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One-Pot Substitution of Aliphatic Alcohols Mediated by Sulfuryl Fluoride

Jia Yi Mo [ł a], Maxim Epifanov [ł a], Jack W. Hodgson [a], Rudy Dubois [a] and Glenn M. Sammis [*a]

Abstract: The Mitsunobu reaction is a powerful transformation for the one-pot activation and substitution of aliphatic alcohols. Significant efforts have focused on modifying the classic conditions to overcome problems associated with purification from phosphine-based by-products. Herein, we report a phosphine free method for alcohol activation and substitution that is mediated by sulfuryl fluoride. This new method is effective for a wide range of primary alcohols using phthalimide, di-*tert*-butyl-iminodicarboxylate, and aromatic thiol nucleophiles in 74% average yield. Activated carbon nucleophiles and a deactivated phenol were also effective for this reaction in good yields. Secondary alcohols were also successful substrates using aryl thiols, affording the corresponding sulfides in 56% average yield with enantiomeric ratios up to 99:1. This new protocol has a distinct synthetic advantage over many existing phosphine-based methods as the by-products are readily separable. This feature was exploited in several examples that did not require chromatography for purification. Furthermore, the mild reaction conditions enabled further *in situ* derivatization for the one-pot conversion of alcohols to amines or sulfones. This method also provides a boarder nucleophile scope compared to existing phosphine-free methods.

Since the two seminal publications in 1967,[1] the Mitsunobu reaction has become the preferred one-pot method to activate alcohols for nucleophilic substitution.[2] A major limitation of this classic reaction, however, is the use of stoichiometric azodicarboxylates and phosphines, both of which often lead to difficulties in product purification.[3] The most common method to circumvent this issue has been to use modified variants of these reagents, [4] A complementary, and relatively unexplored, approach to Mitsunobu reactions is to utilize non-phosphine activating agents (Scheme 1). Early investigations focused on using the Vilsmeier reagent (Scheme 1, A).[5] Cyclopropenium ions, derived from the corresponding cyclopropenones (**3**), have also been shown to effectively activate alcohols for mesylate displacements (Scheme 1, B).[6] Finally, Lewis and Brønsted acids can be used to activate alcohols for intramolecular cyclization to the corresponding oxa-, aza-, and thiacycles (Scheme 1, C).[7] Despite these important advances in phosphine-free methods, they require multiple steps and elevated temperatures (Scheme 1, A), or lack the nucleophile scope of phosphine-based Mitsunobu protocols (Scheme 1, B, C). Herein, we report a mild sulfuryl fluoride-mediated, one-pot substitution reaction that is effective with nitrogen, sulfur, oxygen and carbon nucleophiles (Scheme 1, D).

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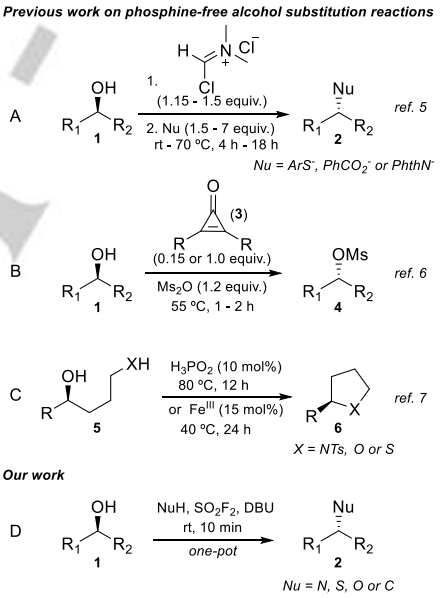
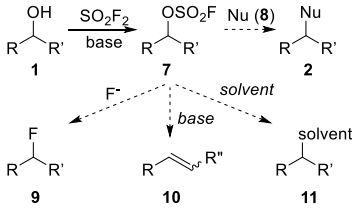
Sulfuryl fluoride (SO_2F_2) has been used as a commodity chemical for over 50 years, but it has only recently received significant attention as a reagent for organic synthesis.[8] Despite the recent surge of interest, there are only a few reports on the use of SO_2F_2 to activate aliphatic alcohols.[9] The most significant problem with aliphatic alcohol activation is that the corresponding fluorosulfate intermediate (Scheme 2, **7**) is highly reactive and is prone to undesired side reactions, such as fluoride substitution (**9**),[10] elimination (**10**),[9a] or substitution with solvent (**11**).[9c] This problem is exemplified in a recent study by Ishii and coworkers on the nucleophilic substitution of alkyl fluorosulfates.[9b] While Appel-type reactions were successful, sulfur- and nitrogen-containing nucleophiles were largely inefficient due to competing fluoride displacement.



Scheme 1. Phosphine-free approaches to one-pot alcohol substitution reactions.

We previously demonstrated that the high reactivity of fluorosulfate **7** (Scheme 2) can be attenuated through the use of 1,1-dihydrofluoroalcohols (**1**, R = perfluoroalkyl, R' = H) as the fluorine substituents decrease the rate of undesired product formation.[11,12] A large excess of the 1,1-dihydrofluoroalcohol was also required for successful amine and thiol 1,1-dihydrofluoroalkylation. Both of these solutions are too restrictive for a general substitution method because using 1,1-dihydrofluoroalcohols narrows the substrate scope, and the alcohol typically is the limiting reagent. To date, there have been no high-yielding sulfuryl fluoride-based methods for aliphatic alcohol activation and substitution using nitrogen or sulfur nucleophiles.



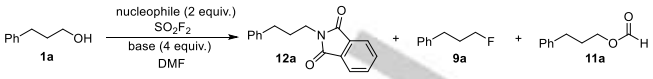
Scheme 2. Possible reaction pathways from alkyl fluorosulfate **7**.

We began our investigation into sulfuryl fluoride-mediated aliphatic alcohol activation and substitution by examining the reaction between a primary alcohol, 3-phenyl-1-propanol (**1a**), and phthalimide (PhthNH, Table 1). No reaction was observed when SO_2F_2 was bubbled through a solution of **1a** and phthalimide in the absence of base (entry 1). Using DIPEA as a base[13] resulted in a 1:10 ratio of product **12a** to starting material **1a**, along with a significant amount of formate **11a** (entry 2). Switching to triethylamine, which was utilized by Ishii and coworkers,[9b] resulted in higher conversion to product (**12a**), along with an increase in the amount of both fluoride product **9a** and **11a** (entry 3). Tetramethylguanidine (TMG) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) both led to clean formation of the desired amine alkylated product (**12a**) in only 20 minutes, with the latter having a slight advantage in reaction rate (entries 4 and 5). Optimization of the solvent found DMF was optimal, although the reaction was also successful in ethyl acetate, acetonitrile, THF, and 1,4-dioxane.[14] Decreasing the amount of DBU to 1.9 and 1.5 equivalents led to a slower reaction rate and a concomitant increase in the amount of formate (entries 6 and 7).[15]

DBU may be playing two roles in this reaction; it may be simply serving as a base or it may be also acting as a catalyst.[16] To test whether DBU is solely acting as a base to form a high concentration of the phthalimide salt in situ, we explored the reaction of a fully deprotonated phthalimide in the presence of a weaker, less nucleophilic base. Replacing phthalimide with potassium phthalimide in the presence of triethylamine led to the formation of **12a** in 73% conversion (entry 8). The increase in conversion relative to triethylamine alone (entry 3) suggests that the basicity of DBU is a major factor in this reaction. However, the lower conversion compared to DBU alone (entry 5) implies that it may also play another role in the reaction. To further test this, we explored the reaction of potassium phthalimide, triethylamine, and a catalytic amount of DBU (entry 9) and observed an increase in the amount of the desired product (**12a**) along with a concomitant decrease in the amount of formate (**11a**). The increased yield is consistent with DBU having a dual role in the reaction mechanism, both in deprotonation of the phthalimide as well as catalytic activation.[17]

With the optimized conditions in hand, we then explored the alcohol scope using phthalimide (Table 2). Increasing the sterics from 3-phenyl-1-propanol to cyclohexyl derivative **1b** led to a slight drop in the isolated yield of desired product **12b**. Benzyl alcohol was an effective substrate, affording **12c** in 69% yield. Electron poor derivatives **12d** and **12e** were also synthesized in 76% and 85% yield, respectively, but electron rich derivative **12f** was formed in poor yield, presumably due to the high reactivity of the fluorosulfate intermediate. We next examined phenethyl derivatives, which are potentially prone to elimination. Gratifyingly,

Table 1. Base optimization of the one-pot phthalimide substitution of aliphatic alcohols mediated by sulfuryl fluoride.

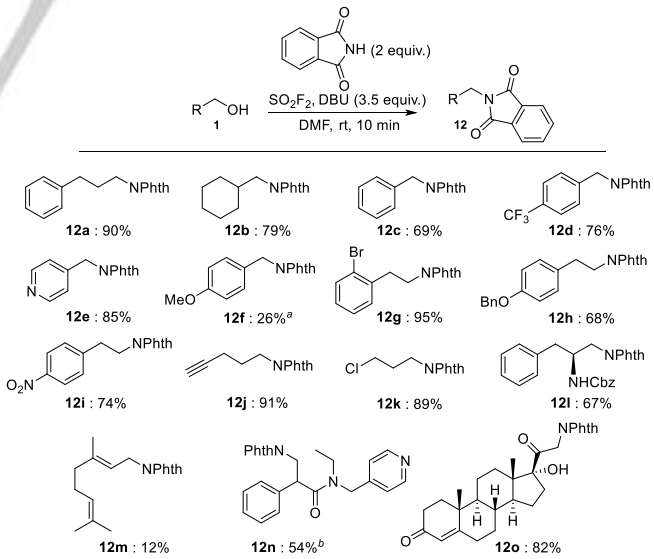


entry	base	nucleophile	1a	12a	9a	11a
1	none	PhthNH	100	0	0	0
2	DIPEA (4 equiv.)	PhthNH	72	7	0	21
3	Et_3N (4 equiv.)	PhthNH	15	22	15	48
4	TMG (4 equiv.)	PhthNH	24	76	0	0
5	DBU (4 equiv.)	PhthNH	0	100	0	0
6	DBU (1.9 equiv.)	PhthNH	4	92	2	2
7	DBU (1.5 equiv.)	PhthNH	23	71	0	6
8	Et_3N (4 equiv.)	$PhthN^-K^+$	5	73	1	21
9	Et_3N (3.7 equiv.) DBU (0.3 equiv.)	$PhthN^-K^+$	0	91	0	9

All reactions were carried out on 0.6 mmol scale of 1a. The ratio of products was determined by ^1H NMR analysis of the crude reaction mixture after 20 minutes.

12g-**12i** were all synthesized in high isolated yields with only minimal elimination product detected. The reaction was tolerant of alkyne (**12j**, 91% yield) and chloride (**12k**, 89% yield) substitution, as well as Cbz-protected amines (**12l**, 67% yield). Geraniol (**1m**) was not effective, largely due to competing S_N2' degradation pathways. More complex substrates tropicamide (**1n**) and cortexolone (**1o**) were also effective substrates for the reaction, affording **12n** and **12o** in 54% and 82% isolated yields, respectively. Secondary alcohols were not as effective (<40% yields) as they were prone to side reactions, such as elimination or nucleophilic attack by DMF leading to **10** and **11** (Scheme 2).[18]

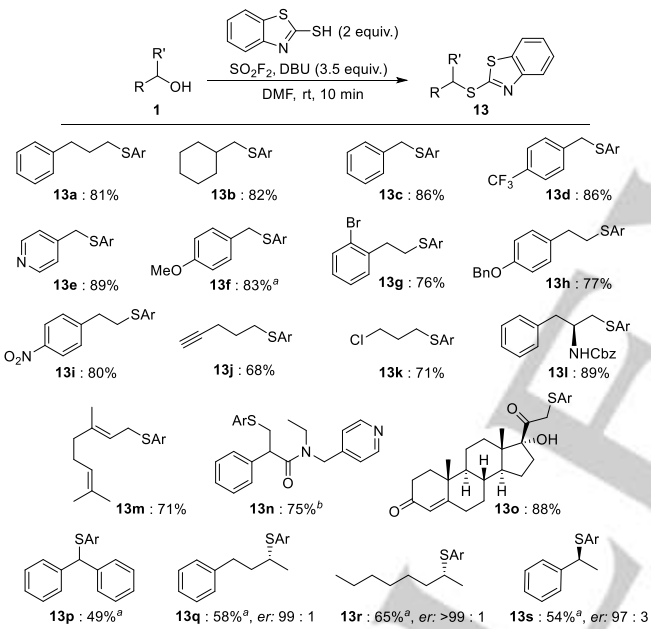
Table 2. Reaction scope for alcohol activation and substitution with phthalimide.



Reaction conditions: SO_2F_2 (4.3 equiv.) was bubbled through a solution of alcohol (1 equiv.), DBU (3.5 equiv.) and nucleophile (2 equiv.) in DMF at room temperature for 3 minutes, and then the reaction was stirred for an additional 7 min. All reactions were run on 0.6 mmol scale of alcohol unless otherwise indicated. Isolated yields are reported. [a]Reaction was run in THF instead of DMF. [b]The isolated yield has been corrected for the elimination by-product. See SI for details.

We next explored the alcohol scope using sulfur nucleophiles (Table 3). While the reaction between benzothiazole thiol and primary alcohol **1a** provided a slightly lower yield of **13a** compared to the analogous reaction with phthalimide (Table 2), increasing the sterics had little effect on the reaction yield (**13b**). Benzyl alcohol (**1c**) and electron poor benzyl alcohol derivatives were also effective, affording **13c**-**13e** in 86-89% isolated yields. Unlike the reaction with phthalimide, electron rich derivative **1f** was also a viable substrate, affording thiol adduct **13f** in 83% isolated yield. Substrates that are prone to elimination, such as **1g**-**1i**, were successfully converted to the corresponding sulfides in 75%, 77%, and 80% yield, respectively. Functionalized substrates **13j**-**13o** were also synthesized in generally high yields. Benzothiazole was an effective nucleophile for symmetric secondary alcohol (**13p**). Enantiopure alcohols **1q**-**1s** could be cleanly inverted to sulfides **13q**-**13s**, although a slight degradation in the enantiomeric ratio was observed in the conversion to the latter product.

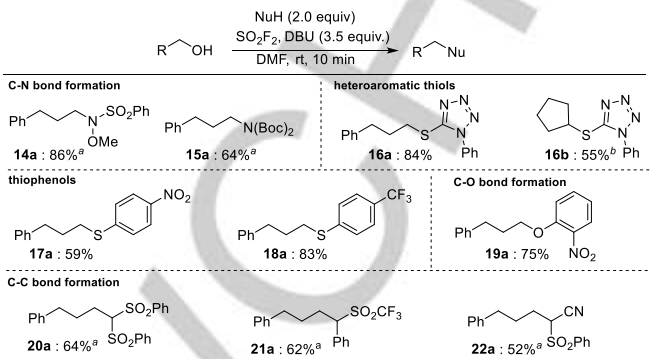
Table 3. Substrate scope for alcohol activation and displacement with benzothiazole thiol.



Reaction conditions: SO_2F_2 (4.3 equiv.) was bubbled through a solution of alcohol (1 equiv.), DBU (3.5 equiv.) and nucleophile (2 equiv.) in DMF, at room temperature for 3 minutes, and then the reaction was stirred for an additional 7 min. All reactions were run on 0.6 mmol scale of alcohol unless otherwise indicated. Isolated yields are reported. [a]Reaction was strirred for 30 minutes in THF instead of DMF. [b]The isolated yield has been corrected for the N-alkylated by-product. See SI for details.

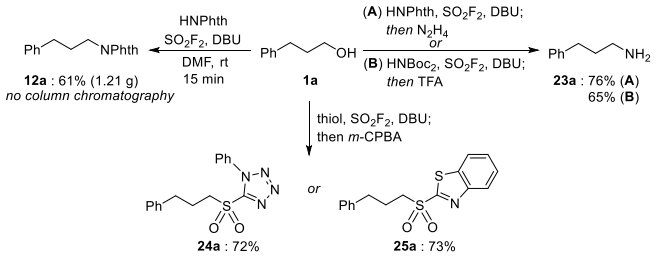
We then explored the nucleophile scope using 3-phenyl-1-propanol (**1a**). More acidic *N*-methoxybenzenesulfonamide[19] and di-*tert*-butyl-iminodicarboxylate[19] were effective nucleophiles for the reaction, providing **14a** and **15a** in 86% and 64% yield, respectively. An examination of thiol nucleophiles revealed that 1-phenyltetrazole-5-thiol and electron deficient thiols were effective for this reaction, providing **16a** to **18a** in good yields.[20] Deactivated phenol also afforded the ether product **19a** in 75% isolated yield. Gratifyingly, carbon nucleophiles could also be successfully employed in this reaction to form **20a**, **21a**, and **22a** in good yields.[21] Less acidic nucleophiles, such as phenols or electron rich thiophenols, were not effective as they react competitively with sulfuryl fluoride.

Table 4. Nucleophile scope for alcohol activation and displacement.



Reaction conditions: SO_2F_2 (4.3 equiv.) was bubbled through a solution of alcohol (1 equiv.), DBU (3.5 equiv.) and nucleophile (2 equiv.) in DMF, at room temperature for 3 minutes, and then the reaction was stirred for an additional 7 min. All reactions were run on 0.6 mmol scale of alcohol unless otherwise indicated. Isolated yields are reported. [a]Higher amounts of nucleophile and/or SO_2F_2 were used. See SI for details. [b]Reaction was run in THF instead of DMF.

The SO_2F_2-mediated reactions were generally clean and the only major byproducts were sulfate derivatives. This feature may enable simplified reaction purification or combining several processes in a single reaction pot. The former was investigated in the gram-scale synthesis of **12a** (Scheme 3). No column chromatography was required and **12a** was isolated in 61% yield.[22] The latter was first explored in the conversion of alcohol **1a** to the corresponding amine in a single reaction pot. This could be accomplished in high yields either by first converting alcohol **1a** to the corresponding phthalimide (**12a**) followed by in situ hydrazine deprotection (Scheme 3, A), or by displacement of 1a with di-*tert*-butyl-iminodicarboxylate, followed by deprotection with TFA (Scheme 3, B). A one-pot conversion of alcohol **1a** to the corresponding sulfones (**24a** or **25a**) can similarly be achieved in high yields through SO_2F_2-mediated sulfide formation followed by oxidation.[23,24]



Scheme 3 Gram scale substitution and one-pot conversion of 3-phenyl-1-propanol (**1a**) to the corresponding amine (**23a**) and sulfone (**24a** or **25a**).

Overall, we have demonstrated the first example of an efficient method for SO_2F_2-mediated activation and substitution of aliphatic alcohols. This protocol allows the formation of C-N and C-S bonds starting from a wide range of alcohols, including the bioactive molecules tropicamide and cortexolone. In addition, three carbon nucleophiles and a deactivated phenol were also

effective for this reaction. We have also demonstrated that chiral secondary sulfides can be accessed in high enantiomeric ratios. The nucleophile scope complements existing phosphine-free methods. Notably, all of the reactions are complete in less than 30 minutes and can be run at room temperature under ambient conditions. These mild reaction conditions facilitate reaction purification and enable telescoping multiple reactions in a single pot. Efforts to explore this new methodology in the context of complex pharmaceuticals are currently underway.

Acknowledgements

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Keywords: alkyl fluorosulfate • nucleophilic substitution • sulfuryl fluoride • amines • alkylation

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[14] See the SI for further details on solvent optimization.

[15] See the SI for further details on base optimization.

[16] Sharpless and co-workers proposed that catalytic amount of DBU can facilitate the nucleophilic attack on the S-F bond in Ar-OSO_2F through the fluoride-proton interaction. See: J. Dong, K. B. Sharpless, L. Kwisnek, J. S. Oakdale and V. V. Fokin, *Angew. Chem., Int. Ed.*, **2014**, *53*, 9466–9470.

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[19] Predicted pK_a values from SciFinder®: HNPhth pK_a = 10.39 ± 0.20, $HNBoc_2$ pK_a = 8.25 ± 0.46, and $PhSO_2NHOMe$ pK_a = 6.24± 0.40.

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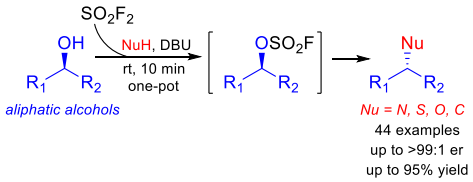

A method for alcohol activation and substitution that is mediated by sulfuryl fluoride (SO_2F_2) is described. This new process is effective for a wide range of primary alcohols using N, S, O, and C nucleophiles. This new protocol has a distinct synthetic advantage over many existing phosphine-based methods as the by-products are readily separable, which was exploited in several examples that did not require chromatography for purification.