Use of Polyethylene Glycol in the Synthesis of Alkyl Fluorides from Alkyl Sulfonates

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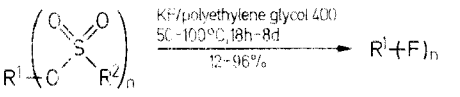
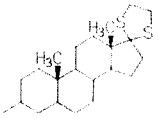
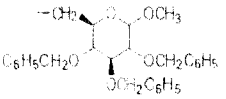
In the synthesis of monofluorinated organic compounds, the reaction of potassium fluoride with mesylates and tosylates of alcohols affords fluoro derivatives when polyethylene glycol 400 is used as solvent and catalyst. The limitation of this reaction is the solvolysis of the leaving group by the solvent; the phenomenon is controlled by the degree of steric hindrance around the reaction centre.

Much effort has been devoted to the synthesis of fluorinated compounds[1] such as steroids, antibiotics, sugars, and amino acids because of their biological activities. Although many methods[2] are known to transform aliphatic and alicyclic alcohols into the corresponding fluorinated compounds, the reaction of activated alcohol derivatives with alkalimetal fluorides seems to be the most important and simple method on a preparative scale. Starting from alkyl or aryl sulfonates, nucleophilic substitution of the sulfonate by the fluoride anion in an aprotic dipolar solvent,[3] in apolar solvents using crown ethers,[4] under phase-transfer catalytic conditions,[5] or using polymer-supported reagents[6] gives poor yields and often suffers some limitations due to the high reaction temperature, the catalyst deterioration, and the cost and toxicity of both the catalyst and the solvent. An interesting example is the conversion of 1-chlorooctane into 1-fluorooctane under phase-transfer conditions. In this reaction, the best yields are obtained in the presence of 0.33 mol equivalents of water with respect to the fluoride ion.[7] The reaction of alkyl sulfonates with fluoride ions affords poor yields when carried out in protic solvents such as methanol[8] or ethylene glycol;[9] yields are somewhat better in diethylene glycol.[10] Of the numerous polyethylene glycols tested by us as solvents in the preparation of C-fluoro compounds from the corresponding sulfonates, polyethylene glycol 400 was chosen for its low cost, its low volatility, and its capacity to dissolve some inorganic salts; if necessary, a co-solvent can be added.



1, 2	R^1	n	f	R^2
a	n-C_8H_{17}	1	g	CH_3
b	n-C_6H_{13}–CH	2	h	4-$CH_3C_6H_4$
c	$(CH_3)_3CCH_2$	1	i	2-naphthyl
		1	j	2,4,6-$(CH_3)_3C_6H_2$
d			1fk	$C_6H_5(CH_2)_2Br$
e		1		
f	$C_6H_5(CH_2)_2$	1		

The reaction of 5 mmol of potassium fluoride with 1 mmol of octyl mesylate (**1ag**) in 5 mL of polyethylene glycol 400 gave 1-fluorooctane (**2a**) almost pure (96% purity, 4% hydrolyzed compound, no trace of elimination products), but with poor recovery of the reaction products, this being mainly due to the reaction of the substrate with the solvent under fluoride ion catalysis; in fact, the reaction of the more hindered tosylate **1ah**, after a shorter reaction time, provided an equally pure fluoro compound, but with higher recovery of the reaction products. We carried out a second series of experiments with 2-phenylethylsulfonates, taking into consideration that with these compounds the elimination reaction proceeds more readily than with the octyl sulfonates **1ag** and **1ah**. To test the described methodology, substrates of biological interest were also submitted to the reaction. Thus, α-methyl-6-tosyl-6-deoxytri-*O*-benzylglucopyranoside (**1eh**) and 17,17-(1,2-ethanediyldithio)-3α-tosyloxy-5α-androstane (**1dh**) were transformed into the corresponding fluoro derivatives **2e** and **2d**, respectively. Increase in temperature promotes the reaction of the solvent hydroxy groups with the starting material. Sulfonates of cyclic alcohols give elimination products in high yield. With the examined sulfonic esters we noticed that when either the sulfonic acid part or the alcohol part of the molecule is hindered, the reactivity of the substrates towards the solvent hydroxy groups strongly decreases, thus favoring the desired fluorination reaction. Modified polyethylene glycols are now under investigation.

GLC analyses were carried out with a glass capillary column OV-1 (20 mt, 40 m, 0.25 mm ID; program: 2 min at 50°C, 20°C/min for 5 min

Table 1. Preparation of Alkyl Fluorides **2** from Alkyl Sulfonates **1**

Alkyl Sulfonate	Reaction Conditions		Yields[a]			b.p. (°C/Torr) of Product **2**	Molecular Formula[b] or b.p. (°C/Torr) reported
	Co-solvent	Time, Temperature	Alkyl Fluoride	Alkene	Alcohol		
1ag	–	50 h, 50–55°C	**2a**[c] 35 (96)	(–)	(4)	142–143/760	144.4/760[5]
1ah	–	27 h, 50–55°C	**2a** 59 (87)	(–)	(4)		
1bg	–	48 h, 50–55°C	**2b**[c] 59 (78)	(13)	(9)	57/42	54/38[5,6]
1bh	–	18 h, 50–55°C	**2b** 70 (75)	(17)	(7)		
1ch	–	60 h, 100°C	no reaction				
1dh[e]	DMF	8 d, 60°C	**2d** 12[d]	65[d]	(–)	m.p. 128–130	$C_{21}H_{33}FS_2$[6] (368.6)
	diglyme	8 d, 60°C	**2d** 24[d]	52[d]	(–)		
1eh[f]	–	44 h, 70°C	**2e** 63[d]	(–)	5[d]	oil	$C_{28}H_{31}FO_5$[12] (466.5)
1fk	–	30 h, 50–55°C	**2f** 10 (25)	(68)	(–)	53–54/10	50–51/10[13]
1fg	–	7 d, 50–55°C	**2f** 63 (92)	(5)	(3)		
1fh	–	43 h, 50–55°C	**2f** 81 (94)	(4)	(2)		
1fj	–	3 d, 60–65°C	**2f** 88 (86)	(4)	(10)		
1fi	–	40 h, 55–60°C	**2f** 80 (90)	(3)	(6)		

[a] Yield of isolated product, based on alkyl sulfonate **1** submitted to the reaction. The relative percentage of the three reaction products, determined using GLC analysis, is given in brackets.
[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.25, N ±0.30.
[c] 1-Fluorooctane and 2-fluorooctane were purified by distillation of the crude product. They were used together with 1-octene and 2-octene as standards in GLC analysis.
[d] Purified by column chromatography.
[e] The starting alcohol was prepared according to Ref. 16.
[f] α-Methyl 6-hydroxy-2,3,4-tri-*O*-benzylglucopyranoside was prepared according to Ref. 17.

Table 2. NMR Data of Some Fluoro Compounds **2**

Compound	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)	^{19}F-NMR (acetone-d_6/$CFCl_3$) δ, *J*(Hz)
2d	1.32 (s, 3H); 1.09–2.52 (m, 20H); 2.76–3.08 (m, 4H); 3.54–3.80 (m, 4H); 4.49 (d, 1H, J_{H-F} = 48)	
2e		−232.2 (dt, J_{H^6-F} = 48, J_{H^5-F} = 28)
2f	2.9 (dt, 2H, J_{H-F} = 24); 4.5 (dt, 2H, J_{H-F} = 48); 7.2 (s, 5H)	

at 180°C). ^{1}H-NMR spectra were recorded on Varian XL-200 or Perkin Elmer-Hitachi R-24 spectrometers. An ^{19}F-NMR spectrum was registered with a Varian XL-200 spectrometer.

Potassium fluoride (Merck) was dehydrated at 100°C/1 Torr for 2 h, and PEG 400 (Fluka) at 135°C/17 Torr for 4 h. Methane sulfonic and *p*-toluenesulfonic esters were prepared as described in Refs. 14 and 15. Octanol, 2-octanol, 2,2-dimethylpropanol (neopentyl alcohol), 1-octene, D-glucose, 3α-hydroxy-5α-androstan-17-one, 2-phenylethanol, 2-bromoethylbenzene, and styrene were supplied by FLUKA AG, CH-9470 Buchs.

1-Fluoro-2-phenylethane (2f); Typical Procedure:
To a stirred solution of 2-phenylethyl tosylate (**1fh**; 2.137 g, 8.52 mmol) and polyethylene glycol 400 (23 mL), potassium fluoride (2.47 g, 42.6 mmol) is added. The mixture is stirred at 50–55°C for 43 h, then diluted with saturated NaCl solution (230 mL), and extracted with Et_2O (3 × 15 mL). The extract is dried (Na_2SO_4), passed through a column of silica gel (20 g) to eliminate polyethylene glycol 400 which is present in the organic solvent after the extraction, and evaporated. For analytical purposes, the crude material (842 mg) is subjected to GLC analysis [Composition of the mixture: *1-fluoro-2-phenylethane* (**2f**), 94%; *styrene*; 4%; *2-phenylethanol*, 2%]. For preparative purposes, product **2f** is purified by distillation; yield: 666 mg (63%); b.p. 53–54°C/10 Torr.[13]

17,17-(1,2-Ethanediyldithio)-3β-fluoro-5α-androstane (2d):
17,17-(1,2-Ethanediyldithio)-3α-tosyloxy-5α-androstane (**1dh**; 304 mg, 0.58 mmol), potassium fluoride (170 mg, 2.9 mmol), PEG 400 (3 mL), and diethylene glycol dimethyl ether (diglyme; 3 mL) are mixed with stirring and this mixture is allowed to react for 8 days at 55–60°C. The mixture is then diluted with saturated NaCl solution (50 mL), and extracted with Et_2O (3 × 10 mL). The organic extract is dried (Na_2SO_4), the solvent is evaporated *in vacuo*, and the residue is separated by column chromatography on silica gel using petroleum ether as eluent to give the following two main components:

17,17-(1,2-Ethanediyldithio)-5α-Δ²-androstene; yield: 106 mg (52%).
^{1}H-NMR ($CDCl_3$): δ = 0.6–2.6 (m, 26H); 2.9–3.4 (m, 4H); 5.6 (br. s, 2H).

17,17-(1,2-Ethanediyldithio)-3β-fluoro-5α-androstane (**2d**); yield: 53 mg (24%); m.p. 128–130°C. (see Tables).

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