Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: F. Ammadi, M. M. Chaabouni, H. Amri & A. Baklouti (1993) Synthesis of α-Cyano-β-fluoro-α-hydroxyesters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:17, 2389-2395, DOI: 10.1080/00397919308011124

To link to this article: http://dx.doi.org/10.1080/00397919308011124

SYNTHETIC COMMUNICATIONS, 23(17), 2389-2395 (1993)

SYNTHESIS OF α-CYANO-β-FLUORO-α-HYDROXYESTERS

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ABSTRACT : The ring opening fluorination of glycidic gem-cyanoesters was achieved by action of pyridine polyhydrofluoride at 25°C in dichloromethane. The regioselective nucleophilic substitution reaction allows the synthesis of a new class of fluorohydrins with OH, CN and CO_2R on the same carbon atom.

The synthesis of fluorohydrins from the ring opening reaction of epoxides by hydrogen fluoride[1], pyridine polyhydrofluoride[2], trimethylamine dihydrofluoride[3], triethylamine[4] and diisopropylamine[5] trishydrofluoride, silicon tetrafluoride[6] and potassium hydrogendifluoride with certain additives[7] has been widely investigated . The choice of fluorinating reagent depends most of the time on the structure of the starting oxiranes[8] . Thus in the case of α-cycano-α,β-epoxyesters, the action of amines hydrofluorides at 100°C yields polymers. At a lower temperature (60°C) the starting material was recovered with a considerable amount of polymerization products. When the pyridine polyhydrofluoride (HF/Pyridine 70% w/w) is used, the ring opening fluorination reaction takes place. Table 1 gives the prepared functionalized fluorohydrins at 25°C in dichloromethane used as solvent .

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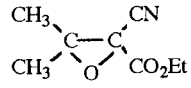
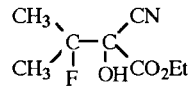
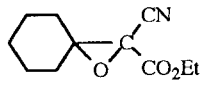
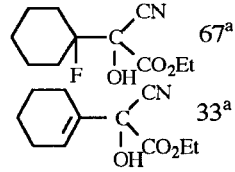
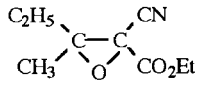
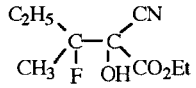
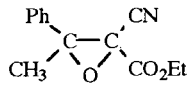
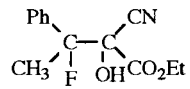
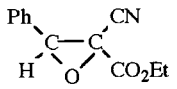
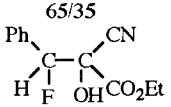
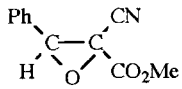
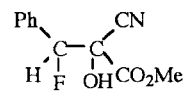
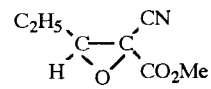
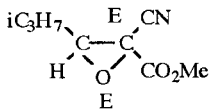
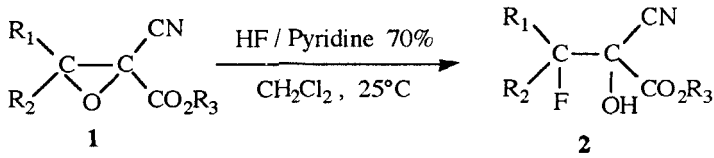
Table 1 : Reaction of α-cyano-α,β-epoxyesters with HF/Pyridine (70%w/w) at 25°C in CH_2Cl_2.

Entry	Epoxide **1**	Time (h)	Fluorohydrin **2** (D_1/D_2)[b]	Yield(%)
a		28		**80**
b		30	 67[a] 33[a]	**60**
c	 Z/E	40	 55/45	**61**
d	 Z/E : 40/60	40	 65/35	**73**
e	 E	96	 60/40	**75**
f	 E	96	 60/40	**60**
g		96	no reaction	—
h	 E	96	no reaction	—

a : Ratio has been determined by GC .

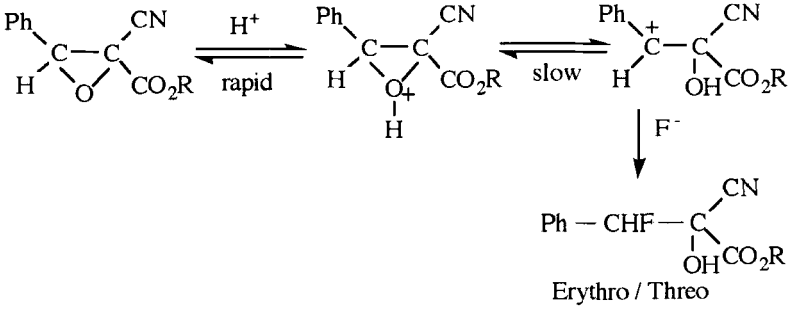
b : Diastereoisomers D_1,D_2 had been determined by ^{19}F NMR .



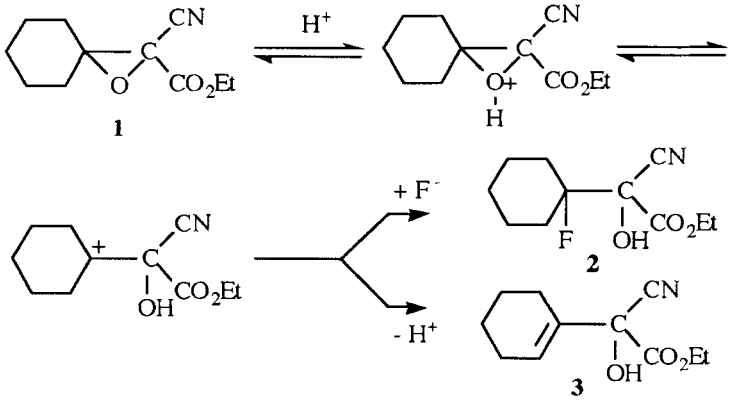
1 2

These bifunctional fluorohydrins with the hydroxy, cyano and ester groups on the same carbon atom are described for the first time. Examination of the results in table 1 allows the determination of the reaction mechanism :

- The formation of erythro-threo fluorohydrins mixture from the (**E**) epoxides (**1e**) and (**1f**) can't be explained without assuming, since the medium is acidic, the existence of an epoxonium-benzylic carbocation equilibrium. Furthermore the reaction regioselectivity, indicates that the fluoride anion reacts on the benzylic carbocation intermediate as shown below.



- The carbocation intermediate formation may be deduced from the results related to cyclohexanic compound (**1b**) . The mixture of fluorohydrin (**2**) and ethylenic compound (**3**) is due to the two possibilities of carbocation evolution (combination with fluoride anion or loss of α proton).



- The ring opening reaction does'nt take place with the oxiranes (**1g**) and (**1h**) for which the starting product is recovered. In this case the secondary carbocations intermediates, much less stable than tertiary and benzylic ones, are not formed.The very rapid equilibrium epoxide $\rightleftharpoons$ epoxonium is therefore limited .

All these results show that the mechanism of the reaction is a monomolecular nucleophilic substitution.

EXPERIMENTAL

^1H NMR spectra were obtained on a Jeol NM-PMX apparatus (60 MHz) using TMS as internal standard and ^{19}F NMR spectra on a Bruker AC 200 (188,3 MHz) using $CFCl_3$ as internal standard . Mass spectra were obtained on a Hewlett Packard 5989 A spectrometer. Infrared spectra were recorded on a Perkin-Elmer 681 instrument. Epoxides **1(a-h)** were prepared by the reaction of an aqueous solution of sodium hypochlorite with the corresponding ethylenic cyanoesters in the presence of alumina as catalyst[9].

Synthesis of fluorohydrins

General procedure : All the reactions were carried out in a polyethylene flask. To a solution of 70 % HF/Pyridine (10 ml) in CH_2Cl_2 (10 ml), glycidic gem -

cyanoester (15 mmol) dissolved in CH_2Cl_2 (5 ml) was added dropwise at 25°C. The reaction mixture was stirred at this temperature for 28 to 96 hours. The mixture was shaken with cold water (50 ml) and extracted with diethylether . The combinated organic extracts were washed with aqueous (5%) solution of sodium carbonate then with water and finally dried over $MgSO_4$. After evaporation of the solvent, the residue was distilled or purified by flash chromatography on silicagel.

Ethyl-2-cyano-3-fluoro-2-hydroxy-3-methylbutanoate (2a) :

bp : 68°C/0,05torr. IR($CHCl_3$,ν cm^{-1}) : 3500(OH) ; 2250(C≡N) ; 1750(C=O) . ^1H NMR(CCl_4, δppm) : 1,40(t,3H, J=7,0Hz); 1,41(d,3H, J=21,1Hz) ; 1,60(d,3H, J=21,1Hz); 4,41(q,2H, J=7,0Hz); 4,50(s,1H). ^{19}F NMR($CDCl_3$, δppm): -148,0(heptuplet, J=21,4Hz). Mass m/z(%) : 39(14) ; 41(6) ; 43(18) ; 45(18) ; 54(10) ; 57(10) ; 61($C_3H_6F^+$,100) ; 70(30) ; 101(10); 102(13) ; 117(10) ; 129(21).

Ethyl-2-cyano-2-(1-fluorocyclohexyl)-2-hydroxyacetate (2b) :

Yellow oil (hexane / ethylacetate 6:4). IR($CHCl_3$,νcm^{-1}): 3500(OH) ; 2240(C≡N) ; 1750(C=O). ^1H NMR($CDCl_3$, δppm): 1,33(t,3H,J=7,1Hz); 1,40-2,30(m,10H); 3,97(s,1H); 4,36(q,2H, J=7,1Hz). ^{19}F NMR($CDCl_3$,δ ppm): -167,8(m). Mass m/z(%): 27(28) ; 28(12); 29(38) ; 39(16) ; 41(23) ; 53(13) ; 55(14) ; 59(12) ; 79(11) ; 81($C_6H_9^+$,100) ; 82(9) ; 101($C_6H_{10}F^+$,31) ; 129(6); 202($M^{+\cdot}$-HCN,1).

Ethyl-2-cyano-2-(cyclohex-1-enyl)-2-hydroxyacetate (3b) :

Yellow oil (hexane / ethylacetate 6:4) . IR ($CHCl_3$, νcm^{-1}) : 3500(OH); 2240(C ≡N); 1750(C=O); 1650(C=C). ^1H NMR($CDCl_3$, δ ppm): 1,40(t,3H, J=7,1Hz); 1,40-2,3(m,8H) ; 4,17(s,1H) ; 4,42(q,2H, J=7,1Hz) ; 6, 23(m,1H). Mass m/z(%) : 27(74) ; 28(26) ; 29(80) ; 39(43) ; 41(39) ; 51(19) ; 52(15) ; 53(57); 67(39) ; 77(21) ; 79(60) ; 80(18) ; 81(95) ; 109($C_7H_9O^+$, 100) ; 136(20) ; 182($M^{+\cdot}$-HCN,1) ; 209($M^{+\cdot}$, 1) .

(Erythro-Threo)-Ethyl-2-cyano-3-fluoro-2-hydroxy-3-methylpentan--oate (2c):

bp : 100°C/0,01torr . IR($CHCl_3$,δppm) : 3500(OH) ; 2260(C≡N) ; 1750(C=O). ^1H NMR(CCl_4, δppm): 1,03 (t,3H, J=7,2Hz) ; 1,13-1,90(m,8H) ; 4,45 (q,2H, J=7,2Hz) ; 3,83(s,1H). ^{19}F NMR($CDCl_3$,δppm) : D_1(55%): -157,3(m). D_2(45%): -158,0(m) . Mass m/z(%): 39(24) ; 41(17) ; 43(17) ; 45(17) ; 47(67) ; 53(15) ; 54(18) ; 55(100) ; 69(23) ; 75($C_4H_8F^+$, 94) ; 84(48) ; 101(18) ; 102(30) ; 129(14) ; 176($M^{+\cdot}$-HCN, 2).

(Erythro-Threo)-Ethyl-2-cyano-3-fluoro-2-hydroxy-3-phenylbutan--oate (2d) :

Yellow oil (hexane / diethylether 9:1). IR ($CHCl_3$, νcm^{-1}) : 3500(OH) ; 2260(C≡N); 1750(C=O). ^1H NMR($CDCl_3$,δppm): D_1(65%): 1,16(t,3H,J=7,0Hz); 1,90(d,3H , J=23,0Hz) ; 4,20 (q,2H, J=7,0 Hz) ; 7,37(s,5H). D_2(35 %) : 1,23 (t,3H, 7,0 Hz) ; 1,96(d,3H, J=23,0 Hz) ; 3,46(q,2H, J=7,0 Hz) ; 7,42(s, 5H) . ^{19}F NMR($CDCl_3$, δppm) : D_1(65%) : -174,0 (q, J=23,5 Hz). D_2(35 %): - 169,8 (q, J=23,5 Hz) . Mass m/z (%) : 29(10) ; 77(11) ; 103(21) ; 123($C_8H_8F^+$, 100) ; 224(M^+-HCN, 3).

(Erythro-threo)-Ethyl-2-cyano-3-fluoro-2-hydroxy-3-phenylpropan--oate (2e) :

Yellow oil (hexane / diethylether 9:1) . IR($CHCl_3$,νcm^{-1}) : 3500(OH) ; 2260(C≡N) ; 1750(C=O) ; ^1H NMR($CDCl_3$,δppm): D_1(60%) :1,33(t,3H, J=7Hz) ; 3,40 (q,2H, J=7,0 Hz) ; 5,76 (d,1H, J=44,0 Hz) ; 7,35 (s,5H). D_2(40%): 1,28 (t,3H, J=7,0 Hz) ; 4,35(q,2H, J=7,0 Hz) ; 5,66 (d,2H, J=44,0 Hz) ; 7,38(s,5H) . ^{19}F NMR($CDCl_3$,δppm): D_1(60%): -187,3(d, J=44,0Hz). D_2(40%): -185,8(d,

J=44,0Hz). Mass m/z(%): 29(32) ; 83(13) ; 109($C_7H_6F^+$, 100) ; 100(8) ; 210($M^{+\cdot}$-HCN, 4).

(Erythro - Threo) - Methyl-2-cyano-3- fluoro-2-hydroxy-3-phenyl - -propanoate (2f) :

Yellow oil (hexane / diethylether 9:1) . IR($CHCl_3$,νcm^{-1}) : 3500(OH) ; 2260(C≡N) ; 1750(C=O) ; ^1H NMR($CDCl_3$,δ ppm): D_1(60%) : 3,95 (s, 3H) ; 5,75(d,1H, J=44,0Hz) ; 7,40(s,5H). D_2(40%): 3,86(s,3H); 5,63(d,1H,J=44Hz); 7,35(s,5H). ^{19}F NMR($CDCl_3$, δppm): D_1(60%): -187,3 (d, J=43,9Hz). D_2(40%): - 185,9(d, J=43,9Hz). Mass m/z(%) : 15(15) ; 39(10) ; 59(15); 83(20) ; 109($C_7H_6F^+$, 100) ; 196($M^{+\cdot}$-HCN, 2).

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(Received in The Netherlands 16 April 1993)