Organic LETTERS

Letter

pubs.acs.org/OrgLett

Trifluoromethyl Sulfoxides from Allylic Alcohols and Electrophilic SCF_3 Donor by [2,3]-Sigmatropic Rearrangement

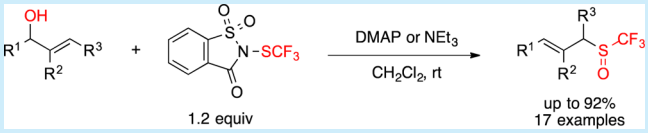
Mayaka Maeno,[†,‡] Norio Shibata,[‡] and Dominique Cahard*[,†]

[†]UMR 6014 CNRS C.O.B.R.A., Université de Rouen, INSA de Rouen, 1 rue Tesnière, 76821 Mont Saint Aignan, France

[‡]Department of Nanopharmaceutical Science, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

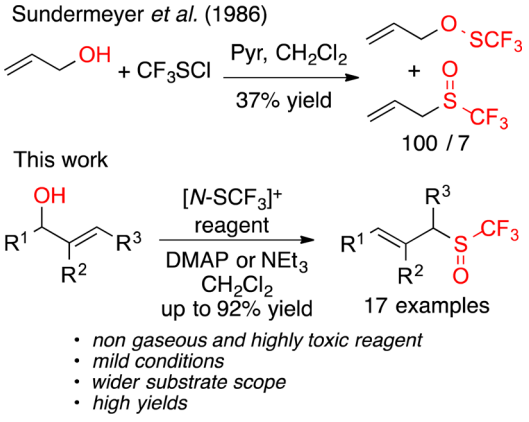
Supporting Information

ABSTRACT: An electrophilic trifluoromethylthiolation of allylic alcohols produces the corresponding allylic trifluoromethanesulfenates, which spontaneously rearrange into trifluoromethyl sulfoxides via a [2,3]-sigmatropic rearrangement. The reaction is straightforward and proceeds in good to high yields for the preparation of various allylic trifluoromethyl sulfoxides.



The electron-withdrawing trifluoromethyl group (CF_3) in combination with sulfur atom at different oxidation states is in the mainstream of organofluorine chemistry in ways that reflect a renaissance of an under-investigated research field.[1] Rapid progress in modern synthetic chemistry associated with a better understanding of fluorine effects[2] has led to a re-examination of the chemistry of $S(O)_nCF_3$-bearing molecules (n = 0, 1, or 2). Indeed, outstanding recent contributions have supplied the toolbox with new reagents and enabled the development of synthetic methods for many $S(O)_nCF_3$ molecules. Of the fluorinated motifs in vogue, the trifluoromethylthio group, SCF_3, occupies a place of choice by virtue of its exceptional lipophilicity that it confers to molecules (Hansch hydrophobic parameter: π = 1.44 versus 0.55 for SO_2CF_3, 0.88 for CF_3, and 1.04 for OCF_3).[3] In terms of electron-withdrawing character, the $SOCF_3$ and chiefly the SO_2CF_3 groups have much higher Hammett substituent constants than the SCF_3 and the CF_3 group.[4] Taft's σ^* parameters that describe the steric effects of substituents are 2.73, 4.30, and 4.41 for SCF_3, $SOCF_3$, and SO_2CF_3, respectively.[5] The class of $SOCF_3$ molecules remained under-developed compared to the many examples of both lower and higher oxidation state congeners SCF_3 and SO_2CF_3. Notwithstanding, the $SOCF_3$ motif is found in a wide variety of *N*-arylpyrazoles that include the Rhône–Poulenc insecticide Fipronil. Indeed, the $SOCF_3$ group is very appealing for the conception of new drugs and agrochemicals with potential excellent biological profiles. Current methods for the construction of the $SOCF_3$ motif include the difficult selective monooxidation of CF_3 sulfides and the nucleophilic trifluoromethylation of sulfinyl halides or sulfinic esters with $TMSCF_3$.[1a] The direct trifluoromethylsulfinylation was performed on (het)arenes with the aid of triflinate salts CF_3SO_2M (M = Na, K) in the presence of triflic acid[6] or phosphoryl chloride,[7] or with *N*-$SOCF_3$ succinimide as $CF_3S(O)^+$ donor source.[8] These literature surveys clearly point out a lack of methods, and thus it is highly desirable to develop alternative routes to further explore the potential of $SOCF_3$–featuring molecules. As part of our ongoing research toward new ways of synthesizing trifluoromethyl sulfur compounds,[9] we discovered by serendipity the formation of trifluoromethyl sulfoxides in reactions employing allylic alcohols as reactants and an electrophilic SCF_3 source. Inspection of the literature revealed a single case of such a reaction, which was carried out with gaseous and highly toxic CF_3SCl reagent on 2-propen-1-ol. Moreover, the yield was low and a mixture of sulfenate/sulfoxide was obtained (Scheme 1).[10] Therefore, we focused our attention, on the one hand, on the replacement of CF_3SCl and, on the other hand, on a wider range of allylic alcohols as a general and easily available class of reactants for the construction of relevant new trifluoromethyl sulfoxides (Scheme 1).

Scheme 1. Direct Access to Trifluoromethyl Sulfoxides from Allylic Alcohols



At the onset, 1-phenyl-2-propen-1-ol (**1a**) was chosen as a model allylic alcohol to study its reactivity with *N*-trifluor-

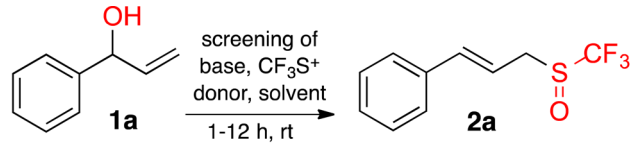
Received: March 14, 2015
Published: April 1, 2015

DOI: 10.1021/acs.orglett.5b00750
Org. Lett. 2015, 17, 1990–1993

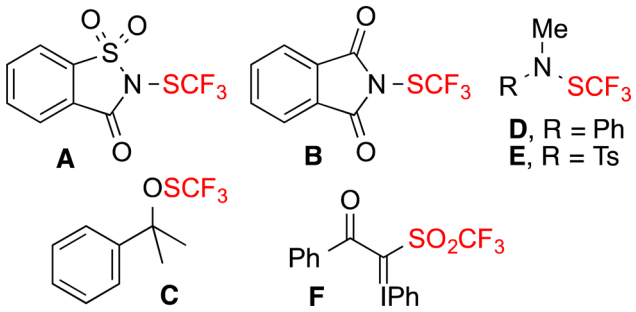
omethylthiosaccharin, Shen's reagent **A**, which has been presented as the most efficient trifluoromethylthiolation agent for alcohols.[11] What is worthy of note, however, is that we did not obtained the thioperoxide like for nonallylic alcohols but instead the allylic trifluoromethyl sulfoxide **2a**. Results of the optimization of the reaction conditions that include screening of the solvent, the base, and the CF_3S^+ donor source are listed in Table 1. Among the solvents evaluated, CH_2Cl_2 proved to be the most appropriate over CH_3CN, THF, and toluene in the presence of triethylamine as the base (entries 1−4). Next, other bases were tested, and we found that DMAP gave improved yields, in particular when the amount of base was optimized to 1.2 equiv (entries 5−9). Other tertiary amines gave lower yields, whereas inorganic bases failed to produce the allylic trifluoromethyl sulfoxide **2a**. By using 10 mol % of base only, we could reach a moderate yield of 47% (entry 10). This result indicated that once *N*-trifluoromethylthiosaccharin has reacted, it liberated a strong base able to deprotonate the allylic alcohol. Next, a screening of other CF_3S^+ donor sources was performed (entries 11−15). The structurally related *N*-SCF_3-phthalimide, Munavalli's reagent **B**,[12] reacted to provide **2a** in 39% yield as compared to the 84% by means of reagent **A**. Shen's sulfenate **C** gave a moderate 49% yield.[13] Disappointingly, neither Billard's reagents **D** and **E**[14] nor Shibata's reagent **F** were effective in this reaction.[15] Finally, the influence of the order of addition of the reaction components on the yield of **2a** revealed a clear preference for an addition of the CF_3S^+ donor onto a mixture of starting allylic alcohol and base in CH_2Cl_2.

With the optimized reaction conditions in hand (Table 1, entry 9), we next sought to examine the substrate scope (Scheme 2). A wide range of 1-aryl-2-propen-1-ols (**1a**−**i**) were subjected to the trifluoromethylthiolation with the aryl group featuring either electron-donating substituents at different positions (Me, MeO) or electron-withdrawing substituents (Cl, CF_3, CN, CO_2Et). Whatever the nature of aryl substituents, the

Table 1. Screening of reaction parameters



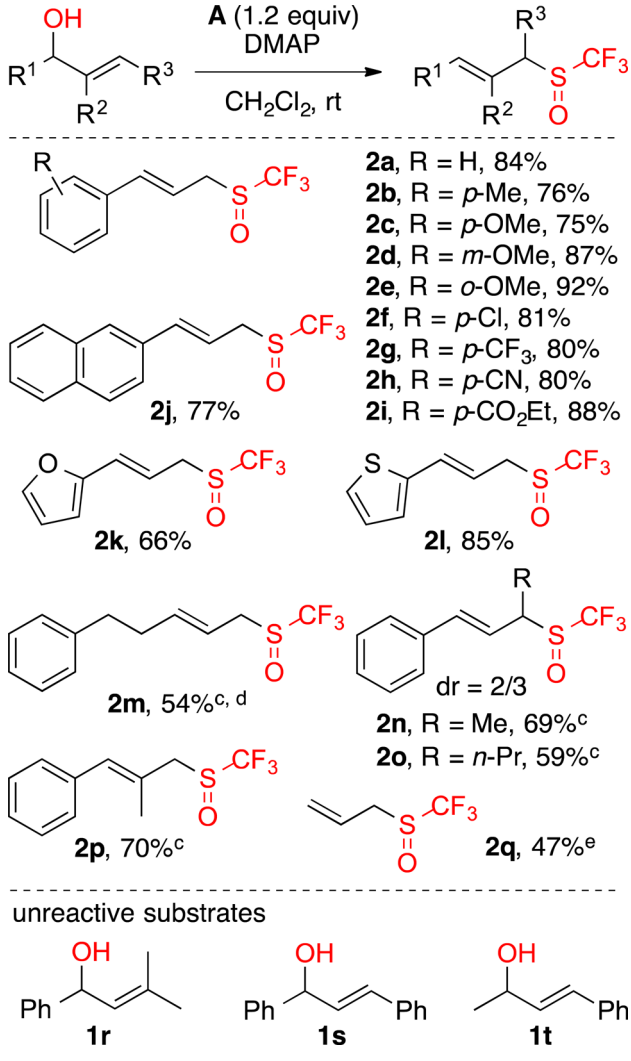
[*N*-SCF_3]$^+$ reagents



run	base	solvent	CF_3S^+ donor	yield (%)[a]
Screening of Base and Solvent[b]				
1	NEt_3	CH_2Cl_2	**A**	70
2	NEt_3	MeCN	**A**	57
3	NEt_3	THF	**A**	51
4	NEt_3	toluene	**A**	47
5	DMAP	CH_2Cl_2	**A**	72
6	DMAP	MeCN	**A**	68
7	DABCO	CH_2Cl_2	**A**	65
8	DIPEA	CH_2Cl_2	**A**	18
Variation of the Amount of base				
9	DMAP (1.2 equiv)	CH_2Cl_2	**A**	84
10	DMAP (0.1 equiv)	CH_2Cl_2	**A**	47
Screening of the CF_3S^+ Donor Source				
11	DMAP	CH_2Cl_2	**B**	39
12	DMAP	CH_2Cl_2	**C**	49
13	DMAP	CH_2Cl_2	**D**	0
14	DMAP	CH_2Cl_2	**E**	0
15	DMAP	CH_2Cl_2	**F**	0

[a]Yields were determined by ^{19}F NMR using trifluorotoluene as an internal standard. [b]Reaction conditions: **1a** (1 equiv, [**1a**] = 0.05 M), base (2.2 equiv), CH_2Cl_2, 30 min, then **A** (1.2 equiv in CH_2Cl_2), room temperature, 1 to 12 h (TLC monitoring). DMAP = 4-dimethylaminopyridine. DABCO = 1,4-diazabicyclo[2.2.2]octane. DIPEA = *N*,*N*-diisopropylethylamine.

Scheme 2. Substrate Scope and Limitations[a,b]



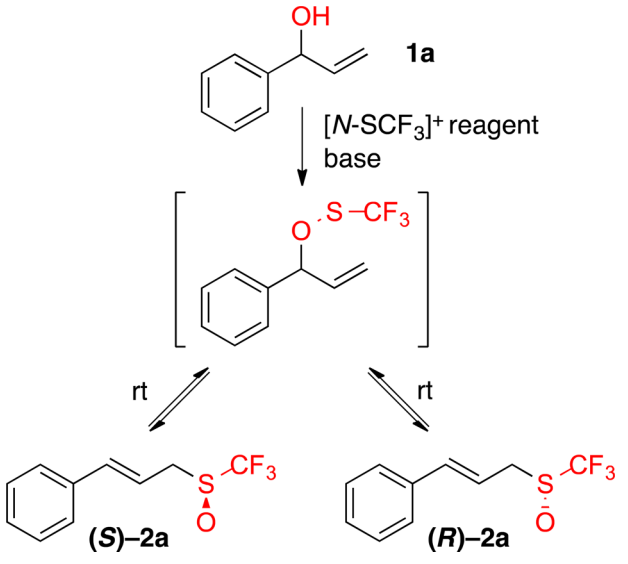
[a]Yields of isolated pure products. [b]Reaction conditions: **1** (1 equiv, [**1**] = 0.05 M), base (1.2 equiv), CH_2Cl_2, 30 min, then **A** (1.2 equiv in CH_2Cl_2), room temperature, overnight. [c]NEt_3 was used instead of DMAP. Reaction time: 1 h. [d]**2m** was obtained in equilibrium with 3% of sulfenate. [e]Contains 20% of sulfenate. Yield was determined by ^{19}F NMR using trifluorotoluene as an internal standard.

DOI: 10.1021/acs.orglett.5b00750
Org. Lett. 2015, 17, 1990−1993

corresponding allylic trifluoromethyl sulfoxides **2a−i** were obtained in good yields in the range 75−92%. The sterically more demanding naphthyl group as well as the 2-furyl- and the 2-thienyl heteroaromatics also led to high yields (**2j−l**). All these allylic trifluoromethyl sulfoxides **2a−l** were readily synthesized definitely owing to their stable conjugated olefin-(het)arene motif. If ones deviate from this pattern, the reaction was still possible, but it led to a lower yield of 54% as in the case of phenethyl derivative **2m** (Scheme 2). We found that triethylamine gave better yields than DMAP for this substrate and the following ones **2m−q**. Starting allylic alcohols bearing a disubstituted olefin moiety are suitable substrates to allow the reaction to take place in moderate to good yields (branched **2n−o** and terminal **2p** products). This is true as far as alkyl groups (Me, Bu) are considered, but substrates **1s** and **1t** featuring a phenyl substituted olefin failed to produce the corresponding sulfoxides. In these two cases, the primary reaction products were the sulfenates, which were obtained within a short reaction time, but they decomposed rather than rearranged into the desired sulfoxides. As to the issue of trisubstituted olefinic substrate **1r**, the sulfenate was formed but rapidly evolved to the corresponding conjugated diene by elimination.[16] Finally, the simplest allylic alcohol, 2-propen-1-ol, was engaged in the reaction to yield sulfoxide **2q** accompanied by the corresponding sulfenate (47%, sulfoxide/sulfenate = 1.35:1).

From a mechanistic point of view, ^{19}F NMR monitoring of the reaction of **1a** clearly indicated the formation of the intermediate sulfenate (δ = −53.1 ppm), which quickly turned into the allylic trifluoromethyl sulfoxide **2a** (δ = −72.7 ppm) (Scheme 3). This

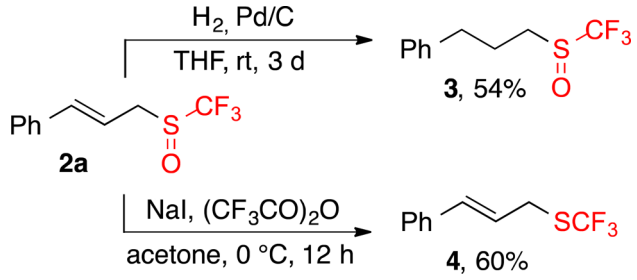
Scheme 3. Enantiomerization of Trifluoromethylsulfoxides via [2,3]-Sigmatropic Rearrangement



is the result of a [2,3]-sigmatropic rearrangement similar to the rearrangement of allyl *p*-tolyl sulfoxides discovered by Mislow in 1966 and of allyl trichloromethyl sulfoxide reported by Braverman in 1967.[17] Obviously, the cyclic rearrangement mechanism is inaccessible to simple alkyl and aryl trifluoromethyl sulfenates.[11] The rearrangement is facilitated by the presence of the electron-withdrawing CF_3 group and easily occurs at room temperature. With the aim of preparing enantiomerically enriched trifluoromethyl sulfoxides, we engaged (*R*)-1-phenyl-2-propen-1-ol in the trifluoromethylthiolation to end up with **2a** but unfortunately as a racemic compound. The reaction is an equilibrium lying far to the side of the sulfoxide during which the intermediate sulfenate racemizes. Support of the rapid interconversion of sulfoxide enantiomers came from HPLC analysis, which showed incomplete peak coalescence at rt with a plateau-type "Batman" elution profile. At 5 °C, enantiomers of **2a** were separated by HPLC, collected and kept at 5 °C for 72 h without any enantiomerization until the sample was warmed up to rt, which has the effect of triggering the enantiomerization. It follows from this study that stereospecific construction of trifluoromethyl sulfoxides is jeopardized.[18]

This novel methodology offers an unprecedented access to several new fluorinated sulfoxides likely to be useful intermediates in organic synthesis.[19] The sulfoxides could easily undergo further chemical transformations as illustrated in Scheme 4 with the chemoselective reduction of either the olefin or the sulfoxide function.[20]

Scheme 4. Functional Group Interconversions of Allylic Trifluoromethylsulfoxide 2a



In conclusion, we have reported the synthesis of trifluoromethyl sulfoxides via a [2,3]-sigmatropic rearrangement of the intermediate sulfenates that were generated in situ by trifluoromethylthiolation of allylic alcohols. The reaction does not require gaseous and highly toxic reagent and is suitable for a wide range of reactants to give the desired trifluoromethyl sulfoxides in good to high yields under mild conditions. A unique feature of these fluorinated molecules is their rapid enantiomerization around room temperature, whereas nonfluorinated sulfoxides require higher temperature. The present methodology expands the toolbox of organic chemists for the preparation of trifluoromethylsulfur compounds at different oxidation states.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dominique.cahard@univ-rouen.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

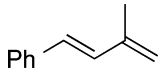
This research was partially supported by the Centre National de la Recherche Scientifique (CNRS), University of Rouen, INSA Rouen, and Labex SynOrg (ANR-11-LABX-0029). M.M. is grateful to the French ministry of foreign affairs for an Eiffel excellence doctorate scholarship. The authors thank Dr. T.

DOI: 10.1021/acs.orglett.5b00750
Org. Lett. 2015, 17, 1990−1993

Billard (ICBMS-UMR 5246, Université de Lyon 1) for the gift of reagents **D** and **E**.

REFERENCES

(1) (a) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (b) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, 2415.
(2) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135.
(3) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.
(4) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(5) Brändström, A. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1855.
(6) Wakselman, C.; Tordeux, M.; Freslon, C.; Saint-Jalmes, L. *Synlett* **2001**, 550.
(7) Billard, T.; Greiner, A.; Langlois, B. R. *Tetrahedron* **1999**, *55*, 7243.
(8) Romanenko, V. D.; Thoumazet, C.; Lavallo, V.; Tham, F. S.; Bertrand, G. *Chem. Commun.* **2003**, 1680.
(9) Dai, X.; Cahard, D. *Synlett* **2015**, *26*, 40.
(10) Holoch, J.; Sundermeyer, W. *Chem. Ber.* **1986**, *119*, 269.
(11) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316.
(12) Munavalli, S.; Wagner, G. W.; Hashemi, B.; Rohrbaugh, D. K.; Durst, H. D. *Synth. Commun.* **1997**, *27*, 2847.
(13) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *J. Org. Chem.* **2015**, *80*, 3012.
(14) (a) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *J. Org. Chem.* **2008**, *73*, 9362. (b) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551. (c) Alazet, S.; Zimmer, L.; Billard, T. *Chem.—Eur. J.* **2014**, *20*, 8589.
(15) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782.
(16) Structure of the diene obtained by reaction of **1r** with *N*-trifluoromethylthiosaccharin.



(17) (a) Rayner, D. R.; Miller, E. G.; Bickart, P.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc.* **1966**, *88*, 3138. (b) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (c) Braverman, S.; Stabinsky, Y. *J. Chem. Soc., Chem. Commun.* **1967**, 270. (d) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956.
(18) We found that electron-withdrawing substituents on the aryl moiety of the allylic alcohol slowed down enantiomerization of sulfoxides. A complete study of this phenomenon is under investigation in our laboratory.
(19) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
(20) Beeler, A. B.; Schlenk, D. K.; Rimoldi, J. M. *Tetrahedron Lett.* **2001**, *42*, 5371.

DOI: 10.1021/acs.orglett.5b00750
Org. Lett. 2015, 17, 1990−1993