functionalized by this system to regioselectively provide their corresponding SCF_2H analogues (Figure 1b). During the preparation of this paper, another approach for difluoromethylthiolation using HCF_2SO_2Cl was reported by the Yi and Zhao groups independently, although the conditions, reaction scope, and mechanism are very different.[14]

We selected 2-naphthol (**3a**) as a model substrate to optimize the reaction conditions using the HF_2CSO_2Na/Ph_2PCl combination (Table 1). We first attempted the reaction of **3a** with HF_2CSO_2Na/Ph_2PCl in MeCN at 25 °C for 12 h, but a reaction

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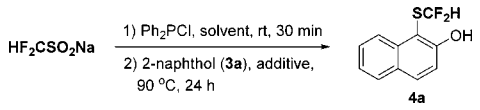
Table 1. Optimization of Reaction Conditions[a]



entry	additive (mol %)	solvent	yield (%)[b]
1[c]		MeCN	0
2		MeCN	14
3	$AlCl_3$ (20)	MeCN	<5
4	$TsOH/H_2O$ (20)	MeCN	19
5	TfOH (100)	MeCN	18
6	Me_3SiOTf (100)	MeCN	33
7	Me_3SiCl (150)	MeCN	50
8	Me_3SiCl (150)	DMF	26
9	Me_3SiCl (150)	EtOAc	trace
10	Me_3SiCl (150)	dioxane	trace
11	Me_3SiCl (150)	toluene	40
12[d]	Me_3SiCl (150)	MeCN	62
13[e]	Me_3SiCl (150)	MeCN	83

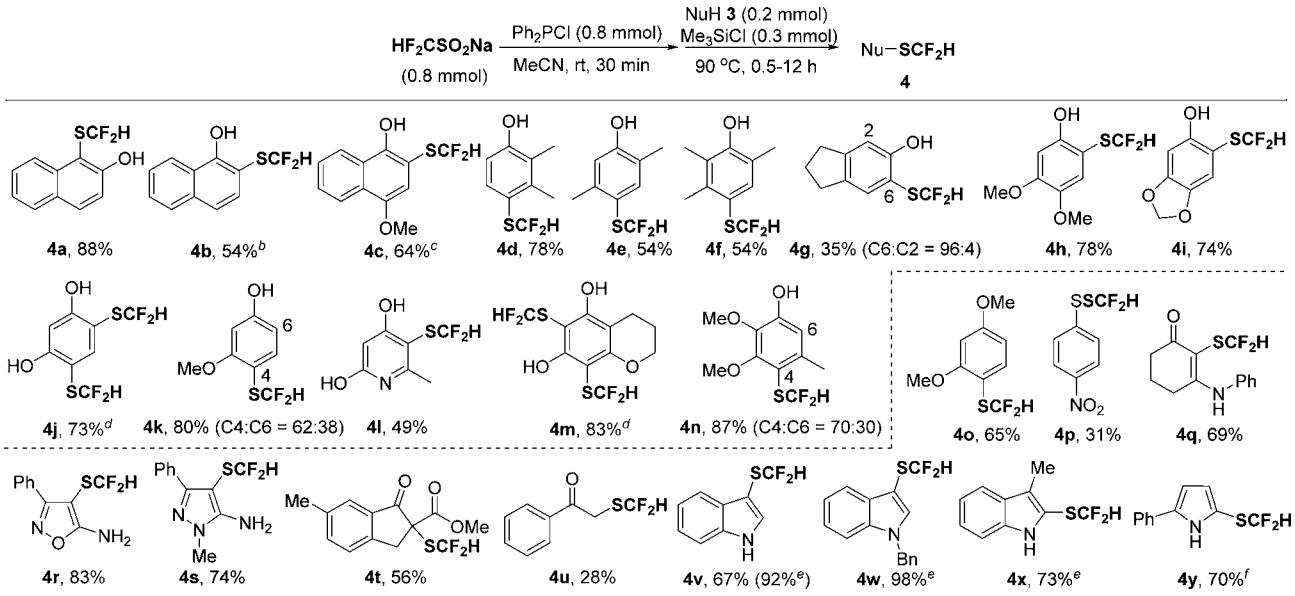
[a]Reaction conditions: HF_2CSO_2Na (0.2 mmol) in 0.75 mL of solvent, Ph_2PCl (0.2 mmol) was added, stirred at room temperature for 30 min. Then, 2-naphthol (**3a**, 0.1 mmol) in 0.25 mL of solvent was added in the presence of additives. [b]Yields were determined by ^{19}F NMR spectroscopy with trifluoromethylbenzene as the internal standard. [c]The reaction was conducted at 25 °C. [d]3.0 equiv of HF_2CSO_2Na/Ph_2PCl was used. [e]4.0 equiv of HF_2CSO_2Na/Ph_2PCl was used.

did not take place (Table 1, entry 1). When the same reaction was carried out at reflux temperature (bath temp, 90 °C), 14% of 1-((difluoromethyl)thio)naphthalen-2-ol (**4a**) was obtained (entry 2). We next examined the effect of additives on yield. After several additives were screened (entries 1−7), Me_3SiCl was found to be suitable, furnishing **4a** in 50% yield (entry 7). Solvent screening was next carried out, but yields did not improve (entries 8−11). The suitable choice of phosphine ligands was crucial (for more details, see Table S1 in the Supporting Information). The best result was obtained with a combination of 4.0 equiv of HCF_2SO_2Na and Ph_2PCl with 1.5 equiv of Me_3SiCl in MeCN at 90 °C to furnish **4a** in 83% yield (entry 13).

With optimized reaction conditions in hand, substrate generality was investigated (Scheme 1). Naphthols **3a−c** smoothly and regioselectively transformed to corresponding SCF_2H products **4a−c** in moderate to good yields (54−88%). Phenols were also nicely difluoromethylthiolated under the same conditions to provide the SCF_2H phenols **4d−j** regioselectively with the exception of **4k**. Difluoromethylthiolation of resorcinol (**3j**) provided bis-SCF_2H product **4j** in 73% using 6.0 equiv of HF_2CSO_2Na/Ph_2PCl. Pyridine-2,4-diol (**3l**) also regioselectively afforded the corresponding compound **4l** in 49% yield. Difluoromethylthiolation of chromane **3m** provided corresponding SCF_2H product **4m** in good yields. Iridol (**3n**), an intermediate in the synthesis of ubiquinone, was directly difluoromethylthiolated by this method, resulting in **4n** as a mixture of isomers in 87% yield. Direct difluoromethylthiolation of other nucleophiles such as 1,3-dimethoxybenzene, 4-nitrobenzenethiol, enamine, 5-aminoisozazole, 5-aminopyrazole, *β*-keto ester, ketone, indoles, and pyrrole was efficiently difluoromethylthiolated by the same system, yielding the corresponding SCF_2H products **4o−y** in satisfactory to good yields (Scheme 1).

Direct difluoromethylthiolation of natural products or pharmaceutically important compounds is an ideal and practical route to modify the molecules. The difluoromethylthiolation of natural products, chromone **5a** and coumarin **5b**, 4-hydroxycoumarin (**5c**), 2-aminochromone (**5d**), 3-indoleacetic acid (**5e**), provided corresponding SCF_2H products **6a−e** in satisfactory to good yields. Thymol (**5f**) is a natural product

Scheme 1. Difluoromethylthiolation of Nucleophiles 3[a]



[a]Reaction conditions: HF_2CSO_2Na (0.8 mmol) in 1.0 mL of MeCN, Ph_2PCl (0.8 mmol) was added, stirred at room temperature for 30 min; NuH (0.2 mmol) in 0.5 mL of MeCN was added; after that, Me_3SiCl (0.3 mmol) was added and then heated at 90 °C for 0.5−12 h. The position ratio was calculated from ^{19}F NMR. All yields given are isolated yields. [b]At 90 °C for 2 h [c]At 90 °C for 0.5 h. [d]HF_2CSO_2Na (1.2 mmol) and Ph_2PCl (1.2 mmol) were used. [e]CSA (20 mol %) was used to replace Me_3SiCl as catalyst in DMF, 100 °C for 2 h. [f]HF_2CSO_2Na (0.4 mmol) and Ph_2PCl (0.4 mmol) were used at 90 °C for 0.5 h.

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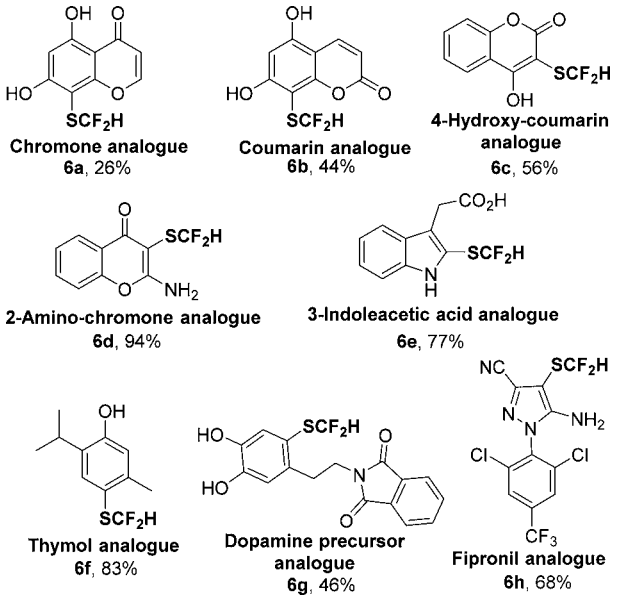
and has antibacterial and antifungal activities.[15] The difluoromethylthiolation of **5f** provided SCF_2H-thymol (**6f**) in 83% yield. Direct difluoromethylthiolation of pharmaceutically important dopamine derivative **5g** and pesticide fipronil **5h** furnished the SCF_2H products **6g** and **6h** in 46% and 68% yields, respectively. The results demonstrate the utility of the protocol. The regioselectivity of the reaction is sometimes obvious but not always (Schemes 1 and 2). It could be explained by the steric and/or electronic effects, and further investigation is required.

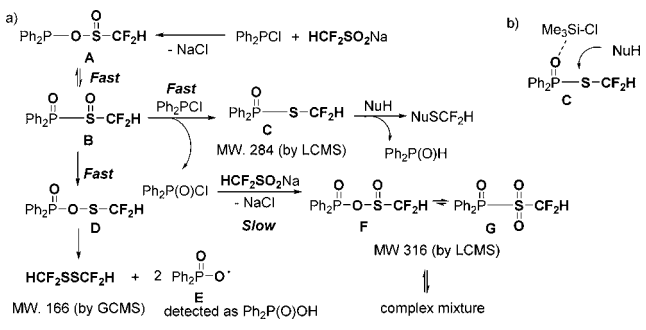
Scheme 2. Difluoromethylthiolation of Natural Products or Pharmaceutically Important Compounds[a]



[a]Reaction conditions: HF_2CSO_2Na (0.8 mmol) in 1.0 mL of MeCN; Ph_2PCl (0.8 mmol) was added, stirred at room temperature for 30 min; NuH (0.2 mmol) in 0.5 mL of MeCN was added; after that, Me_3SiCl (0.3 mmol) was added and then heated at 90 °C for 12 h.

Although the reaction mechanism is not clear yet, we hypothesize the generation of reactive SCF_2H species **C** via **A** and **B** under a substitution/rearrangement/reduction process (Scheme 3a).[6,16,17] First, HF_2CSO_2Na reacts with Ph_2PCl to afford intermediate **A** with the elimination of NaCl and converts to intermediate **B** via an intramolecular rearrangement. **B** is converted into a reactive species after reduction by a second Ph_2PCl to generate reactive species **C** for electrophilic difluoromethylthiolation. **C** is rather unreactive and can be highly activated in the presence of Me_3SiCl as a Lewis acid when heated (Scheme 3b). The formation of **C** is also strongly supported by the literature data that the reaction of $NaSO_2Ar$ and 2 equiv of Ph_2PCl gave $Ph_2P(O)SAr$ accompanied by $Ph_2P(O)$-Cl.[17,18] The requirement of excess reagent can be explained by the side reactions, such as the rearrangement of **B** to **D** followed by radical decomposition[6c] with the elimination of **E** ($Ph_2P(O)$-OH was detected by LCMS).

Scheme 3. (a) Plausible Reaction Mechanism and (b) Plausible Role of Me_3SiCl



In conclusion, we disclose a novel $HF_2CSO_2Na/Ph_2PCl/Me_3SiCl$ system for the direct difluoromethylthiolation of phenols and naphthols. Corresponding SCF_2H compounds are regioselectively obtained in good yields under mild conditions. Other C_{sp2} and C_{sp3} nucleophiles such as indoles, pyrroles, pyrazoles, enamines, ketones, and β-keto esters were also transformed to corresponding SCF_2H products in good yields. This system is effective for the late-stage direct difluoromethylthiolation of a number of natural products and pharmaceutically attractive molecules without any pretreatment of the substrates. Further potential of this system and the isolation and preparation of the proposed reactive intermediate are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00113.

Table S1, experimental procedures, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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