The Synthesis of Aryl Fluoromethyl Sulfoxides

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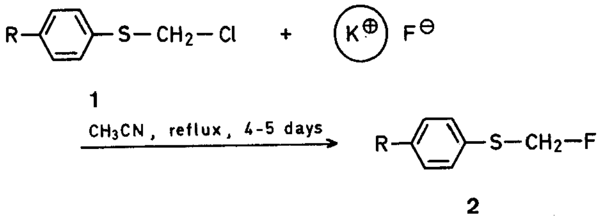
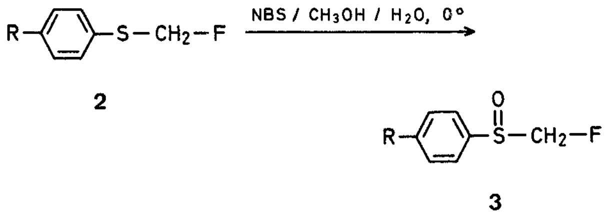
In connection with our interest in synthetic chemistry of organosulfur compounds we had occasion to prepare a series of mono-α-haloalkyl sulfoxides[1]. A survey of the literature indicated that several methods are available for the synthesis of α-chloro-[1,2], α-bromo-[1,3], as well as α-iodoalkyl sulfoxides[1,4] whereas no report of mono-α-fluoroalkyl sulfoxides was found[5]. We would like to report a convenient synthetic route to aryl α-fluoromethyl sulfoxides, using a method made possible by the recent discovery of Liotta and Harris[6] of crown ether-assisted nucleophilic substitution reactions of potassium fluoride with activated organochlorides.

We have found that potassium fluoride in the presence of 18-crown-6 may be used in the conversion of the readily available[7] aryl chloromethyl sulfides (**1**) to aryl fluoromethyl sulfides (**2**) if longer reaction periods are employed (4–5 days) than used previously with the activated chlorides (5–20 h)[6]. The yields of aryl fluoromethyl sulfides are good (79–85%) and the products are obtained in high purity (Table 1).

These conditions are considerably more severe than those reported recently in the crown ether-induced conversion of ethyl trichloromethyldithioacetate to ethyl trifluoromethyldithioacetate, a process which was complete within 3 h at room temperature[8]. The commercial anhydrous potassium fluoride used in our work was dried under vacuum in an oil bath at 160° for 24 h. A slower reaction was observed when the potassium fluoride was heated in an oven at 120° at atmospheric pressure for 12 h[6].



Lack of success was reported[9] in the attempted synthesis of chloromethyl phenyl sulfoxide by oxidation of chloromethyl phenyl sulfide. Likewise we found that sodium metaperiodate was not useful for the oxidation of aryl fluoromethyl sulfides to the corresponding sulfoxides. However, a modification of an older oxidation procedure of Tagaki et al.[10] employing *N*-bromosuccinimide afforded excellent yields in the conversion of aryl fluoromethyl sulfides to aryl fluoromethyl sulfoxides. In place of water or 70% methanol/water, methanol or tetrahydrofuran with only a few drops of added water proved to be effective. It is also important to maintain the temperature at 0°. Under these conditions the aryl α-fluoroalkyl sulfoxides are produced in greater than 90% yield (Table 2).



Fluoromethyl *p*-Tolyl Sulfide (2a):

To a solution of 18-crown-6 (0.264 g, 1.0 mmol) in anhydrous acetonitrile (10 ml) is added dry potassium fluoride (1.16 g, 20 mmol) and this is stirred for 1 h under nitrogen. Chloromethyl *p*-tolyl sulfide[7a] (1.73 g, 10 mmol) is added and the reaction mixture is heated with rapid stirring under reflux for 100 h. The reaction mixture is cooled in an ice bath and diluted with ice water (10 ml). It is then extracted with dichloromethane (3 × 40 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give an oily residue. This is distilled immediately to give the product **2a** as a colorless oil; yield: 1.33 g (85%); b.p. 60° (bath)/0.01 torr; n_D^{22} = 1.5415.

C_8H_9FS	calc.	C 61.52	H 5.80	S 20.52
(156.2)	found	61.33	5.55	20.75

Table 1. Preparation of Aryl Fluoromethyl Sulfides (**2**)

Product	R	Reaction time	Yield[a] [%]	m.p. or n_D^{22}	Molecular formula	¹H-N.M.R. ($CDCl_3$) δ [ppm]
2a	CH_3	100 h	85	1.5415	C_8H_9FS (156.2)[b]	7.5–7.0 (m, 4 H_{arom}); 5.63 (d, 2H, J = 53 Hz); 2.30 (s, 3H)
2b	H	100 h	83	1.5503	C_7H_7FS (142.2)	7.6–7.2 (m, 5 H_{arom}); 5.65 (d, 2H, J = 53 Hz)
2c[c]	Cl	110 h	79	1.5630	C_7H_6ClFS (176.6)	7.5–7.2 (m, 4 H_{arom}); 5.67 (d, 2H, J = 52 Hz)
2d	NO_2	110 h	81	98°[d]	$C_7H_6FNO_2S$ (187.2)	8.50 (d, 2H, J = 9 Hz); 7.52 (d, 2H, J = 9 Hz); 5.80 (d, 2H, J = 52 Hz)

[a] Yield of distilled product.

[b] Gave satisfactory microanalysis.

[c] Chloromethyl *p*-chlorophenyl sulfide was purchased from Aldrich Chemical Company.

[d] Recrystallized from methanol.

Table 2. Preparation of Aryl Fluoromethyl Sulfoxides (3)

Product	R	Yield [%]	m.p. or n_D^{22}	Molecular formula[a]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
3a	CH$_3$	95	52° (hexane)	C_8H_9FOS (172.2)	7.7–7.2 (m, 4H$_{arom}$); 5.03 (d, 2H, J=48Hz); 2.40 (s, 3H)
3b	H	96	1.5575	C_7H_7FOS (158.2)	7.7–7.2 (m, 5H$_{arom}$); 5.06 (d, 2H, J=48Hz)[b]
3c	Cl	91	74° (hexane)	C_7H_6ClFOS (192.6)	7.57 (s, 4H$_{arom}$); 5.08 (d, 2H, J=48Hz)
3d	NO$_2$	92	145° (CH$_3$OH)	$C_7H_6FNO_3S$ (203.2)	8.30 (d, 2H, J=9Hz); 7.95 (d, 2H, J=9Hz); 5.22 (d, 2H, J=48Hz)

[a] All products gave satisfactory microanalyses (C ±0.2%, H ±0.2%, S ±0.2%).

[b] In deuteroacetone the —CH$_2$F group appeared as an ABX pattern centered at δ=5.27 ppm with coupling constants of 9 and 48 Hz. An unusually large $\Delta\delta$ value of 16 Hz was observed for the two diastereotopic hydrogens in acetone-d_6.

Fluoromethyl *p*-Tolyl Sulfoxide (3a):

To a solution of **2a** (0.78 g, 5.0 mmol) in methanol (10 ml) is added *N*-bromosuccinimide (0.89 g, 5.0 mmol) and water (0.2 ml). This is stirred for 30 min at 0° and then diluted with cold water (20 ml). The product is extracted with dichloromethane (3 × 50 ml), dried (Na$_2$SO$_4$), and concentrated under vacuum to give **3a** as a slightly yellow solid (m.p. 50–51°); yield: 0.817 g (95%); m.p. 52° (from hexane).

		C	H	S
C_8H_9FOS	calc.	55.80	5.26	18.62
(172.2)	found	55.96	5.28	18.48

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