A Convenient and Efficient Synthesis of Trifluoromethyl Vinyl Sulfoxide and Its Reactivity in Addition Reactions

Liubov V. Sokolenko,* Irina I. Maletina, Lev M. Yagupolskii,† Yurii L. Yagupolskii

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya Str. 5, 02094 Kiev, Ukraine
Fax +38(044)5732643; E-mail: sokolenko_liubov@mail.ru

Received 26 May 2010

Abstract: We report a novel high-yielding approach to trifluoromethyl vinyl sulfoxide from 2-mercaptoethanol and trifluoromethyl iodide. Additionally, the principal ability of this compound to react with N-, O-, and S-nucleophiles is demonstrated.

Key words: trifluoromethylation, oxidation, nucleophilic addition, bromination, vinyl sulfoxides

Perfluoroalkyl vinyl sulfoxides are promising precursors for the preparation of more complex molecules containing CF_3SO group. Double bond of such a building block is activated by fluorinated sulfoxy moiety being the strong electron acceptor.[1] It opens various ways to modification of unsaturated part of such sulfoxides. To the best of our knowledge, there are only three fluoroalkyl vinyl sulfoxides containing trifluoromethyl (**1**),[2] tridecafluorohexyl (**2**),[3a] and ethyl difluoroacetyl (**3**)[3b] groups described in the literature (Figure 1). The compound of significant interest is the simplest representative of the family – trifluoromethyl vinyl sulfoxide (**1**).

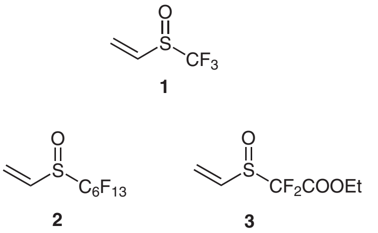


Figure 1 Three fluoroalkyl vinyl sulfoxides described in the literature

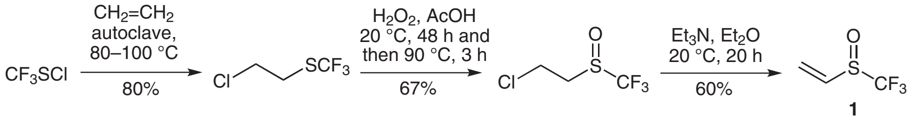
This molecule was first synthesized in our laboratory in 1967[2] as shown in Scheme 1. However, this method includes the use of the toxic trifluoromethanesulfenyl chloride and gives only 32% overall yield of compound **1**. Fluoroalkyl vinyl sulfoxides **2** and **3** were obtained by Wakselman and co-workers starting from 2-mercaptoethanol and perfluorohexyl iodide or ethyl bromodifluoroacetate.[3] It should be mentioned here that only aza-Michael reaction of compounds **2** and **3** with primary,[4] secondary,[4] and macrocyclic[5] amines was investigated.

In this letter we wish to describe the practical high-yielding preparation of trifluoromethyl vinyl sulfoxide (**1**) using readily available starting materials on each stage. Additionally, we have shown the principal ability of alkene **1** to undergo addition reactions with various nucleophilic and electrophilic agents.

The initial route towards compound **1** was chosen by analogy with Wakselman's work[3] and started from 2-mercaptoethanol (**4**) and CF_3I (Scheme 2). Nevertheless, the present method differs from previously described methodology; our strategy involves cheaper reactants (Oxone® instead of trifluoroperacetic acid and triethylamine instead of DBU) and leads to the more convenient isolation of intermediates and higher overall yield of the desired product.

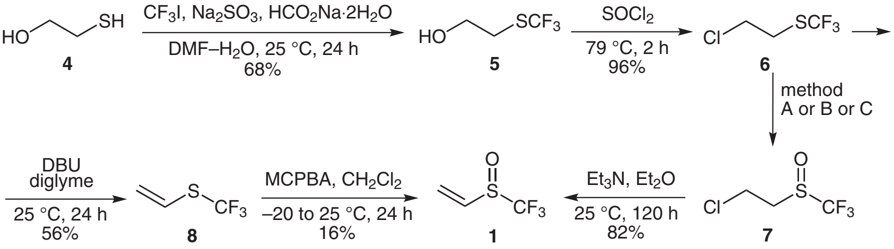
The reaction between 2-mercaptoethanol and CF_3I occurs in the presence of sodium formate/sodium sulfite mixture in DMF–water solution.[6] However, 2-mercaptoethanol does not react with CF_3Br under these conditions. Alcohol **5** was converted into chloride **6** in nearly quantitative yield by the action of sulfinyl chloride under reflux.[7] Oxidation of compound **6** proceeds under the action of MCPBA (method A), freshly prepared trifluoroperacetic acid (method B), or Oxone® (method C, Table 1).

It is noteworthy to mention that the best results were achieved with Oxone®,[8] in this case yield of sulfoxide is nearly quantitative, and product separation is easy and convenient. Trifluoromethyl vinyl sulfoxide (**1**) was prepared by elimination of HCl from the compound **7** according to the procedure described earlier,[2] but we have found that increasing of the reaction time from 20 hours to 120 hours led to significant enlargement of the desired product yield.



Scheme 1 Synthesis of trifluoromethyl vinyl sulfoxide described earlier

SYNLETT 2010, No. 14, pp 2075–2078
Advanced online publication: 22.07.2010
DOI: 10.1055/s-0030-1258515; Art ID: G13710ST



Scheme 2

Table 1 Oxidation of Sulfide **6** to Sulfoxide **7**

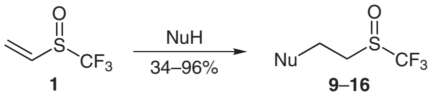
Method	Oxidant (equiv)	Solvent	Time (h)	Temp (°C)	Yield (%)
A	MCPBA (1)	CH_2Cl_2	24	0–25	70
B	CF_3CO_3H (1)	CF_3CO_2H	24	–20 to 25	76
C	Oxone® (1.5)	CH_2Cl_2–H_2O	120	25	96

DBU was also used for elimination of HCl from **7**, but in this case reaction was accompanied by substantial resinification and yield of compound **1** was only 60%. Additionally, attempt to obtain trifluoromethyl vinyl sulfoxide (**1**) by another way was undertaken. Compound **6** was converted to trifluoromethyl vinyl sulfide (**8**)[9] under the action of equivalent amount of DBU. Oxidation of sulfide **8** by MCPBA (1 equiv) leads to sulfoxide **1**.

Nevertheless, yields of compounds **8** and **1** in this strategy are low due to the low boiling point (26–27 °C)[9] of product **8** and its high volatility.

Trifluoromethyl vinyl sulfoxide (**1**) is the typical Michael acceptor in which double bond is activated by the strong electron-withdrawing substituent – the trifluoromethylsulfonyl group ($\sigma_p = 0.69$[1]). Therefore, the reactivity of this compound is of interest.

In our study we also explored ability of alkene **1** to react with different N-, O-, and S-nucleophiles. These interactions could be described by general equation shown in Scheme 3. The results are summarized in Table 2.



Scheme 3 Reactions of trifluoromethyl vinyl sulfoxide (**1**) with nucleophiles

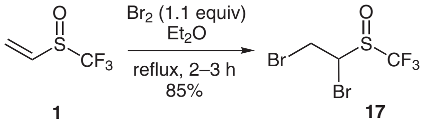
Remarkably, trifluoromethyl vinyl sulfoxide (**1**) reacts with cyclic and aliphatic amines (entries 1 and 2) readily with excellent yields. Michael adducts **9** and **10** could be isolated in a pure form after the removal of the solvent without further purification. It should be noted that in the case of (*R*)-(+)-phenylethylamine product **10** (entry 2) was obtained as a 1:1 mixture of diastereomers.

Aromatic amines (aniline and 4-fluoroaniline, entries 3 and 4) react with **1** in the presence of catalytic amounts of acetic acid under severe conditions (without solvent at heating).

We supposed that these reactions proceed as electrophilic addition initiated by protonation of the double bond of alkene **1**. Substantial polymerization is observed in these cases, and yields of products **11** and **12** are moderate.

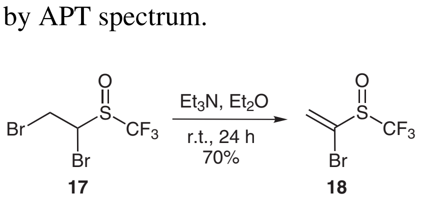
Aliphatic alcohols and mercaptanes as well as phenols and thiophenols (entries 5–8) were shown to react with alkene **1** under the basic catalysis. Sodium hydride was found to be the most suitable base in these reactions. Amount of base depends on the nature of nucleophile, and it is evident that the weaker nucleophile needs the greater quantity of NaH.

We have found that bromine addition to the compound **1** proceeds in ether solution at reflux (Scheme 4). The product of this interaction **17** was obtained as mixture of diastereomers in a ratio of 3:1.



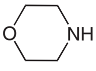
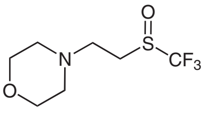
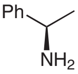
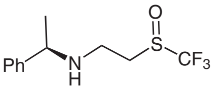
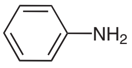
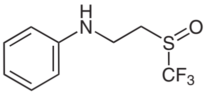
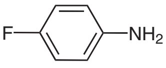
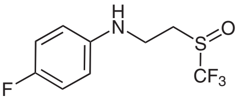
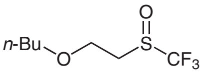
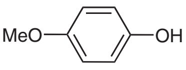
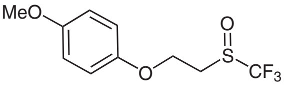
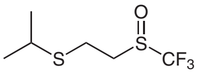
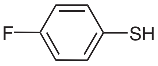
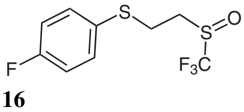
Scheme 4

Elimination of HBr from **17** occurs easily in the presence of triethylamine and leads to the alkene **18** in good yield (Scheme 5). The structure of compound **18** was confirmed by APT spectrum.



Scheme 5

Table 2 Reactions of Trifluoromethyl Vinyl Sulfoxide **1** with Nucleophiles

Entry	Nucleophile (equiv)	Cat. (mol%)	Solvent	Time (h)	Temp (°C)	Product	Mp (°C)	Bp (°C) (bar)	Yield (%)
1	 (1)	–	Et_2O	24	r.t.	 **9**	23–24	75–78 ($6.7 \cdot 10^{-5}$)	97 (91)[a]
2	 (1)	–	Et_2O	24	r.t.	 **10**	oil	–	96
3	 (1)	AcOH (10)	–	3	120–140	 **11**	126–127	–	48
4	 (1)	AcOH (10)	–	3	110	 **12**	110–111	–	34
5	*n*-BuOH (1)	NaH (2.5)	–	0.5	r.t.	 **13**	–	96 ($1.3 \cdot 10^{-2}$)	50
6	 (1)	NaH (5)	–	3	100–110	 **14**	61–62	–	55
7	*i*-PrSH (1)	NaH (0.5)	–	0.5	r.t.	 **15**	–	70 ($1.3 \cdot 10^{-2}$)	76
8	 (1)	NaH (0.5)	Et_2O	24	r.t.	 **16**	oil	–	70

[a] Yield of **9** after distillation.

In summary, we have reported a convenient and efficient synthesis of trifluoromethyl vinyl sulfoxide (**1**) in four steps (51% overall yield) from commercial starting materials. Furthermore, the conditions for interaction of this alkene with different nucleophiles and electrophiles were found. A series of compounds containing the (trifluoromethylsulfinyl)ethyl moiety was synthesized. Further studies on the reactivity of trifluoromethyl vinyl sulfoxide are currently in progress.

References and Notes

(1) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(2) Knunyants, I. N.; Rozhkov, I. N.; Alexandrov, A. M.; Yagupolskii, L. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1967**, *37*, 1210.

(3) (a) Magnier, E.; Tordeux, M.; Goumont, R.; Magder, K.; Wakselman, C. *J. Fluorine Chem.* **2003**, *124*, 55.
(b) Moïse, J.; Goumont, R.; Magnier, E.; Wakselman, C. *Synthesis* **2004**, 2297.

(4) Magnier-Bouvier, C.; Blazejewski, J.-C.; Larpent, C.; Magnier, E. *Tetrahedron Lett.* **2006**, *47*, 9121.

(5) de Castries, A.; Magnier, E.; Monmotton, S.; Fensterbank, H.; Larpent, C. *Eur. J. Org. Chem.* **2006**, 4685.

(6) **2-[(Trifluoromethyl)thio]ethanol (5)**
Reaction was carried out in the three-neck flask equipped by condenser (–80 °C), mechanical stirrer, and bubbler. To the stirred suspension of sodium sulfite (113.5 g, 0.9 mol) and sodium formate (93.6 g, 0.9 mol) in DMF–H_2O (600 mL:180 mL) mixture mercaptoethanol (70 g, 0.9 mol) in DMF (100 mL) was added in a single portion at 0 °C under argon. CF_3I (216 g, 1.1 mol) was bubbled into the reaction mixture for 2–3 h at r.t. After stirring at r.t. for 24 h the solution was poured into H_2O (300 mL). Product was extracted by Et_2O (5 × 300 mL), organic layer was washed by diluted HCl (3 × 50 mL), H_2O (5 × 200 mL) and dried ($MgSO_4$). Solvent was removed by distillation at atmospheric pressure, and product was purified by distillation. Yield 90 g, 68%; bp 124–126 °C. ^1H NMR (299.5 MHz, DMSO-d_6): $\delta = 3.06$ (t, $^3J = 6.2$ Hz, 2 H, CH_2), 3.64 (t, $^3J = 6.2$ Hz, 2 H, CH_2), 5.01–5.35 (br s, 1 H, OH). ^{19}F NMR (282.2 MHz, DMSO-d_6): $\delta = -39.96$ (s,

SCF_3). Anal. Calcd for $C_3H_5F_3OS$: C, 24.66; H, 3.45; S, 21.94. Found: C, 24.87; H, 3.40; S, 22.03.

(7) **2-Chloroethyl Trifluoromethyl Sulfide (6)**
$SOCl_2$ (25 mL, 0.33 mol) was added dropwise to the alcohol **5** (45 g, 0.31 mol) at 0 °C over 30 min. The reaction mixture was stirred under reflux for 2 h. After cooling to r.t. H_2O (0.3 mL), followed by K_2CO_3 (2 g), was added, and the resulting mixture was allowed to stand overnight. Product **6** was purified by vacuum distillation ($6.7 \cdot 10^{-5}$ bar) over K_2CO_3 into cooled trap and following distillation at atmospheric pressure. Yield 49 g, 96%; bp 94–96 °C. ^1H NMR (299.5 MHz, $CDCl_3$): $\delta = 3.21$ (t, $^3J = 7.5$ Hz, 2 H, CH_2), 3.72 (t, $^3J = 7.5$ Hz, 2 H, CH_2). ^{19}F NMR (282.2 MHz, DMSO-d_6): $\delta = -41.38$ (s, SCF_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 31.8$ (q, $^3J_{CF} = 2.5$ Hz, α-CH_2), 42.2 (s, β-CH_2), 130.7 (q, $^1J_{CF} = 306.9$ Hz, CF_3).

(8) **Oxidation of Sulfide 6 to Sulfoxide 7 Using Oxone®**
To the stirred mixture (mechanical stirrer) of SiO_2 (340 g) and H_2O (135 mL) Oxone® (125 g, 0.41 mol of $KHSO_5$) and a solution of sulfide **6** (45 g, 0.27 mol) in CH_2Cl_2 (700 mL) were added in a single portion. The reaction mixture was stirred at r.t. for 120 h (monitoring by ^{19}F NMR). Silica gel was filtered off and washed with CH_2Cl_2 (ca 300 mL). The organic layer was washed with a $FeSO_4$ solution, dried ($MgSO_4$), and filtered. Solvent was removed at atmospheric pressure, and product was purified by distillation. Yield 47 g, 96%; bp 64 °C ($9.3 \cdot 10^{-3}$ bar). ^1H NMR (299.5 MHz, $CDCl_3$): $\delta = 3.17$–3.27 (m, 1 H, CH_2), 3.44–3.51 (m, 1 H, CH_2), 3.88–4.06 (m, 2 H, CH_2). ^{19}F NMR (282.2 MHz, $CDCl_3$): $\delta = -74.15$ (s, $SOCF_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 35.5$ (s, β-CH_2), 51.4 (q, $^3J_{CF} = 2.5$ Hz, α-CH_2), 125.4 (q, $^1J_{CF} = 333.3$ Hz, CF_3).

(9) Harris, J. F. Jr. *J. Org. Chem.* **1967**, *32*, 2063.