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Direct Perfluoroalkylthiolation of Few Chalcogenols

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Trifluoromethanesulfenamide reagent can react with alcohols, in basic conditions, or with thiols, in catalytic acid conditions, to afford the corresponding trifluoromethanesulfenates or trifluoromethyldisulfides. The use of higher homologs of this reagent leads to synthesis of the nearly unknown perfluoroalkanesulfenates and perfluoroalkyldisulfides.

Keywords perfluoroalkylthiolation, perfluoroalkyldisulfide, perfluoroalkanesulfenate, trifluoromethylthiolation, trifluoromethanesulfenamide

Introduction

Since the elementary fluorine isolation by Moissan,[1] the development of fluorine chemistry has considerably grown.[2] Such an interest is essentially due to the exceptional properties of fluorinated compounds.[2b,2c,3] From materials to life sciences, all the fields of applications are impacted by fluorine characteristics.[3c,4]

Modulation of molecules properties for various utilizations can be achieved by introducing diverse fluorinated substituents. Among all fluorinated groups, the association of a CF_3 part with sulfur atom is of particular interest.[5] Thus, the high lipophilicity induced by the CF_3S group (Hansch parameter $\pi_R = 1.44$)[6] can contribute to favor transmembrane permeation of CF_3S-substituted molecules, which, consequently, present an improved bioavailability.[7] Furthermore, higher perfluorinated groups can also present interesting properties,[8] as illustrated by Fulvestrant, an estrogen receptor antagonist used in treatment of hormone receptor-positive metastatic breast cancer.[9]

Consequently, the association of fluoroalkyl groups with several heteroatoms could contribute to expand the molecules properties modulations. Such a concept has been already validated by designing the CF_3SN group which presents a higher lipophilicity than CF_3S.[10] Therefore, because of specific properties of chalcogens such as oxygen or sulfur,[11] fluoroalkylsulfenates (R_FSO) and fluoroalkyldisulfides (R_FSS) substituents could bring interesting new properties.

To this day, only a few methods to obtain compounds bearing these substituents have been described, and almost mainly in CF_3 series. Trifluoromethyldisulfides can be synthetized by reaction of organolithium reagents with non-commercially available bis(trifluoromethyl) trisulfide.[12] Direct trifluoromethylthiolations of thiols have been also described with CF_3SCl[13] or a CF_3S-pyrrole derivative[14] (arising from CF_3SCl). Alternatives to these previous toxic reagents[15] have been more recently developed by employing other electrophilic reagents such as *N*-trifluoromethylthiophthalimide,[16] *N*-trifluoromethylthiosaccharin[17] or the 1st generation of trifluoromethanesulfenamide.[18]

Trifluoromethanesulfenates have been less studied and only CF_3SCl,[19] the CF_3S-pyrrole derivative[14] and *N*-trifluoromethylthiosaccharin[17,20] have been able to react with alcohols. A specific rearrangement of hypervalent species could also lead to few trifluoromethanesulfenates.[21]

If trifluoromethylthiochalcogenides have been still little described, the fluoroalkyl versions descriptions are still more sporadic. Some difluoromethyldisulfides have been obtained with *N*-difluoromethylthiosaccharin reagent[22] and the methyl heptafluoroisopropylsulfenate has been described from heptafluoroisopropylsulfenyl chloride.[19]

Trifluoromethanesulfenamides constitute an efficient family of shelf-stable reagents (**BB** reagents-Figure 1), easy to obtain in multigram scale at low cost (up to 100 g at 15 €/g), to perform various trifluoromethylthiolation reactions.[23] Furthermore, higher homologs of these reagents have been also described.[24] Therefore, the reactivity of fluoroalkylsulfenamides with chalcogenols has been studied to easily access fluoroalkylthiochalcogenides.

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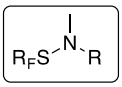


$R_F = CF_3$: **BBx3** R = Ph : **BB1x**
$R_F = CF_2CF_3$: **BBx5** R = Ts : **BB2x**
$R_F = CF_2CF_2CF_3$: **BBx7**

Figure 1 **BB** reagents.

Experimental

General procedure for the perfluoroalkylthiolation of thiols

To a tube equipped with a magnetic stirrer were added thiols **1** (0.50 mmol, 1.0 equiv.), dry DCM (1 mL) and **BB2x** (0.6 mmol, 1.2 equiv.). The reaction mixture was stirred for 1 min followed by the addition of TfOH (0.1 mmol, 20 mol%). The reaction mixture was stirred at 40 ℃ for 15 h. Conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was partitioned between DCM and water. The aqueous layer was extracted with DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness (under moderate vacuum: 400 mbar at 25 ℃). The crude residue was purified by flash chromatography to afford the desired product **2** (or **3** or **4**).

General procedure for the perfluoroalkylthiolation of alcohols

To a flame-dried-tube equipped with a magnetic stirrer were added alcohols **5** (0.50 mmol, 1.0 equiv.) and dry THF (1 mL). The flask was evacuated and refilled with nitrogen three times and the reaction mixture cooled to 0 ℃. *n*-BuLi (0.55 mmol, 1.1 equiv.) was added at 0 ℃ and the reaction let stirred for 5 min before the addition of **BB2x** (0.60 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 ℃ under nitrogen for 3 h. Conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was partitioned between Et_2O and water and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness (under moderate vacuum: 400 mbar at 25 ℃). The crude residue was purified by flash chromatography to afford the desired product **6** (or **7** or **8**).

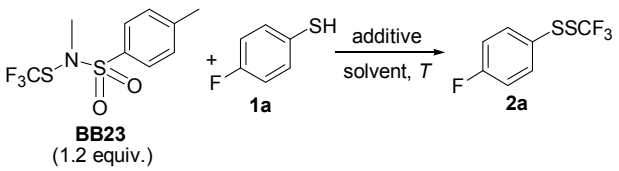
Results and Discussion

The 2nd generation of trifluoromethanesulfenamides (**BB2**) being more reactive,[23a] this family of fluoroalkylated reagents (**BB2x**) has been selected.

The reactivity with thiols has been first studied and the optimal conditions have been sought with CF_3 reagents (**BB23**) and 4-fluorobenzenethiol (Table 1).

By simply mixing **BB23** with thiol **1a**, in acetonitrile, a modest amount of **2a** has been observed; heating seems to be deleterious to the reaction (Table 1, Entries 1—2). Activation of thiol, in basic conditions, did not lead to expected reaction. In acid conditions, electrophilicity of reagent **BB23** is exacerbated. If Lewis acid $ClSiMe_3$ was not very efficient (Table 1, Entries 5—7), protic acid TfOH, in catalytic amount, gave rise to good results (Table 1, Entries 8—12). If a better yield was obtained by increasing temperature from 20 to 40 ℃, no effect was observed at 80 ℃ (Entries 8—10). Catalytic amount of triflic acid could be decreased while retaining a satisfactory yield (Table 1, Entries 11—12). In a mechanistic point of view, proton from TfOH certainly activates **BB23**, through an interaction with nitrogen, which becomes electrophilic enough to react with thiol **1a**. The released proton from thiol can, then, activate another **BB23**, justifying the catalytic amount of TfOH.

Table 1 Reactivity of **BB23** with 4-fluorobenzenethiol



BB23 (1.2 equiv.) **1a** **2a**

Entry	Additive	Solvent	*T*/℃	*t*/h	**2a**[a]/%
1	—	CH_3CN	80	19	25
2	—	CH_3CN	20	19	36
3	—	CH_2Cl_2	20	23	<1
4	BuLi (1.1 equiv.)	THF	20	15	0
5	$ClSiMe_3$ (1.1 equiv.)	CH_3CN	20	17	13
6	$ClSiMe_3$ (0.2 equiv.)	CH_3CN	40	17	36
7	$ClSiMe_3$ (0.2 equiv.)	CH_3CN	80	17	30
8	TfOH (0.2 equiv.)	CH_2Cl_2	20	15	79
9	TfOH (0.2 equiv.)	CH_2Cl_2	40	15	98
10	TfOH (0.2 equiv.)	DCE[b]	80	15	98
11	TfOH (0.1 equiv.)	CH_2Cl_2	40	15	92
12	TfOH (0.05 equiv.)	CH_2Cl_2	40	15	75

[a] Yield of products, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] DCE: 1,2-dichloroethane.

With the optimal conditions (Table 1, Entry 9), some perfluoroalkylthiolations of thiols have been performed (Figure 2).

The reaction leads to medium to excellent yields in aromatic, heteroaromatic and aliphatic series. There is no major influence of aromatic substituents. Steric hindrance appears also to be not deleterious in aromatic or aliphatic series. Pentafluoroethyl- and heptafluoropropyl-disulfides can be also obtained in the same conditions with satisfactory yields.

Pefluoroalkylthiolation of alcohols to obtain perfluoroalkanesulfenates has been also envisaged. In contrast with thiols, alcohols did not react under acid activation. However, in basic conditions, the in situ generated alkoxides underwent the expected electrophilic

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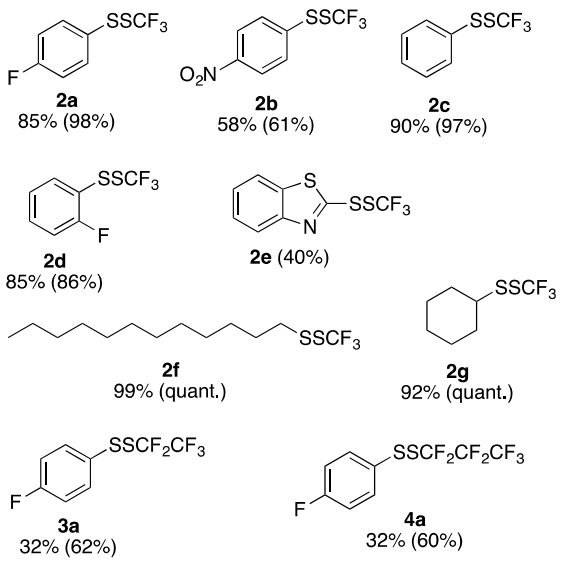
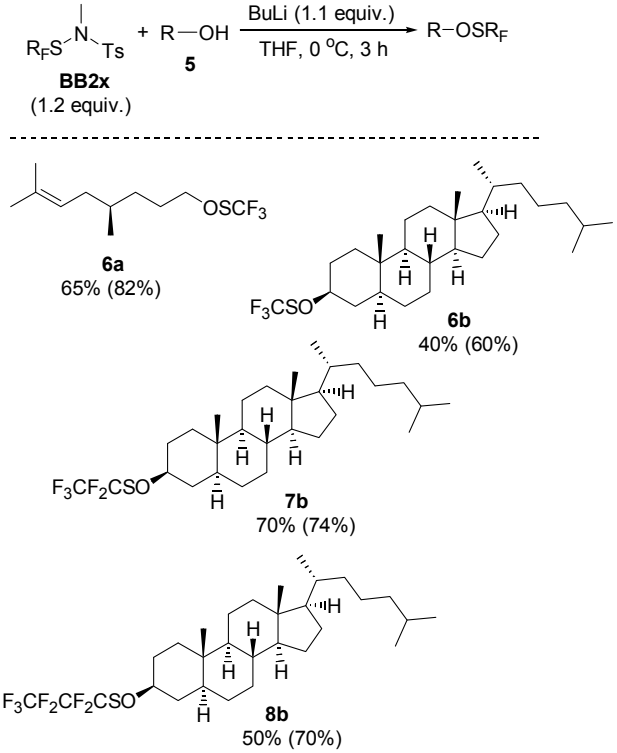


Figure 2 Perfluoroalkylthiolations of some thiols. Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

perfluoroalkylthiolation. This has been illustrated with cholestenol (**5b**) and the corresponding perfluoroalkanesulfenates have been obtained with good yields (Scheme 1).

Scheme 1 Perfluoroalkylthiolation of some alcohols (Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.)



Conclusions

To conclude, 2nd generation of trifluoromethanesulfenamide (**BB2**) turns out electrophilic enough to react with chalcogenols and, thus, joins the few reagents able to perform such a reaction, particular with alcohols. The possibility to obtain higher homologs of this reagent has opened the way to the synthesis of various perfluoroalkyldisulfides or perfluoroalkanesulfenates, which have been scarcely described. These results introduce new fluorinated groups which could be of interest for further applications.

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