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Sulfilimines and Sulfoximines by Reaction of Nitriles with Perfluoroalkyl Sulfoxides

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The species obtained by activation of perfluoroalkylated sulfoxides with trifluoromethanesulfonic anhydride behaves as highly electrophilic entities. Their reaction with nitriles allows a Ritter-like process leading to the new fluorinated acylsulfilimines **1**–**21** after hydrolysis. This flexible methodology allows some variation of both the sulfoxide and nitrile components. Derived acylsulfoximines **22**–**25** or free sulfoximines **26**–**28** could be selectively obtained, as needed, by further controlled oxidation with the cheap and nontoxic potassium permanganate. This oxidation may be performed either after isolation of the intermediate sulfilimine, or more conveniently in a one-pot process directly from fluorinated sulfoxides. This versatile, solvent and metal free, reaction is thus an opening way through the synthesis of new ligands or electrophilic trifluoromethylating reagents.

Introduction

The introduction of the trifluoromethyl group has grown in importance in all fields of chemistry thanks to the modifications induced by its presence. Materials science, agrochemistry, pharmaceuticals and ligand chemistry have taken advantage of this substituent through the development of molecules possessing original properties and/or increased stability.[1] In this context, we have recently developed a research program devoted to the preparation of electrophilic trifluoromethylating reagents and proposed a general one step synthesis of trifluoromethyl sulfonium salt derivatives.[2] Our simple methodology has unlocked the access to these kind of reagents, previously limited by their cumbersome preparation,[3] which are now complemented by new reagents proposed recently by Togni and Shibata.[4,5] During this work, we were intrigued by the uncommon reactivity of the species obtained by activation of a trifluoromethyl sulfoxide with trifluoromethanesulfonic anhydride. We and others have shown that this intermediate can react easily with weak nucleophiles like aromatics to produce trifluoromethylating agents (vide supra) or more curiously is subjected to a reduction process leading ultimately to a trifluoromethyl thioether in the absence of an external nucleophile.[2,6] This points to a very high electrophilic reactivity which seems to have been overlooked previously.[7]

Results and Discussion

These remarks led us to envisage that the active species could also react with other weak nucleophilic entities. In this work, we described its novel reaction with nitriles opening an easy access to fluorinated sulfilimines.[8] To the best of our knowledge, only one example of nitrile as nitrogen source for the production of sulfilimines (nonfluorinated) has been described.[9] This later function is an emergent group in organic chemistry due to numerous and increased applications in medicinal chemistry, organic synthesis and also catalysis as coordination ligands.[10] Extensive synthetic works are devoted to their preparation with recent special emphasis to enantioselective synthesis.[10,11] They are usually obtained by reaction of a thioether or a sulfoxide with various elaborated imination reagents both assisted or unassisted by a transition metal catalyst.[12]

Our metal free methodology involves a simple mix of phenyl trifluoromethyl sulfoxide with acetonitrile and trifluoromethanesulfonic anhydride affording, after a quench with water, the corresponding *N*-acylsulfilimine **1** (Table 1, entry 1). This process is very simple, solvent free and highly versatile. Indeed, the length of the perfluorinated chain can be increased without loss of efficiency as depicted by entries **2**, **6**, **11** and **12**. The substitution pattern of the aromatic has also been studied. With an electron-donating group like methyl, we noticed a beneficial effect on the isolated yield

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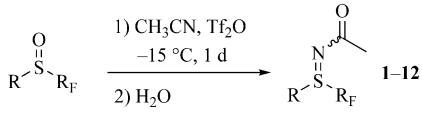
whatever its position on the ring (entries 3 to 5). Halogen substitution is well tolerated (entries 7 to 11) with a decrease of yield in the case of the meta position (entry 8) as expected for an electrophilic reaction. We also succeed in the preparation of the methylsulfilimine **12** but obtained unreproducible results with nonfluorinated sulfoxide like methyl phenyl sulfoxide or diphenyl sulfoxide. All the sulfilimines are stable compounds and can be kept at room temperature for many weeks.

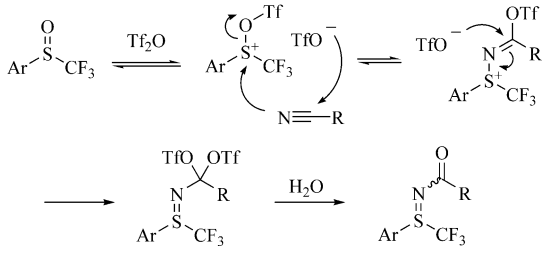
Table 1. Preparation of perfluoroalkylated sulfilimines.



Entry	R	R_F		% Yield of isolated product[a]
1	Ph	CF_3	**1**	75
2	Ph	C_4F_9	**2**	80
3	*o*-Me-C_6H_4	CF_3	**3**	87
4	*m*-Me-C_6H_4	CF_3	**4**	94
5	*p*-Me-C_6H_4	CF_3	**5**	97
6	*p*-Me-C_6H_4	C_4F_9	**6**	97
7	*o*-Cl-C_6H_4	CF_3	**7**	78
8	*m*-Cl-C_6H_4	CF_3	**8**	50
9	*p*-Cl-C_6H_4	CF_3	**9**	96
10	*p*-Br-C_6H_4	CF_3	**10**	99
11	*p*-Br-C_6H_4	C_4F_9	**11**	81
12	CH_3	C_8F_{17}	**12**	56

[a] In all cases 1.5 equiv. of CH_3CN and 1.5 equiv. of Tf_2O are introduced.

We propose the following mechanism (Scheme 1). At low temperature (–15 °C) the activated species (complex of sulfoxide and trifluoromethanesulfonic anhydride) is stable enough to be attacked by the nitrogen atom with concomitant addition of the triflate anion on the carbon of the nitrile function. The resulting sulfonium species is then converted into a more stable acetal intermediate and further transformed into the desired sulfilimine by addition of water during the final quenching step.[13]



Scheme 1. Tentative mechanism proposal.

The structure of all these new sulfilimines has been ascertained by classical analytical data and secured for compounds **5** and **10** by X-ray analysis.[14] Figure 1 discloses the structure of molecule **5**. Interestingly, it appears that the S–CF_3 bond lies almost perpendicular to the plane defined by the aromatic ring. This very particular conformation has already been observed for dibenzothiophenium salts.[15]

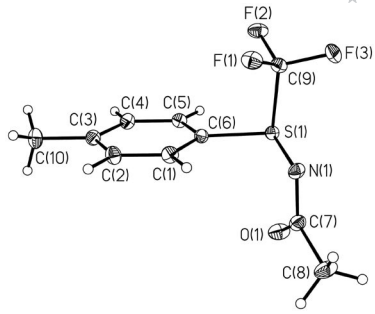
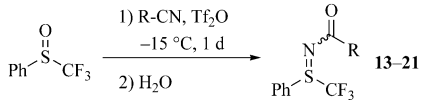


Figure 1. X-ray structure of sulfilimine **5**.

We also studied the possibility of variation of the nitrile engaged in this reaction. Such modifications will allow the description of a rich family of sulfilimines with varied functionalities for further applications. Table 2 illustrates the wide range of chemical functions compatible with the reaction conditions. Aliphatic, benzylic, ether and aromatic nitriles gave rise to target sulfilimines with correct yield (entries 1 to 6). The main limitation seems to be the presence of an electron-withdrawing group on the benzene ring decreasing the nucleophilic character of the nitrogen reagent and consequently resulting in modest isolated yield (entries 7 to 9).

Table 2. Variation of the nitrile.



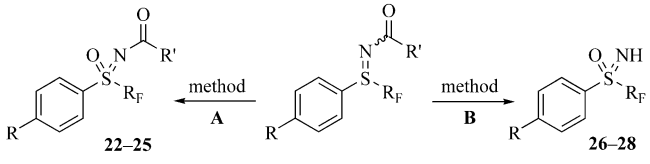
Entry	R		% Yield of isolated product
1	*n*Pr	**13**	64
2	*cyclo*-Pr	**14**	75
3	$MeOCH_2$	**15**	74
4	$PhCH_2$	**16**	63
5	Ph	**17**	60
6	*p*-Me-C_6H_4	**18**	63
7	*p*-Br-C_6H_4	**19**	44
8	*o*-Br-C_6H_4	**20**	44
9	*m*-O_2N-C_6H_4	**21**	22

With sulfilimines at hand, their oxidation to highly praised sulfoximines seemed to be a logical extension to the present study as they are also key intermediates for the synthesis of this sulfur(VI) heteroatomic group.[16] Many synthetic efforts have been devoted to preparation of the latter for biological purposes or the development of chiral auxiliaries.[17]

The chemistry of fluorinated sulfoximines has been initiated by the group of Yagupolskii and continued by us.[18,19] These highly electron-withdrawing derivatives have found applications for liquid crystals and more recently for the invention of electrophilic trifluoromethylating reagents.[20,5] Nevertheless, their preparation is cumbersome, especially the imination step which is undertaken by heating an oleum solution of sodium azide and sulfoxide.[21]

We tried to ameliorate oxidation conditions to be able to give rise either to the sulfoximine with the keto functionalization kept on the nitrogen atom or free sulfoximine. Amongst the classical reagents tested, disappointing results (partial transformations, lack of selectivity) occurred with metachloroperbenzoic acid, trifluoroperacetic acid, ruthenium dioxide and hydrogen peroxide.[22–25] We were pleased to observe that the cheap and nontoxic potassium permanganate was the candidate of choice.[26] The controlled oxidation of sulfilimines has been undertaken with excellent to modest (due to incomplete conversion of the starting material) yields depending on substrate (Table 3, entries 1–4). When the same reaction was run in the presence of a base, deprotection of the nitrogen atom occurs concomitantly (entries 5–7).

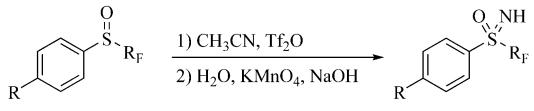
Table 3. Oxidation to sulfoximines.



Entry	R	R′	R_F	Method	Compound	% Yield
1	H	CH_3	CF_3	**A**[a]	**22**	69
2	Me	CH_3	CF_3	**A**	**23**	95
3	Br	CH_3	C_4F_9	**A**	**24**	40
4	H	CH_2Ph	CF_3	**A**	**25**	44
5	H	CH_3	CF_3	**B**[b]	**26**	48
6	Me	CH_3	CF_3	**B**[b]	**27**	72
7	Br	CH_3	C_4F_9	**B**[c]	**28**	36

[a] One equiv. of $KMnO_4$ in water. [b] One equiv. of $KMnO_4$ and two equiv. of NaOH in water. [c] See footnote b, but 5 equiv. of $KMnO_4$ for this sluggishly reacting substrate.

In order to avoid the isolation of the sulfilimine for the production of sulfoximine, we have also studied a one pot process. After completion of sulfilimine formation, the oxidant and the base are directly added to the reaction medium (Scheme 2). Sulfoximines were thus formed in excellent yields, better in fact than those obtained via the two step process. This new smooth and convenient pathway now allows the preparation of original fluorinated sulfoximine like **27** and the easy synthesis of a precursor **26** of recently described new electrophilic trifluoromethylating reagent.[5,27]



R = H, $R_F = CF_3$, **26**, 88 %
R = Me, $R_F = CF_3$, **27**, 94 %
R = Br, $R_F = C_4F_9$, **28**, 63 %

Scheme 2. One-pot preparation of sulfoximines.

Conclusions

In summary, we have developed a new methodology for straightforward synthesis of either fluorinated sulfilimines or sulfoximines by simple mix of sulfoxide, nitrile and trifluoromethanesulfonic anhydride. This versatile pathway allows the introduction of functional diversity. The synthetic potential of this new reaction and of the new compounds is under evaluation in our laboratory.

Experimental Section

General Procedure for the Synthesis of Sulfilimines Compounds as Exemplified by the Preparation of 1: Trifluoromethanesulfonic anhydride (1.3 mL, 7.5 mmol, 1.5 equiv.) was added under argon to a precooled (–15 °C) mixture of phenyl trifluoromethyl sulfoxide[28] (0.97 g, 5 mmol) and acetonitrile (0.4 mL, 7.5 mmol, 1.5 equiv.). The reaction mixture was stirred for 24 h at –15 °C, then hydrolyzed with water (5 mL), extracted with CH_2Cl_2 (3 × 15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (diethyl ether/pentane, 7:3) to give 0.89 g (75%) of a yellow oil. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –64.7 (s, 3 F) ppm. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.87 (d, J = 8.3 Hz, 2 H, ArH), 7.72–7.57 (m, 3 H, ArH), 2.22 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 183.7, 134.3, 130.2, 128.7, 127.3, 124.2 (q, J = 324 Hz, CF_3), 24.0 ppm. Pos. ESI MS: m/z = 189 ([MNa – CF_3]$^+$), 258 [MNa^+], 493 ($2MNa^+$). $C_9H_8F_3NOS$ (235.03): calcd. C 45.95, H 3.43, N 5.95; found C 45.54, H 3.53, N 5.89.

General Procedure for the Basic Oxidation of Sulfilimines Compounds as Exemplified by the Preparation of 26:[5] A mixture of *N*-[phenyl(trifluoromethyl)-λ^4-sulfanylidene]acetamide (**1**) (118 mg, 0.5 mmol), sodium hydroxide (40 mg, 1 mmol, 2 equiv.) and potassium permanganate (80 mg, 0.4 mmol, 1 equiv.) in water (2 mL) was heated at 110 °C for 2 h. The mixture was cooled, cleared with $Na_2S_2O_4$, then diluted with water (3 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative plate (diethyl ether/pentane, 3:7) to give 50 mg (48%) of a white solid; m.p. 89 °C ± 0.2 °C. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –79.3 (s, 3 F) ppm. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.16 (d, J = 7.3 Hz, 2 H, ArH), 7.83–7.75 (m, 1 H, ArH), 7.69–7.61 (m, 2 H, ArH), 3.62 (br. s for NH, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 35.5, 131.6, 130.6, 129.5, 120.9 (q, J = 332 Hz, CF_3) ppm. Pos. ESI (m/z): 210 [MH^+], 232 [MNa^+], 441 ($2MNa^+$).

General Procedure for the Oxidation of Sulfilimines Compounds as Exemplified by the Preparation of 22: A mixture of **1** (118 mg, 0.5 mmol) and potassium permanganate (80 mg, 0.5 mmol, 1 equiv.) in water (5 mL) was stirred at room temperature overnight and then treated and purified as above to give 87 mg (69%) of an oil. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.9 (s, 3 F) ppm. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.06 (d, J = 7.7 Hz, 2 H, ArH), 7.87–7.80 (m, 1 H, ArH), 7.73–765 (m, 2 H, ArH), 2.27 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.6, 136.2, 130.4, 130.2, 130.1, 120.3 (q, J = 328 Hz, CF_3), 26.8 ppm. pos. ESI (m/z): 251 [MNa^+]. $C_9H_8F_3NO_2S$ (251.02): calcd. C 43.03, H 3.21, N 5.58; found C 43.19, H 3.35, N 5.61.

General Procedure for the One-Pot Synthesis of Sulfoximines: After the water hydrolysis (vide supra), sodium hydroxide (2 equiv.) and potassium permanganate (1 equiv.) were added, the reaction heated at 110 °C for 2 h and then treated and purified as above.

Supporting Information (see also the footnote on the first page of this article): Crystal data and X-ray structures for compounds **5**, **10** and **23**. ^{19}F NMR spectra of the crude mixture as experimental

proofs of the proposed mechanism; analytical data of all the compounds including copies of the NMR spectra.

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[13] Some evidence for a bis triflate acetal intermediate has been obtained by ^{19}F NMR spectroscopy. See the corresponding spectra in Supporting Information.

[14] X-ray structure of sulfoximine **23** has also been obtained. The crystal data for **5**, **10** and **23** are detailed in the Supporting Information. CCDC-724941 (**5**), -724942 (**10**) and -724943 (**23**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[21] ***Safety remark:*** When this reaction is conducted on a large scale (10 g of sulfoxide or more), the addition of sodium azide can set the reaction mixture on fire.

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