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Preparation of Trifluoromethyl Sulfides or Selenides from Trifluoromethyl Trimethylsilane and Thiocyanates or Selenocyanates

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Abstract : Trifluoromethyl sulfides (or selenides) are easily obtained in one pot at 0°C from thiocyanates (or selenocyanates), commercial trifluoromethyl trimethylsilane and catalytic amounts of tetrabutylammonium fluoride (TBAF). Copyright © 1996 Elsevier Science Ltd

The biological importance of products bearing the very lipophilic CF_3S substituent (Π_R = 1.44),[1] has initiated a very active search for the synthesis of such compounds,[2] especially by direct introduction of trifluoromethyl moieties on sulfur-containing substrates. If the trifluoromethylation of thiols[3] or disulfides[4] with bromotrifluoromethane is probably the simplest, safest and cheapest route to trifluoromethyl sulfides on a large scale, the gaseous nature of CF_3Br can impede the rapid preparation of these products for screening purposes on the laboratory scale. On the other hand, though it can be suspected that trifluoromethyl selenides are more lipophilic than trifluoromethyl sulfides, the synthesis of such compounds is hardly documented at the moment : most of the related papers report tedious trifluoromethylations of oxygen-sensitive selenolates (generated *in situ*)[5] or rather unstable selenenyl chlorides.[6] Thus, new rapid and general routes to trifluoromethyl chalcogenoethers are still needed.

Very recently, we have described a one-pot access to trifluoromethyl sulfides (or selenides) from disulfides (or diselenides), 2 equivalents of commercial trifluoromethyl trimethylsilane (CF_3SiMe_3, **1**) and 2 equivalents of tetrabutylammonium fluoride (TBAF).[7] However, this technique suffers from the use of an excess of TBAF (which can behave as an undesirable base or nucleophile) and, more important, from the fact that only one thiyl (or selenenyl) moiety of the disulfide (or deselenide) leads to the desired compound, the second one being lost as thiolate (or selenolate), which must be oxidized before recycling. On the other hand, if alkyl disulfides provide trifluoromethyl sulfides in fair to good yields by this technique, the results are more disappointing with less reactive ones, like diphenyl disulfide. Thus, we focused our attention on more electrophilic substrates bearing only one sulfur (or selenium) atom attached to a small and good leaving group. Organic thiocyanates (or selenocyanates) fulfil these requirements. A very recent patent[8] mentioned the preparation of only one aryl trifluoromethyl selenide (2-(trifluoromethylseleno)biphenyl, used for the preparation of electrophilic trifluoromethylating reagents), from the corresponding selenocyanate, CF_3SiMe_3

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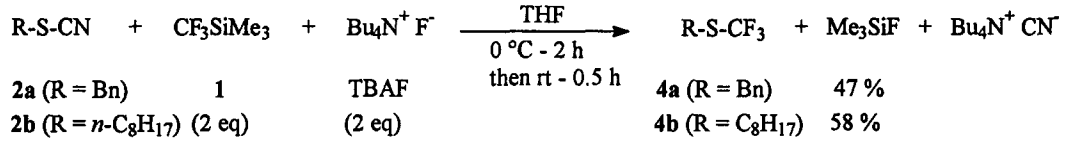
(1) and rather large quantities of fluoride anions. This little documented publication prompted us to report here our own simultaneous and independent results concerning a similar, but general, route to trifluoromethyl sulfides, as well as selenides, from thiocyanates (or selenocyanates), **1** and TBAF.

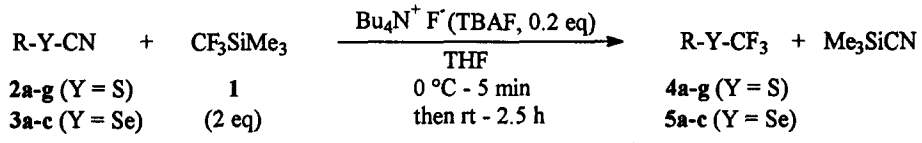
Following the procedure used for the treatment of disulfides with **1**,[7] we first dropped, by means of a syringe-pump, 2 equiv of TBAF (as 1M solution in THF) onto a ice-cooled solution of **1** (2 equiv) and benzyl thiocyanate **2a** (or *n*-octyl thiocyanate **2b**) in anhydrous THF (1 mL/1 mmol RSCN). The corresponding trifluoromethyl sulfides were obtained in moderate yields only (Scheme 1).



Scheme 1

The rather disappointing yield obtained from benzyl thiocyanate (compared to that delivered by dibenzyl disulfide)[7], led us to consider that benzyl trifluoromethyl sulfide could be sensitive to large concentrations of cyanide anion. Consequently, a catalytic amount of TBAF (0.2 equiv) was added to an ice-cooled solution of **2a** (or **2b**) and **1** in THF. The resulting mixture was first stirred at 0 °C for 5 min, then at room temperature for 2.5 h. As expected, the corresponding trifluoromethyl sulfides were obtained in much higher yields (87 % and 76 %, resp.).

This optimized technique has been applied to the preparation of other trifluoromethyl sulfides and selenides from the corresponding thiocyanates and selenocyanates (Scheme 2).[9]



Scheme 2

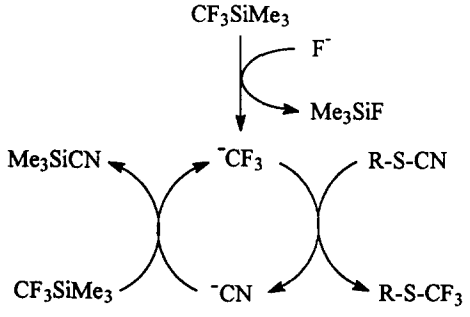
As reported in Table 1, good yields were obtained from primary or benzylic thiocyanates (entries 1,2) and selenocyanates (entries 8,9). Secondary thiocyanates (entry 7) are a little bit more sensitive to steric hindrance than disulfides concerning their reaction with **1**. However, phenyl thiocyanate (entry 3) and selenocyanate (entry 10) gave far better yields than the corresponding disulfide and diselenide when opposed to **1** (cf. ref. 7 for comparison). This situation reflects the fact that the sulfur p-electrons are less conjugated with aromatic systems in thiocyanates than in disulfides. Nevertheless, the influence of substituents on the aromatic nucleus is not completely clear at the moment. Preliminary observations led us to consider that side-reactions of **2d** (entry 4) and **2f** (entry 6) with fluoride as well as steric effect of *ortho*-substituents (entry 5) could be responsible for the lower yields of **4d-f**.

Entry	Substrate			Product			
	Compd	R	Y	Compd	Yield (%)	^{19}F NMR δ (ppm)[a]	^{13}C NMR $^{3}J_{CF}$ (Hz)[b]
1	**2a**	$PhCH_2$	S	**4a**	87	- 42.15	2.30
2	**2b**	*n*-C_8H_{17}	S	**4b**	76	- 41.73	1.97
3	**2c**	Ph	S	**4c**	70	- 43.37	2.10
4	**2d**	4-O_2N-C_6H_4	S	**4d**	58	- 41.81	2.10
5	**2e**	2,4-$(MeO)_2C_6H_4$	S	**4e**	30	- 44.15	1.50
6	**2f**	1-Me-2-pyrolyl	S	**4f**	32	- 46.01	-
7	**2g**	*c*-C_6H_{11}	S	**4g**	33	- 39.60	1.50
8	**3a**	$PhCH_2$	Se	**5a**	70	- 35.00	1.70
9	**3b**	n-C_8H_{17}	Se	**5b**	75	- 34.68	1.38
10	**3c**	Ph	Se	**5c**	58	- 36.60	1.50

a) 188 MHz - solv. : $CDCl_3$ - Ref. : $CFCl_3$ b) for C-Y-CF_3 at 75 MHz in $CDCl_3$

Table 1 : Preparation of trifluoromethyl sulfides and selenides from **1** and thiocyanates or selenocyanates

Owing to the fact that fluoride can be used in catalytic amounts, we assume that CN^- forms stronger bonds than $^-CF_3$ with silicon and is able to generate a trifluoromethyl anion from **1**. Thus, the following mechanism could be proposed :



In conclusion, alkyl and aryl trifluoromethyl sulfides or selenides are easily obtained, in one step under very mild conditions, from the corresponding thiocyanates or selenocyanates, trifluoromethyl trimethylsilane and catalytic amounts of tetrabutylammonium fluoride. This reaction is often more attractive than the similar one performed with disulfides or diselenides[7] since :

- yields are generally higher, especially in the aromatic series,
- fluoride is used only as catalyst,
- as cyanide is by-produced instead of thiolate, this process respects the "atom economy" concept to a larger extend and can be applied to more sophisticated substrates,
- organic thiocyanates and selenocyanates are easily prepared from inorganic thiocyanates or selenocyanates, either through nucleophilic or electrophilic processes.[10]

Such a technique allowed us to prepare aliphatic trifluoromethyl selenides which were until now unknown.

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