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New sulfuryl fluoride-derived alkylating reagents for the 1,1-dihydrofluoroalkylation of thiols[†]

Paul J. Foth, Frances Gu, Trevor G. Bolduc, Sahil S. Kanani and Glenn M. Sammis D *

Herein, we report a new method for the one-pot synthesis of 1,1-dihydrofluoroalkyl sulfides by bubbling sulfuryl fluoride (SO_2F_2) through a solution of the corresponding alcohol and thiol. The reaction proceeds through a new class of bis(1,1-dihydrofluoroalkyl) sulfate reagents, to afford the desired 1,1-dihydrofluoroalkyl sulfides in 55–90% isolated yields. The bis(1,1-dihydrofluoroalkyl) sulfates are highly chemoselective for thiol alkylation, and are unreactive with competing, unprotected nucleophiles, including amines, alcohols, and carboxylic acids.

Sulfuryl fluoride (SO_2F_2) has been utilized since the 1960s as an industrial fumigant,¹ but it has only recently attracted significant attention as a reagent for organic synthesis.^{1b,2} Studies have demonstrated that oxygen nucleophiles, such as alcohols (1),^{3,4} phenol derivatives (2),^{1b,5} oximes (3),⁶ and carboxylic acids (4),⁷ react with sulfuryl fluoride to form fluorosulfate derivatives (Scheme 1).² The addition of a second equivalent of the oxygen nucleophile is kinetically slow, which allows fluorosulfate 5 to undergo subsequent transformations.⁸ Fluorosulfates (5) have been utilized as key reactants in a diverse range of reactions, including metal-catalyzed cross couplings,^{5e,9} click reactions,^{1b,5d} deoxyfluorinations,^{5b} alkylations,^{3a,4} nitrile syntheses,⁶ and the formation of amide bonds.^{7a}





This work: new SO₂F₂-derived bis(1,1-dihydrofluoroalkyl) sulfate intermediates.



Scheme 1 Representative examples of sulfuryl fluoride-mediated processes that utilize fluorosulfate reactive intermediates (5) and a new bis(trifluoroalkyl) sulfate (6).

All current synthetic methods rely on a very similar protocol for the formation of the fluorosulfate intermediate. Sulfuryl fluoride is bubbled through a solution of the requisite oxygen nucleophile and a base, which is usually *N*,*N*-diisopropylethylamine (DIPEA), triethylamine, or a carbonate salt.^{1b,2-7} Despite the expansion of the use of sulfuryl fluoride, the only reactive intermediates that have been identified are fluorosulfate derivatives (5), and no other sulfuryl fluoride-derived reactive intermediates have been explored.¹⁰

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We previously reported that bubbling sulfuryl fluoride through a solution of 2,2,2-trifluoroethanol (1a) and an amine base, such as DIPEA or triethylamine, afforded trifluoroethyl fluorosulfate (5a, $R'' = CH_2CF_3$) in >90% yield.^{3a,11} Following up on the synthesis and reactivity of fluorosulfate 5a in new transformations, we serendipitously discovered that even moderately more basic reagents,¹² such as 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) with a p K_{aH} of 12,¹³ afforded bis(trifluoroethyl) sulfate (6a) as the major product, and only trace amounts of fluorosulfate 5a were detected by ¹⁹F NMR spectroscopy. Bis(trifluoroethyl) sulfate (6a) is an intriguing species as there are only two previous methods for its synthesis,¹⁴⁻¹⁶ and there are no studies investigating its reactivity.¹⁷

We elected to study the reactivity of this new bis(trifluoroethyl) sulfate intermediate (**6a**) for the 1,1-dihydrofluoroalkylation of thiols for two reasons: (1) the resulting fluoroalkyl sulfides are important fluorinated motifs in pharmaceuticals and agrochemicals,^{18–20} and (2) the more common sulfuryl fluoride-derived reagent, trifluoroethyl fluorosulfate **5a**, is not an effective intermediate for thiol alkylation. Previous studies by Shreeve and coworkers indicated that the reaction between methane thiol (7), triethylamine, and **5a** afforded the corresponding fluoroalkyl sulfide (**8**) in only 31% yield and a 2.2 : 1 preference for reactivity at carbon compared to sulfur (Scheme 2A).¹⁴

To examine the viability of bis(trifluoroethyl) sulfate (6a) as a thiol alkylating reagent, we treated a solution of 6a and DBU

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada . E-mail: gsammis@chem.ubc.ca

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A. Reactivity of fluorosulfate 5a with methane thiol.¹⁴

$$F^{O} \xrightarrow{O} CF_{3} \xrightarrow{CH_{3}SH(7), NEt_{3}}_{-196 °C to rt} \xrightarrow{H_{3}C} CF_{3} \xrightarrow{CF_{3}}_{31\%}$$

B. Reactivity of bis(trifluoroethyl) sulfate (6a) with benzyl mercaptan.



C. Reactivity of fluorosulfate 5a with benzyl mercaptan.



Scheme 2 Investigations into thiol alkylation using fluorosulfate (5a) and bis(trifluoroethyl) sulfate (6a). The yields in (B) and (C) were determined by ¹⁹F NMR spectroscopy using trifluorotoluene as an internal standard.

with benzyl mercaptan (9a), which led to a 99% ¹⁹F NMR yield of 1,1-dihydrofluoroalkylated product 10a (Scheme 2B). The analogous reaction with a solution of DIPEA and fluorosulfate 5a with 9a afforded only 52% yield of 10a (Scheme 2C), which is comparable to the result reported by Shreeve and coworkers.¹⁴ The addition of DBU and benzyl mercaptan to a solution of DIPEA and 5a improved the vield: however, the reaction led to an increase in the amount of free trifluoroethanol in solution, presumably resulting from nucleophilic attack at sulfur.21

This initial result is noteworthy as it represents the first example of the direct conversion of an unactivated 1,1-dihydrofluoroalcohol to the corresponding fluoroalkyl sulfide in a one-pot process. Thiol 1,1-dihydrofluoroalkylation can be achieved through nucleophilic displacement of activated trifluoroalkyl moieties,14,22 copper-catalyzed reactions with

Table 1 Optimization of the one-pot, 1,1-dihydrofluoroalkylation of benzyl mercaptan (9a)^a

	SH 9a	SO ₂ F ₂ DBU trifluoroethanol (1a) conditions	\bigcirc	∼s∕⊂cF₃ 10a
Entry	Solvent	Temp (°C)		¹⁹ F NMR yield ^{b} (%)
1	DMF	25		71
2	DMF	40		86
3	DMF	60		85
4	THF	40		81
5	ACN	40		77
6	Hexane	40		75
7	Benzene	40		67
8	DCM	40		38

^a All reactions were carried out following a one-pot procedure on 0.30 mmol scale of 9a and a 1:1 v/v trifluoroethanol: solvent ratio. Yield after 20 minutes, as determined by ¹⁹F NMR spectroscopy using trifluorotoluene as an internal standard.

trifluoroalkyl iodide23 or trifluorodiazoalkanes,24 or reductive trifluoroalkylthiolations.²⁵ All previous work relies on activated trifluoroalkyl moieties. This is particularly problematic for select activated trifluoroethyl derivatives and longer chain 1,1dihydrofluoroalkyl groups that are only available from the corresponding alcohols, and thus require additional synthetic steps to activate.

With an established protocol for a one-pot, sequential reaction, investigations next focused on a one-step process, where the alkylation proceeds by bubbling sulfuryl fluoride through a solution of trifluoroethanol (1a), benzyl mercaptan (9a), and DBU. At room temperature, the reaction proceeded efficiently to afford desired trifluoroethylated product 10a in 71% yield (Table 1, entry 1). The yield increased at 40 °C (entry 2), but there was no further improvement when the reaction was run at 60 °C (entry 3). We next examined the reaction performance in different solvents (entries 4-8).26 Overall, the reaction was robust in a range of solvents, providing good yield in both polar aprotic (entries 4 and 5) and nonpolar solvents (entries 6 and 7).



Scheme 3 Substrate scope for the 1,1-dihydrofluoroalkylation of thiols. Reaction conditions: SO_2F_2 (2.9 equiv.) was bubbled through a solution of 9 (1 equiv.), DBU (5.9 equiv.) in 1 : 1 TFE/DMF (v/v), at 40 °C for 3 minutes, and then the reaction was stirred for an additional 17 min. All reactions were run on 1 mmol scale of thiol unless otherwise indicated. Isolated yields for the one-pot reaction are reported, with ¹⁹F NMR yields (using trifluorotoluene as the internal standard) provided in parentheses. ^aThe isolated yield has been corrected to account for disulfide or solvent impurities. See the ESI† for details. ^bThe reaction was conducted on 0.5 mmol scale. ^cThe product was not isolated due to volatility. ^dThe reaction was stirred for 2 hours. ^ePentafluoropropanol : DMF (1 : 2 v/v) was used to form the reagent, and then the thiol was added to the reaction mixture. The reaction was stirred for 30 minutes.

DCM was not as effective for this transformation, with product **10a** observed in only 38% yield (entry 8).²⁷

The one-pot reaction generally affords high yields of the desired thioalkylated product regardless of the steric bulk or the electronics of the thiol (Scheme 3). Benzyl mercaptan (9a) and furfuryl mercaptan (9b) were both efficiently trifluoroethylated to form the corresponding sulfides 10a and 10b in good yields. 1-Decanethiol (9c), 2-phenylethanethiol (9d), methyl thiolglycolate (9e), and 1,9-nonanedithiol (9f) were effective substrates for this transformation, affording mono- and dialkylated products 10c-10f in 58% to 73% isolated yields. The reaction was insensitive to steric bulk alpha to the thiol, with both cyclohexyl mercaptan (9g) and triphenylmethanethiol (9h) alkylated in comparable yields (10g and 10h, respectively). Electron rich and electron poor thiophenol derivatives were well tolerated, regardless of the position of the substituents (10i-q). Importantly, longer chain 1,1-dihydrofluoroalcohols, such as 2,2,3,3,3-pentafluoropropanol (1b), were viable starting materials; however extended reaction times were required. The isolated yields of 11a and 11c were increased to 90% and 89%, respectively, by conducting the reaction in a sequential one-pot manner,28 where sulfuryl fluoride was first bubbled through a solution of DBU and trifluoroethanol followed by the addition of the requisite thiol.

We next examined the functional group tolerance of this new thiol 1,1-dihydrofluoroalkylation (Scheme 4). In substrates in which there is competition between alcohol and thiol alkylation, the reaction cleanly afforded good yields of the desired thiol 1,1-dihydrofluoroalkylation products (**10r** and **11r**). Carboxylic acids were also tolerated, with good isolated yields of thiol alkylated product **10s** using either the standard one-pot or the sequential one-pot protocols. The reaction was selective for the thiol over potential competing reactivity at the nitrogen atom of aniline and pyridine derivatives (**10t**, **11t**, and **10u**). As primary nitrogen derivatives were competent nucleophiles in reactions with trifluoroalkyl fluorosulfate, we next examined the reaction of L-cysteine ethyl ester. Under our sequential one-pot conditions, reactivity was only observed at sulfur to give **10v** in 63% isolated yield.²⁹

Finally, we investigated whether we could achieve selective 1,1-dihydrofluoroalkylation using glutathione (**9w**). Glutathione is a challenging substrate as it has two carboxylic acids, an amine, and two amides that may interfere with the desired thiol fluoroalkylation. Gratifyingly, under our sequential, one-pot reaction conditions, the thiol was selectively alkylated in 92% ¹⁹F NMR yield and 59% isolated yield. Under similar reaction conditions, trifluoroethyl triflate only afforded moderate yields of **10w**.

Intrigued by the chemoselectivity of the bis(trifluoroethyl) sulfate reagent (6a), we next investigated its selectivity compared to trifluoroethyl fluorosulfate $(5a)^{30}$ in a competition experiment between benzyl mercaptan (9a) and piperidine $(12)^{31}$ (Scheme 5).³² Addition of 9a and 12 to a preformed solution of trifluoroethyl fluorosulfate and DIPEA afforded only a slight preference for thiol alkylation (Scheme 5A). Trifluoroethanol (1a) was liberated in the course of the reaction, which is likely



Scheme 4 Functional group tolerance of the 1,1-dihydrofluoroalkylation reaction. Reaction conditions: SO_2F_2 (2.9 equiv.) was bubbled through a solution of 9 (1 equiv.), DBU (5.9 equiv.) in 1 : 1 TFE/ DMF (v/v), at 40 °C for 3 minutes, and then the reaction was stirred for an additional 17 min. All reactions were run on a 1 mmol scale unless otherwise indicated. Isolated yields for the one-pot reaction are reported, with ¹⁹F NMR yields (using trifluorotoluene as the internal standard) provided in parentheses. ^aThe one-pot reaction was stirred for 2 hours. ^bThe sequential, one-pot reaction was stirred for 30 minutes after addition of thiol. ^cThe product was converted to an HCl salt, and the reported yield has been corrected for solvent impurities.







C. Bis(trifluoroethyl) sulfate (6a) reactivity



D. Bis(trifluoroethyl) sulfate (6a) reactivity using pyrrolidine as the competition substrate



Scheme 5 Competition experiments with sulfur and nitrogen nucleophiles.

the result of the addition of thiol to the sulfur center of the fluorosulfate reagent.^{33,34} Better selectivity for thiol *versus* amine alkylation could be achieved by adding DBU with **9a** and **12**;³⁵ however, there was also a concomitant increase in the amount of **1a** (Scheme 5B). Increasing the amount of fluorosulfate reagent **5a** resulted in more amine alkylated product (**13**), but did not lead to a significantly better yield of **10a**. In contrast, formation of bis(trifluoroethyl) sulfate (**6a**) followed by addition of **9a** and **12** led to 90% yield of thiol alkylated product **10a**, and only trace amounts of **13** and trifluoroethanol (Scheme 5C). Further increasing the equivalents of the alkylating reagent led to near quantitative yield of **10a** (>97%). Even when pyrrolidine (**14**), a more nucleophilic amine,³⁶ was used in a competition experiment, trifluoroethyl sulfide **10a** was obtained almost exclusively (Scheme 5D).³⁷

Overall, we have developed a new method for the 1,1-dihydrofluoroalkylation of thiols using a previously unexplored, sulfuryl fluoride derived bis(trifluoroethyl) sulfate reagent (6a). This protocol enables the one-pot activation and thiolation of 1,1-dihydrofluoroalcohols to afford industrially relevant moieties in high yields, regardless of the sterics or electronics of the starting thiol. In situ generated bis(trifluoroethyl) sulfate (6a) is highly selective for thiols, even in the presence of unprotected alcohols, carboxylic acids, or amines, allowing for possible latestage functionalization. Compared to trifluoro-ethyl fluorosulfate, the new bis(trifluoroethyl) sulfate reagent displays superior thiol alkylation chemoselectivity over both competing amine alkylation and reactivity at the sulfate center. Efforts to further explore this new class of bis(1,1-dihydrofluoroalkyl) reagents in the context of other reactions are currently underway.

Conflicts of interest

There are no conflicts to declare.

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- 28 Under the standard one-pot conditions, sulfuryl fluoride can react with the thiol, which leads to disulfides, among other products. The sequential, one-pot conditions prevent this side reaction from occurring. For a discussion of this disulfide, see the ESI.[†]
- 29 ¹⁹F NMR spectroscopic analysis of the crude reaction mixture indicated that no amine 1,1dihydrofluoroalkylation products were observed.
- 30 Reactivity was compared to fluoroalkyl fluorosulfates, such as **5a**, because they are the only other sulfuryl fluoridederived reagent that can be generated from any **1**,**1**dihydrofluoroalcohol, and used in a one-pot process.
- 31 Piperidine was selected for the competition experiment as it was an effective substrate for amine trifluoroethylation (see ref. 3a).
- 32 For full reactions conditions, see the ESI.†
- 33 As attack at the sulfur atom with nitrogen was not typically seen under these conditions (see ref. 3a), the reagent degradation is likely to be due to thiol attack at sulfur.
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