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Electrophilic Trifluoromethylthiolation of Allylsilanes with Trifluoromethanesulfanamide

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ABSTRACT

A CH_3COCl-promoted allylic trifluoromethylthiolation of allylsilanes with trifluoromethanesulfanamide has been described. The method allows for an efficient synthesis of a wide range of allylic trifluoromethylthiolated compounds under mild conditions.

The trifluoromethylthio moiety (CF_3S-) is one of the key structural units found in pharmaceuticals and agrochemicals mainly due to its strong electron-withdrawing effect and extremely high lipophilicity.[1] Consequently, extensive efforts have been devoted to the incorporation the CF_3S group into a series of pharmaceutically and agrochemically related agents. Earlier studies in this area primarily focused on indirect methods, including nucleophilic fluorination of perchloroalkyl sulfides[2] and trifluoromethylation of sulfur-containing precursors,[3] while more attention has been recently turned toward the direct and attractive trifluoromethylthiolation.[4−11] For example, significant progress has been made in the construction of $C-SCF_3$ bonds using CF_3SM or CF_3SNMe_4 as a nucleophilic CF_3S source, including nucleophilic substitution[5] of aryl halides or diazonium salts and trifluoromethylthiolations of aryl

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(1) (a) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525. (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207. (c) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827.

(2) Wakselman, C.; Tordeux, M. *J. Org. Chem.* **1985**, *50*, 4047.

(3) (a) Tordeux, M.; Wakselman, C.; Langlois, B. *J. Org. Chem.* **1989**, *54*, 2452. (b) Soloshonok, V.; Kukhar, V.; Pastrait, Y.; Nazaretian, V. *Synlett* **1992**, 657. (c) Koshechko, V. G.; Kiprianova, L. A.; Fileleeva, L. I. *Tetrahedron Lett.* **1992**, *33*, 6677. (d) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156. (e) Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **1996**, *37*, 6865. (f) Quiclet-Sire, B.; Saicic, R. N.; Zars, S. Z. *Tetrahedron Lett.* **1996**, *37*, 9057. (g) Billard, T.; Large, S.; Langlois, B. R. *Tetrahedron Lett.* **1997**, *38*, 65. (h) Billard, T.; Roques, N.; Langlois, B .R. *J. Org. Chem.* **1999**, *64*, 3813. (i) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848. (j) Pooput, C.; Medebielle, M.; Dolbier, W. R. *Org. Lett.* **2003**, *6*, 301. (k) Pooput, C.; Dolbier, W. R.; Medebielle, M. *J. Org. Chem.* **2006**, *71*, 3564. (l) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754.

(4) For radical trifluoromethylthiolation, see: (a) Harris, J. F.; Stacey, F. W. *J. Am. Chem. Soc.* **1961**, *83*, 840. (b) Harris, J. F. *J. Am. Chem. Soc.* **1962**, *84*, 3148. (c) Sheppard, W.; Andreades, S.; Harris, J. F. *J. Org. Chem.* **1964**, *29*, 898. (d) Harris, J. F. *J. Org. Chem.* **1966**, *31*, 931. (j) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Wagner, W. G.; Durst, H. D. *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 1021.

(5) (a) Adams, D. J.; Clark, J. H. *J. Org. Chem.* **2000**, *65*, 1456. (b) Adams, D. J.; Goddard, A.; Clark, J. H.; Macquarrie, D. J. *Chem. Commun.* **2000**, 987. (c) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2003**, *119*, 101.

(6) (a) Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun.* **1993**, 918. (b) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7312. (c) Zhang, C.-P.; Vicic, D. A. *J. Am. Chem. Soc.* **2011**, *134*, 183. (d) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1548.

(7) (a) Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2492. (b) Zhang, C.-P.; Vicic, D. A. *Chem.—Asian J.* **2012**, *7*, 1756.

(8) Chen, C.; Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 12454.

(9) (a) Sheppard, W. A. *J. Org. Chem.* **1964**, *29*, 895. (b) Bogdanowicz-Szwed, K.; Kawalek, B.; Lieb, M. *J. Fluorine Chem.* **1987**, *35*, 317. (c) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237.

(10) (a) Ferry, A. l.; 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) Ferry, A.; Billard, T.; Bacqué, E.; Langlois, B. R. *J. Fluorine Chem.* **2012**, *134*, 160. (d) Baert, F.; Colomb, J.; Billard, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10382.

(11) Yang, Y.; Jiang, X.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 7538.

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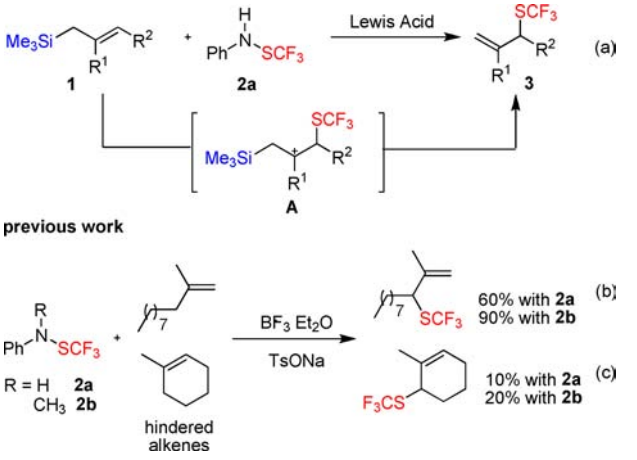
halides,[6] aryl boronic acids,[7] and terminal alkynes[8] in the presence or absence of transition metal catalysts. These methods allowed efficient access to a wide range of CF_3S-containing compounds under relatively mild reaction conditions. However, the utility of electrophilic trifluoromethylthiolating reagents to construct C−SCF_3 bonds, which would broaden the scope of direct trifluoromethylthiolation reactions, remains less extensively explored. Until now, only several examples of the direct electrophilic trifluoromethylthiolation reactions have been reported.[9−11] Steppard[9a] and Bogdanowicz-Szwed[9b] respectively reported the electrophilic reactions of arylmagnesium halides and enamines with CF_3SCl as the electrophile. Remarkably, Daugulis and co-workers described the first example of a copper-promoted direct trifluoromethylthiolation of aryl C−H bonds using CF_3SSCF_3 as the electrophilic trifluoromethylthiolating reagent.[9c] Nevertheless, these electrophilic protocols have significant limitations including the modest substrate scope/generality and the use of gaseous and/or highly hazardous reagents. Recently, Billard and Langlois reported that trifluoromethanesulfanamides (**2**)[10] could be used as a new and easy-to-handle electrophilic CF_3S source, enabling the direct trifluoromethylthiolation of a series of nucleophiles, such as alkenes, alkynes,[10b] electron-rich arenes,[10c] and organometallic reagents[10d] in the presence of acidic initiators. Most recently, our group also accomplished an acid-promoted trifluoromethylthiolation−cyclization cascade with trifluoromethanesulfanamide **2a**.[11] In our continuing efforts to develop new and efficient trifluoromethylation and trifluoromethylthiolation reactions, herein we describe a Lewis acid promoted electrophilic trifluoromethylthiolation of allylsilanes to afford a range of allylic trifluoromethylthiolated products under mild conditions (Scheme 1a).

Compounds carrying a fluoroalkyl group at their allylic positions are versatile building blocks for the synthesis of a variety of fluoroalkyl-containing compounds.[12] Currently, strategies for the preparation of allylic CF_3 compounds have been developed.[13] For example, Buchwald's,[13a] Liu's,[13b] Wang's,[13c] and our group[13d] successively reported the Cu-catalyzed allylic trifluoromethylation of olefins, providing a series of trifluoromethylated allylic compounds. To further expand the substrate scope of these reactions, Sodeoka[14a] and Gouverneur[14b] subsequently developed the Cu-catalyzed trifluoromethylation of allylsilanes using Togni's reagent.[14] However, a similar transformation employed in the trifluoromethylthiolation, which would be an efficient method to access allylic SCF_3 compounds, has hardly been demonstrated. A single example of this type of reaction was disclosed by Billard and co-workers, in which allylic SCF_3 products were obtained when hindered olefins were employed in the electrophilic trifluoromethylthiolation of alkenes with trifluoromethanesulfanamides (Scheme 1b, 1c).[10b] The scope of the reaction was considerably limited, and the reaction efficiency was low. Inspired by the work of Sodeoka's and Gouverneur's groups,[14] we surmised that the utility of allylsilanes as the substrates, in which the pendant trimethylsilyl group could enhance the nucleophilicity of olefins and control the regioselectivity via the β-silyl effect, would facilitate the selective formation of allylic SCF_3 products in the electrophilic trifluoromethylthiolation reactions (Scheme 1a).

Scheme 1. Electrophilic Trifluoromethylthiolation Reactions with Trifluoromethanesulfanamides



Considering the fact that an acidic initiator is required for the transfer of the SCF_3 group from the electrophilic trifluoromethanesulfanamides,[10,11] we initially examined various Bronsted acids and Lewis acids for the electrophilic trifluoromethylthiolation of allylsilanes (Table 1). (2-Phenylallyl)trimethylsilane **1a** was chosen as a model substrate, and the reaction was conducted with trifluoromethanesulfanamide **2a** as a source of the electrophilic CF_3S reagent at room temperature in dichloromethane (Table 1, entries 1−5). However, $BF_3\cdot OEt_2$ and $TsOH\cdot H_2O$, the most common Lewis acid and Bronsted acid employed for the electrophilic trifluoromethylthioltion reactions,[10b,c,11] gave the desired product **3** in 26% and 13% yield, respectively (entries 1 and 2). Both a weak acid (CH_3COOH) and strong acid (CF_3COOH) were found to be ineffective in the current reaction, leaving reagent **2a** essentially untouched (entries 3 and 4). The biggest problem is that most of the allylsilane substrate underwent desilylation under the acidic reaction conditions to give the desilylated byproduct **4a** and/or its dimers (entries 1−4). To overcome this problem, we surmised that a proper acidic initiator, which would preferentially activate

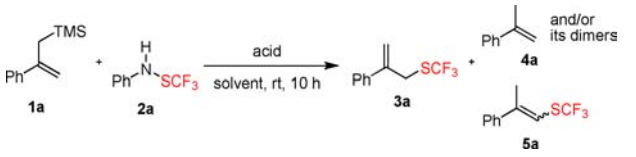
(12) (a) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004. (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford, 2006. (c) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.

(13) (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (b) Xu, J.; Fu, Y.; Luo, D. F.; Jiang, Y. Y.; Xiao, B.; Liu, Z. J.; Gong, T. J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (c) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. (d) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106.

(14) (a) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577. (b) Mizuta, S.; Galicia-López, O.; Engle, K. M.; Verhoog, S.; Wheelhouse, K.; Rassias, G.; Gouverneur, V. *Chem.—Eur. J.* **2012**, *18*, 8583.

trifluoromethanesulfanamide rather than allylsilane, should be employed.

Table 1. Optimization of the Reaction Conditions[a]



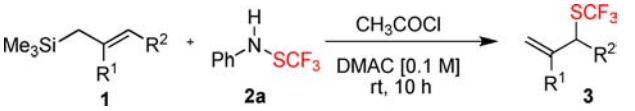
entry	Lewis acid (equiv)	solvent [0.05M]	yield of **3a** (%)[b]
1	$BF_3 \cdot Et_2O$ (5.0)	CH_2Cl_2	26
2[c]	$TsOH \cdot H_2O$ (2.4)	CH_2Cl_2	13
3	CH_3CO_2H (2.4)	CH_2Cl_2	none
4	CF_3CO_2H (2.4)	CH_2Cl_2	trace
5	CH_3COCl (2.4)	CH_2Cl_2	37
6	CH_3COCl (2.4)	CH_2Cl_2	29
7	CH_3COCl (2.4)	MeOH	25
8	CH_3COCl (2.4)	DMSO	23
9	CH_3COCl (2.4)	DMF	78
10	CH_3COCl (2.4)	DMAC	84
11[d]	CH_3COCl (2.4)	DMAC	86
12[d,e]	**CH_3COCl (2.4)**	**DMAC**	**92 (75)**[f]

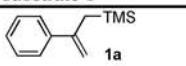
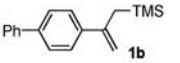
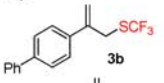
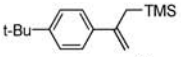
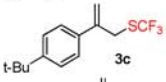
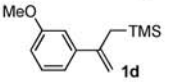
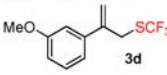
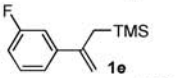
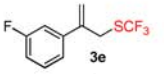
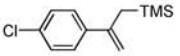
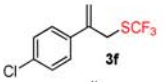
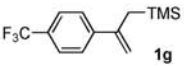
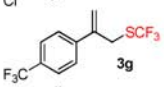
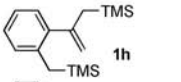
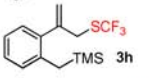
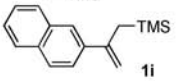
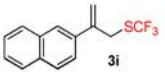
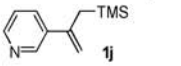
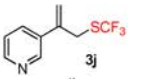
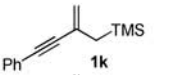
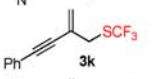
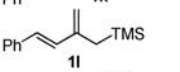
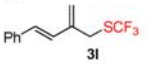
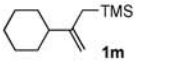
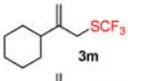
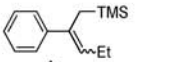
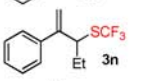
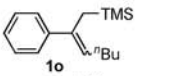
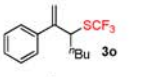
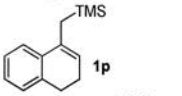
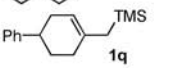
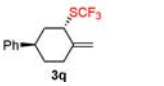
[a] Reaction conditions: **1a** (0.1 mmol), acid, **2a** (0.1 mmol, 1.0 equiv), solvent (2 mL), room temperature, 10 h. [b] Yield was determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard. [c] Reaction was conducted at 50 °C. [d] **2a** (0.12 mmol, 1.2 equiv). [e] DMAC (1 mL). [f] Isolated yield.

After surveying some other Lewis acids, we found that the trifluoromethylthiolation proceeded in the presence of CH_3COCl, affording the desired product in 37% yield as well as certain amounts of byproducts **4a** and **5a** (entry 5). Interestingly, the use of CH_3COCl as an acidic initiator in the trifluoromethylthiolation has not been reported. Based on previous studies,[10,11] we conjectured that the *in situ* generated acetylated form of reagent **2a** was the reactive intermediate in this reaction. Consistent with the hypothesis proposed by Langlois and Billar that the acid-promoted trifluoromethylthiolation reactions with trifluoromethanesulfanamides might proceed via an S_N1 pathway,[10c] we expected that the acetylated species would be more reactive to transfer the CF_3S group than its related protonated species due to the better leaving group ability of the acetanilide moiety than the aniline group. More importantly, the observation of a large amount of acetanilide implied that the reaction between CH_3COCl and trifluoromethanesulfanamide **2a** occurs faster than the one between CH_3COCl and allylsilane **1a**, providing a promising model for retarding the undesired desilylation of allylsilanes.

To improve the reaction efficiency further, various solvents were screened (entries 5–10). Gratifyingly, the use of *N*,*N*-dimethylformamide (DMF) and its analogue *N*,*N*-dimethylacetamide (DMAC) as a solvent could reduce the amount of the desilylated byproduct **4a** to less than 10% (determined by GC-MS) (entries 9 and 10). Particularly, DMAC significantly improved the yield of the trifluoromethylthiolation reaction to 84% (entry 10).

Table 2. CH_3COCl-Promoted Trifluoromethylthiolation of Allylsilanes[a]



entry	substrate **1**	product **3**	yield (%)[b]
1			75 (88)[b]
2[c]			52
3			74
4			80
5			89
6			57
7			80
8			71
9			72
10			77
11			40
12			52
13[c]			61 (52)[d]
14[e]			55
15[f]			56
16			53
17			44

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), CH_3COCl (2.4 mmol), DMAC (10 mL), rt, 10 h, isolated yields. [b] On a 10 mmol scale, isolated yield is given in parentheses. [c] At the end of reaction, CH_3COOH (0.4 equiv) and TBAF (1.0 M in THF, 4.0 equiv) were added and the resulting mixture was stirred for another 10 h at room temperature; please see Supporting Information for details. [d] Under the standard conditions, the ^{19}F NMR yield is given in parentheses. [e] **1n** used as a mixture of isomer, Z/E = 1.8:1. [f] **1o** used as a mixture of isomer, Z/E = 1.7:1.

A slightly higher yield was observed when reagent **2a** was used in excess (entry 11). Further investigation of the substrate concentration showed that the highest yield could be obtained by increasing the reaction concentration to 0.1 M (entry 12).[15]

With the optimized conditions in hand, we next investigated the substrate scope of allylsilanes (Table 2). A series of 2-substituted allylsilanes were found to undergo the desired trifluoromethylthiolation smoothly under the standard reaction conditions, affording the corresponding allylic SCF_3 products in 40−89% yields (Table 2, entries 1−11). Several functional groups, including chloro, heteroaromatic rings, trimethylsilyl, and alkynyl groups, are easily tolerated under the acidic conditions (entries 6, 8, 10−11). The position and electronic nature of the substituents on the aromatic rings have no significant influence on the reaction efficiency, and the substrates bearing electron-donating or -withdrawing substituents on the *ortho*-, *meta*-, or *para*-positions could be trifluoromethylthiolated in moderate to good yields (entries 1−8). Additionally, 2-naphtyl, 2-pyridyl, 2-phenylalkynyl, 2-styryl, and even 2-cyclohexyl substituted allylsilanes were compatible with this protocol, and all reactions occurred smoothly to give the desired products (**3i**−**3m**) in moderate yields, albeit with slightly lower yields of products **3k**, **3l**, and **3m** (entries 9−13).

Next, more substituted allylsilanes were examined to evaluate the electrophilic trifluoromethylthiolation reaction further. Both acyclic and cyclic allylsilanes bearing substituents at both the 2- and 3-position are acceptable substrates, generating the branched allylic SCF_3 compounds in 44−56% yields (entries 14−17). However, the yields of these transformations were generally lower than those of the 2-monosubstituted allylsilanes, probably due to the steric hindrance effects (Table 2). In addition, the reaction of **1a** on a 10 mmol scale also proceeded efficiently, indicating the good scalability and reliability of the transformation (entry 1). Notably, manipulation of the trifluoromethylthiolation reactions is very simple, and all reactions are carried out at room temperature on unprotected systems without the need for solvent purification (Table 2).

In conclusion, a mild and convenient method for the efficient allylic trifluoromethylthiolation of allylsilanes based on a combination of trifluoromethanesulfanamide and CH_3COCl has been developed. The utility of CH_3COCl as an acidic initiator was observed to play a pivotal role in the success of this trifluoromethylthiolation. Due to the potential utility of the resulting allylic SCF_3 compounds, the mild conditions employed, and the simple manipulation, we expect this method to be widely applied in the pharmaceutical and agrochemical fields.

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Supporting Information Available. Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) To further illustrate the important role of the pendant trimethylsilyl group, the reaction of α-methylstyrene **4a** with trifluoromethanesulfanamide **2a** was conducted under the optimal reaction conditions, while the desired product **3a** and byproduct **5a** were obtained in 9% and 8% yield (determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard), respectively.

The authors declare no competing financial interest.