Synthesis of Sterically Hindered Fluorous Aryl Perfluoroalkyl Sulfides

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Abstract: The sodium salt of 2,6-dimethyl-4-tert-butyl-benzene-thiol was reacted in dimethyl formamide with a series of perfluoroalkyl iodides and 1,8-diiodoperfluorooctane to afford the corresponding perfluoroalkyl sulfides and 1,8-bis(arylthio)perfluorooctane in good yields.

Keywords: fluorous sulfides, perfluoroalkyl iodides, perfluoroalkylation

Inspired by the introduction of Fluolead™ by Umemoto et al. [1] as a novel fluorinating reagent and with the early publication on the preparation of some aryl(trifluoromethyl)difluorosulfuranes by Yagupolskii et al. [2] we aimed at to synthesize ArSF₂R₃n type sulfuranes (4) (Scheme 1).

Such perfluoroalkyl substituted reagents are expected to have unique physical-chemical properties similar to that of fluorocarbons and allowing easy separation of used reagents from products [3].

Here we disclose the optimized synthesis of precursor aryl perfluoroalkyl sulfides (3a-e) based on spontaneous perfluoroalkylation of thiols without initiators under similar conditions that reported for simple thiols by Feiring and Boiko [4][Scheme 1].

Sterically hindered aryl perfluoroalkyl sulfides 3a-e were prepared in good to excellent isolated yields using the reaction of the sodium salt of 1 with a slight excess of 1-iodoperfluoroalkanes (R₁nI, 2a-d) or with that of 1,8-diiodoperfluorooctane (2e) in absolute DMF at room temperature for 20 to 40 h. The purified new fluorous sulfides 3a-e were appropriately characterized. It is worth to mention that mass spectrometric measurements by APCI technique were highly facilitated by using a 1:1 vol/vol solvent mixture of CH₃CN and CF₃CH₂OH for sample preparation. The synthesis of the analogue trifluoromethyl sulfide (R₁n = CF₃) was effected by using CF₃I dissolved in DMF as a perfluoroalkylating reagent and reported earlier by us [5].

Our attempts for oxidative fluorination of 3 to 4 (R₁n = CF₃) with the use of Br₂/KF/CH₂Cl₂ and some other reagent systems however has not succeeded yet [6].
Experimental

$^1$H, $^{13}$C- and $^{19}$F-NMR spectra were recorded on Bruker Avance 250 instrument using a 5 mm inverse $^1$H/$^{13}$C/$^{31}$P/$^{19}$F probe head at room temperature. Chemical shifts ($\delta$) are given in parts per million (ppm) units relatively solvent (CDCl$_3$) residual peaks ($\delta$=7.26 for $^1$H, $\delta$=77.0 for $^{13}$C) and to CFCl$_3$ as external standard ($\delta$=0.00 for $^{19}$F). Determination of molecular mass was performed by atmospheric pressure chemical ionization mass spectrometry (APCI-MS) on a Bruker Daltonics Esquire 3000 plus (Germany) ion trap mass spectrometer. Samples were dissolved in acetonitrile – trifluoroethanol solvent mixture (50:50, V/V). Mass spectra were acquired in the 50-1500 m/z range yielding singly charged radical cations (M$^+$). Nebulizer gas pressure was 25 psi, drying gas flow was 5 L/min, the heated capillary temperature was 250 °C and the vaporizer temperature was 450 °C. Samples were injected into the ion source in a flow rate of 10 µL/min using a syringe pump. Melting point s were determined on a Böetius micro-melting point apparatus and are uncorrected.

Gas chromatographic analysis of volatile products was performed using a Hewlett-Packard 5890 Series II instrument with PONA [crosslinked methylsilicone gum] 50 m x 0.2mm x 0.5 mm column, H$_2$ carrier gas, FID detection; Program: 120 °C, 5 min, 10 °C/min, 250 °C, 5 min, Inj.: 250°C, Det.: 280°C.

General Procedure for the Synthesis of Aryl Perfluoroalkyl Sulfides (GP) [7]

4-($^{\text{tert}}$-Butyl)-2,6-dimethylbenzenethiol [8] (1.93 g, 10 mmol) was suspended in absolute DMF (15 mL) and reacted with sodium hydride (11 mmol) in small portions, prepared by washing under an argon atmosphere a 57% w/w sodium hydride – white oil dispersion with pentane (3 x 5 mL). When the evolution of hydrogen ceased the perfluoroalkyl iodide (2a-d, C$_n$F$_{2n+1}$I, [n=4,6,8,10], 11.0 mmol) or 1,8-diiodoperfluoroctane (2e, I(CF$_2$)$_8$I, 5.50 mmol) was added and the mixture was stirred at room temperature for 20 h (3a-c) or 40 h (3d-e) under an N$_2$ atmosphere. Then the reaction mixture was poured into water (100 mL) and extracted with diethyl ether (3 x 20 mL), the combined organic extracts were washed with water (3 x 20 mL) and saturated aq-NaCl solution (20 mL). The ether phase was separated and dried (Na$_2$SO$_4$), then the ether was removed by distillation and the product was purified by vacuum distillation or crystallization.

(4-$(^{\text{tert}}$-Butyl)-2,6-dimethylphenyl)(perfluorobutyl)sulfide (3a)

Yield: 2.90 g (71 %) colourless liquid, obtained by short path distillation; 20 Hgmm@160°C bath. It solidifies in the freezer. GC assay: 98%+, t$_{\text{ref}}$: 14.47 min. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 1.33 (s, 9H, C(CH$_3$)$_3$), 2.57 (s, 6H, CH$_3$), 7.22 (s, 2H, Ar CH). $^{13}$C NMR (62.5 MHz, CDCl$_3$): $\delta$ 22.88, 31.43, 34.97, 118.81, 126.34, 145.98, 154.82. $^{19}$F NMR (243 MHz, CDCl$_3$): $\delta$ -81.50 (m, 3F, CF$_3$), -85.96 (m, 2F, CF$_3$), -121.29 (m, 2F, CF$_3$), -126.01 (m, 2F, CF$_3$). MS (APCI, M$^+$): calcd. for C$_{16}$H$_{17}$F$_9$S = 412.1; measured: 412.0.
(4-(tert-Butyl)-2,6-dimethylphenyl)(perfluorohexyl)sulfide (3b)

Yield: 3.50 g (68 %) white waxy solid with mp = 32-34 °C, obtained by short path distillation; 20 Hgmm@170°C bath. GC assay: 98%, t_REF: 15.90 min. 1H NMR (250 MHz, CDCl3): δ 1.32 (s, 9H, C(CH3)3), 2.56 (s, 6H, CH3), 7.21 (s, 2H, Ar CH). 13C NMR (62.5 MHz, CDCl3): δ 22.89, 31.44, 34.97, 118.81, 126.34, 145.99, 154.82. 19F NMR (243 MHz, CDCl3): δ -81.33 (m, 3F, CF3), -85.74 (m, 2F, CF2), -120.38 (m, 2F, CF2), -121.85 (m, 2F, CF2), -123.28 (m, 2F, CF2), -126.63 (m, 2F, CF2). MS (APCI, M⁺): calcd. for C35H31F13S = 512.1; measured: 511.9.

(4-(tert-Butyl)-2,6-dimethylphenyl)(perfluoroctyl)sulfide (3c)

Yield: 5.30 g (86 %) white crystals with mp = 53-54 °C, obtained by short path distillation; 0.5 Hgmm@120°C bath. GC assay: 98%, t_REF: 17.31 min. 1H NMR (250 MHz, CDCl3): δ 1.31 (s, 9H, C(CH3)3), 2.55 (s, 6H, CH3), 7.20 (s, 2H, Ar CH). 13C NMR (62.5 MHz, CDCl3): δ 22.90, 31.45, 34.98, 118.82, 126.34, 145.98, 154.81. 19F NMR (243 MHz, CDCl3): δ -81.28 (m, 3F, CF3), -85.72 (m, 2F, CF2), -120.33 (m, 2F, CF2), -121.65 (m, 2F, CF2), -122.35 (m, 4F, CF2), -123.24 (m, 2F, CF2), -126.62 (m, 2F, CF2). MS (APCI, M⁺): calcd. for C35H31F13S = 612.1; measured: 611.8.

(4-(tert-Butyl)-2,6-dimethylphenyl)(perfluorodecyl)sulfide (3d)

Yield: 5.70 g (76 %) white crystals with mp = 72-75 °C, obtained by short path distillation; 0.5 Hgmm@140°C bath. 1H NMR (250 MHz, CDCl3): δ 1.31 (s, 9H, C(CH3)3), 2.55 (s, 6H, CH3), 7.20 (s, 2H, Ar CH). 13C NMR (62.5 MHz, CDCl3): δ 22.90, 31.46, 34.98, 118.82, 126.33, 145.97, 154.81. 19F NMR (243 MHz, CDCl3): δ -81.26 (m, 3F, CF3), -85.72 (m, 2F, CF2), -120.33 (m, 2F, CF2), -121.64 (m, 2F, CF2), -122.24 (m, 8F, CF2), -123.20 (m, 2F, CF2), -126.58 (m, 2F, CF2). MS (APCI, M⁺): calcd. for C35H31F16S2 = 712.1; measured: 711.8.

(Perfluoroocatane-1,8-diyi)bis((4-(tert-butyl)-2,6-dimethylphenyl)sulfide (3e)

The crude product was recrystallization from acetone (15 mL). Yield: 2.80 g (50 %) white crystals with mp = 100-101 °C. 1H NMR (250 MHz, CDCl3): δ = 1.32 (s, 9H, C(CH3)3), 2.56 (s, 6H, CH3), 7.21 (s, 2H, Ar CH). 13C NMR (62.5 MHz, CDCl3): δ = 22.90; 31.45; 34.98; 118.82; 126.34; 145.98; 154.81. 19F NMR (243 MHz, CDCl3): δ = -85.67 (m, 4F, CF2), 120.31 (m, 4F, CF2), -121.62 (m, 4F, CF2), -122.22 (m, 4F, CF2). MS (APCI, M⁺): calcd. for C35H31F16S2 = 786.2; measured: 786.0.
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6. Unpublished results of PhD student Mr. Bálint Menczinger, Institute of Chemistry, Eötvös Loránd University, Budapest.
