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Perfluoroalkylation of Thiosulfonates: Synthesis of Perfluoroalkyl Sulfides

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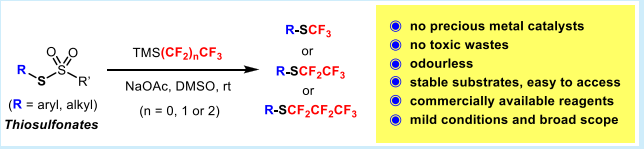
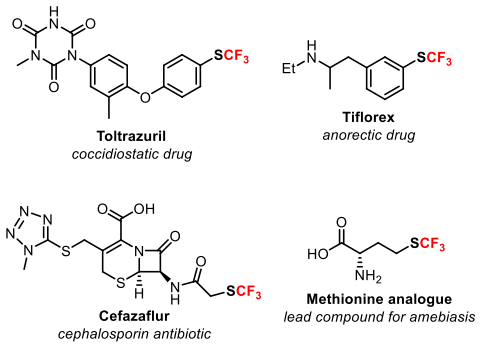
ABSTRACT: A practical synthesis of perfluoroalkyl sulfides is described. The method employs stable and readily accessible thiosulfonates as new electrophiles with commercial nucleophilic perfluoroalkylating reagents. The mild reaction conditions allow access to a wide variety of both aryl- and alkyl-substituted perfluoroalkyl sulfides amenable to pharmaceutical development. Furthermore, the reaction operation is straightforward, odorless, does not produce toxic wastes, and, therefore should appeal to practitioners in industrial-scale productions.



One of the major challenges in drug discovery is the search for pharmacophores that can increase lipophilicity. Heteroatoms attached to fluorinated groups are known to have high lipophilicity. The trifluoromethylthio group ($-SCF_3$) possesses an extremely high Hansch lipophilicity parameter (π = 1.44), even higher than that of the trifluoromethyl group (π = 0.88).[1] This unique property of trifluoromethylthiolated molecules could greatly enhance the transmembrane permeation and therefore improve their pharmacokinetics and efficacy as drug candidates.[2] The rapidly increasing number of marketed drugs containing aryl and alkyl SCF_3 moieties (Scheme 1) is a testament to their importance in pharmaceutical and medicinal applications.[3]

Scheme 1. Bioactive compounds containing SCF_3 group



The high demand for trifluoromethylthiolated compounds has stimulated significant development of synthetic methods for the incorporation of SCF_3 group into organic molecules.[4] Traditional syntheses of trifluoromethyl sulfides as early as 1960 involved hazardous chlorination of $ArSCH_3$ to $ArSCCl_3$, followed by Cl−F exchange with SbF_3 to produce $ArSCF_3$.[5] Modern approaches since 2011 utilizing transition-metal-catalyzed/-mediated "direct trifluoromethylthiolation" have drastically improved reaction efficiency and operational safety.[4b] This includes palladium-,[6] copper-,[7] nickel-,[8] and silver-catalyzed/-mediated[9] trifluoromethylthiolation with $MSCF_3$ reagents, albeit expensive $AgSCF_3$ was often employed as the source of "SCF_3" in superstoichiometric amounts. More recent electrophilic trifluoromethylthiolation reagents and methods have broadened the reaction scope remarkably;[10,4b−d] however, the availability and preparation of some of these reagents might not be trivial.

Conceptually, nucleophilic trifluoromethylation of a sulfur electrophile RSX is the simplest way to reach $RSCF_3$ without the need for any transition-metal catalysts (Scheme 2a). This approach is attractive due to the abundant choice of commercial nucleophilic CF_3 sources.[11] However, the development and application of such methodology lags far behind other areas of trifluoromethylthiolation, possibly due to the limitation of suitable sulfur electrophiles and practical reaction conditions. A series of earlier seminal works described the nucleophilic trifluoromethylation of sulfur compounds using $TMSCF_3/F^-$ systems (Scheme 2b).[12a−c] Yagupolskii's method employed arenesulfenyl chlorides (RSCl) which had severe limitations on substrate scope; no alkyl variants were demonstrated.[12a] Langlois et al. opted to use disulfides (RSSR) which broadened the alkyl substrate scope, but diphenyl disulfide gave poor yield.[12b] Another drawback was that 1 equiv of thiolate was released which needed to be oxidized before recycling, and upon protonation it could

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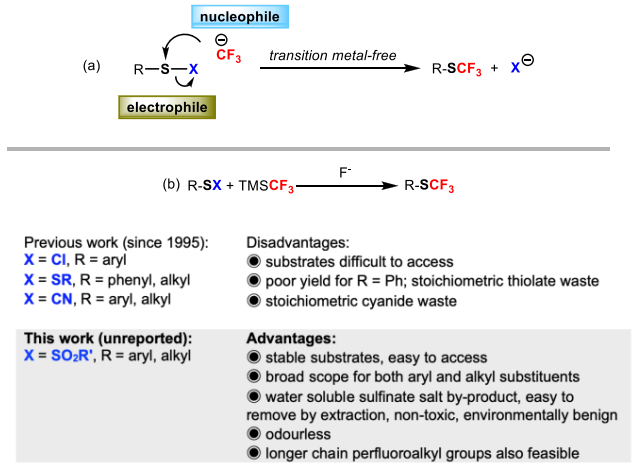
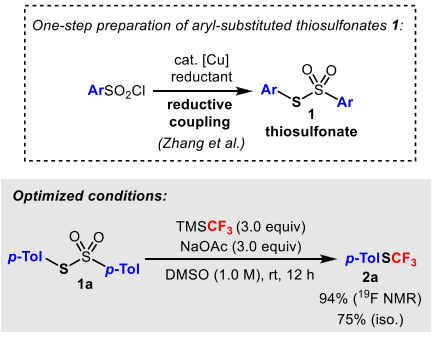
Scheme 2. Nucleophilic Trifluoromethylation of Sulfur Electrophiles with $TMSCF_3$



produce foul-smelling thiols. An improvement was made in both alkyl and aryl scope by using thiocyanates (RSCN),[12c] which have become staple substrates in nucelophilic trifluoromethylations;[12d−g] however, stoichiometric amounts of cyanides are produced as byproducts which are highly toxic to human health and detrimental to the environment for industrial-scale production. In the context of our continuing interests in developing practical trifluoromethylation methods[13] using easy-to-handle and commercial Ruppert−Prakash reagent[14] ($TMSCF_3$, liquid, bp = 54−55 °C), we herein offer a solution to the above challenges by employing *thiosulfonates* ($RSSO_2R'$) as a new class of sulfur electrophile for accessing both alkyl- and aryl-substituted trifluoromethyl sulfides and their longer chain perfluoroalkyl variants via a transition-metal-free, odorless, nucleophilic perfluoroalkylation reaction.

Thiosulfonates have been known to react with carbon- and heteroatom-based nucleophiles at the S(II) atom in nucleophilic substitution reactions.[15] As a valuable sulfenylating reagent, they are more stable and easier to handle than sulfenyl chlorides and are more reactive than disulfides, and the byproduct generated is a sulfinate salt which is water-soluble, odorless, nontoxic, and environmentally benign. Contemporary synthesis of thiosulfonates has overcome the earlier challenges to their access; for example, aryl-substituted thiosulfonates **1** can be conveniently prepared in one step from commercial arenesulfonyl chlorides via a Cu-catalyzed reductive coupling by Zhang's method.[15b] We envisioned that the nucleophilic attack of a CF_3 anion (from $TMSCF_3$) to the S(II) atom of thiosulfonate would directly lead to trifluoromethyl sulfide. To the best of our knowledge, this straightforward approach has not been reported to date. The hypothesis was tested by reacting tolyl-substituted thiosulfonate **1a** with $TMSCF_3$ using NaOAc (initiator for $TMSCF_3$) in DMSO at room temperature (Scheme 3).[16] The corresponding *p*-tolyl trifluoromethyl sulfide **2a** was indeed obtained in excellent yield (94%). Several factors were found to be important to ensure high yields during optimization studies:[17] (1) higher concentration; (2) polar aprotic solvent; (3) use of acetate as initiator; and (4) excess of $TMSCF_3$. For example, compared with the optimized conditions, the reaction yield at 0.1 M concentration was poor (42%). Less polar solvents such as THF and toluene gave no conversions. Using NaOAc as an initiator was more convenient since it is cheaper, less hygroscopic, and more

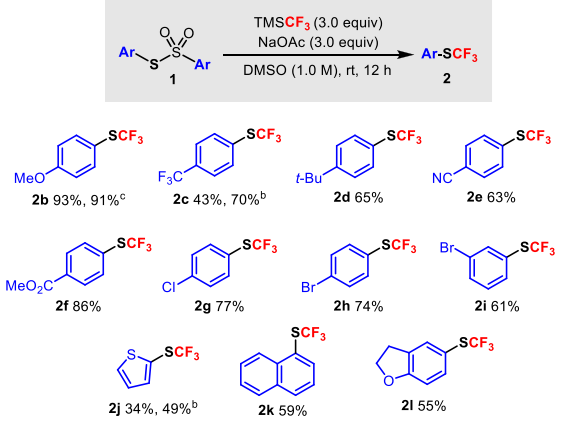
Scheme 3. Synthesis of *p*-Tolyl Trifluoromethyl Sulfide 2a from Thiosulfonate 1a



reactive than fluorides such as KF (79% yield). On the other hand, use of catalytic amounts of NaOAc (0.2 equiv, 63% yield) or no initiator (8% yield) was ineffective. Reaction at higher temperature (40 °C) caused a decrease in yield (68%), and smaller amounts of $TMSCF_3$ (2.0 equiv) also lowered the yield (68%).

By applying the optimized conditions, a series of aryl-substituted trifluoromethyl sulfides were successfully synthesized from the corresponding thiosulfonates (Scheme 4).

Scheme 4. Scope of Aryl-Substituted Trifluoromethyl Sulfides[a]



[a]Unless specified otherwise, reactions were carried out using **1** (0.2 mmol) under argon. Isolated yield. [b]Yield determined by ^{19}F NMR using benzotrifluoride as internal standard. [c]1.0 mmol scale.

Electron-donating (**2b**) and -withdrawing (**2c**) groups at the *para* position were compatible. The lower isolated yield for **2c** was due to volatility of the product. The sterically encumbering *tert*-butyl group was tolerated (**2d**). Electrophilic groups such as nitrile (**2e**) and ester (**2f**) remained intact. Chloride (**2g**) and bromide (**2h**,**i**) were tolerated at the *para* and *meta* positions, which are good coupling partners for further transformations. Heteroaromatic (**2j**) and polycyclic (**2k**, **2l**) systems were also compatible. Reaction on a larger scale (1.0 mmol) was demonstrated to give equally good yield (**2b**).

Next, the scope of alkyl-substituted trifluoromethyl sulfides was explored (Scheme 5). Most reported methods have addressed *either* aryl- or alkyl-substituted substrates for trifluoromethylthiolation,[12] and a set of general conditions to handle *both* types of substrates would be highly attractive. The alkyl-substituted thiosulfonates **1** can be prepared conveniently

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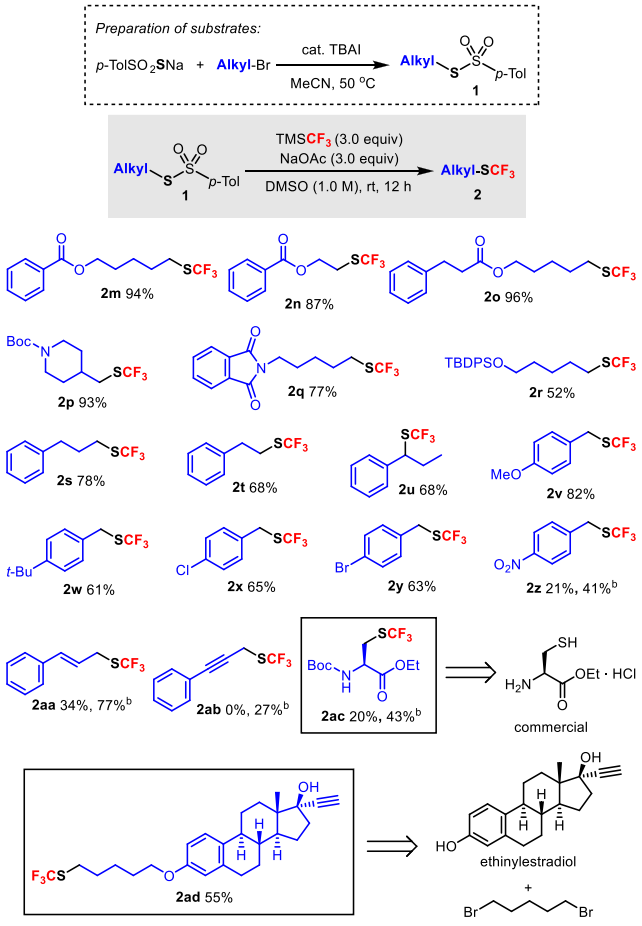
Scheme 5. Scope of Alkyl-Substituted Trifluoromethyl Sulfides[a]

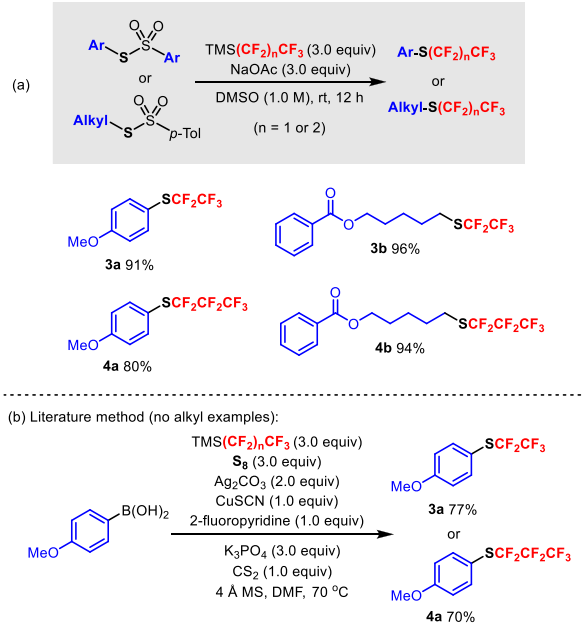


[a]Unless specified otherwise, reactions were carried out using **1** (0.2 mmol) under argon. Isolated yield. [b]Used $NaHCO_3$ (1.0 equiv) instead of NaOAc.

from sodium 4-methylbenzenesulfonothiolate and a wide variety of alkyl bromides.[15d] Under the "standard conditions", alkyl-substituted trifluoromethyl sulfides were smoothly synthesized tolerating ester (**2m−o**), *tert*-butyl carbamate (**2p**), phthalimide (**2q**), and silyl ether (**2r**) functionalities of various chain lengths. Linear (**2s,t**) and branched (**2u**) products were both obtained. In the benzyl series, aryl substituent groups including electron-rich (**2v**), sterically hindered (**2w**), and halogens (**2x,y**) were compatible. Several substrates, including nitro-substituted benzyl (**2z**), cinnamyl (**2aa**), and propargyl (**2ab**), were found to be unstable under the current conditions resulting in poor yields. However, using 1.0 equiv of $NaHCO_3$ instead of 3.0 equiv NaOAc could improve the yields. The amino acid derivative **2ac** was synthesized from commercial *L*-cysteine ethyl ester hydrochloride via an alternative substrate preparation route.[15f] Late stage trifluoromethylthiolation of a bioactive compound ethinylestradiol (EE, estrogen medication) was demonstrated in product **2ad** where the pharmacophore core is tethered with SCF_3 group by an alkyl chain. Such strategy could be valuable for structure−activity relationship (SAR) studies in medicinal chemistry.

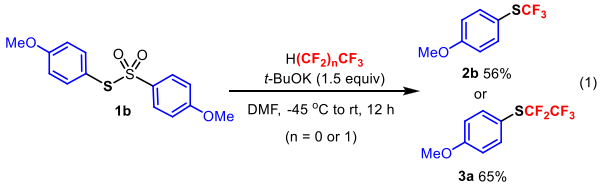
The nucleophilic reaction design allowed us to easily extend the method to install longer chain perfluoroalkyl groups onto sulfur by employing commercially available $TMS(CF_2)_nCF_3$ (n = 1 and 2) reagents (Scheme 6a). As a proof of concept, both

Scheme 6. (a) Pentafluoroethylthiolation and Heptafluoropropylthiolation of Thiosulfonates. (b) Copper-Mediated Oxidative Method Using Aryl Boronic Acids



aryl- and alkyl-substituted *pentafluoroethylthiolated* (**3a,b**) and *heptafluoropropylthiolated* (**4a,b**) products were successfully synthesized in good to excellent yields. Compared to a known literature method employing the same nucleophiles (Scheme 6b),[18] our conditions are more streamlined, avoiding the use of excess metal salts and multiple reagents.

Fluoroform (HCF_3),[19a−e] a low-cost industrial gaseous byproduct, was tested as a CF_3 source for this reaction using substrate **1b** in the presence of a base (eq 1). The results were encouraging, affording product **2b** in a moderate yield. Pentafluoroethane (HCF_2CF_3), an inexpensive gaseous fire suppression agent and refrigerant,[19f,g] was also employed in the pentafluoroethylthiolation, providing product **3a** in a decent yield. The alkyl-substituted substrates were found to be less stable under such conditions. These investigations demonstrated the feasibility of turning an industrial waste or low-cost bulk materials into valuable compounds, which is especially important nowadays for an increasing demand of sustainable synthesis.



In conclusion, a new protocol for perfluoroalkylation of thiosulfonates was developed that allows access to a wide variety of both aryl- and alkyl-substituted perfluoroalkyl sulfides. The substrates are stable and readily accessible from commercial building blocks with tunable structures amenable to drug discovery. The reaction conditions are mild and simple, functional group tolerant, do not produce harmful or foul-

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smelling byproducts, and employ commercial nucleophilic reagents. These practical qualities should appeal to industrial-scale preparation of pharmaceutically relevant perfluoroalkyl sulfides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02235.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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