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Journal of Fluorine Chemistry 105 (2000) 41–44

JOURNAL OF FLUORINE CHEMISTRY

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Perfluoroalkylation of aliphatic thiols in the presence of sodium hydroxymethanesulfinate

Elsa Anselmi, Jean-Claude Blazejewski, Marc Tordeux, Claude Wakselman*

SIRCOB, ESA CNRS 8086, Université de Versailles, 45 Avenue des Etats-Unis, 78035 Versailles, France

Received 18 February 2000; accepted 16 March 2000

Abstract

Direct perfluoroalkylation of aliphatic thiols was performed in the presence of sodium hydroxymethanesulfinate (Rongalite). Reaction of mercaptoalkanoic esters with trifluoromethyl bromide gave the corresponding trifluoromethylthio ethers. Condensation of alkane dithiols with perfluoroalkyl iodides led mainly to fluorinated dithioethers. These alkylation reactions are interpreted as occurring via in situ formation of dialkyldisulfides.

Keywords: Perfluoroalkyl sulfides; Thiols; Trifluoromethyl bromide; Disulfides; Hydroxymethanesulfinate

1. Introduction

Owing to its high lipophilicity and its electron-withdrawing ability, the trifluoromethylthio group has long attracted the interest of chemists [1–3]. Numerous methods are now available for the synthesis of trifluoromethylthioaromatic compounds [3,4].[1] The introduction of this group in the aliphatic series, however, is more problematic because the spontaneous condensation of alkyl thiolates with perfluoroalkyl halides can produce a notable quantity of disulfide [5]. The occurrence of this secondary reaction was reported to be reduced when the perfluoroalkylation of thiols by perfluoroalkyl iodides was performed in the presence of triethylamine [6]. In our hands, an attempt to use this procedure for the condensation of trifluoromethyl bromide with ethyl mercaptoacetate gave in fact the corresponding disulfide (see Section 3).

On the other hand, disulfides themselves can be transformed to perfluoroalkylthioethers by the action of perfluoroalkyl halides in the presence of sulfoxylate radical anion precursors [7,8]. It appeared that a combination of the two transformations (in situ formation of the disulfide from the thiol and its alkylation) should be useful when the disulfide is not easily available or is thermally fragile. We report here the results of the perfluoroalkylation reaction of mercaptoalkanoic esters and alkanedithiols.

2. Results and discussion

The condensation of thiolates with perfluoroalkyl halides may be envisaged as occurring by either of the two competitive processes: an halogenophilic mechanism (S_N2 attack on the larger halogen followed by an anionic chain process) and a radical-anion chain mechanism initiated by a single electron transfer process [9,10]. Moreover, formation of disulfides can compete with both of these mechanisms (Scheme 1 and Scheme 2), and is often the major pathway.

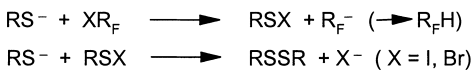
With aliphatic thiolates, disulfide formation often limits the yield of these spontaneous perfluoroalkylation reactions [5]. Disulfides can themselves be perfluoroalkylated in the presence of sulfoxylate radical anion precursors, such as sodium hydroxymethanesulfinate (Rongalite) [7,8] (Scheme 3).

In principle, combination of these two successive condensations, that is, in situ disulfide formation and subsequent reduction with SO_2 radical anion, should lead to aliphatic perfluoroalkylthioethers (Scheme 4). Consequently, a direct perfluoroalkylation of aliphatic thiols was attempted in the presence of sodium hydroxymethanesulfinate (Rongalite) in aqueous DMF. Sodium phosphate was placed in the medium in order to transform the thiol to its corresponding thiolate and, after, to neutralize the sulfur dioxide formed in the reaction.

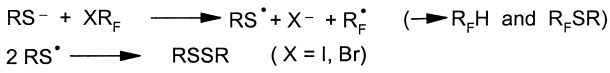
* Corresponding author. Tel.: +33-01-39-25-44-11; fax: +33-01-39-25-44-52.

[1] For references on the recent methods of preparation of trifluoromethyl sulfides in the aliphatic or aromatic series, see [4].

0022-1139/00/$ – see front matter
PII: S0022-1139(00)00286-4

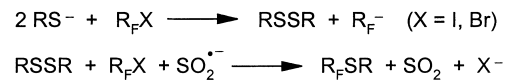


Scheme 1.

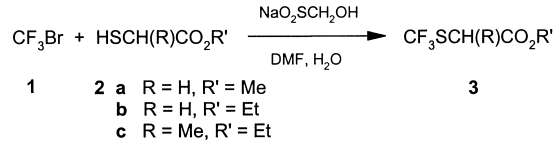


Scheme 2.

Scheme 3.



Scheme 4.



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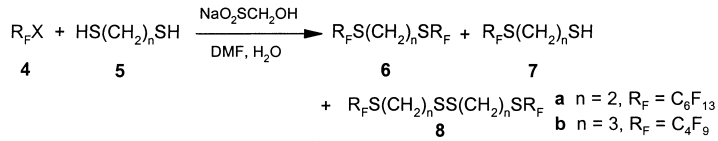

Scheme 6.

Mercaptoalkanoic esters were chosen as substrates owing to the thermal fragility of their corresponding disulfides.[2] The perfluoroalkylation was performed with trifluoromethyl bromide (**1**) because trifluoromethylthioacetic esters (**3**) are interesting synthons [11,12]. The desired derivatives were indeed obtained in 33–52% isolated yields (Scheme 5). Some trifluoromethanesulfinate has also been detected on the NMR spectra of the crude products. Formation of this product can be explained as shown on Scheme 4. This salt can also arise from the direct transformation of trifluoromethyl bromide by Rongalite [13].

The reactivity of alkanedithiols (**5**) has also been studied. Cyclic disulfides or oligomeric disulfides can be produced in situ from these substrates. Whatever their structure may be, they can react following the process written on Scheme 4. Bis-perfluoroalkylation can occur as shown by the isolation of the fluorinated dithioethers (**6**) in 30–45% isolated yields (Scheme 6). Detection of compound **8** is in agreement with the in situ formation of disulfide (Scheme 4).

The yield was not increased by addition of an excess of perfluoroalkyl iodide or of a greater excess of sodium hydroxymethanesulfinate.

The reaction of perfluorohexyl iodide with ethanedithiol in the presence of two equivalents of triethylamine in dimethylformamide did not give the fluorinated sulfide. With propanedithiol, we obtained a mixture of the starting iodide (53%), perfluorohexyl-1-hydride (21%), 1,3-bis-(tridecafluorohexylthio)propane (11%), 1,8-(tridecafluorohexythio)-4,5-dithiaoctane (2%) and an unknown product of higher molecular weight.

[2] We have observed that distillation of these disulfides often result in the loss of product and the formation of high boiling materials.

3. Experimental

3.1. General

NMR spectra were recorded as $CDCl_3$ solutions, on a Bruker AC-300 spectrometer. Reported coupling constants and chemicals shifts were based on a first order analysis. Internal reference was the residual peak of $CHCl_3$ (7.27 ppm) for ^1H (300 MHz), central peak of $CDCl_3$ (77 ppm) for ^{13}C (75 MHz) spectra and internal $CFCl_3$ (0 ppm) for ^{19}F (282 MHz) NMR spectra. IR spectra were recorded as CCl_4 solutions on an Impact 400D Nicolet spectrophotometer. GCMS were performed with Chrompack CP Sil 19 CB chromatography column, length 30 m, diameter 0.25 mm, film thickness 0.25 μm, initial temperature 50°C over 2 min, gradient 10°C/min, final temperature 250°C on a HP 5989B quadrupolar mass spectrometer. High resolution mass spectra were performed with a Finnigan MAT 95S spectrometer. Boiling points were determined by the Siwoloboff method on a Buchi melting point apparatus.

Sodium hydroxymethanesulfinate (Rongalite) was purchased from Aldrich.

3.2. Preparation of trifluoromethyl sulfides **3a-c**

Methyl [(trifluoromethyl)thio]acetate (**3a**). A mixture of methyl mercaptoacetate (5 g, 47 mmol) and sodium phosphate (7.72 g, 47 mmol) in DMF (100 ml) was magnetically stirred for 15 min in a heavy walled glass flask (Parr apparatus). Water (4.5 ml) and Rongalite (10.9 g, 70 mmol) were then quickly introduced. The flask was immediately evacuated (5 mm Hg) before being connected to a bromotrifluoromethane pressure cylinder. The pressure was maintain at 4.5 bar, with constant shaking, during the absorption process which takes ca. 8 h. The apparatus was vented, the supernatant liquor was removed and diluted with 50 ml of water. The remaining salts were taken up in diethyl ether (50 ml), filtered, and washed with 100 ml of diethyl ether. Combined liquid phases were washed with water (5×100 ml) and brine (100 ml). After drying ($MgSO_4$), the solvents were removed under reduced pressure. Short path distillation of the residue (15 mm Hg) afforded sulfide **3a** (3.9 g, 48%) which had: HRMS (found: 173.9960 $C_4H_5O_2F_3S$ needs 173.9962); bp 120–122°C (lit. [14] 50°C/15 mm Hg); ^{1}H NMR 3.66 (2H, s, CH_2S) and 3.76 (3H, s, CH_3O) ppm; ^{19}F NMR −42.9 (s, CF_3) ppm; ^{13}C NMR 31.5 (q, $^3J_{CF}$=2.6 Hz, CH_2S), 53.0 (CH_3O), 130.0 (q, $^1J_{CF}$=307 Hz, CF_3) and 168.0 (CO) ppm; ν_{max} (CCl_4) 1095, 1154, 1448, 1764, 2850 and 2962 cm^{-1}, EI (*m/z*) 174 (M^+, 65), 114 (100) and 69 (40%).

Compounds prepared in the same way were

Ethyl [(trifluoromethyl)thio]acetate (**3b**), (52%) which had: bp 142–144°C (lit. [14] 68°C/35 mm Hg); ^{1}H NMR 1.28 (3H, t, J_{HH}=7.1 Hz, CH_3), 3.65 (2H, s, CH_2S) and 4.23 (2H, q, J_{HH}=7.1 Hz, CH_2O) ppm; ^{19}F NMR −42.8 (s, CF_3) ppm; ^{13}C NMR 13.7 (CH_3), 31.7 (q, $^3J_{CF}$=2.6 Hz,[3] CH_2S), 62.2 (CH_2O), 130.1 (q, $^1J_{CF}$=306 Hz, CF_3) and 167.5 (CO) ppm; ν_{max} (CCl_4) 1037, 1304, 1143, 1748, 1755 and 2989 cm^{-1}; EI (*m/z*) 188 (M^+, 20), 143 (14), 115 (100) and 69 (41%).

Ethyl 2-[trifluoromethyl)thio]propanoate (**3c**), (33%) which had: bp 140–142°C (lit. [14] 44°C/8 mm Hg); ^{1}H NMR 1.29 (3H, t, J_{HH}=7.1 Hz, CH_3CH_2), 1.59 (3H, d, J_{HH}=7.2 Hz, CH_3CH), 3.92 (1H, q, J_{HH}=7.2 Hz, CH) and 4.22 (2H, apparent dq: AB part of an ABX_3 spin system, J_{HH}=7.1 and 4.4 Hz, CH_2O) ppm; ^{19}F NMR −41.1 (s, CF_3) ppm; ^{13}C NMR 13.9 (CH_3CH_2), 18.3 (CH_3CH), 41.6 (q, $^3J_{CF}$=2.3 Hz, CH), 62.1 (CH_2O), 130.1 (q, $^1J_{CF}$=307 Hz, CF_3) and 171.1 (CO) ppm; ν_{max} (CCl_4) 1090, 1154, 1448, 1764, 2946 and 2994 cm^{-1}, EI (*m/z*) 202 (M^+, 16), 129 (100) and 69 (11%).

3.3. Condensation of methyl mercaptoacetate with bromotrifluoromethane in the presence of triethylamine

A mixture of methyl mercaptoacetate (2 g, 17 mmol) and triethylamine (2.4 g, 24 mmol) in DMF (25 ml) was introduced into a Parr apparatus. The flask was evacuated (5 mm Hg) before being connected to a bromotrifluoromethane pressure cylinder. Pressure was maintained at 4.5 bar over 17 h, with constant shaking. ^{19}F NMR analysis of the crude mixture did not show the presence of SCF_3 compounds. The resulting liquor was removed and diluted with 50 ml of water. After extraction with diethyl ether (3×50 ml), the organic phase was washed with water (5×30 ml) and brine (100 ml). After drying ($MgSO_4$), the solvents were removed under reduced pressure. Column chromatography of the residue (SiO_2, CH_2Cl_2) afforded 0.52 g (27%) of diethyl (2,3-dithiabutane)-1,4-dicarboxylate which had: bp 275–280°C dec. (lit. [15] 122°C/0.5 mm Hg); ^{1}H NMR 1.27 (6H, t, J=7.1 Hz, CH_3), 3.55 (4H, s, CH_2S) and 4.18 (4H, q, J=7.2 Hz, CH_2O) ppm. ^{13}C NMR 14.0 (CH_3), 41.3 (CH_2S), 61.6 (CH_2O) and 169.2 (CO) ppm; EI (*m/z*): 238 (M^+, 23), 192 (37), 165 (22), 119 (49), 59 (100%).

3.4. Condensation of dithiols with iodoperfluoroalkanes

3.4.1. Condensation of ethane-1,2-dithiol (**4a**) with 1-iodotridecafluorohexane (**5a**)

A mixture of ethane-1,2-dithiol (**4a**) (0.94 g, 0.01 mol) and sodium phosphate (3.3 g, 0.02 mol) in DMF (20 ml) was stirred at room temperature for a quarter of an hour. Then sodium hydroxymethanesulfinate (4.65 g, 0.03 mol) and water (1 ml) were introduced followed by 1-iodo-tridecafluorohexane (**5a**) (9 g, 0.02 mol). The mixture was stirred over 17 h, then poured into water (150 ml) and extracted three times with diethyl ether. The organic phase was washed three times with 1 N hydrochloric acid, 10% sodium carbonate and water, dried over magnesium sulfate and evacuated under vacuum. GCMS of the mixture (3.9 g) showed the presence of 2-(tridecafluorohexylthio)ethanethiol (**7a**), 1,2-bis-(tridecafluorohexylthio) ethane (**6a**) and 1,6-(tridecafluorohexylthio)-3,4-dithiahexane (**8a**) (9.6, 10.9, 20.2 min) in the ratio 0.06/0.74/0.20. Individual samples of these compounds were obtained by preparative thin layer chromatography on silica gel, using pentane as eluant. The dithioether migrated with the front of the solvent. The rf of the sulfide-thiol **7a** was 0.9 and the rf of the **6a** disulfide **8a** 0.3.

The fluoro chemical shifts of the three corresponding compounds are exactly the same: ^{19}F NMR −81.3, −87.3, −120.0, −121.9, −123.2 and −126.7 ppm. 1,2-Bis-(tridecafluorohexylthio)ethane (**6a**), yield 30%, had: HRMS (found: 729.9364 $C_{14}H_4F_{26}S_2$ needs 729.9380); ^{1}H NMR 3.22 (s) ppm; EI (*m/z*): 730 (M^+, 14), 411 (32), 379 (100) and 319 (14%). 2-(tridecafluorohexylthio)ethanethiol (**7a**) (3% yield) had: ^{1}H NMR 3.24 (1H, t, J=7.1 Hz, SH), 2.85 (2H, q, J=7.1 Hz, CH_2SH) and 1.45 (2H, t, J=7.1 Hz, R_FSCH_2); GCMS m=412; EI (*m/z*): 412 (M+, 100), 379 (21), 365 (19) and 319 (11%). 1,6-(Tridecafluorohexylthio)-3,4-dithiahexane (**8a**), yield 8%, had: ^{1}H NMR 3.28 (2H, t, J=7.1 Hz) and 3.03 (2H, t, J=7.1 Hz); GCMS m=822; EI (*m/z*): 504 (2), 445 (13), 379 (100), 265 (7) and 319 (6%).

[3] We must point out this differs from the reported value of 7.8 Hz [14].

*3.4.2. Condensation of propane-1,3-dithiol (**4b**) with 1-iodo-nonafluorobutane (**5b**)*

Using the same experimental conditions as for Section 3.4.1 with propane-1,3-dithiol (**4b**) (1.08 g) and 1-iodo-nonafluorobutane (**5b**) (7 g), we isolated a mixture (3.4 g) of fluorinated products shown by GCMS to be composed of 3-(nonafluorobutylthio)propanethiol (**7b**), 1,3-bis-(nonafluorobutylthio)propane (**6b**) and 1,8-(nonafluorobutylthio)-4,5-dithiaoctane (7.45, 8.85, 18.54 min) in the ratio 22/70/8. This residue was chromatographed on silica gel plates, using pentane as eluant. The dithioether **6b** migrated with the solvent front. The rf of the sulfide-thiol **7b** was 0.9 and the rf of the disulfide **8b** 0.3. The fluorine chemical shifts of the three corresponding compounds are exactly the same: ^{19}F NMR −81.3, −87.3, −121.4 and −126.2 ppm. 1,3-Bis-(nonafluorobutylthio)ethane (**6b**), yield 45%, had: HRMS (found: 543.9609 $C_{11}H_6F_{18}S_2$ needs 543.9624); ^{1}H NMR 3.09 (4H, t, J=7.1 Hz, CH_2S) and 2.14 (2H, quint, J=7.1 Hz, $CH_2CH_2CH_2$) ppm; EI (*m/z*) 325 (45), 324 (39), 293 (14), 265 (23), 106 (100) and 105 (49%); CI (*m/z*) 545 (2.3), 544 (11), 543 (6), 325 (51) and 106 (100%). 3-(Nonafluorobutylthio)propanethiol (**7b**), yield 14%, had: ^{1}H NMR 3.09 (1H, t, J=7.1 Hz, SH), 2.09 (2H, quint, J=7.1 Hz, $CH_2CH_2CH_2$), 2.67 (2H, q, J=7.1 Hz, CH_2SH) and 1.45 (2H, t, J=7.1 Hz, R_FSCH_2) ppm; EI (*m/z*) 327 (0.7), 326 (M^+, 2.4), 325 (1.7), 131 (4.5), 119 (2.4), 107 (100) and 106 (51.4%); CI (*m/z*) 325 (94), 324 (47), 107 (100) and 106 (59%). 1,8-(Nonafluorobutylthio)-4,5-dithiaoctane (**8b**), yield 5%, had: ^{1}H NMR 3.09 (4H, t, J=7.1 Hz, CH_2S), 2.09 (4H, quint, J=7.1 Hz, $CH_2CH_2CH_2$) and 2.82 (4H, t, J=7.1 Hz, R_FSCH_2) ppm; EI (*m/z*) 651 (3), 649 (6), 325 (53), 293 (11), 265 (16.5), 107 (57) and 106 (100%); CI (*m/z*) 651 (57), 650 (71), 649 (71), 325 (100) and 106 (66%).

4. Conclusion

Direct perfluoroalkylation of aliphatic thiols and polythiols can be performed in the presence of sodium hydroxymethanesulfinate or of other sulfoxylate radical anion precursors (sodium dithionite, combination of sulfur dioxide with a reductant such as zinc or sodium formate ...). This method appears useful when the intermediate disulfide is fragile or not easily available.

Acknowledgements

This work enters in the frame of the European TMR programme ERB FMRX-CT970120, entitled 'Fluorine As a Unique Tool for Engineering Molecular Properties'. We thank Atochem for the generous gifts of perfluoroalkyl halides.

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