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Communication

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One-Pot 1,1-Dihydrofluoroalkylation of Amines using Sulfuryl Fluoride

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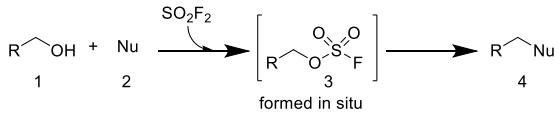
Supporting Information Placeholder

ABSTRACT: Sulfuryl fluoride, SO_2F_2, has been known and used as a fumigant for over 50 years but it has only recently gained widespread interest as a reagent for organic synthesis. Herein we report a novel application of sulfuryl fluoride gas in a new 1,1-dihydrofluoroalkylation reaction, which simply involves bubbling SO_2F_2 through a solution of amine, 1,1-dihydrofluoroalcohol, and diisopropylethylamine. The reaction is successful for a wide range of primary and secondary amines, as well as several 1,1-dihydrofluoroalcohols, to afford the 1,1-dihydrofluoroalkylated amines in 42% to 80% isolated yields. The reaction also displays excellent functional group tolerance. The ease of the one-pot activation and alkylation, combined with the wide substrate scope make this new procedure an attractive alternative to existing 1,1-dihydrofluoroalkylation methodologies.

Sulfuryl fluoride (SO_2F_2) is a commodity chemical manufactured by Dow, and has been widely used as a fumigant for over 50 years.[1] Sharpless and coworkers have recently sparked interest in this reagent in the context of organic chemistry with the development of Sulfur-Fluoride Exchange (SuFEx) chemistry,[2] in which sulfuryl fluoride rapidly reacts with an aryl alcohol to form the corresponding aryl fluorosulfate. These fluorosulfates are relatively stable and can be used as intermediates in click reactions with O-silylated phenols,[3] as triflate surrogates for transition metal-catalyzed couplings,[2,4] or as activating agents in nucleophilic deoxyfluorinations of phenols.[5] In contrast, there are significantly fewer methods that utilize SO_2F_2 to activate aliphatic alcohols.[6] The rapid reaction of alcohols with SO_2F_2, coupled with the triflate-like behavior of the resulting alkyl fluorosulfates, presents the intriguing possibility of using SO_2F_2 to effect a substitution reaction where the alcohol activation step and the substitution step occur in a single reaction pot (Scheme 1). The success of this strategy hinges upon a thorough understanding of both the kinetics of the desired reaction, as well as the relative rates of all the undesired reaction pathways.

This new strategy using SO_2F_2 was investigated in the context of the 1,1-dihydrofluoroalkylation of amines (Scheme 1, R = fluoroalkyl, Nu = R'R"NH). The products from this reaction are valuable motifs present in many biologically-active molecules[7] and have traditionally been made from the corresponding iodide or sulfonates, such as tosylates or triflates.[8] These processes involve two synthetic steps from the corresponding 1,1-dihydrofluoroalcohol and often require forcing reaction conditions. Recently, Denton and coworkers developed a new, one pot trifluoroethylation methodology that uses trifluoroacetic acid under reducing conditions.[9] We envisioned that we may be able to achieve a one-pot 1,1-dihydrofluoroalkylation by using SO_2F_2 and the appropriate alcohol. Procedurally, this new approach would be more convenient than existing methods as the alkylations could be performed simply by bubbling sulfuryl fluoride through a mixture of an alcohol and a nucleophile in a one-pot process.

Scheme 1. Proposed one-pot alkylation strategy using SO_2F_2.



A one-pot activation and substitution presents many interesting selectivity and reactivity challenges (Figure 1). For the first step, there will be a competition between the reaction of SO_2F_2 and 1,1-dihydrofluoroalcohol **1** and the undesired capture of SO_2F_2 by the amine (**2**). Even if **3** could preferentially be formed, the displacement with amine **2** to afford **4** has no direct literature precedence.[10] All previous reports involving treatment of alcohol with SO_2F_2 indicate the formation of alkyl fluoride **5**[6] or **6**[11] as the major products. Further complicating matters, treatment of amines with trifluoroethyl fluorosulfate (**3a**, R = F), generated through a different method, exclusively form trifluoroethyl sulfamate (**7**, R = F),[11] To tackle these formidable selectivity challenges, we opted to investigate this reaction using a combination of standard synthetic optimization coupled with process analytical technology (PAT),[12] to provide real-time in-situ kinetic data.

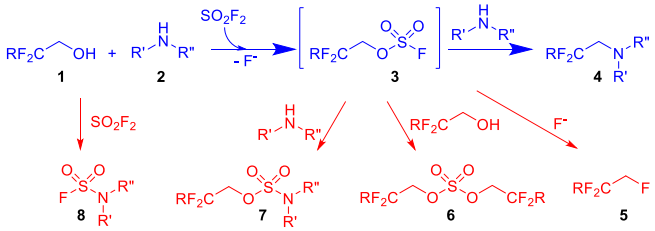


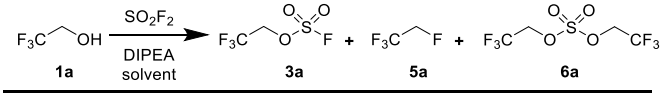
Figure 1. One-pot 1,1-dihydrofluoroalkylation mediated by SO_2F_2 (blue), and associated undesired reaction pathways (red)

1,1-Dihydrofluoroalkyl fluorosulfates have been investigated, but there have been no reports of their direct formation and isolation from SO_2F_2.[11, 13] We anticipated that trifluoroethyl

fluorosulfate (**3a**) would be more stable than non-fluorinated analogs as fluorine alpha to the electrophilic center has been shown to decrease the rate of substitution reactions.[14] Initial experiments revealed that trifluoroethyl fluorosulfate (**3a**) was facile to prepare by bubbling SO_2F_2[15] through a solution of trifluoroethanol (TFE, **1a**) and DIPEA in a variety of polar aprotic solvents (Scheme 2).[16, 17] After an aqueous work-up, it is stable for up to a week as a solution in CH_2Cl_2. A factor that significantly influenced the reaction was the choice of base; DIPEA was found to afford **3a** in higher purity than triethylamine, but bases such as potassium carbonate and DBU led to the formation of 43% and 100% of bis(trifluoroethyl)sulfate (**6a**) respectively. No trifluoroethyl fluorosulfate (**3a**) was formed in the absence of base. These conditions represent the first time **3a** has been synthesized from SO_2F_2.

Scheme 2. Synthesis of trifluoroethyl fluorosulfate (3a).

We were encouraged by the remarkable stability of fluorosulfate **3a**. Once synthesized in DMF, **3a** is stable in the reaction environment, displaying a linear decomposition profile with an approximate observed rate constant of 1.88×10^{-4} min^{-1} (Figure 2). This observed decomposition is an aggregate of both fluoride and TFE (**1a**) reacting with **3a**, giving alkyl fluoride **5a** and sulfate **6a** respectively. This small rate constant was exceptionally promising, as it demonstrated that unwanted nucleophilic capture should not be competitive with alkylation between trifluoroethyl fluorosulfate (**3a**) and the amine (**2**).



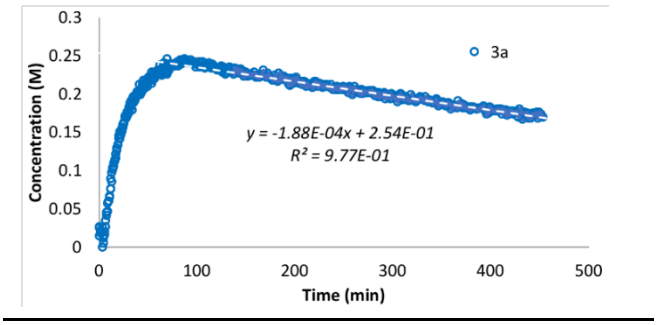
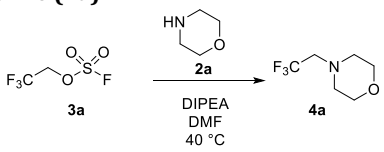


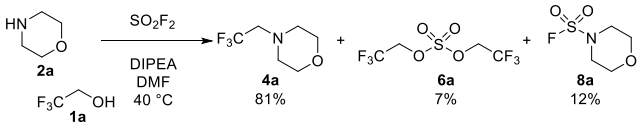
Figure 2. Reaction progress curve showing the formation and stability of trifluoroethyl fluorosulfate (3a) using SO_2F_2, DIPEA, TFE (1a) in DMF. Concentration profile generated by React-IR, monitoring absorbance at 1241 cm^{-1}.

Facile generation of trifluoroethyl fluorosulfate (**3a**) allowed us to evaluate the subsequent substitution reaction with a representative amine, morpholine (Scheme 3, **2a**).[17] Analysis of this reaction revealed two important features. First, reaction between morpholine (**2a**) and **3a** proceeded exclusively via displacement of fluorosulfate affording trifluoroethylmorpholine (**4a**) and not sulfamate **7a**. This represents the first example of **3a** acting as an amine alkylating agent.[18] Second, the relative rate of formation of trifluoroethyl fluorosulfate **3a** is ~4x the rate of its consumption through reaction with morpholine (**2a**). This suggests that we expect **3a** to accumulate in the course of the one-pot process. The kinetic experiments thus far provided information about the formation of trifluoroethyl fluorosulfate (**3a**), and its subsequent reactivity to form the fluoroethylated amine product (**4a**) and possible side products (**5**, **6**, and **7**).

Scheme 3. Reactivity of trifluoroethyl fluorosulfate (3a) with morpholine (2a).



The last piece of information required for this one-pot process is the rate of the reaction between SO_2F_2 and an amine, such as morpholine (**2a**), to form fluorosulfamide **8**. In-situ React-IR studies revealed that the reaction between alcohol (**1a**) or amine (**2a**) and SO_2F_2 have similar rate constants. This was encouraging as selective formation of **3a** in the presence of morpholine (**2a**) can be achieved by simply leveraging a concentration difference between the two. Gratifyingly, this concentration strategy allowed for a viable one-pot procedure; optimization of the amount of TFE relative to morpholine revealed that a 10:1 mixture resulted in the optimal yield of **4a** while minimizing the total volume of TFE.[17] Monitoring the one-pot process via ReactIR confirmed that capture of SO_2F_2 by **1a** is more rapid than fluoroalkylation of **2a** to give **4a**, allowing trifluoroethyl fluorosulfate (**3a**) to accumulate in-situ (Figure 3).



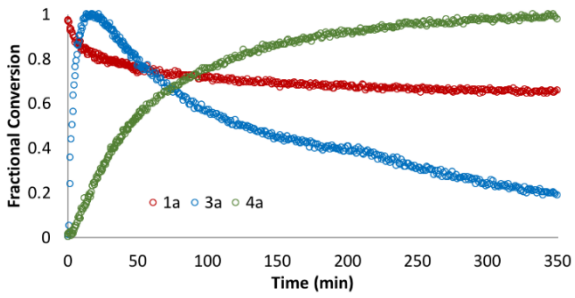
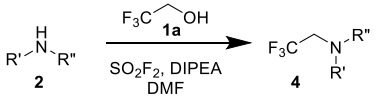


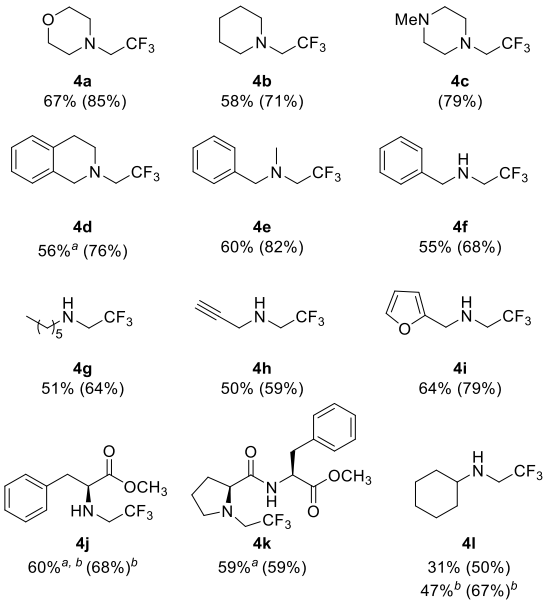
Figure 3. Reaction progress curve for the one-pot 1,1-dihydrofluoroalkylation of morpholine (2a) using SO_2F_2, DIPEA, TFE (1a) in DMF. Concentration profile generated by React-IR; O = 949 cm^{-1},O = 1241 cm^{-1},O = 1273 cm^{-1}.

The scope of this new reaction was then explored with both primary and secondary amines (Scheme 4). Consistent with what we observed during optimization, **2a** was effectively trifluoroethylated to afford **4a**, although the equivalents of sulfuryl fluoride had to be increased on larger scale.[19] Secondary amines, such as piperidine, *N*-methylpiperazine,[20] and benzylic secondary amines, were trifluoroethylated in high yields to the corresponding fluoroalkylated products **4b**-**4e**, respectively. Primary amines, such as benzylamine, *n*-hexylamine and propargylamine, were also viable substrates, affording **4f**, **4g** and **4h** respectively, although the reaction rates were slightly slower. The reaction was also compatible with a pendant furan, affording **4i**. Phenylalanine methyl ester

required a second addition of SO_2F_2 and DIPEA to achieve good isolated yields of **4j**. Other substrates with steric bulk alpha to the amine, such as cyclohexylamine (**2l**), also needed the second addition due to slow reaction rates. Further increasing the steric bulk of the amine, such as with diisopropylamine, led to no conversion. Aniline derivatives were also poor substrates for this reaction. Overall, this reaction scope is comparable with current state-of-the-art methodologies.[7, 8]

Scheme 4. Trifluoroethylation of amines



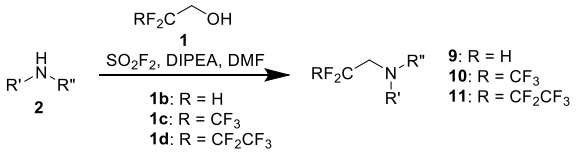


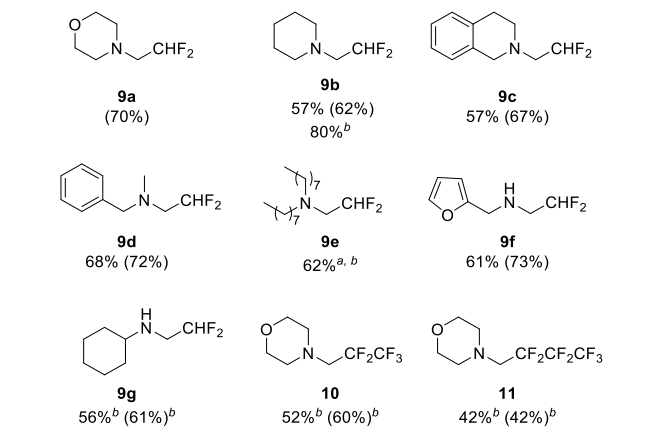
All reactions were run on 0.6 mmol scale. Unless otherwise indicated, 2M HCl in ether was added after purification, and the products were isolated as the HCl salt. Isolated yields are reported with NMR yields in parentheses. [a]The product was isolated as the neutral amine. [b]A second addition of SO_2F_2 was used.

Studies then focused on whether this new methodology could be applied to the activation of other 1,1-dihydrofluoroalcohols (Scheme 5). We initially focused on synthesizing *N*-difluoroethyl morpholine (**9a**) using difluoroethanol (**1b**). Initial optimization experiments identified that the in situ-generated difluoroethyl fluorosulfate was less stable than the analogous **3a**. To maximize the yield of the desired difluoroethylation, the temperature was decreased to ambient temperature and silica gel was added to the reaction mixture. Using these new conditions, **9a** was successfully formed in 70% NMR yield in only 20 minutes.[21] Overall, the scope was comparable to that of trifluoroethylation, although select substrates needed a second addition of SO_2F_2 and DIPEA. Pentafluoropropanol and heptafluorobutanol were also viable alcohols when the reaction was run at 40 °C, although longer reaction times were required to achieve comparable yields of the 1,1-dihydrofluoroalkylated products **10** and **11**.

To further examine the functional group compatibility of this new method, substrates with pendant nucleophiles were explored (Scheme 6). The reaction was tolerant of amines, such as indole (**2m**) and pyridine (**2n**), and no trifluoroethylation of the pendant groups was observed by ^{19}F NMR spectroscopy. We next explored the reaction with (*1S,2R*)-(+)-norephedrine (**2o**), which contains both an unprotected amine and an unprotected alcohol. Despite the possible side reactions, trifluoroethylation of **2o** under the standard one-pot reaction conditions afforded trifluoroethyl product **4o** in 72% yield.[22]

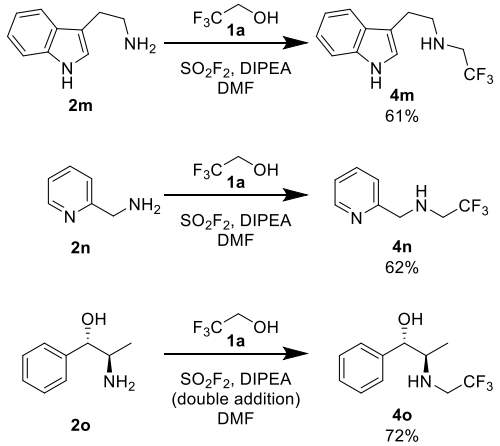
Scheme 5. 1,1-Dihydrofluoroalkylation of amines





All reactions were run on 0.6 mmol scale. Unless otherwise indicated, 2M HCl in ether was added after purification, and the products were isolated as the HCl salt. Isolated yields are reported with NMR yields in parentheses. [a]The product was isolated as the neutral amine. [b]A second addition of SO_2F_2 was used.

Scheme 6. Functional group compatibility studies.



As this is the first example of the 1,1-dihydrofluorination of amines with fluorosulfate derivatives, we next explored the relative reactivity of trifluoroethyl fluorosulfate (**3a**) com-

pared to existing activating groups, such as iodides, tosylates, mesylates, or triflates. Under our standard reaction conditions with morpholine, trifluoroethyl iodide, trifluoroethyl tosylate, and trifluoroethyl mesylate were completely unreactive.[23] While trifluoroethyl triflate is more reactive, it is significantly more unstable, particularly under aqueous basic conditions. Furthermore, replacement of sulfuryl fluoride with triflic anhydride in our one-pot process did not afford the desired product.[23]

Overall, we have developed a novel 1,1-dihydrofluoroalkylation method which simply involves bubbling SO_2F_2 through a solution of the starting amine with DIPEA and the requisite 1,1-dihydrofluoroalcohol. This process is effective for both primary and secondary amines using either trifluoroethanol or difluoroethanol as the fluoroalkyl precursors. Longer linear 1,1-dihydroperfluoroalkyl alcohols, such as pentafluoropropanol and heptafluorobutanol, were also viable, although longer reaction times were required. The reaction also displays good functional group tolerance. Compared to other fluoroalkylation methods that start from 1,1-dihydrofluoroalcohols, this is the only method that can be performed in a single synthetic step. Furthermore, the 1,1-dihydrofluoroalkyl fluorosulfate intermediate has a useful balance between reactivity and stability. Our methodology also compares favorably to the Denton strategy as we can achieve comparable results under non-reductive conditions. Additional applications in late-stage pharmaceutical derivatization and materials chemistry are currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and methods; kinetic studies and optimization data; MS, IR, and NMR data including ^{1}H, ^{13}C, and ^{19}F NMR spectra.

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Notes

The authors declare no competing financial interests.

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(10) While there are no examples of nitrogen reactivity at the carbon of trifluoroethyl fluorosulfate, reactivity at the carbon has been demonstrated for soft nucleophiles, such as sulfur and bromide. See reference 11a.

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(15) Sulfuryl fluoride can be purchased as a gas cylinder or it can be prepared from Sulfur(VI) derivatives. For a recent example, see: Veryser, C.; Demaerel, J.; Bieliūnas, V.; Gilles, P.; De Borggraeve, W. M. *Ex Situ* Generation of Sulfuryl Fluoride for the Synthesis of Aryl Fluorosulfates. *Org. Lett.* **2017**, *19*, 5244–5247.

(16) The reaction was successfully completed both using a tank of SO_2F_2, or generation of SO_2F_2 from sulfuryl diimidazole, KF, and TFA in a procedure adapted from reference 15.

(17) For optimization details, see the SI.

(18) Methyl fluorosulfates are known to react with nitrogen nucleophiles. For representative examples, see: (a) Ahmed, M. G.; Alder, R. W. Methyl basicity and nucleophilicity: the *N*- and *O*-alkylation of carbamates. *Chem. Commun.* **1969**, 1389–1390. (b) Grigg, R.; Sweeney, A.; Dearden, G. R.; Jacksen, A. H.; Johnson, A. W. *N*-methylation of octaethylporphyrin and octaethylchlorin. *Chem. Commun.* **1970**, 1273–1274.

(19) When the reaction was scaled from 0.28 mmol to 0.6 mmol, the amount of SDI had to be increased to 2.9 equivalents to maintain the pressure of SO_2F_2 in the larger reaction vessels.

(20) Substrate **9c** was challenging to separate from DIPEA due to similar physical properties.

(21) Difluoroethylmorpholine was difficult to separate from DIPEA due to similar physical properties.

(22) Another ~2.9 equiv. of SO_2F_2 was bubbled through the solution after 20 minutes.

(23) For details see the Supporting Information.

Graphical Abstract