REGIOSELECTIVE HYDROFLUORINATION OF α,ω-DIOL DIGLYCIDYL ETHERS

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ABSTRACT: Ring opening of diepoxides using three kinds of fluorinating reagents has been realized. Regioselectivity of the hydrofluorination depends essentially on acidity of the used reagent. Thus, highest yields and best selectivity were obtained with the less acidic reagent.

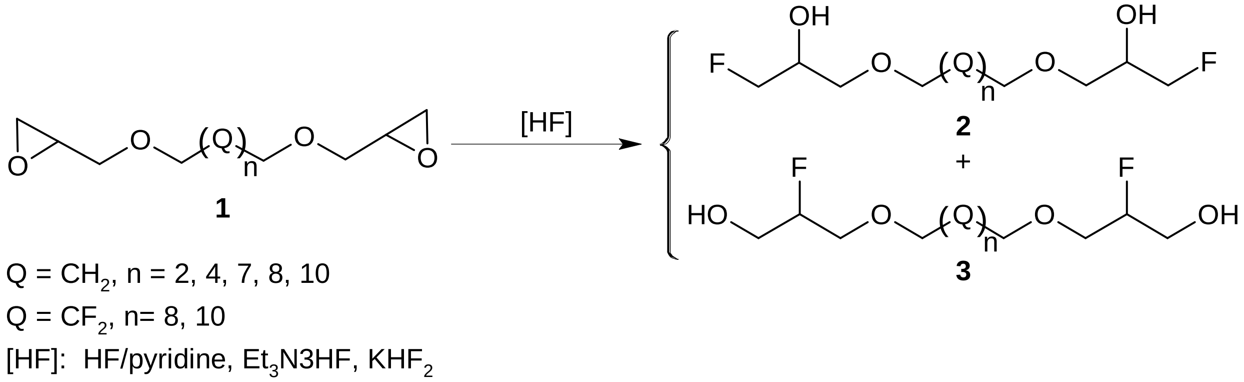
Key Words: diepoxide, hydrofluorination, fluorohydrin.

INTRODUCTION

Hydrocarbon and fluorocarbon diepoxides are considered as versatile intermediates in organic synthesis, particularly in cyclization, polymerization, resins preparation, enzyme inhibition and anti-bacterial drugs formulation [1-11].

In the last decades, many fluorinating reagents have been used in ring opening of oxiranes. Thus, pyridinium poly(hydrogen fluoride) (Olah reagent), alkylamine hydrogen fluoride, potassium dihydrogen trifluoride, tetrabutylammonium bifluoride, tetrabutylammonium dihydrogentrifluoride, boron trifluoride and potassium hydrogen fluoride were the most frequently used reagents to introduce fluorine atom into oxiranic derivatives [12-19].

We report herein the hydrofluorination of hydro- and fluorocarbon diepoxides **1** using HF/pyridine (method A), triethylamine trishydrofluoride (method B) and potassium hydrogen fluoride (method C) (scheme 1) [3].



Scheme 1

We grouped in table I the overall regioisomeric ratios and yields of fluorohydrins **2** and **3** obtained according to methods A, B and C.

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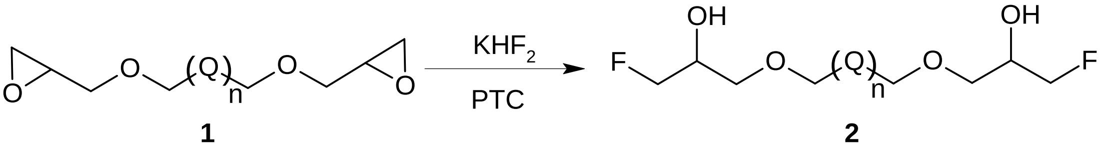
Table I: Ring opening of diepoxides **1**

Method[a]	Q/n	Overall ratio of fluorohydrins[b] **2**:**3**	Overall yield (%)
A	CH_2/8	52:48	53
B	CH_2/8	72:28	74
C	CH_2/8	97:03	87

[a] A: HF/pyridine, B: $Et_3N,3HF$ and C: KHF_2

[b] Viscous oils

The results presented in table I denote that, (i) whatever the fluorinating reagent, the dissymmetrical fluorohydrins are not observed as indicated by ^{19}F NMR, and (ii) yields and regioselectivity improve when going from method A to C [19]. Therefore, method C, using potassium hydrogen fluoride in phase transfer catalysis (PTC), constitutes an interesting way for fluorohydrins **2** preparation (scheme 2).



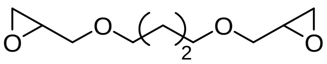
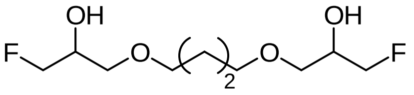
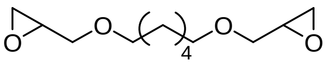
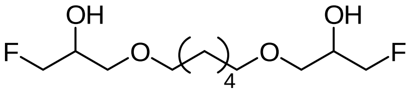
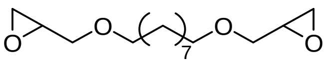
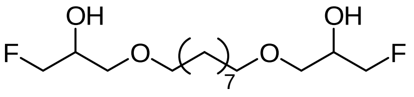
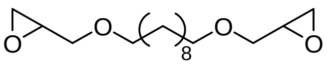
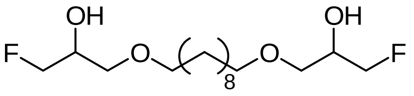
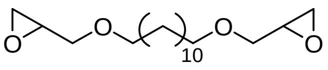
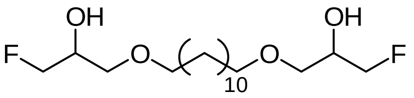
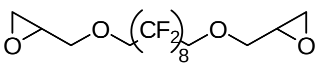
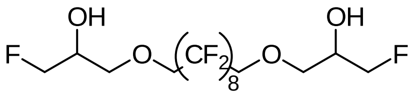
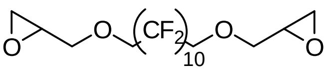
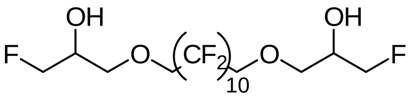
Q = CH_2, n = 2, 4, 7, 8, 10

Q = CF_2, n= 8, 10

Scheme 2

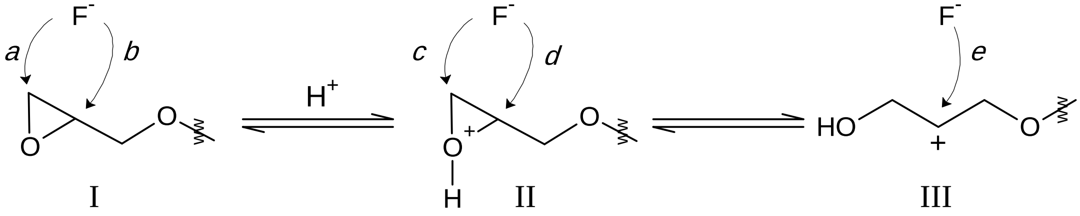
Fluorohydrins **2** obtained by this method are grouped in table II. Moderate yields of fluorohydrins **2f** and **2g** may be due to the lesser solubility of the corresponding fluorinated diepoxides **1f** and **1g**.

Table II: fluorohydrins **2** prepared according to method C

Diepoxide **1**	Fluorohydrin **2**	Reaction time (h)	Isolated yield (%)
 **1a**	 **2a**	21	80
 **1b**	 **2b**	21	82
 **1c**	 **2c**	25	81
 **1d**	 **2d**	25	87
 **1e**	 **2e**	25	80
 **1f**	 **2f**	36	52
 **1g**	 **2g**	36	53

RESULTS AND DISCUSSION

The acidic/nucleophilic character of reagents is presumably the main factor from which depend the results. So, in method A, the most acidic reagent (HF/pyridine) leads to species II and III in which attacks *d* and *e* furnish fluorohydrin **3**, whereas attack *c* leads to **2** (scheme 3). With the less acidic reagent KHF_2, only species I may be involved. Hence, on the basis of steric effect, fluoride ion reacts essentially with the terminal carbon of oxiranic ring (attack *a*) leading to fluorohydrin **2**.



Scheme 3

CONCLUSION

Regioselective hydrofluorination of α,ω-diol diglycidyl ethers was accomplished using three fluorinating reagents: Olah reagent, triethylamine trishydrofluoride and potassium hydrogen fluoride. This latter was the best reagent in terminal fluorine fluorohydrins synthesis. In the present investigation, nonfluorinated diepoxides were more reactive than the fluorinated analogues.

EXPERIMENTAL SECTION

IR spectra were recorded on a Bruker IFS 66V/S spectrometer. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker AC 300 at 300 MHz for ^{1}H, 282 MHz for ^{19}F and 75 MHz for ^{13}C. TMS was used as standard reference for ^{1}H and ^{13}C NMR spectra and $CFCl_3$ for ^{19}F NMR spectra. The following abbreviations are used to denote multiplicity of the signals in the NMR spectra (s, singlet; t, triplet; m, multiplet; dm, doublet of multiplet and b, broad). Analytical TLC was conducted using percolated aluminium TLC plates: silica gel/UV 254. Column chromatography was carried out with silica gel (silica gel, 0.060-0.200 mm, 40 Å).

Hydrofluorination of diepoxides: General Procedure

Method A

To a solution of diepoxide **1** (4.9 mmol) in CH_2Cl_2 (2 mL) in a polyethylene flask cooled to 0°C, was added pyridinium poly(hydrogen fluoride) (70%) (5 mL) dissolved in dichloromethane (5 mL). The mixture was magnetically stirred, first at 0°C for 15 min and then at room temperature until completion of the reaction (TLC, eluent ethyl acetate /petroleum ether 80/20). The mixture was poured into ice water (20 mL) and extracted with $CHCl_3$ (3×30 mL). The combined organic layers were washed with saturated aqueous K_2CO_3 and dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate/petroleum ether 80/20) to yield fluorohydrin **2** (viscous oil).

Method B

A mixture of diepoxide **1** (7.6 mmol) and $Et_3N.3HF$ (4.9 ml, 30 mmol) was stirred at 100°C for 5-15 h. It was poured into $CHCl_3$ (30 mL) and neutralized with saturated aqueous K_2CO_3. The organic layer was separated. After extraction with $CHCl_3$ (4×40 mL) the organic phases were combined and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the obtained viscous oil was purified by column chromatography (eluent: ethyl acetate/petroleum ether 80:20).

Method C

A mixture of diepoxide **1** (7.5 mmol), KHF_2 (1.56 g, 20 mmol) and TBAHS (0.2 g, 0.6 mmol) was stirred progressively at 110°C for 21-36 h. Then, it was diluted with $CHCl_3$ (100 mL) and filtrated. The solvent was evaporated and the residue was purified by column chromatography (eluent: ethyl acetate / petroleum ether 80:20) to obtain compound **2** (viscous pale yellow oil).

1,12-difluoro-4,9-dioxadodecane-2,11-diol (2a)

Yield: 80%. IR: ν (cm^{-1}): ν_{C-F} = 1015, ν_{C-O-C} = 1102, ν_{O-H} = 3406. ^{1}H NMR ($CDCl_3$/TMS): δ (ppm) 1.35 (m, 4H, $(C\underline{H}_2)_2$), 2.60 (b, 2H, 2×$O\underline{H}$), 3.45 (m, 4H, 2×$OC\underline{H}_2(CH_2)_2$), 3.60 (ddm, 4H, 2×$OC\underline{H}_2CHOHCH_2F$), 3.84 (m, 2H, 2×$C\underline{H}OHCH_2F$), 4.45 (dm, 4H, 2×$C\underline{H}_2F$). ^{13}C NMR ($CDCl_3$/TMS): δ (ppm) 45.00 (s, C, $(\underline{C}H_2)_2$), 68.67 (d, C, $\underline{C}HOHCH_2F$, $^{2}J_{CF}$ = 19.49 Hz), 68.85 (s, C, $O\underline{C}H_2(CH_2)_2$), 71.34 (d, C, $O\underline{C}H_2CHOHCH_2F$, $^{3}J_{CF}$ = 6.49 Hz), 83.35 (d, C, $\underline{C}H_2F$, $^{1}J_{CF}$ = 170.32 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ (ppm) -70.92 (dt, 2F, $CH_2\underline{F}$, $^{2}J_{HF}$ = 47.15 Hz, $^{3}J_{HF}$ = 18.52 Hz). Anal. Calcd. for $C_{10}H_{20}F_2O_4$, C, 49.58, H, 8.32. Found, C, 49.43, H, 8.16.

1,14-difluoro-4,11-dioxatetradecane-2,13-diol (2b)

Yield: 82%. IR: ν (cm^{-1}): ν_{C-F} = 1020, ν_{C-O-C} = 1100, ν_{O-H} = 3416. ^{1}H NMR ($CDCl_3$/TMS): δ (ppm) 1.45 (m, 8H, $(C\underline{H}_2)_4$), 2.80 (b, 2H, 2×$O\underline{H}$), 3.52 (m, 4H, 2×$OC\underline{H}_2(CH_2)_4$), 3.62 (ddm, 4H, 2×$OC\underline{H}_2CHOHCH_2F$), 3.82 (m, 2H, 2×$C\underline{H}OHCH_2F$), 4.40 (dm, 4H, 2×$C\underline{H}_2F$). ^{13}C NMR ($CDCl_3$/TMS): δ (ppm) 42.65 (s, C, $(\underline{C}H_2)_4$), 67.95 (d, C, $\underline{C}HOHCH_2F$, $^{2}J_{CF}$ = 19.45 Hz), 68.12 (s, C, $O\underline{C}H_2(CH_2)_4$), 69.85 (d, C, $O\underline{C}H_2CHOHCH_2F$, $^{3}J_{CF}$ = 6.47 Hz), 84.44 (d, C, $\underline{C}H_2F$, $^{1}J_{CF}$ = 169.13 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ (ppm) -70.12 (dt, 2F, $CH_2\underline{F}$, $^{2}J_{HF}$ = 49.71 Hz, $^{3}J_{HF}$ = 18.45 Hz). Anal. Calcd. for $C_{12}H_{24}F_2O_4$, C, 53.32, H, 8.95. Found, C, 53.11, H, 8.03.

1,17-difluoro-4,14-dioxaheptadecane-2,16-diol (2c)

Yield: 81%. IR: ν (cm^{-1}): ν_{C-F} = 1009, ν_{C-O-C} = 1105, ν_{O-H} = 3408. ^{1}H NMR ($CDCl_3$/TMS): δ (ppm) 1.61 (m, 14H, $(C\underline{H}_2)_7$), 2.80 (b, 2H, 2×$O\underline{H}$), 3.55 (m, 4H, 2×$OC\underline{H}_2(CH_2)_7$), 3.65 (ddm, 4H, 2×$OC\underline{H}_2CHOHCH_2F$), 3.85 (m, 2H, 2×$C\underline{H}OHCH_2F$), 4.42 (dm, 4H, 2×$C\underline{H}_2F$). ^{13}C NMR ($CDCl_3$/TMS): δ (ppm) 45.50 (s, C, $(\underline{C}H_2)_7$), 67.92 (d, C, $\underline{C}HOHCH_2F$, $^{2}J_{CF}$ = 19.28 Hz), 68.57 (s, C, $O\underline{C}H_2(CH_2)_7$), 70.08 (d, C, $O\underline{C}H_2CHOHCH_2F$, $^{3}J_{CF}$ = 6.49 Hz), 84.75 (d, C, $\underline{C}H_2F$, $^{1}J_{CF}$ = 168.49 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ (ppm) -70.32 (dt, 2F, $CH_2\underline{F}$, $^{2}J_{HF}$ = 45.71 Hz, $^{3}J_{HF}$ = 20.02 Hz). Anal. Calcd. for $C_{15}H_{30}F_2O_4$, C, 57.67, H, 9.68. Found, C, 57.33, H, 9.45.

1,18-difluoro-4,15-dioxaoctadecane-2,17-diol (2d)

Yield: 87%. IR: ν (cm^{-1}): ν_{C-F} = 1010, ν_{C-O-C} = 1105, ν_{O-H} = 3406. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.65 (m, 16H, $(C\underline{H}_2)_8$), 2.70 (b, 2H, 2×$O\underline{H}$), 3.60 (m, 4H, 2×$OC\underline{H}_2(CH_2)_8$), 3.67 (ddm, 4H, 2×$OC\underline{H}_2CHOHCH_2F$), 3.82 (m, 2H, 2×$C\underline{H}OHCH_2F$), 4.40 (dm, 4H, 2×$C\underline{H}_2F$). ^{13}C NMR ($CDCl_3$/TMS) δ (ppm) 35.82 (s, C, $(\underline{C}H_2)_8$), 67.86 (d, C, $\underline{C}HOHCH_2F$, $^{2}J_{CF}$ = 19.43 Hz), 68.94 (s, C, $O\underline{C}H_2(CH_2)_8$), 72.32 (d, C, $O\underline{C}H_2CHOHCH_2F$, $^{3}J_{CF}$ = 6.58 Hz), 83.76 (d, C, $\underline{C}H_2F$,$^{1}J_{CF}$ = 169.18 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ (ppm) -70 (dt, 2F, $CH_2\underline{F}$, $^{2}J_{HF}$ = 49.23 Hz, $^{3}J_{HF}$ = 18.29 Hz). Anal. Calcd. for $C_{16}H_{32}F_2O_4$, C, 58.87, H, 9.88. Found, C, 58.69, H, 9.72.

1,20-difluoro-4,17-dioxadecadecane-2,19-diol (2e)

Yield: 80%. IR: ν (cm^{-1}): ν_{C-F} = 1010, ν_{C-O-C} = 1105, ν_{O-H} = 3406. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 1.47 (m, 20H, $(C\underline{H}_2)_{10}$), 3.10 (b, 2H, 2×$O\underline{H}$), 3.50 (m, 4H, 2x$OC\underline{H}_2(CH_2)_{10}$), 3.62 (ddm, 4H, 2x$OC\underline{H}_2CHOHCH_2F$), 3.80 (m, 2H, $C\underline{H}OHCH_2F$), 4.46 (dm, 4H, 2×$C\underline{H}_2F$). ^{13}C NMR ($CDCl_3$/TMS) δ (ppm) 38.53 (s, C, $(\underline{C}H_2)_{10}$), 68.17 (d, C, $\underline{C}HOHCH_2F$, $^{2}J_{CF}$ = 19.47 Hz), 68.88 (s, C, $O\underline{C}H_2(CH_2)_{10}$), 72.32 (d, C, $O\underline{C}H_2CHOHCH_2F$, $^{3}J_{CF}$ = 6.47 Hz), 83.76 (d, C, $\underline{C}H_2F$, $^{1}J_{CF}$ = 167.38 Hz). ^{19}F NMR ($CDCl_3$/ $CFCl_3$) δ (ppm) - 70 (dt, 2F, $CH_2\underline{F}$, $^{2}J_{HF}$ = 47.01 Hz, $^{3}J_{HF}$ = 20.25 Hz). Anal. Calcd. for $C_{18}H_{36}F_2O_4$, C, 60.99, H, 10.24. Found, C, 60.68, H, 10.01.

Octadecafluorotetradecane-2,13-diol (2f)

Yield: 52%. IR: ν (cm^{-1}): ν_{C-F} = 1085, ν_{C-O-C} = 1102, ν_{O-H} = 3406.^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 3.10 (b, 2H, 2×$O\underline{H}$), 3.65 (m, 4H, $OC\underline{H}_2CH(OH)CH_2F$), 3.85 (m, 2H, $C\underline{H}OHCH_2F$), 4.10 (m, 4H, $OC\underline{H}_2(CF_2)_8$), 4.40 (dm, 4H, $C\underline{H}_2F$).^{13}C NMR ($CDCl_3$/TMS) δ (ppm) 60.05 (d, C, $O\underline{C}H_2(CF_2)_8$, $^{3}J_{CF}$ = 6.47 Hz), 67.68 (s, C, $O\underline{C}H_2CHOHCH_2F$), 68.52 (d, C, $\underline{C}HOHCH_2F$, $^{2}J_{CF}$ = 20.24 Hz), 87.2 (d, C, $\underline{C}H_2F$, $^{1}J_{CF}$ = 166.8 Hz), 104.67 (m, C, $(\underline{C}F_2)_8$). ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ (ppm) -119.12 (m, 4F, 2×$CH_2C\underline{F}_2$), -121.5 (m, 4F, 2×$CH_2CF_2C\underline{F}_2$), -123.73 (m, 8F, 2×$CH_2(CF_2)_2(C\underline{F}_2)_2$), -70 (dt, 2F, $CH_2\underline{F}$, $^{2}J_{HF}$ = 48.45 Hz, $^{3}J_{HF}$ = 19.34 Hz). Anal. Calcd. for $C_{16}H_{16}F_{18}O_4$, C, 31.28, H, 2.63. Found, C, 31.11, H, 2.34.

Docasafluorohexadecane-2,15-diol (2g)

Yield: 53%. IR: ν (cm^{-1}): $\nu_{C\text{-}F}$ = 1080, $\nu_{C\text{-}O\text{-}C}$ = 1105, $\nu_{O\text{-}H}$ = 3420. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 3.68 (m, 4H, $OC\underline{H}_2CHCH_2F$), 3.80 (b, 2H, 2×$O\underline{H}$), 3.88 (m, 2H, $C\underline{H}OHCH_2F$), 4.15 (m, 4H, $OC\underline{H}_2(CF_2)_{10}$), 4.45 (dm, 4H, $C\underline{H}_2F$). ^{13}C NMR ($CDCl_3$/TMS) δ (ppm) 61.12 (t, C, $O\underline{C}H_2(CF_2)_{10}$, $^{2}J_{CF}$ = 20.70 Hz), 67.68 (d, C, $O\underline{C}H_2CHOHCH_2F$, $^{3}J_{CF}$ = 6.84 Hz), 68.52 (d, C, $\underline{C}HOHCH_2F$, $^{2}J_{CF}$ = 19.84 Hz), 87.2 (d, C, $\underline{C}H_2F$, $^{1}J_{CF}$ = 166.8 Hz), 106.67-129.50 (m, C, $(\underline{C}F_2)_{10}$). ^{19}F NMR ($CDCl_3$/$CFCl_3$) δ (ppm) -118.92 (m, 4F, 2×$CH_2C\underline{F}_2$), -122.12 (m, 4F, 2×$CH_2CF_2C\underline{F}_2$), -125.73 (m, 12F, 2×$CH_2(CF_2)_2(C\underline{F}_2)_3$), -72,11 (dt, 2F, $CH_2\underline{F}$, $^{2}J_{HF}$ = 47.12 Hz, $^{3}J_{HF}$ = 18,75 Hz). Anal. Calcd. for $C_{18}H_{16}F_{22}O_4$, C, 30.27, H, 2.26. Found, C, 30.22, H, 2.12.

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