A New Simple Access to Trifluoromethyl Thioethers or Selenoethers from Trifluoromethyl Trimethylsilane and Disulfides or Diselenides
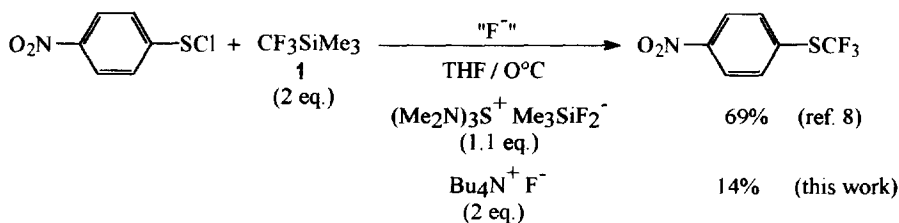
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Abstract : Trifluoromethyl thioethers (or selenoethers) are easily obtained in one pot at 0°C from disulfides (or diselenides), commercial trifluoromethyl trimethyl silane and TBAF.
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As the most lipophilic substituent known at the moment ($\Pi_R = 1.44$),[1] the trifluoromethylthio group is more and more involved in the conception of biologically-active compounds, both in pharmaceutical[2] and agrochemical[3] fields. For example, original action modes have been described for new insecticides, like Fripronil,[4] bearing the CF_3S moiety. Numerous methods, recently reviewed,[5] have been reported to introduce it on organic substrates. However, if some of them are of huge value on the industrial scale, most of these techniques are somewhat difficult to carry out on the laboratory scale since they involve sophisticated, corrosive or toxic reagents. On the other hand, bromotrifluoromethane, which has been extensively studied for the preparation of aromatic trifluoromethyl sulfides,[6] needs a pressure apparatus and sodium trifluoromethane-sulfinate[7] is not yet commercially available.

Recently, a new preparation of aryl trifluoromethyl thioethers have been described from sulfenyl chlorides and trifluoromethyl trimethylsilane (CF_3SiMe_3, **1**), in the presence of tris-dimethylaminosulfonium difluorotrimethylsilicate [TASF: $(Me_2N)_3S^+$ $Me_3SiF_2^-$] as anhydrous source of fluoride anions.[8] **1**, commercially available now, is a very useful formal source of trifluoromethyl anions, able to add on C=O, N=O and S=O functions or to substitute organic halides.[9] However, the Yagupolskii's method[8] suffers from two drawbacks. First, few sulfenyl halides are commercially available and, if aromatic sulfenyl chlorides can be obtained rather easily from thiophenols,[10] aliphatic ones are more difficult to prepare from disulfides.[10,11] Secondly, we observed that TASF is probably the only source of fluoride suitable in this process, since, in our hands, 4-nitrophenyl trifluoromethyl sulfide was obtained in a disapointing yield from **1** and the corresponding sulfenyl chloride when TASF was replaced by very cheaper tetrabutylammonium fluoride (TBAF), which is the most usual fluoride used to activate **1**.[9] This yield (14%) was not improved by increasing the amounts of **1** and TBAF or by introducing the commercial solution of TBAF (in THF) with a syringe-pump. The difference in water content for the two fluorides (anhydrous TASF vs. hydrated commercial TBAF (Bu_4N^+ F^-, 3 H_2O)) could explain these results : first, sulfenyl chlorides are known to be sensitive to hydrolysis and, secondly, the nucleophilicity of water is enhanced by hydrogen bonding with the fluoride anion.[12]

$$O_2N\text{—}\langle\text{—}\rangle\text{—SCl} + \underset{\underset{\text{(2 eq.)}}{\textbf{1}}}{CF_3SiMe_3} \xrightarrow[\text{THF / 0°C}]{\text{"F}^-\text{"}} O_2N\text{—}\langle\text{—}\rangle\text{—SCF}_3$$

$$\underset{\text{(1.1 eq.)}}{(Me_2N)_3S^+\ Me_3SiF_2^-} \qquad 69\% \quad (\text{ref. 8})$$

$$\underset{\text{(2 eq.)}}{Bu_4N^+\ F^-} \qquad 14\% \quad (\text{this work})$$

Generally, sulfenyl chlorides are prepared from disulfides but it is known that, in some cases, the latter substrates can also behave as electrophiles. Thus, we examined the behaviour of disulfides towards **1** in the presence of TBAF. Indeed, in such conditions, trifluoromethyl thioethers were obtained in fair to good yields. The influence of the different parameters and the optimization of the yield were studied first with di-n-octyl disulfide as model substrate (Table 1).
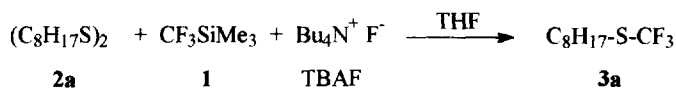
$$\underset{\textbf{2a}}{(C_8H_{17}S)_2} + \underset{\textbf{1}}{CF_3SiMe_3} + \underset{\text{TBAF}}{Bu_4N^+\ F^-} \xrightarrow{\text{THF}} \underset{\textbf{3a}}{C_8H_{17}\text{-S-CF}_3}$$

Table 1 : Formation of n-octyl trifluoromethyl sulfide from **1** and di-n-octyl disulfide.

Entry	1 (eq.)	TBAF (eq.)	TBAF dropping [a]	Temp. (°C)	Yield 3a [b] (%)
1	1	1	A	20	18
2	1	1	A	0	36
3	1	1	B	0	60
4	1	2	A	0	50
5	2	2	A	0	70
6	2	2	B	0	96
7	2	1	B	0	90
8	2	0.5	B	0	75

[a] **method A** : by the mean of a dropping funnel; **method B** : by the mean of a syringe-pump.
[b] from ^{19}F NMR analysis with $PhOCF_3$ as internal standard.

Table 1 shows that the reaction must be performed around 0°C (entries1,2), TBAF being advantageously introduced very slowly by the mean of a syringe-pump. Best results were obtained with the following reagent ratio : 1/TBAF/RSSR = 2/2/1. However, the excess of **1** seemed to be more crucial than the excess of TBAF (entries 3, 6, 7). It must be also noted that, even with 0.5 equivalent of TBAF (entry 8), the yield of n-octyl trifluoromethyl thioether exceeded 50%. That means that by-produced thiolate was also able to react, to some extend, with **1** to generate $^-CF_3$ anions. Thus, by analogy with the mechanism given for the

addition of **1** to carbonyl compounds,[9] the reaction of **1** with disulfides can be rationnalized in the following way.

$$CF_3SiMe_3 + F^- \longrightarrow {}^-CF_3 + Me_3SiF$$

$${}^-CF_3 + RS\text{-}SR \longrightarrow RS\text{-}CF_3 + RS^-$$

$$RS^- + CF_3SiMe_3 \xrightarrow{\text{partially}} {}^-CF_3 + RS\text{-}SiMe_3$$
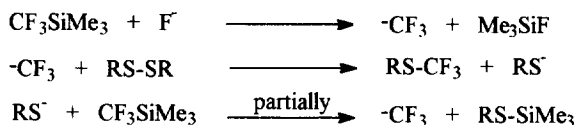
The standard conditions[13] have been then applied to the preparation of alkyl and aryl trifluoromethyl thioethers. Morever, the same technique allowed the synthesis of phenyl trifluoromethyl selenoether from diphenyl diselenide (Table 2). Though delivering a medium yield of phenyl trifluoromethyl selenoether, this process is the first one to provide this compound so simply, avoiding the use of specific and toxic reagents like CF_3SeCu[14] or CF_3SeCl.[15]
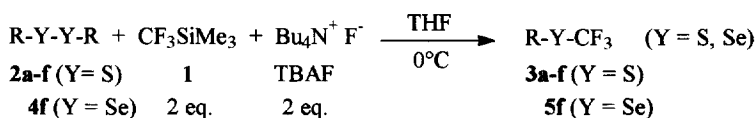
$$R\text{-}Y\text{-}Y\text{-}R + CF_3SiMe_3 + Bu_4N^+F^- \xrightarrow[0°C]{THF} R\text{-}Y\text{-}CF_3 \quad (Y = S, Se)$$

| **2a-f** (Y= S) | **1** | TBAF | | **3a-f** (Y = S) |
| **4f** (Y = Se) | 2 eq. | 2 eq. | | **5f** (Y = Se) |

Table 2 : Preparation of trifluoromethyl thio- and seleno- ethers from **1**.

Substrate			Product		
Compound	R	Y	Compound	Crude yield [a] (%)	Isolated yield (%)
2a	$n\text{-}C_8H_{17}$	S	**3a**	96	80
2b	CH_3	S	**3b**	47 [b]	-
2c	$c\text{-}C_6H_{11}$	S	**3c**	51	46
2d	$t\text{-}C_4H_9$	S	**3d**	4	-
2e	$C_6H_5CH_2$	S	**3e**	79	70
2f	C_6H_5	S	**3f**	32	25
4f	C_6H_5	Se	**5f**	43	40

[a] From ^{19}F NMR with internal standard ($PhOCF_3$)
[b] This very volatile product was probably present in higher yields before work-up.

Table 2 shows that the reaction is very sensitive to steric hindrance. The reactivity of disulfides is in the order : primary > secondary >> tertiary.

This process is also sensitive to the polarizability of the S-S bond which is connected to the electron density around sulfur atoms. For example, diphenyl disulfide **2f**, in which sulfur p-electrons are conjugated with ring Π-electrons, is less reactive than aliphatic disulfides. In the same way, diphenyl diselenide **4f**, which is less conjugated than **2f** (4p-2p orbital overlap is less efficient than 3p-2p one), is more reactive than **2f**.

In conclusion, trifluoromethyl thioethers, even volatile ones, are rapidly obtained, in one pot under mild conditions, from disulfides, trifluoromethyl trimethylsilane 1 and cheap tetrabutylammonium fluoride. They are isolated very easily. Moreover, trifluoromethyl selenoethers can be prepared from dilesenides by the same simple process which will probably favour, in a soon future, the study of such relatively unknown products.

References and notes

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13. To an ice-cooled solution of **2a-f** or **4f** (around 1 mmol) and **1** (2 eq.) in anhydrous THF (about 1 ml), maintained under nitrogen, was dropped, with a syringe-pump (1 ml/h), 2 eq. of TBAF (as 1M solution in THF). The reaction was monitored by GPC and ^{19}F NMR (δ (CDCl$_3$, CFCl$_3$) : around -41 ppm (CF$_3$S) or -36 ppm (CF$_3$Se)). After stirring 1 hour at r.t., the crude mixture was deposited at the top of a column filled with silica (Geduran SI60) then eluted with petroleum ether.
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