COMMUNICATIONS

Organic Fluorine Compounds Part XLIV[1]. Preparation and Reactions of Epifluorohydrin

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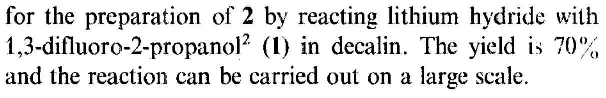
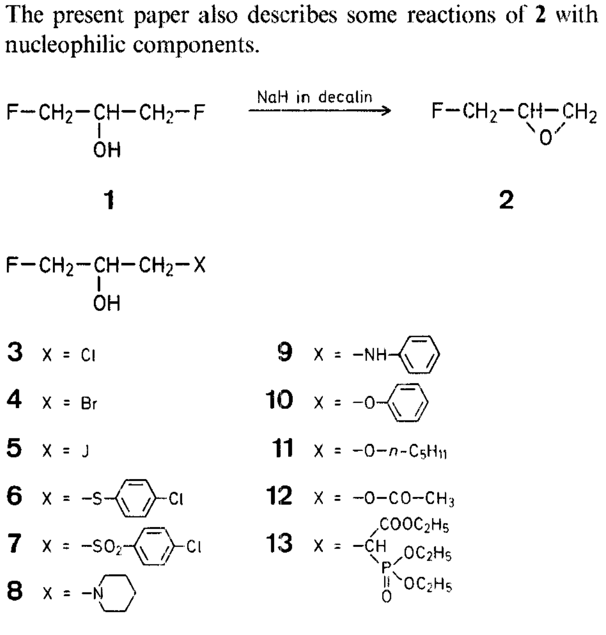
The best previously known method for the preparation of epifluorohydrin[2] (2) is rather tedious and gives a low overall yield. This result may be the reason that except for polymerization studies[3,4] the reactions of 2 have been little investigated[2,5,6]. We have developed a new method for the preparation of 2 by reacting lithium hydride with 1,3-difluoro-2-propanol[2] (1) in decalin. The yield is 70% and the reaction can be carried out on a large scale.

The present paper also describes some reactions of 2 with nucleophilic components.





The reactions of 2 with aqueous hydrochloric, hydrobromic, and hydroiodic acids give the corresponding 3-chloro- (3), 3-bromo- (4), and 3-iodo-1-fluoropropanols (5). Mercaptans do not react without a catalyst, even on heating, but in the presence of a small amount of potassium hydroxide in methanol, the corresponding hydroxy sulfides (e.g. 6) are obtained. Compound 6 was oxidized to the crystalline sulfone 7.

Amines also react with 2. The reaction with piperidine in the cold yields 3-fluoro-1-piperidino-2-propanol (8); brief heating of 2 with aniline yields 1-anilino-3-fluoro-2-propanol (9).

The reaction of 2 with hydroxy compounds is less fruitful. Phenol reacts with 2 only under basic conditions to give 3-fluoro-1-phenoxy-2-propanol (10) in low yield. A similarly low yield of 3-fluoro-1-pentoxy-2-propanol (11) is obtained with pentanol under acidic conditions. 1-Acetoxy-3-fluoro-2-propanol (12) was isolated in moderate yield from the reaction of 2 with acetic acid.

As an example of the reaction of an active methylene group, diethyl ethoxycarbonyl-lithiomethanephosphonate was reacted with 2; a low yield of 13 was obtained.

Compounds 1 and 3–13 exhibit characteristic N.M.R. spectra of the F—CH$_2$—CH(OH)-group. The CH$_2$F group gives a double doublet with $J_{HF_{gem}}=45$–50 Hz and $J_{HH_{vic}}=4$–5 Hz. The I.R. spectra show a broad absorption at $\nu_{max}=3300$–$3500\ cm^{-1}$ for the hydroxy groups.

Epifluorohydrin (2):

1,3-Difluoro-2-propanol[2] (192 g, 2 mmol) was added slowly and with cooling to a suspension of lithium hydride (17.5 g) in decalin (170 ml). The mixture was refluxed for 15 min. and distilled; yield: 108 g (71%); b.p. 85–88°. The N.M.R. spectrum of 2 is very complicated, but has been fully resolved[7,8].

1-Bromo-3-fluoro-2-propanol (4):

Epifluorohydrin (7.6 g, 0.1 mol) was added slowly with cooling (ice water) to 48% hydrobromic acid (30 g). After 20 min. at 0° and 1 hr at room temperature, dichloromethane was added, followed by potassium carbonate until the upper layer was basic. The organic phase was worked up by washing to neutrality, drying with magnesium sulfate, and evaporation in vacuo. The residue was distilled at reduced pressure; yield: 15.5 g (95%); b.p. 70°/20 mm.

C_3H_6BrFO	calc.	F 12.1	Br 50.9
	found	11.8	50.6

N.M.R. (CCl$_4$): $\delta=4.50$ (d,d, 2H, CH$_2$F, $J_{HF_{gem}}=46$ Hz, $J_{HH_{vic}}=4$ Hz), 4.12 (1H, α to hydroxy, centre of m), 3.48 (d,d, 2H, CH$_2$Br, $J_{HH_{vic}}=5$ Hz, $J_{HF(1,3\,coupling)}=2$ Hz). This spectrum is typical of all compounds described in this study. It was recorded on a "Varian T-60" using TMS as an internal reference.

1-Chloro-3-fluoro-2-propanol (3)

was obtained analogously; yield: 90%; b.p. 145–149°[2].

3-Fluoro-1-iodo-2-propanol (5)

was obtained analogously; yield: 80%; b.p. 89–90°/20 mm.

C_3H_6FJO	calc.	J 62.3
	found	61.9

1-(4-Chlorophenylthio)-3-fluoro-2-propanol (6):

To a solution of epifluorohydrin (8.4 g, 0.11 mol) and 4-chlorothiophenol (15.5 g, 0.11 mol) in methanol (60 ml), a solution of potassium hydroxide (0.5 g) in 60% methanol (6 ml) was added with stirring. An exothermic reaction occurred. After 5 min., the reaction mixture was poured into very dilute acetic acid, extracted with chloroform, and treated in the usual way; yield: 12 g (50%); b.p. 135–137°/1 mm.

$C_9H_{10}ClFOS$	calc.	C 49.0	H 4.5	F 8.6
	found	48.9	4.4	8.6

1-(4-Chlorophenylsulfono)-3-fluoro-2-propanol (7)

was prepared by oxidation of **6** with hydrogen peroxide in acetic acid and was recrystallized from benzene/hexane; yield: 70%; m.p. 85°.

$C_9H_{10}ClFO_3S$	calc.	C 42.8	H 4.0	F 7.6
	found	42.7	3.9	7.6

3-Fluoro-1-piperidino-2-propanol (8):

To a cooled solution of epifluorohydrin (9.5 g) in methanol (15 ml), a solution of piperidine (15 g) in methanol (30 ml) was added. The mixture was kept in ice for 12 hr and at room temperature for 24 hr. It was then evaporated and the residue was distilled in vacuo; yield: 19.5 g (95%); b.p. 64–65°/0.5 mm.

$C_8H_{16}FNO$	calc.	F 11.8	N 8.7
	found	11.7	8.6

1-Anilino-3-fluoro-2-propanol (9):

A solution of epifluorohydrin (7.6 g) and aniline (17 g) in methanol (20 ml) was refluxed for 15 min. It was then allowed to stand at room temperature for 2 days. The solvent was evaporated in vacuo and the residue distilled in vacuo; yield: 19 g (80%); b.p. 120–121°/0.8 mm.

$C_9H_{12}FNO$	calc.	C 63.9	H 7.1	F 11.2
	found	64.3	6.8	11.0

3-Fluoro-1-phenoxy-2-propanol (10):

To a solution of epifluorohydrin (7.6 g) and phenol (9.5 g) in methanol (40 ml), a solution of potassium hydroxide (1 g) in 80% methanol (5 ml) was added. The mixture was refluxed for 1 hr and after a further 12 hr at room temperature it was poured into water and extracted with benzene. The organic phase was washed with cold 10% aqueous sodium hydroxide solution and worked up in the usual manner; yield: 3.5 g (20%); b.p. 96°/0.9 mm.

$C_9H_{11}FO_2$	calc.	C 63.5	H 6.5	F 11.2
	found	63.3	6.5	11.0

3-Fluoro-1-pentoxy-2-propanol (11):

To a mixture of epifluorohydrin (7.6 g) and pentanol (10 g), conc. sulfuric acid (0.2 ml) was added with stirring. After the exothermic reaction had subsided, the mixture was allowed to stand at room temperature overnight and was then poured into benzene. The organic phase was washed with saturated potassium carbonate solution and worked up in the usual manner; yield: 1.5 g (10%); b.p. 104–106°/30 mm. A considerable amount of pentanol was recovered.

$C_8H_{17}FO_2$	calc.	C 58.5	H 10.4	F 11.6
	found	58.7	10.4	11.5

N.M.R. (CCl_4): $\delta = 4.20$ (d, d, 2H, CH_2F, $J_{HF_{gem}} = 47$ Hz, $J_{HH_{vic}} = 5$ Hz), 3.90 (1H, centre of m), 3.46 (m, $—CH_2—O—CH_2—$).

1-Acetoxy-3-fluoro-2-propanol (12):

Epifluorohydrin (7.6 g) was slowly added to a boiling solution of conc. sulfuric acid (1 g) in acetic acid (7 ml). The mixture was heated at 120–130° (bath) for 2 hr, dissolved in dichloromethane, washed with potassium carbonate solution, and worked up as usual; yield: 5 g (47%); b.p. 70–75°/1.5 mm.

$C_5H_9FO_3$	calc.	F 14.0
	found	14.2

Ethyl 2-Diethylphosphono-5-fluoro-4-hydroxypentanoate (13):

To a suspension of lithium hydride (0.8 g) in benzene, a solution of ethyl diethylphosphonoacetate (22.4 g) in benzene was added. The mixture was refluxed for 20 min. Then epifluorohydrin (7.6 g) was added and heating was continued for 1.5 hr. The reaction mixture was cooled, washed with dilute hydrochloric acid, and worked up as usual; yield: 6 g (20%); b.p. 139–141°/1 mm.

$C_{11}H_{22}FO_6P$	calc.	C 44.0	H 7.3	P 10.3
	found	44.1	7.2	9.9

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