CHEMISTRY LETTERS, pp. 2405-2408 1992.

Anodic Preparation of N-(2,2,2-Trifluoroethylidene)sulfenamides and Their Application to the Synthesis of Trifluoromethylated Amines, Aminoketone, and Aminoalkanoates[1)]

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N-(2,2,2-Trifluoroethylidene)sulfenamides (trifluoromethylated sulfenimines) were easily prepared in one step by anodic oxidation of 2,2,2-trifluoroethylamine and diaryl disulfides in $MeCN/Et_4NClO_4$ using $MgBr_2$ as a redox mediator. The sulfenimines were highly useful building blocks for the preparation of trifluoromethylated amines, aminoketone, and aminoalkanoates.

A great deal of interest has been focused on partially fluorinated organic molecules. Among them, β-fluorinated amines and amino acids have attracted much attention as potent inhibitors of various enzymes.[2)] In addition, such compounds are highly useful precursors to synthetic fluorinated peptides.[3)] Although a number of fluorinated building blocks have been developed,[4)] preparation of desired β-fluorinated amines and amino acids is not always straightforward.

N-Alkylidenesulfenamides (sulfenimines) are versatile building blocks for the preparation of secondary and tertiary amines.[5)] Therefore, fluoroalkylated sulfenimines should be useful building blocks for the preparation of N-fluoroalkylamino compounds. However, no paper described on such sulfenimines has been reported so far.

Here, we report anodic preparation of novel trifluoromethylated sulfenimines and their application to the synthesis of trifluoromethylated amines, aminoketone, and aminoalkanoates. Torii and Tanaka *et al.*, have reported that direct transformation of α-aminoalkanoates and disulfides to the corresponding sulfenimines was performed by electrolysis in a two-phase system using a redox mediator.[6)] In this reaction, an electron-withdrawing ester group seems to play an important role, namely the ester group facilitates deprotonation of the sulfenamide intermediate formed in the course of the electrolysis. Since a trifluoromethyl group is also strong electron-withdrawing, this electrolytic method seems to be promising for our purpose.

Table 1. Electrosynthesis of sulfenimines from 2,2,2-trifluoroethylamine

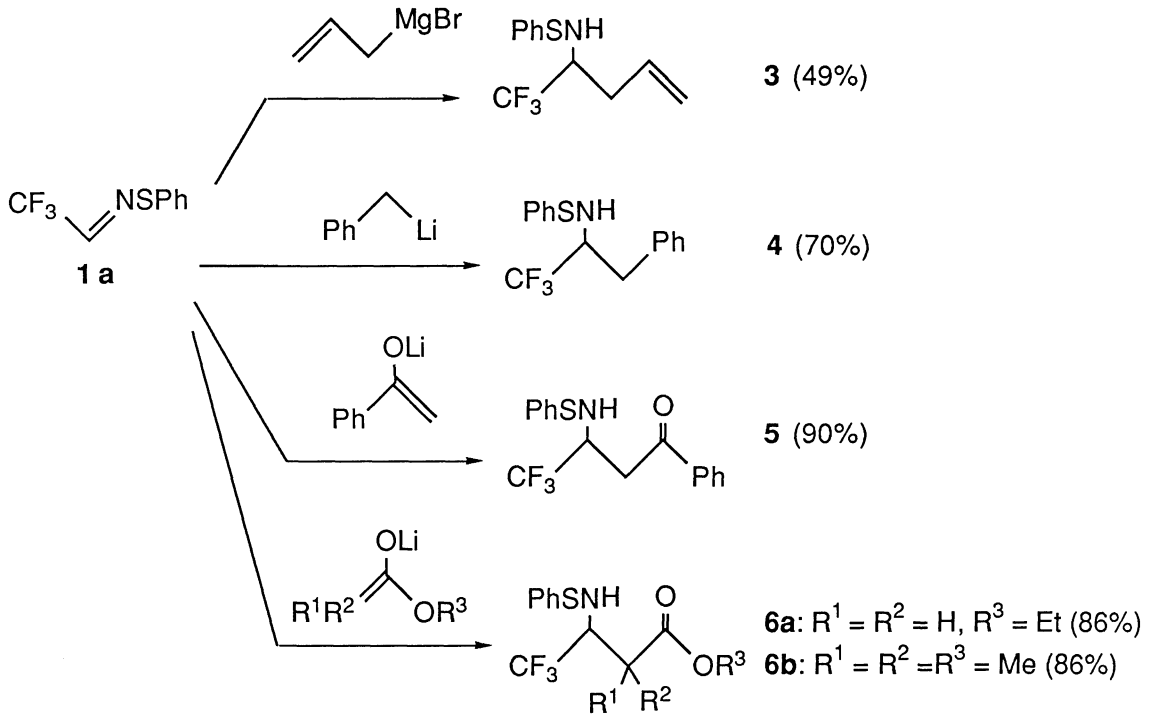
$$CF_3CH_2NH_2 + ArSSAr \xrightarrow{-e - H^+} \underset{\mathbf{2}}{[CF_3CH_2NHSAr]} \xrightarrow{-2e - H^+} \underset{\mathbf{1}}{CF_3CH{=}NSAr}$$

Run	Ar	Method[a)]	Electricity 96480 C mol^{-1}	Product **1** Yield / %
1	Ph	A	3.0	55 (**1a**)
2	*p*-Tol	A	3.0	33 (**1b**)
3	Ph	B	3.5	72 (**1a**)
4	*p*-Tol	B	3.5	58 (**1b**)

a) See text.

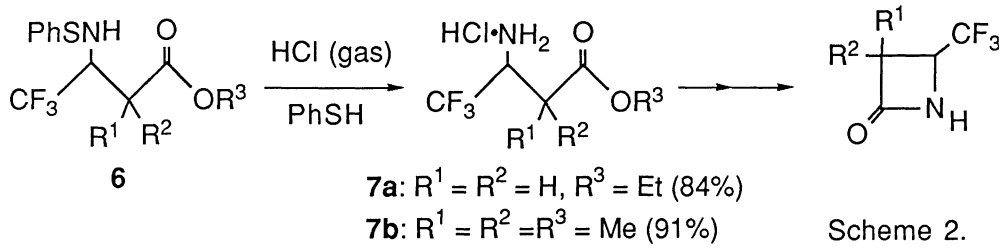
With this in mind, we have attempted electrolytic transformation of readily available 2,2,2-trifluoroethylamine and diaryl disulfides to the corresponding trifluoromethylated sulfenimines **1**. At first, anodic oxidation was carried out in a two-phase system (CH_2Cl_2/H_2O) using magnesium halides as a redox mediator (method A) in a manner similar to that reported.[6] Although $MgCl_2$ failed to give the desired product **1**, $MgBr_2$ was effective for this reaction. Di-*p*-tolyl disulfide gave the corresponding sulfenimine **1b** in a low yield (run 2) while diphenyl disulfide provided the sulfenimine **1a** in a moderate yield (run 1). After many attempts, the yield of **1** increased when the electrolysis was done in a homogeneous system ($MeCN/Et_4NClO_4/MgBr_2$) (method B).[7] Here again, diphenyl disulfide gave much higher yield compared to the case of di-*p*-tolyl disulfide (runs 3 and 4). This indirect oxidative reaction seems to proceed *via* a sulfenamide intermediate **2** in a similar mechanism as proposed previously.[6, 8]

In order to demonstrate the synthetic utility of **1**, an addition reaction of various kinds of carbon nucleophiles to **1** was attempted. As shown in Scheme 1, the reactions with alkyllithium, allylmagnesium bromide, lithium enolate, and lithium enolester were successfully carried out to provide trifluoromethylated amines,[9] aminoketone, and aminoalkanoates as the corresponding sulfenamide derivatives in good to high yields. In our previous paper, we have shown that reductive cleavage of an S-N bond is easily performed by treatment with H_2S.[10] However, H_2S was not effective for the cleavage of the S-N bond of the sulfenamide derivatives **3** - **6**. Finally, we have found that the deprotection of a phenylsulfenyl group was easily achieved by the treatment with HCl gas in the presence of thiophenol at room temperature. For example, trifluoromethylated β-aminoalkanoates were obtained in excellent yields as shown in Scheme 2.



Scheme 1.

Trifluoromethylated β-aminoalkanoate **7a** has been prepared from ethyl trifluoroacetoacetate.[11] However, this method requires multi steps and can not be applied to the preparation of other types of aminoalkanoates such as **7b**. The aminoalkanoates **7** are known to be useful precursors to trifluoromethylated β-lactams.[11]



Scheme 2.

In summary, we have demonstrated that anodically prepared trifluoromethylated sulfenimines are highly versatile building blocks for the preparation of various types of amino compounds bearing a trifluoromethyl group.

We are grateful to Prof. Tsutomu Nonaka of Tokyo Institute of Technology of his valuable suggestion.

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7) The electrolysis was carried out at Pt electrodes (3 x 4 cm^2) in MeCN containing 2,2,2-trifluoroethylamine (6 mmol) , disulfide (12 mmol), NaBr (2 mmol), and Et_4NClO_4 (2 mmol) at room temperature. During the electrolysis, the cell voltage was kept at 3 V (current density: 2.4 - 1.0 mA/cm^2). After 3.5 x 96480 C/mol of electricity was passed, the solvent was removed under reduced pressure and the product was extracted repeatedly with ether. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane-AcOEt, 30:1) to provide pure **1b**. In the case of **1a**, further purification was done by distillation under reduced pressure. **1a**: BP 52 °C/15 Torr; ^{19}F NMR ($CDCl_3$, ext. CF_3COOH) δ 9.25 (d, J_{F-H} = 3.6 Hz); ^1H NMR ($CDCl_3$) δ 7.36 - 7.68 (m, 6H, C<u>H</u>=N & Ph); MS m/z 205 (M^+), 136 (M^+-CF_3), 109 (PhS^+). **1b**: ^{19}F NMR ($CDCl_3$, ext. CF_3COOH) δ 8.92 (d, J_{F-H} = 3.6 Hz); ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 7.20 - 7.46 (m, 5H, C<u>H</u>=N & C_6<u>H_4</u>); MS m/z 219 (M^+), 123 (*p*-$TolS^+$).

8) The sulfenamide intermediate **2** was detected by MS in the course of the electrolysis. For example: **2a** (Ar = Ph): MS (75 eV) m/z 207 (M^+), 138 (M^+-CF_3), 109 (PhS^+).

9) Recently, Uno and Suzuki *et al.* have reported boron trifluoride-assisted reaction of perfluoroalkyllithiums with imines providing perfluoroalkylated amines. However, they did not show the preparation of trifluoromethylated amines: H. Uno, Y. Shiraishi, K. Shimokawa, and H. Suzuki, *Chem. Lett.*, **1988**, 729.

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(Received September 3, 1992)