Synthetic Methods

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Direct Dehydroxytrifluoromethylthiolation of Alcohols Using Silver(I) Trifluoromethanethiolate and Tetra-*n*-butylammonium Iodide**

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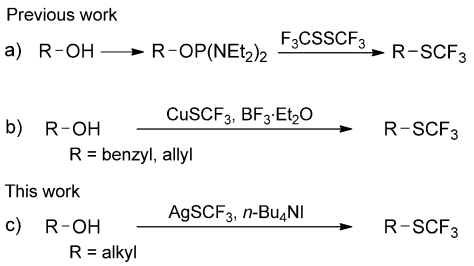
Abstract: *An unprecedented reaction for the direct trifluoromethylthiolation and fluorination of alkyl alcohols using $AgSCF_3$ and nBu_4NI has been developed. The trifluoromethylthiolated compounds and alkyl fluorides were selectively formed by changing the ratio of $AgSCF_3/nBu_4NI$. This protocol is tolerant of different functional groups and might be applicable to late-stage trifluoromethylthiolation of alcohols.*

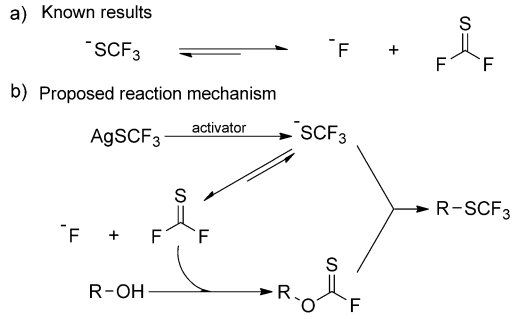
The development of new fluorination and fluoroalkylation methods is currently an active area of research[1] because fluorine-containing compounds are widely used in pharmaceuticals, agrochemicals, and materials.[2] However, most of the synthetic methods are focused on the introduction of fluorinated groups onto aromatic substrates. In contrast, few breakthroughs have been made in the methodology for the preparation of fluorine-containing aliphatic compounds. Thus, the development of new methods for the introduction of fluorinated groups into aliphatic molecules, especially from the simple and easily available materials, is highly desirable.

The trifluoromethanesulfenyl group (CF_3S) has attracted special interest because of its strong electron-withdrawing power and extremely high lipophilicity.[3] Especially during the past several years, CF_3S chemistry has experienced a renewal.[4] The development of new trifluoromethylthiolating agents,[5] as well as new trifluoromethythiolation reactions,[6] have attracted attention. Surprisingly, little attention was paid to the transformation of alcohols into the corresponding trifluoromethyl sulfides. In 1994, Kolomeitsev and co-workers developed a two-step procedure for the preparation of trifluoromethyl sulfides from alcohols via a phosphite intermediate using the toxic and gaseous reagent CF_3SSCF_3 (Scheme 1a).[7] Very recently, Rueping and co-workers reported a direct trifluoromethylthiolation of benzylic and allylic alcohols with $CuSCF_3$ in the presence of stoichiometric amounts of $BF_3{\cdot}Et_2O$ (Scheme 1b).[8] This method suffers from narrow substrate scope and poor functional-group tolerance because of the strong acidic conditions. In continuation of our research interest in trifluoromethylthiolation,[6b,e,g,n,w,ac] we herein report a new strategy for the direct dehydroxytrifluoromethylthiolation of alcohols (Scheme 1c). In this protocol, the readily prepared and stable $AgSCF_3$ is used as the trifluoromethylthiolating agent and the mild reagent nBu$_4$NI was chosen for promoting the transformation.



Scheme 1. Different strategies for dehydroxytrifluoromethylthiolation.

The idea of this work came from the fact that trifluoromethylthiol and the corresponding anion are unstable.[9] It was reported that there is an equilibrium between trifluoromethanethiolate with carbonothioic difluoride and fluoride anion (Scheme 2a).[10] Normally, the trifluoromethanethiolate



Scheme 2. Our new strategy.

is associated with a metal, such as Hg^{II},[11] Ag^{I},[12] or Cu^{I},[13] to stabilize the CF_3S group. Among these stable sources of trifluoromethanethiolate, $AgSCF_3$ is readily prepared and widely used for preparation of other trifluoromethylthiolation agents (such as $CuSCF_3$[13]) and trifluoromethylthiolation reactions.[6] We wondered if it was possible to apply this unique property of trifluoromethanethiolate to develop new reactions, such as direct dehydroxytrifluoromethylthiolation of alcohols. The proposed reaction mechanism is shown in Scheme 2b. The activation of $AgSCF_3$ gives the more active

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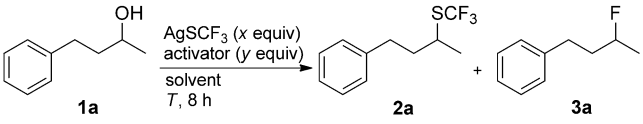
trifluoromethanethiolate, which subsequently decomposes into carbonothioic difluoride and fluoride anion. Then the alcohol reacts with in situ generated carbonothioic difluoride to generate the carbonofluoridothioate intermediate, which subsequently undergoes nucleophilic substitution by trifluoromethanethiolate to provide the trifluoromethylthiolated compound.

In 2000, Adams and Clark reported that treatment of $AgSCF_3$ with nBu$_4$NI led the formation of active source of trifluoromethanethiolate.[14] Based on this work, we started to investigate the dehydroxytrifluoromethylthiolation of alcohols with $AgSCF_3$, and 4-phenylbutan-2-ol (**1a**) was used as the model substrate. Initially, the solvent and temperature were screened (Table 1, entries 1–6). Toluene was found

Table 1: Optimization of reaction conditions.

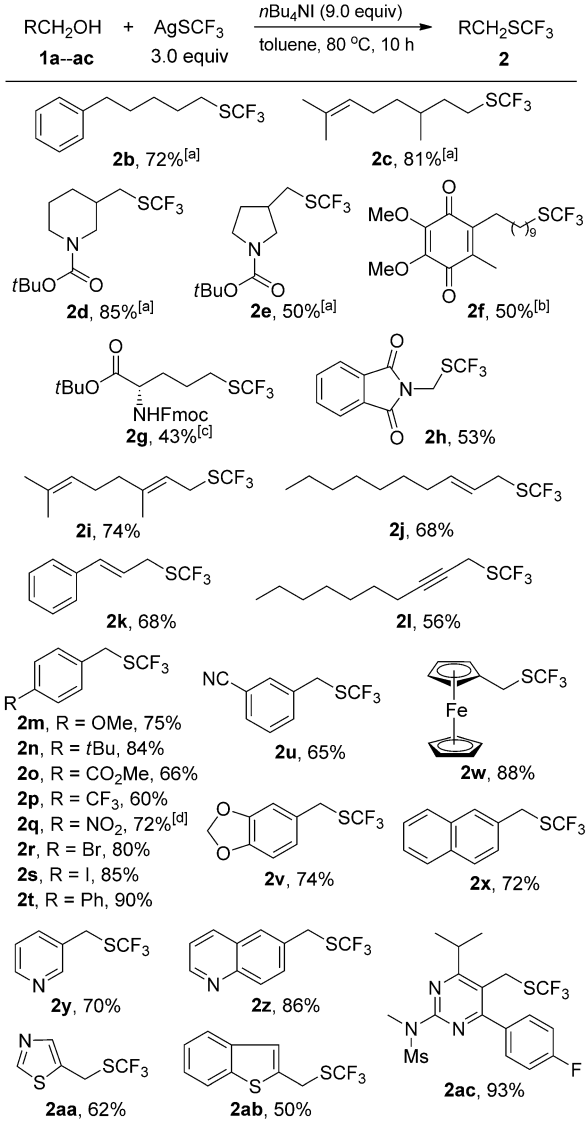


Entry	Activator	x	y	Solvent	T [°C]	Yield [%][a]	
						2a	**3a**
1	nBu$_4$NI	1.5	2.0	toluene	RT	n.d.	n.d.
2	nBu$_4$NI	1.5	2.0	toluene	50	trace	3
3	nBu$_4$NI	1.5	2.0	toluene	80	6	29
4	nBu$_4$NI	1.5	2.0	toluene	100	7	32
5	nBu$_4$NI	1.5	2.0	CH_2ClCH_2Cl	80	trace	n.d.
6	nBu$_4$NI	1.5	2.0	DMSO	80	trace	n.d.
7	nBu$_4$NI	1.5	0	toluene	80	n.d.	n.d.
8	nBu$_4$NI	1.5	1.5	toluene	80	2	36
9	nBu$_4$NI	1.5	3.0	toluene	80	19	20
10	nBu$_4$NI	1.5	4.5	toluene	80	35	15
11	nBu$_4$NI	1.5	6.0	toluene	80	36	16
12	nBu$_4$NI	3.0	9.0	toluene	80	62	trace
13	nBu$_4$NBr	3.0	9.0	toluene	80	48	26
14	nBu$_4$NCl	3.0	9.0	toluene	80	n.d.	36
15	KI	3.0	9.0	toluene	80	n.d.	10
16	nBu$_4$NI	3.0	3.0	toluene	80	4	52

[a] Yields determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard.

better than other solvents and the ideal temperature was 80 °C (entry 3). However, the trifluoromethylthiolated product **2a** was produced in low yield and the alkyl fluoride **3a** was formed as the major byproduct. To increase the yield of **2a**, we decided to change the nBu$_4$NI/$AgSCF_3$ ratio. No reaction occurred in the absence of nBu$_4$NI (entry 7). To our delight, **2a** became major when the nBu$_4$NI/$AgSCF_3$ ratio was changed into 3:1 (entries 8–11). The yield of **2a** was further improved to 62% by increasing both of the amount of $AgSCF_3$ and nBu$_4$NI (entry 12). The additive nBu$_4$NI was crucial to the reaction yield. Lower yield was found when nBu$_4$NBr was added, and **2a** was not detected when nBu$_4$NCl and KI were used as activator (entries 13–15). It was noteworthy that **3a** was formed in 52% yield when using 3.0 equivalents of $AgSCF_3$ and nBu$_4$NI (entry 16).

With the optimized reaction conditions in hand, we next investigated the substrate scope. Various primary alcohols, including alkyl, allyl, propargyl, and benzyl alcohols, were

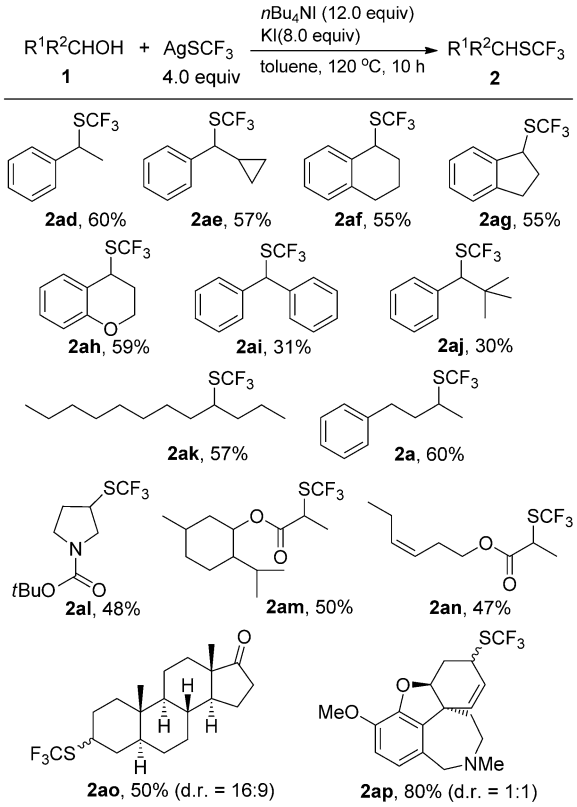


Scheme 3. Dehydroxytrifluoromethylthiolation of primary alcohols. Reaction conditions: **1** (0.4 mmol), $AgSCF_3$ (1.2 mmol), nBu$_4$NI (3.6 mmol), toluene (4.0 mL), 80 °C, 10 h. Yield is that of the isolated product. [a] 120 °C. [b] Additional KI (2.4 mmol) was added. [c] 50 °C, additional KI (2.4 mmol) was added. [d] 100 °C, nBu$_4$NI (1.2 mmol). Fmoc = 9-fluorenylmethoxycarbonyl.

converted into the corresponding trifluoromethyl sulfides in moderate to excellent yield (Scheme 3). In general, higher reaction temperature was needed for long-chain alkyl alcohols and higher yields were obtained for benzyl alcohols. Substrates bearing electron-donating and electron-withdrawing groups, such as methoxy, aryl, carbonyl, cyano, nitro, bromo, and iodo, proceeded well. Esters, amides, and a number of heterocycles, such as piperidine (**1d**), pyrrolidine (**1e**), pyridine (**1y**), quinoline (**1z**), thiazole (**1aa**) and benzo[*b*]thiophene (**1ab**), were well tolerated. It is noteworthy that the dehydroxytrifluoromethylthiolation of Idebenone, a drug for the treatment of Alzheimer's disease, was successful and gave **2f** in 50% yield. The protected L-homoserine **1g** was compatible with the reaction conditions,

thus affording the corresponding trifluoromethyl sulfide **2g** in moderate yield. The intermediate of Rosuvastatin, a member of the drug class of statins, also could be converted into the trifluoromethylthiolated product **2ac** in 93% yield.

In the case of secondary alcohols, the elimination reaction easily occurred to produce olefins as the major byproducts. Thus, the addition of another activator, KI, and higher reaction temperature were needed to achieve moderate yields (Scheme 4). Esters, amides, and heterocycles were tolerated

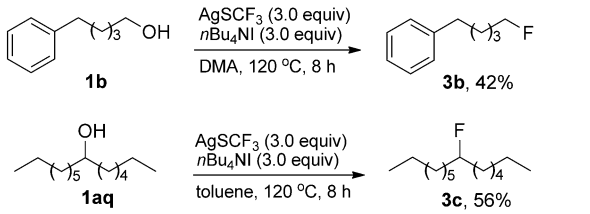


Scheme 4. Dehydroxytrifluoromethylthiolation of secondary alcohols. Reaction conditions: **1** (0.4 mmol), $AgSCF_3$ (1.6 mmol), nBu_4NI (4.8 mmol), KI (3.2 mmol), toluene (4.0 mL), 120°C, 10 h. Yield is that of isolated product.

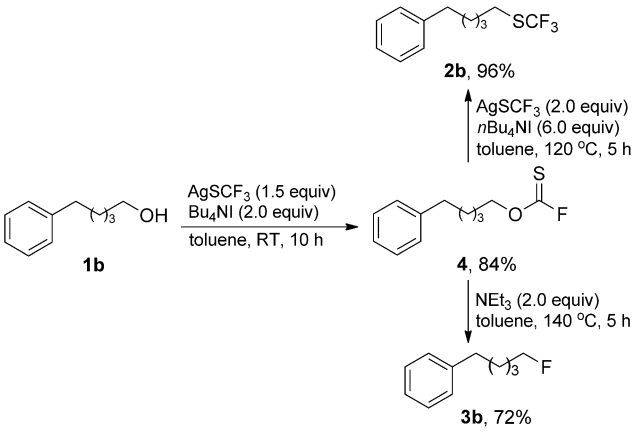
under the reaction conditions. The sterically hindered alcohols **1ai** and **1aj** were also effective, although some starting of the materials were not converted. Tertiary alcohols were not suitable substrates for this transformation. To further demonstrate the utility of this method, the dehydroxytrifluoromethylthiolation of complex compounds were attempted. When epiandrosterone (**1ao**), a steroid hormone with weak androgenic activity, was submitted to the optimal reaction conditions the desired product **2ao** was obtained in 50% yield with 16:9 diastereoselectivity. The reaction of galantamine (**1ap**), a drug used to treat Alzheimer's disease and dementia, proceeded well and afforded the trifluoromethylthiolated product **2ap** in 80% yield with 1:1 diastereoselectivity. The above results show that this protocol might be applicable to late-stage dehydroxytrifluoromethylthiolation of some medicinally relevant compounds.

As shown the entry 16 of Table 1, this protocol could also be used for the direct conversion of the hydroxy group into fluorine. When the ratio of substrate/$AgSCF_3$/nBu_4NI was 1:3:3, both the primary alcohol **1b** and secondary alcohol **1aq** were transformed into the corresponding alkyl fluorides in moderate yields (Scheme 5). This method is a rare example of using a trifluoromethylthiolating agent for a fluorination reaction.

To gain insight of the reaction mechanism, a carbonofluoridothioate intermediate was prepared (Scheme 6). Treatment of **1b** with $AgSCF_3$ and KI gave the carbonofluoridothioate **4** in high yield. The nucleophilic substitution of **4** with in situ generated trifluoromethanethiolate gave the trifluoromethylthiolated product **2b** in 96% yield. In the absence of nucleophiles, the elimination of carbonyl sulfide from **4** gave the alkyl fluoride **3b** in 72% yield.[15] These results proved that the carbonofluoridothioate intermediate is probably involved in this protocol (Scheme 2b).



Scheme 5. Dehydroxyfluorination of alkyl alcohols **1b** and **1aq**. DMA = dimethylacetamide.



Scheme 6. Investigation of the reaction mechanism.

In conclusion, we have designed and accomplished an unusual reaction process for tunable transformation of alcohols into either trifluoromethylthiolated products or alkyl fluorides. The chemoselectivity was controlled only by changing the amount of the activator used. It is well known that trifluoromethylthiolate is unstable and decomposes into carbonothioic difluoride and the fluoride anion. We have successfully used this reactivity for the direct trifluoromethylthiolation of alcohols. This investigation is an excellent example of the use of a side reaction for the development of new reactions in organic chemistry. The wide application of

this method to various alkyl alcohols containing different functional groups and heterocycles will encourage organic chemists to develop new methodologies and to synthesize more fluorinated compounds.

Experimental Section

General procedure for dehydroxytrifluoromethylthiolation: $AgSCF_3$ (250.7 mg, 1.2 mmol, 3.0 equiv) and nBu$_4$NI (1329.7 mg, 3.6 mmol, 9.0 equiv) were combined in a Schlenk tube. The tube was mounted with a reflux condenser and backfilled with N_2 (this process was repeated three times), then toluene (4.0 mL) and alcohol **1** (0.4 mmol, 1.0 equiv) were added via syringe. The tube was placed into a pre-heated oil bath at 80 °C with vigorous stirring. After 10 h, the reaction mixture was cooled to room temperature and filtered through a plug of silica (eluted with EtOAc). The filtrate was concentrated, and the product was purified by column chromatography on silica gel (eluent: hexane) to give product **2**.

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