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New stable reagents for the nucleophilic trifluoromethylation. Part 4: Trifluoromethylation of disulfides and diselenides with hemiaminals of trifluoroacetaldehyde

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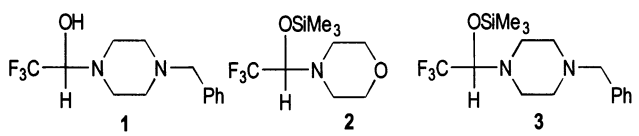
Abstract—Hemiaminals of fluoral and derivatives have been previously described as efficient new reagents for the nucleophilic trifluoromethylation of carbonyl compounds. Their use has been extended to the synthesis of trifluoromethyl sulfides and selenides from disulfides and diselenides. © 2001 Elsevier Science Ltd. All rights reserved.

The trifluoromethylthio moiety is one of the most hydrophobic groups[1] and, thereby, compounds bearing it are potentially important targets in the pharmaceutical and agrochemical fields.[2]

Numerous methods are now available to introduce this function on organic substrates but essentially in the aromatic series.[3] Its introduction on aliphatic compounds has been less described and generally occurs through radical processes.[4] Very few nucleophilic trifluoromethylations around a sulfur atom have been reported,[5] except a convenient synthesis of trifluoromethyl sulfides that we developed from disulfides or thiocyanates and Ruppert's reagent (CF_3SiMe_3).[6] Nevertheless, the use of CF_3SiMe_3, prepared from ecotoxic CF_3Br,[7] does not allow this reaction to be carried out on a large scale.

On the other hand, we recently described the synthesis and use of hemiaminals of fluoral **1**[10], **2**,[8] and **3**,[9] which are efficient trifluoromethylating agents for non-enolizable carbonyl compounds (Scheme 1).

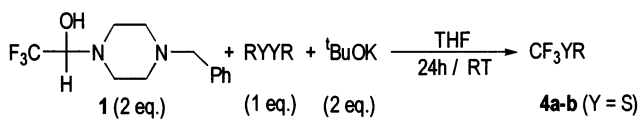


Scheme 1. Hemiaminals of fluoral and derivatives.

These new reagents are easily prepared from fluoroform or fluoral, which are environmentally benign. Continuing our exploration of this new family of promising reagents, we presently report on their reactivity towards disulfides and diselenides, which allows the synthesis of trifluoromethylchalcogeno ethers.

Our work began with hemiaminal **1**, which can be easily obtained from fluoral methyl hemiketal, even in large quantities[10] (Table 1).

Table 1. Reactivity of **1** toward disulfides and diselenides



Entry	RYYR	**4** or **5** (%)[a]
1	PhSSPh	70 (87) **4a**
2	$(p\text{-Cl-PhS})_2$	?[b]
3	$(n\text{-}C_8H_{17}S)_2$	(5) **4b**
4	PhSeSePh	35 (45) **5a**

[a] Isolated yield. In parentheses: crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$).

[b] ^{19}F NMR ($CDCl_3$ versus $CFCl_3$): $\delta = -69.56$ (d, $J = 7.5$ Hz).

Keywords: trifluoromethylation; hemiaminal; trifluoroacetaldehyde; trifluoromethyl sulfides; trifluoromethyl selenides.

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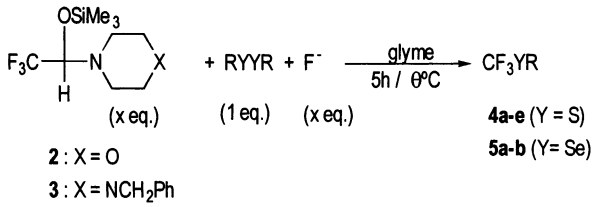
Table 2. Reactivity of **2** or **3** toward disulfides and diselenides



Entry	RYYR	**2** or **3** (x equiv.)	F^-	θ (°C)	**4** or **5** (%)[a]
1	PhSSPh	**2** (2)	CsF	80	(50) **4a**
2	PhSSPh	**2** (2)	TBAT[b]	80	70 (90) **4a**
3	(c-$C_6H_{11}S)_2$	**2** (2)	TBAT	80	82 (90) **4c**
4	PhSSPh	**3** (1)	TBAT	60	(43) **4a**
5	PhSSPh	**3** (2)	TBAT	60	69 (78) **4a**
6	PhSSPh	**3** (2)	TBAT	80	(95) **4a**
7	(c-$C_6H_{11}S)_2$	**3** (1)	TBAT	60	(54) **4c**
8	(c-$C_6H_{11}S)_2$	**3** (2)	TBAT	60	70 (75) **4c**
9	(n-$C_8H_{17}S)_2$	**3** (2)	TBAT	80	87 (97) **4b**
10	(*tert*-BuS)$_2$	**3** (2)	TBAT	80	(5) **4d**
11	(p-Cl-PhS)$_2$	**3** (2)	TBAT	80	86 (95) **4e**
12	PhSeSePh	**3** (2)	TBAT	80	80 (92) **5a**
13	(p-Cl-PhSe)$_2$	**3** (2)	TBAT	80	80 (75) **5b**

[a] Isolated yield. In parentheses: crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$).
[b] TBAT: tetrabutylammonium triphenyldifluorosilicate (De Shong's reagent).

Although the result was satisfactory with diphenyl disulfide (entry 1), it was very disappointing with dioctyl disulfide (entry 3). This low yield could be explained by an α-deprotonation of the disulfide by the basic system, which strongly competed with trifluoromethylation. When di(4-chorophenyl)disulfide was used as substrate, only 35% of an undetermined product was obtained (entry 2). This compound was too unstable to be isolated and characterized.

Because of these limited results, we focused our interest on silylated reagents **2** and **3** (Table 2).

By analogy with our previous studies on the reaction of CF_3SiMe_3 with disulfides, we used a stoichiometric amount of fluoride ions (versus RSSR).[6] The low solubility of CsF in 1,2-dimethoxyethane (glyme) allowed us to obtain medium yields only (entry 1) whereas the soluble, and commercially available, De Shong's fluoride[11] (TBAT: $(Ph_3SiF_2)^-Bu_4N^+$) provided a good result (entry 2).

As with CF_3SiMe_3,[6] the morpholino derivative **2** gave good results when 2 equiv. were used (entries 2 and 3).

We have previously shown that the *N*-benzylpiperazino derivative **3** is more efficient than **2**.[9] Thus, **3** was also opposed to disulfides. Table 2 indicates that medium yields were obtained with 1 equiv. of **3** whereas good yields were reached with 2 equiv. (entries 4–5 and 7–8). Also, the same temperature was required to get similar yields from **2** and **3** (entries 5 and 6). Thus, in contrast with the reaction on ketones, **2** and **3** exhibited the same reactivity towards disulfides. This fact could be explained by the low electrophilicity of disulfides compared to that of carbonyl compounds.

Finally, the optimal results were obtained with 2 equiv. of **2** or **3** and 2 equiv. of TBAT, the reaction being carried out at 80°C for 5 h.[12]

This reaction allows the preparation of trifluoromethyl sulfides in high yields either in the aromatic or the aliphatic series (Table 2). The low yield obtained from di(*tert*-butyl) disulfide can be rationalized by a high steric hindrance around the sulfur atom.

Trifluoromethyl selenides, which are quite unknown compounds, can be also synthesized very easily by this way (entries 12 and 13).

In conclusion, we have demonstrated that hemiaminals of fluoral, which constitute a new family of trifluoromethylating agents, can be also used for the synthesis of trifluoromethylchalcogenides from dichalcogenides. Others investigations on the scope and limitations of these new reagents are currently under study in our laboratory.

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12. *Typical procedure*: TBAT (2 mmol) was added to a solution of **2** or **3** (2 mmol) and disulfide or diselenide (1 mmol) in 2 mL of 1,2-dimethoxyethane (glyme). The mixture was heated at 80°C for 5 h, and then, after cooling, was treated twice with pentane and 6% aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, evaporated and then purified by flash chromatography with pentane as eluent.