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Silver-Catalyzed Nucleophilic Deoxydifluoromethylthiolation of Activated Aliphatic Alcohols with BT–SCF_2H

Matteo Tironi[a, b] and Matthew N. Hopkinson*[a, b]

Deoxygenative conversion of alcohols into difluoromethylthioethers is reported using 2-((difluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium triflate (BT–SCF_2H) as a source of $^{-}SCF_2H$ anions. The presence of silver(I) triflate as a catalyst was found to be crucial for stabilizing the *in situ*-generated anion, while the concomitant formation of a reactive 2-(alkoxy)benzothiazolium electrophile likely ensures a fast onward substitution reaction, avoiding the build-up of $^{-}SCF_2H$. To the best of our knowledge, this process represents the first report of a direct nucleophilic substitution reaction with $^{-}SCF_2H$ and delivers products containing the medicinally relevant difluoromethylthio motif in a single step from widely available alcohols.

Introduction

Substitution of drug or agrochemical candidates with fluorine has become a widespread strategy for improving their bioavailability and *in vivo* activity.[1] While single fluorine atoms and the trifluoromethyl (CF_3) group remain the most widely incorporated fluorine-containing motifs, recent efforts have increasingly focused on so-called emerging fluorinated groups such as OCF_3, SCF_3 or SF_5.[2] These moieties impart differing influences on the parent molecule and their incorporation in place of F atoms or CF_3 groups can result in an improvement or fine-tuning of the compound's lipophilicity and other steric and electronic properties. Partially fluorinated motifs such the difluoromethylthio (SCF_2H) group have been the subject of considerable recent interest.[3] In addition to this group's high hydrophobicity and strong electron-withdrawing properties, the relatively acidic hydrogen atom in SCF_2H is potentially available for hydrogen bonding, opening up new possibilities for beneficial intermolecular interactions *in vivo*.[4] As a result of these attractive features, several pharmaceutical and agrochemical candidates featuring the SCF_2H motif have been developed, including the insecticide Pyriprole and the antibiotic Flomoxef sodium (Scheme 1a).

Difluoromethylthio-substituted molecules are most commonly synthesized via difluoromethylation of the corresponding thiol, disulfide or thiocyanate.[3] Considering the limited availability of such moieties in many organic substrates, one-pot procedures have been developed that involve the *in-situ* synthesis of sulfur-containing intermediate species.[5] Recently, however, a selection of direct difluoromethylthiolation methodologies have been developed, in which the entire SCF_2H group is attached in one step.[3] These approaches do not require the pre-installation of a sulfur-containing moiety onto the substrate and thus extend the scope of compounds amenable for substitution with SCF_2H. The development of difluoromethylthiolation reactions relies on the availability of suitable reagents. Significant progress in this respect has been made for electrophilic and radical difluoromethylthiolation with Shen and co-workers developing several synthetically useful reagents such as *N*-(difluoromethyl)phthalimide (**A**, Scheme 1b) and $PhSO_2SCF_2H$ (**B**).[6–9] Nucleophilic difluoromethylthiolation, on the other hand, has been much less widely applied, largely due to the apparent instability of the $^{-}SCF_2H$ anion.[10] To date, only one metal-SCF_2H complex has been successfully prepared and employed as a source of $^{-}SCF_2H$: the *N*-heterocyclic carbene containing silver(I) species (SIPr)$AgSCF_2H$ (**C**, Scheme 1b, SIPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolinylidene). This compound was introduced by Shen and co-workers in 2015 and has been applied in copper and palladium-catalyzed reactions affording aromatic (difluoromethyl)thioethers from aryl diazonium salts, halides and triflates.[11]

In 2019, we introduced benzothiazolium salts as new nucleophilic reagents for installing valuable fluorine-containing groups into organic molecules.[12,13] Initially, these reagents were employed in deoxygenative trifluoromethylthiolation and selenylation reactions of aliphatic alcohols[12,14] while subsequent work focused on the synthesis of (fluoroalkyl)thio- and selenoesters directly from widely available carboxylic acids.[14b,15,16] In addition to (trifluoromethyl)thiolation using BT–SCF_3, in the latter project, (difluoromethyl)thioesters could

[a] *M. Tironi, Dr. M. N. Hopkinson*
Institute of Chemistry and Biochemistry
Freie Universität Berlin
Fabeckstrasse 34–36, 14195 Berlin, Germany
[b] *M. Tironi, Dr. M. N. Hopkinson*
School of Natural and Environmental Sciences
Newcastle University
Bedson Building, Newcastle upon Tyne, NE1 7RU, UK
E-mail: matthew.hopkinson@newcastle.ac.uk
https://blogs.ncl.ac.uk/matthewhopkinson/

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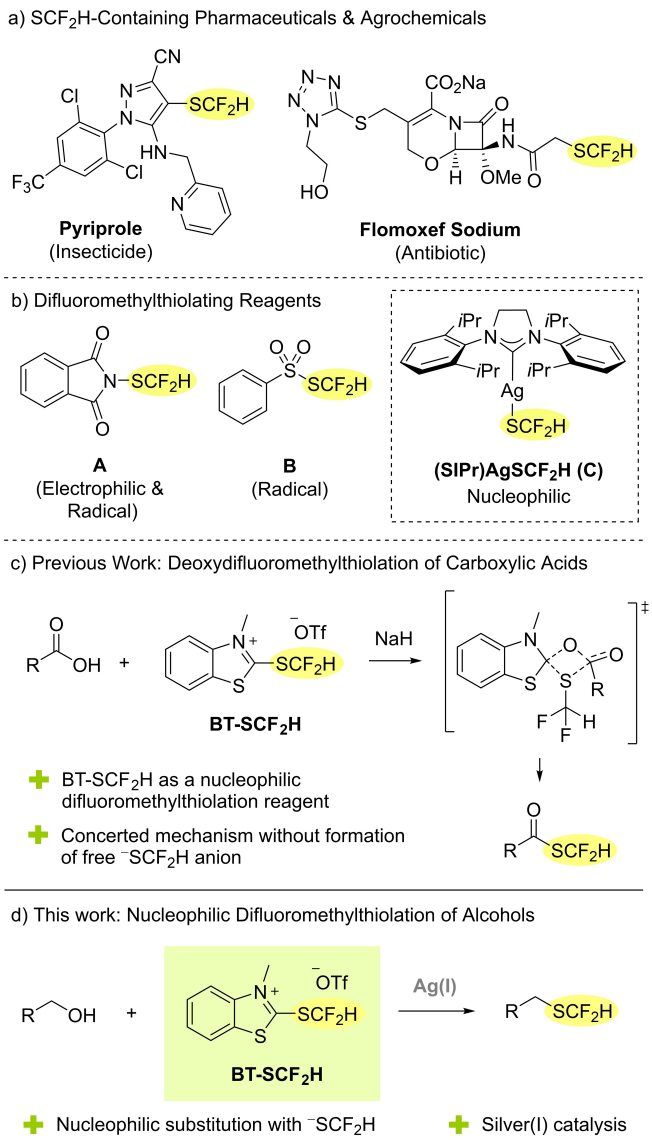
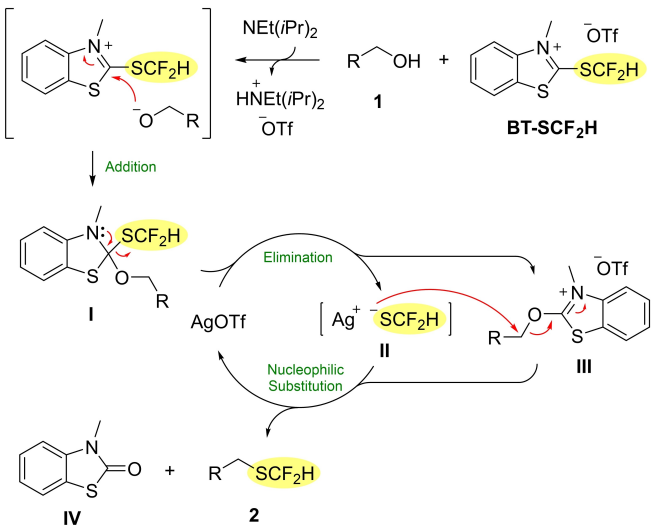


Scheme 1. a) Examples of SCF_2H-containing agrochemicals and pharmaceuticals. b) Difluoromethylthiolation reagents. c) Previous work: Deoxydifluoromethylthiolation of carboxylic acids with BT–SCF_2H. d) This work: Silver-catalyzed deoxygenative nucleophilic difluoromethylthiolation of alcohols with BT–SCF_2H.

be prepared employing 2-((difluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium triflate (BT–SCF_2H, Scheme 1c). This compound, which can be synthesized in two steps from inexpensive 2-(mercapto)benzothiazole (MBT), serves as a nucleophilic source of the SCF_2H group and thus represents only the second such reagent alongside (SIPr)AgSCF_2H (**C**). DFT calculations on the deoxydifluoromethylthiolation reaction, however, suggested that a concerted mechanism involving a four-membered ring transition state was likely operating and that free $^-SCF_2H$ anions were not formed during the process.[12] We therefore became interested in investigating the scope of BT–SCF_2H as a general nucleophilic difluoromethylthiolation reagent and, more specifically, in determining whether BT–SCF_2H could serve as a practical source of $^-SCF_2H$ anions for nucleophilic substitution reactions. Here we report the successful application of BT–SCF_2H in a silver-catalyzed deoxygenative difluoromethylthiolation of alcohols. To the best of our knowledge, this reaction represents the first report of a nucleophilic substitution involving $^-SCF_2H$ and provides (difluoromethyl)thioethers in a single step from simple alcohols (Scheme 1d).

Results and Discussion

The development of a successful nucleophilic deoxydifluoromethylthiolation of alcohols requires that substitution with $^-SCF_2H$ outcompetes any decomposition of the anion. Several features of reactions involving benzothiazolium reagents are well suited to this requirement. Firstly, rather than being present throughout the reaction, $^-SCF_2H$ is instead released in a controlled manner upon addition/elimination of the alcohol to BT–SCF_2H. Furthermore, this step results in the simultaneous generation of a highly reactive 2-(alkoxy)benzothiazolium electrophile, which can then react directly with $^-SCF_2H$, ensuring the concentration of the unstable anion in the reaction mixture remains low (Scheme 2). Initial experiments reacting 4-bromobenzyl alcohol (**1a**) with BT–SCF_2H (1.2 & 0.3 equiv., two additions) and NEt(iPr)$_2$ (2.0 & 2.0 equiv.), however, were not encouraging. After 4 h at −40 °C in MeCN, the desired product **2a** was not observed by ^1H and ^{19}F NMR (Table 1, entry 1). Hypothesizing that the provision of alternative, more covalently binding cations may help to stabilize the *in situ*-generated $^-SCF_2H$ anion, we next tested sources of silver(I). Alcohol **1a** was thus reacted under the same conditions in the presence of 0.1 equiv. of AgOTf. To our delight, difluoromethylthioether **2a** was formed in 30% ^1H NMR yield, while increasing the loading up to 0.5 equiv. provided **2a** in 61% ^1H NMR yield (Table 1, entries 2,3). To the best of our knowledge, this reaction represents the first known example of



Scheme 2. Proposed mechanism for the deoxygenative nucleophilic difluoromethylthiolation of alcohols with BT–SCF_2H.

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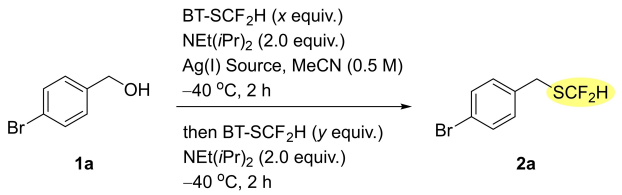
Table 1. Optimization table using **1a** as model substrate.



1a **2a**

Entry[a]	Equiv. BT–SCF_2H (*x* & *y*)	Ag(I) Source	NMR Yield of **2a**[b]
1	1.2 & 0.3	–	–
2	1.2 & 0.3	AgOTf (0.1 equiv.)	30%
3	1.2 & 0.3	AgOTf (0.5 equiv.)	61%
4	1.2 & 0.3	AgOTf (0.7 equiv.)	58%
5	1.2 & 0.3	AgOTf (1.0 equiv.)	37%
6	1.5 (one addition)	AgOTf (0.5 equiv.)	55%
7	1.5 & 0.5	AgOTf (0.5 equiv.)	70%
8	2.0 & 0.5	AgOTf (0.5 equiv.)	69%
9	2.0 & 1.0	AgOTf (0.5 equiv.)	57%
10	1.5 & 0.5	AgOTf (0.2 equiv.)	40%
11	1.5 & 0.5	(SIPr)AgOTf (0.2 equiv.)	55%
12	1.5 & 0.5	(SIPr)AgOTf (0.1 equiv.)	37%

[a] Conditions, **1a** (0.15 mmol), BT–SCF_2H (*x* equiv.), $NEt(iPr)_2$ (2.0 equiv.) in MeCN (0.5 M), −40 °C, 2 h then additional BT–SCF_2H (*y* equiv.), $NEt(iPr)_2$ (2.0 equiv.) added, −40 °C, 2 h. [b] ^1H NMR with CH_2Br_2 as internal reference.

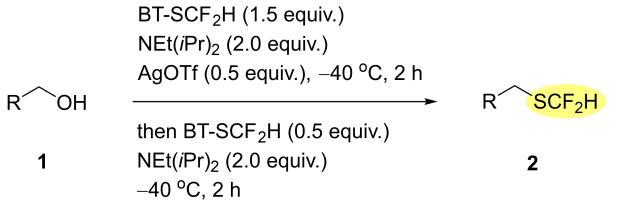
a direct nucleophilic substitution reaction with $^-SCF_2H$ and suggests that even simple silver(I) salts can help to stabilize the anion sufficiently to allow for downstream reactions.

The proposed role of the catalyst is shown in Scheme 2. Addition of the alkoxide to the C2-position of BT–SCF_2H first results in the tetrahedral intermediate **I**. At this stage, an interaction between the sulfur atom and Ag(I) may aid elimination of the difluoromethylthiolate anion, generating an $AgSCF_2H$ species **II**. This salt is expected to be comparatively stable by virtue of the soft, more covalent bonding situation present in silver(I) thiolate complexes. Nucleophilic substitution at the reactive 2-(alkoxy)benzothiazolium species **III** by $AgSCF_2H$ (**II**) would then deliver the product **2**, the thiocarbamate by-product **IV** and regenerate the silver(I) catalyst.

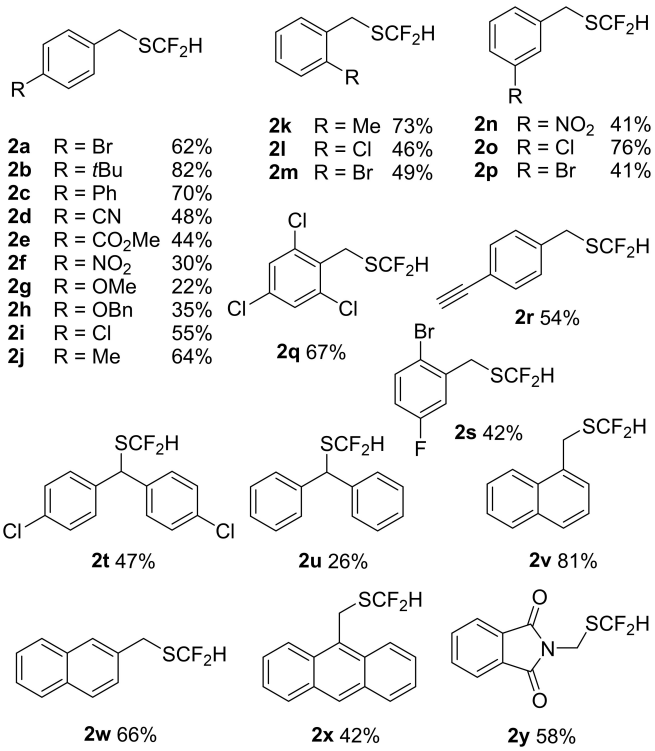
Raising the loading of AgOTf further did not result in an increase in reaction efficiency with 0.7 or 1.0 equiv. delivering **2a** in lower yields (58% and 37%, respectively, Table 1, entries 4,5). Addition of BT–SCF_2H (1.5 equiv) all together at the beginning of the reaction rather than in two separate portions led to a decrease in ^1H NMR yield to 55%, however increasing the overall amount to 2.0 equiv. (1.5 & 0.5 equiv.) delivered **2a** in an improved yield of 70% (Table 1, entries 6,7). Further increasing the equivalents of BT–SCF_2H did not lead to a higher yield of **2a** (Table 1, entries 8,9).

At this point in the study, NHC-coordinated silver(I) complexes were tested as additives in place of AgOTf. While **2a** was provided in only 40% ^1H NMR yield using 0.2 equiv. of AgOTf, this could be improved to 55% when the reaction was conducted using 0.2 equiv. of (SIPr)AgOTf (Table 1, entries 10,11). In this case, the previously reported stable (SIPr)AgSCF_2H (**C**) species would be formed during the reaction. Decreasing the loading of (SIPr)AgOTf further to 0.1 equiv., however, led to a drop in yield to 37% (Table 1, entry 12). Due to its commercial availability and much lower overall cost compared to (SIPr)AgOTf, further studies were conducted AgOTf, despite the requirement for a higher loading of 0.5 equiv.

With optimized conditions in hand, the scope and limitations of the deoxydifluoromethylthiolation reaction with a selection of aliphatic alcohols were investigated (Scheme 3). Using the conditions from Table 1, entry 7, a wide range of primary benzylic alcohols **1a–o** could be successfully converted into the corresponding thioethers **2a–o** in generally good yields. While substrates bearing relatively electron-neutral groups such a 4-*tert*-butyl and 4-phenyl provided the highest yields (**2b** = 82%, **2c** = 70%), strongly electron-withdrawing and electron-donating groups such a 4-nitro and 4-benzyloxy were also tolerated (**2f** = 30%, **2h** = 35%). Halogen substituents amenable to subsequent cross-coupling reactions could be



1 **2**



Scheme 3. Scope and limitations. Conditions: **1** (0.4 mmol), BT–SCF_2H (1.5 equiv.), $NEt(iPr)_2$ (2.0 equiv.), AgOTf (0.5 equiv.) in MeCN (0.5 M), −40 °C, 2 h then additional BT–SCF_2H (0.5 equiv.), $NEt(iPr)_2$ (2.0 equiv.) added, −40 °C, 2 h. Isolated yields.

incorporated successfully with the previously discussed 4-Br as well as the 4-Cl-containing difluoromethylthioethers **2a** and **2i** being delivered in 62% and 55% isolated yield, respectively. Remarkably, despite the well-known susceptibility of terminal alkynes towards activation by silver(I), 4-(ethynyl)benzyl alcohol **1r** reacted smoothly, providing product **2r** in 54% yield. Substitution at the *ortho*- and *meta*-positions was also tolerated, as exemplified for product **2s** (42%). The secondary (diarylmethyl)alcohols **1t** and **1u** could be successfully converted in moderate yields while extended aromatic systems such as naphthyl or anthracyl could be successfully incorporated in place the phenyl group (**2v**=81%, **2w**=66%, **2x**=42%). Unfortunately, however, secondary alcohols featuring one aryl and one alkyl substituent were not suitable substrates. The method was also not limited to alcohols featuring neighboring aromatic groups with the phthalimide-containing product **2y** being delivered in 58% isolated yield. Unfortunately, however, primary or secondary aliphatic alcohols without activating heteroatoms were not suitable substrates.

Conclusion

In conclusion, BT–SCF_2H has been employed as a nucleophilic difluoromethylthiolating reagent in a deoxygenative substitution of activated aliphatic alcohols. The combination of the benzothiazolium reagent and the silver(I) catalyst AgOTf was crucial for overcoming the inherent instability of the $^-SCF_2H$ anion. The method is operationally simple and delivers aliphatic difluoromethylthioethers from readily available alcohols without requiring pre-activation of the electrophile. To the best of our knowledge, this process represents the first reported example of a direct nucleophilic substitution reaction involving $^-SCF_2H$ and further studies exploring BT-reagents as convenient sources of otherwise inaccessible fluorine-containing anions are ongoing in our laboratory.

Experimental Section

General procedure: BT–SCF_2H (1.5 equiv.), silver triflate (0.5 equiv.) and the alcohol (**1**, 1.0 equiv., 0.4 mmol) were added to dry MeCN (0.5 M) under argon. $NEt(iPr)_2$ (2.0 equiv.) was then added, and the reaction mixture was stirred for 2 h at −40 °C. Additional BT–SCF_2H (0.5 equiv.) and $NEt(iPr)_2$ (2.0 equiv.) were then added, and the reaction mixture was stirred for a further 2 h. The solids were subsequently filtered off, the solvent was removed under reduced pressure and the difluoromethylthioethers **2** were finally isolated using flash column chromatography over silica gel.

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Data Availability Statement

Research data are not shared.

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