Synthetic Methods

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Synthesis of Difluoromethyl Thioethers from Difluoromethyl Trimethylsilane and Organothiocyanates Generated In Situ**

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Abstract: *A copper-CF_2H complex generated in situ from copper thiocyanate and TMS–CF_2H smoothly converts organothiocyanates into valuable difluoromethyl thioethers. This reaction step can be combined with several thiocyanation methods to one-pot protocols, allowing late-stage difluoromethylthiolations of widely available alkyl halides and arenediazonium salts. This strategy enables the introduction of difluoromethylthio groups—a largely unexplored substituent with highly promising properties—into drug-like molecules.*

Close to 40% of marketed agrochemicals and 25% of pharmaceuticals contain fluorine atoms. Fluorine-containing residues are central functionalities in such active substances,[1] because they modulate their metabolic stability, lipophilicity, and bioavailability. So-called "fluorine scans", i.e., systematic derivatizations through the introduction of groups such as CF_3,[2] C_2F_5,[3] SCF_3,[4] and OCF_3,[5] have become standard procedure in drug discovery. New fluorine-containing residues and efficient methods for their introduction into functionalized molecules are, thus, constantly sought.

Trifluoromethyl groups are incorporated into bioactive molecules to enhance their membrane permeability.[1d,6] Recent years have witnessed a tremendous development in trifluoromethylation technology. Efficient benzotrifluoride syntheses that can be employed even at late stages within a synthetic sequence have been disclosed for example, by the groups of Prakash,[7] Grushin,[8] Buchwald,[9] and others.[10]

Lately, there is a shift in focus toward trifluoromethylthio groups, because these are even more effective in inducing lipophilicity and membrane permeability (Hansch constants 1.44 vs. 0.88 for CF_3).[11] Contemporary late-stage trifluoromethylthiolations of arenes employ Pd,[12] Cu,[13] Ni,[14] and Ag[12] catalysts.

Difluoromethyl groups, in contrast, are potent hydrogen donors.[15] They serve as lipophilic and membrane permeability-enhancing isosteric and isopolar analogues to OH and SH groups.[1b,16] Difluoromethylations still face challenges, and only few methods reach the efficiency of the corresponding trifluoromethylations.[17]

With SCF_3 receiving increasing attention as an enhanced version of CF_3 in bioactive molecules, one might expect a similar shift in interest from CF_2H to SCF_2H. Indeed, difluoromethylthio residues were shown to be uniquely effective in the β-lactamase-resistant oxcephalosporin antibiotic Flomoxef sodium (Figure 1). In 2-(difluoro[(4-methylpyrimidin-2-yl)thio]methyl)benzoxazole, the SCF_2 bridge is crucial for its activity against HIV-1, whereas the OCF_2-substituted analogue is inactive.[18]

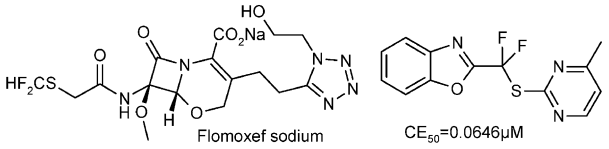
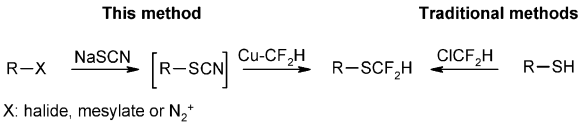


Figure 1. Biologically active α-difluoromethyl thioethers.

The proton in SCF_2H groups is even more acidic than that in CF_2H groups.[19] This underlines the potential of SCF_2H groups as lipophilic OH or NH surrogates. It would be highly desirable to routinely examine SCF_2H substituents during drug discovery. However, no presently available synthetic method is mild and selective enough for their late-stage introduction into drug-like molecules.

Traditional syntheses of SCF_2H moieties are based on the insertion of difluorocarbene into the S–H bond of thiophenols, as first described by Porter et al. in 1957.[20] Originally, the difluorocarbenes were generated from the ozone-depleting chlorodifluoromethane (Scheme 1).[21] The groups of



Scheme 1. Strategies to access difluoromethyl thioethers.

Hu[22] and Dolbier[23] recently utilized TMS–CF_2Br or CF_3H as more environmentally benign CF_2 sources. Thiols and thiophenols can also be difluoromethylated using electrophilic reagents.[24] However, these approaches suffer from the limited availability of thiol substrates, the incompatibility of the strongly basic reaction conditions with sensitive functionalities, and the low selectivity of the CF_2 insertion step.

A method to introduce SCF_2H groups in a single step, using an inexpensive reagent, and substituting a widely available leaving group such as a halide, mesylate, or

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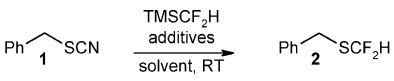
diazotized amino group would be highly desirable. Preformed SCF_3 reagents are laborious to prepare and rather expensive,[12,13,25] and the same limitations must be expected for their presently unknown SCF_2H counterparts. Therefore, we decided to base our difluoromethylthiolation process on a stepwise assembly first of S, introduced by way of an SCN group, then of CF_2H by the in situ conversion of SCN to SCF_2H using a nucleophilic CF_2H source, preferentially TMS–CF_2H, which is easily accessible from the inexpensive Ruppert–Prakash reagent.

Langlois et al.[26] found that SCF_3 groups can be generated from thiocyanates by nucleophilic displacement of the CN group using TMS–CF_3. However, the corresponding reaction between organothiocyanates with TMS–CF_2H has not yet been achieved. Since such a transformation would constitute the pivotal step in our desired synthesis of organodifluoromethyl thioethers, we focused our initial research efforts on this step in isolation. Using the model reaction of benzyl thiocyanate (**1**) with TMS–CF_2H, we investigated a range of reaction conditions, starting with those reported for the analogous trifluoromethylation (TBAF, THF, 0 °C). None of the fluoride sources tested in various solvents promoted the formation of benzyl difluoromethyl sulfide (**2**, Table 1, entries 1–4) in more than trace amounts, confirming that a noncatalyzed introduction of the sensitive CF_2H moiety is not feasible.

Table 1: Optimization of the reaction conditions.[a]

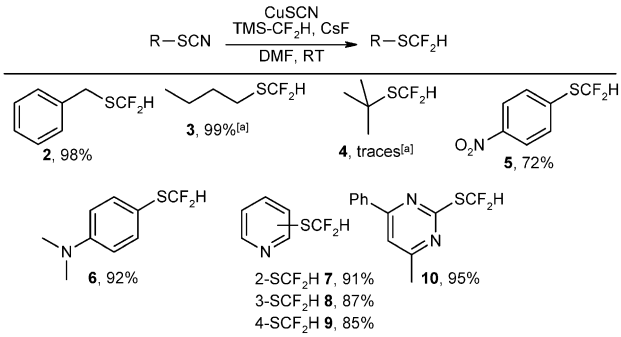


Entry	Additive	Mediator	Solvent	**2** [%][b]
1[c]	TBAF	–	THF	trace
2	CsF	–	THF	0
3	TBAF	–	DMF	trace
4	KF	–	DMF	trace
5	CsF	–	DMF	51
6[d]	CsF	CuSCN	DMF	85
7[e]	CsF	CuSCN	DMF	98

[a] Reaction conditions: 0.5 mmol of benzyl thiocyanate, 1.0 mmol of additive, 1 mL solvent, 1.0 mmol of TMS–CF_2H, RT. [b] Yields were determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard. [c] TMS–CF_2H was added at 0 °C, then the mixture was slowly warmed up to RT. [d] 0.5 mmol of CuSCN. [e] 0.5 mmol of CuSCN and 2.0 mmol of CsF were used.

Systematic investigations of potential mediators identified copper salts, particularly copper thiocyanate, as strong promoters of the desired reaction. NMR investigations showed that Cu–CF_2H is intermediately formed and acts as the actual difluoromethylation reagent (entries 6 and 7).[27] Under optimal conditions, that is, in the presence of CsF and CuSCN in DMF, **1** is converted into benzyl difluoromethyl sulfide (**2**) in quantitative yields within 12 h at room temperature (entry 7).

As illustrated in Scheme 2, the new difluoromethylation protocol extends to aliphatic, aromatic, and heteroaromatic thiocyanates. They include substructures of particular interest, namely a 2-[(difluoromethyl)thio]pyrimidine analogous



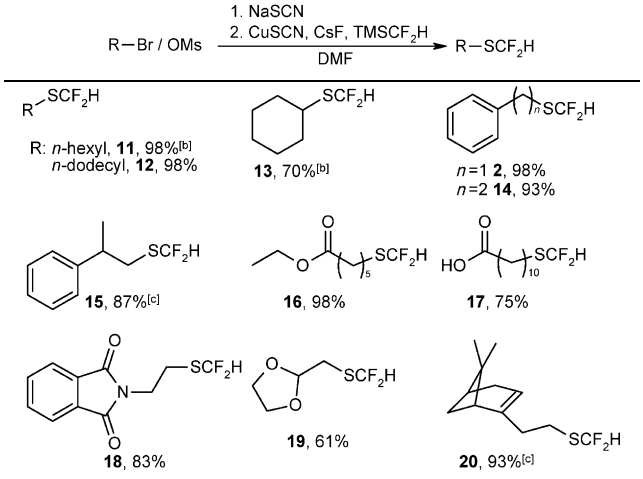
Scheme 2. Cu-mediated difluoromethylation of organothiocyanates. Reaction conditions: 1.0 mmol of organothiocyanate, 1.0 mmol of CuSCN, 4.0 mmol of CsF, 2.0 mmol of TMS–CF_2H in 2 mL of DMF, 12 h, RT. Yields are of isolated products. [a] Yields determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard.

to the above-mentioned anti-HIV-1 agents,[18] and a 2-(difluoromethylthio)pyridine related to the 2-(difluoromethyl)pyridine herbicide thiazopyr.

The discovery of this mild, copper-mediated difluoromethylation of organothiocyanates should be combinable with syntheses of organothiocyanates from various carbon electrophiles, overall leading to one-step synthesis of difluoromethyl thioethers from widely available starting materials. Indeed, upon briefly heating alkyl bromides with sodium thiocyanate in DMF and then adding the difluoromethylation reagent mixture composed of TMS–CF_2H, CsF, and CuSCN, the corresponding alkyl difluoromethyl thioethers were cleanly obtained in high yields and purities.

The scope of this one-pot difluoromethylthiolation is shown in Table 2. Primary and secondary alkyl bromides, as well as mesylates conveniently accessible from ubiquitous

Table 2: One-pot difluoromethylthiolation of alkyl bromides and mesylates.[a]



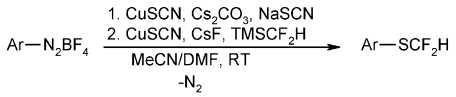
[a] 1.0 mmol of alkyl bromide and 1.2 mmol of NaSCN in 4 mL DMF were heated for 2 h (see SI for detailed conditions). After cooling to RT, 1.0 mmol of CuSCN, 4.0 mmol of CsF, and 2.0 mmol of TMS–CF_2H were added, and stirring continued for 12 h at RT. Yields are of isolated products. [b] Yields determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard. [c] Starting from mesylate.

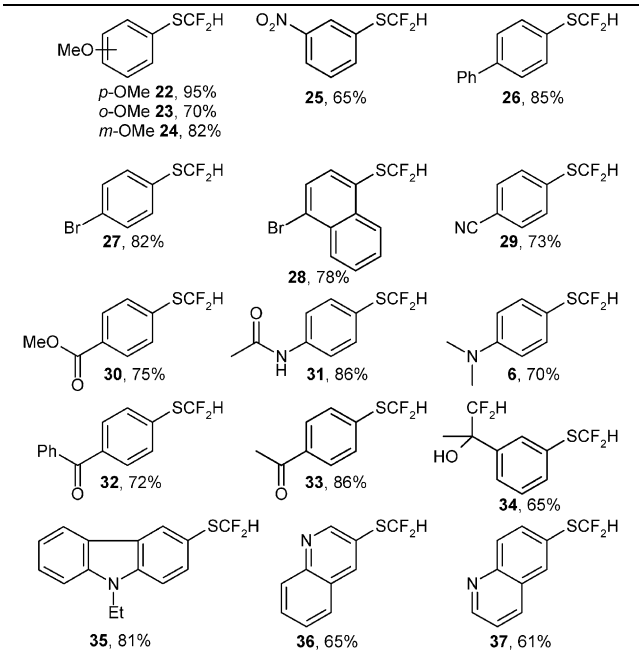
alcohols, were converted in high yields, and a range of common functionalities was tolerated.

The synthesis of aromatic derivatives by this strategy is limited to strongly activated aryl halides capable of undergoing nucleophilic aromatic thiocyanation. Therefore, we sought another protocol for the C–S bond-forming step capable of converting the entire range of aromatic and heteroaromatic substrates. A Sandmeyer-type approach as recently implemented in several fluoroalkylations of diazonium salts[17b,28] appeared to be promising for a generally applicable synthesis of difluoromethylthio arenes.

To probe the viability of this approach, we treated 4-methoxybenzenediazonium tetrafluoroborate (**21**) with sodium thiocyanate and TMS–CF_2H in the presence of copper thiocyanate (Table 3). The optimal literature conditions for the trifluoromethylthiolation of diazonium salts (Cs_2CO_3, MeCN)[28a] did not yield any of the desired difluoromethylthiolated product (see the Supporting Information, SI). However, upon switching to DMF as the solvent, the arenethiocyanate was fully consumed, and the desired product was detected in modest yield along with anisole, diaryl disulfide, and biaryl byproducts. By careful optimization of the conditions, the yield could be increased to a satisfactory 83% by adding both cesium carbonate and cesium fluoride to the reaction mixture. The carbonate base is required for the Sandmeyer step, and CsF promotes the transfer of CF_2H^- from silicon to copper.[17a,b] The ratio between the two cesium bases has a crucial influence on the yield. Both cesium carbonate and sodium thiocyanate interfere with the difluoromethylation step, so that an excess of these reagents must be avoided. Under optimized conditions, the only remaining byproduct is anisole, which results from competing protodediazotization. Further control experiments showed that the Sandmeyer thiocyanation and the formation of Cu–CF_2H species each require one equivalent of CuSCN.[29]

Table 3: Difluoromethylthiolation of arenediazonium salts.[a]





[a] 1.0 mmol of arenediazonium tetrafluoroborate in 2 mL of MeCN was slowly added to a mixture of 1.0 mmol of CuSCN, 0.75 mmol of Cs_2CO_3, and 1.5 mmol of NaSCN in 2 mL of MeCN, and stirred for 1 h at RT. Then MeCN was evaporated, 1.0 mmol of CuSCN, 4.0 mmol of CsF, and 2.0 mmol of TMS–CF_2H in 4 mL DMF were added, stirring was continued for 12 h at RT. Yields are of isolated products.

Having thus identified a highly efficient protocol, we next investigated its scope. The examples in Table 3 illustrate that diversely substituted arenediazonium tetrafluoroborates are smoothly converted into the corresponding aryl difluoromethyl thioethers in high yields. Electron-rich and electron-deficient substrates give similarly high yields, and various heterocycles such as quinolines and carbazoles are smoothly converted. Common functionalities including ester, ether, keto, amino, cyano, and bromo groups are tolerated. Remarkably, in compound **33**, the acetyl substituent in the *para*-position is left intact whereas the same group in the *meta*-position is converted into the corresponding difluoromethyl alcohol (product **34**). The successful synthesis of **22** in 89% yield on a 10 mmol scale demonstrates the scalability of the process.

Control experiments suggest that the reaction indeed proceeds through a Sandmeyer-type mechanism, as proposed also for related fluoroalkyl(thiol)ations. This copper-mediated radical dediazotative thiocyanation step is followed by nucleophilic displacement of a cyanide group by CF_2H via a $CuCF_2H$ species.

In conclusion, a copper-mediated difluoromethylation of organothiocyanates has opened up new opportunities for the synthesis of difluoromethyl thioethers from widely available substrates such as alkyl halides or (hetero)aryl amines via their diazonium salts. The mild and efficient synthetic approach is suitable for the late-stage functionalization of complex molecules and thus meets the requirements of pharmaceutical and agrochemical research. Many difluoromethyl thioethers have thus become accessible for the first time and may now be screened for biological activity.

Keywords: copper · difluoromethylthiolation · fluorine · Sandmeyer reaction · synthetic methods

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