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NEW SYNTHETIC ROUTES TO β-FLUORO β-PHENYLLACTIC ACID DERIVATIVES AND β-FLUOROCYANOHYDRINS

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SUMMARY

Alkyl phenyl 2,3-epoxycarboxylates from the well-known Darzens glycidic esters synthesis react under very mild conditions with pyridinium-poly-hydrogen fluoride to give corresponding 3-fluoro 3-phenyllactates in almost quantitative yields with a high regio and stereoselectivity.

This method can be applied successfully to other glycidic derivatives : glycidoamides, glycidonitriles, glycidoiminoesters...

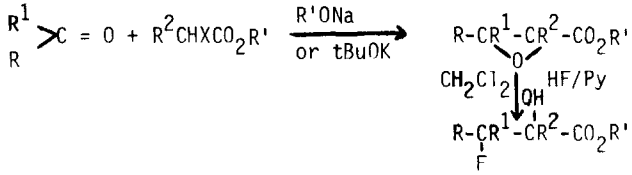
The spectrometric propertities (IR, NMR) are presented.

INTRODUCTION

Many synthetic methods have been described for the preparation of fluorohydrins :

- halogen exchange reaction between chlorohydrins and potassium fluoride [1].
- reaction of epoxides and liquid HF [2] or its complex with THF [3,4] or dialkylamines [5,6].
- reaction of epoxides with boron trifluororide etherate [7,8].

Some of these reactions require high temperatures and moreover are made inconvenient owing to the difficulty in separating the components of the reaction mixtures and to the frequent polymerization or rearrangement that occur. The use of pyridinium-poly-hydrogen fluoride as the source of HF [9,10] for the ring opening of epoxide enables us to obtain almost quantitatively 3-fluoro 3-phenyllactates under mild conditions by the route described in the following scheme :



We have examined the reaction of HF/pyridine with a variety of epoxides (glycidonitriles, glycidamides and glycidoiminoesters) which, under the same conditions give the expected fluorohydrins in almost quantitative yields. The results of the preparations of the various fluorohydrins studied are summerized in the Table II.

RESULTS

Preparation and characterization of the starting glycidates

The starting epoxides have been prepared by the Darzens reaction between a carbonyl compound and an α-haloester using potassium t-butylate (method A) [11,12] or by the oxydation of the α,β-unsaturated esters with m-chloroperbenzoic acid in methylene chloride (method B) [13].

Physical properties of the glycidates prepared and their NMR characteristics are summarized in Table I.

Preparation of the β-fluorolactates and fluorocyanohydrins

The glycidates, glycidonitriles and glycidamides readily available could react with hydrogen fluoride in pyridine solution. The fluoro compounds were isolated in very good yields (Table II).

The course of the reaction has been followed by thin layer chromatography (eluent : hexane/ethylacetate 8/2 v/v).

Identification

(^{1}H and ^{19}F) NMR are good methods to identify these classes of compounds.

The NMR spectra were correlated with structures on the basis of the known configurations [6] of the 3-fluorolactates 22, 28 and 30, and by noting that chemical shifts of fluorine resonances in the all isomers agree with prediction [14].

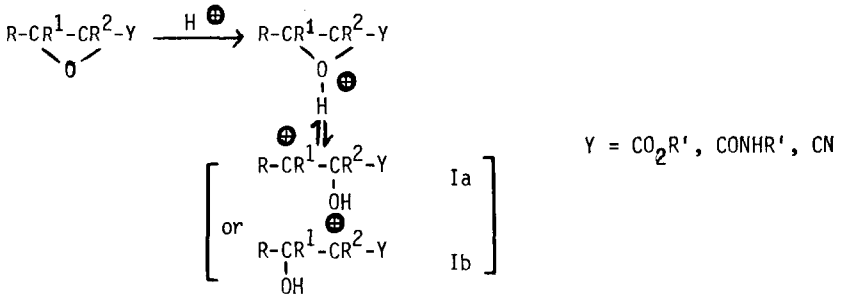
When the compounds prepared carry β-phenyl groups, the fluorine atom (cf. paragraph 'Discussion') is at the benzylic position. J. Jullien and col. [14], observed that in these compounds the fluorine are in the erythro isomers shifts at higher field than in the corresponding threo ones.

On the other hand, the configuration of compound 23b has been proved by its subsequent cyclization with alcoholic potassium hydroxide.

The NMR properties are summerized in the Tables IIIa and IIIb.

DISCUSSION

Since the ring opening of epoxides in acidic solutions occurs through the initial formation of an epoxonium ion, the electron donating or withdrawing character of substituent R groups and the stability of the intermediate carbocation have a major influence on the reaction direction and the conditions required for the ring opening step.



Thus, the epoxonium ion is in an equilibrium with two secondary α-hydroxy carbenium ions (Ia) and (Ib) and the reaction could a priori take place on either of two carbon atoms. When R is a phenylgroup, the carbenium ion (Ia) is highly stabilized and opening the glycidic derivatives 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13, 15, 17, 18, 19 and 20, one could obtain preferentially a single product its fluorine atom being in the benzylic position. For the starting materials 11, 12, 14, 19 and 20, the electron withdrawing effect of carboxylate, amide and cyano groups prevents stretching of the C-O bond contiguous to it and it is the cycloalkyl ring carbon which becomes positive. The reaction led selectively to the products which have the fluorine atom in the β position from Y functional groups.

Substituents in the phenyl, cycloalkyl or in the epoxide ring would not alter the course of the reaction.

Results assembled in Table II, show that the reaction of HF/pyridine with the glycidates is regioselective.

We have also examined the stereoselectivity of the reaction.

1. The reaction of hydrogen fluoride in pyridine solution with the glycidates of known cis and trans isomers compositions (see Table I) led to the corresponding fluorolactates containing the threo and erythro isomers in about the same compositions (Table II).

2. When methyl trans-3-phenylglycidate 3a methyl trans-2-methyl-3-phenylglycidate 6 and trans-3-phenyl glycidamide 13b, were treated with HF/pyridine, they yielded 88 %, 95 % and 92 % of the erythro isomers 23a, 26 and 34 respetivaly. The other products were the threo isomers.

TABLE I

The glycidic derivatives R-CR^1(α)-O-CR^2(β)-Y. Yields, physical constants and ^{1}H NMR (CCl_4/TMS).

N°	R	R^1	R^2	Y	Yield %	$E_{p_{mmHg}}$ °C/ or m.p.	Method	% a cis / trans	^{1}H NMR, δ:pμm ; J:Hz						
									δH_α	δH_β	$J_{\alpha\beta}$	R	Y	R^1	R^2
1	C_6H_5	H	H	CO_2Et	68	$118_{1.5}$	A	22 78	3.80(d) * 3.27(d)	4.10(d) * 4.01(d)	2.5 1.5	7.23	3.95(s) * OCH_2		
2	C_6H_5	H	H	CO_2Me	51	$84_{0.5}$	A	21 79	3.78(d) 3.35(d)	4.15(d) 4.01(d)	2.5 2.1	7.23(s)	3.66(s) 3.73(s)		
3	C_6H_5	H	H	CO_2Me	45	$84_{0.5}$	B	0 100	 3.35(d)	 4.01(d)	 2.1	 7.23(s)	 3.73(s)		
4	C_6H_5	H	H	CO_2iPr	55	$95_{1.5}$	B	0 100	 3.46(d)	 4.06(d)	 2.0	 7.31(s)	1.25(d) 5.10(h)		
5	4-Cl-C_6H_4	H	H	CO_2Et	46	$128_{0.09}$	A	35 65	3.41(d) 3.38(d)	4.10(d) 4.03(d)	2.0 1.7	7.28(m) 7.30(m)	1.33(t) } 4.38(q) } 1.25(t) } 4.26(q) }		
6	C_6H_5	H	CH_3	CO_2Me	80	Liq [b]	B [c]	0 100	 	 4.36(s)	 	7.32(s)	 3.75(s)		1.35(s)
7	C_6H_5	H	C_6H_5	CO_2Me	65	Liq [b]	B	15 85	3.90(s) 4.40(s)	 	 	7.2-7.35 (m)	3.42(s) 3.60(s)		7.2-7.35 (m)
8	C_6H_5	CH_3	H	CO_2Me	55	$84_{0.7}$	B	41 59	3.53(s) 3.30(s)	 	 	7.23(s)	 3.75(s)	 1.80(s)	
9	C_6H_5	i-C_3H_7	H	CO_2Me	58	103_1	A	75 25	3.70(s) 3.50(s)	 	 	7.30(s)	3.67(s) 3.81(s)	1.95(m) } 0.89(d) } 1.90(m) } 1.0(d) }	
10	C_6H_5	CH_3	CH_3	CO_2Me	56	Liq	A	45 55	 	 	 	7.28(s)	3.45(s) 3.74(s)	1.68(s) 1.82(s)	1.28(s) 1.37(s)

11	$-(CH_2)_5-$		H	CO_2Et	71	$75_{0.9}$	A		3.15(s)			1.80-1.65 (m)	4.15(q) 1.30(t) J=7.1Hz			
12	$-(CH_2)_4-$		H	CO_2Et	58	93_{15}	A		3.28(s)			1.73-1.60(m)	4.10(q) 1.37(t) J=7.10Hz			
13	C_6H_5	H	H	$CONH_2$	54	146-147	A	80 20	3.75(d) 3.73(d)	4.20(d) 4.16(d)	1.5	7.30(s)	$CONH_2$ 7.66(broad)			
14	$-(CH_2)_5-$		H	$CONH_2$	50	134.5	A		3.38(s)			1.85-1.60 (m)	$CONH_2$ 7.43 (broad)			
15	C_6H_5	H	H	CNH OEt	40[d]		A									
16	C_6H_5	H	H	CN	51	$86_{0.7}$	A	59 41	3.60(d) 3.23(d)	4.12(d) 4.30(d)	4.1 2.0	7.35(s) 7.30(s)				
17	C_6H_5	CH_3	H	CN	57	$114_{2.5}$	A	56 44	3.47(s) 3.21(s)			7.30(s) 7.26(s)		1.71(s) 1.90(s)		
18	C_6H_5	H	CH_3	CN	60	105_{10}	A	49 51		4.10(s) 4.35(s)		7.31(s) 7.29(s)		1.30(s) 1.35(s)		
19	$-(CH_2)_5-$		H	CN	80	$70_{1.5}$	A		3.26(s)						1.85-1.30(m)	
20	$-(CH_2)_4-$		H	CN	75	64_3	A		3.23(s)						1.75-1.60(m)	

[a] The proportions of the cis and trans isomers have been determined by NMR analysis. [b] A sample containing 43% of the cis isomer have been obtained by the Darzens method. NMR (CCl_4/ TMS) δ 1.73(s,3H,$\alpha C\underline{H}_3$),3.43(s,3H,$OC\underline{H}_3$), 4.06(s,1H,βH), 7.32(s,5H,$C_6\underline{H}_5$). [c] These products were chromatographed over neutral alumina using benzene-hexane (1/1 v/v) as eluent. [d] *This product has been obtained by the reaction of sodium ethoxide with a mixture of* benzaldehyde and chloroacetonitrile 12. The reaction furnished a mixture of 17 (40 %) and 18 (60 %) (total yield 62 %).

* These values have been obtained after irradiation of the signals at 0.9-1.30 ppm.

TABLE II

Preparation of fluorhydrins from glycidic derivatives (Part 1).

N°	HF/Py w/w	Reaction time (H)	Temp°C	Products[a]	% threo / % erythro	N°	Yield %
1	70	1	25	$C_6H_5CHFCHOHCO_2Et$ (n.c.)	20 / 80	21	95
2	45	120	25	$C_6H_5CHFCHOHCO_2Me$	15 / 85	22	90
3a	45	120	25	$C_6H_5CHFCHOHCO_2Me$	12 / 88	23a	90
3b	45	120	25	$C_6H_5CHFCHOHCO_2Me$ [c]	75	23b	85
4	70	2	25	$C_6H_5CHFCHOHCO_2iPr$ [c] (n.c.)	85	24	90
5	45	24	50	$pCl\text{-}C_6H_4CHFCHOHCO_2Et$ (n.c.)	40 / 60	25	85
6	70	1	25	$C_6H_5CHFC(CH_3)OHCO_2Me$	5 / 95	26	95
7	60	24	25	$C_6H_5CHFC(C_6H_5)OHCO_2Me$ [c] (n.c.)	10 / 65	27	80
8	70	4	25	$C_6H_5C(CH_3)FCHOHCO_2Me$	46 / 54	28	95
9	70	4	25	$C_6H_5C(i\text{-}C_3H_7)FCHOHCO_2Me$ [d] (n.c.)	30 / 10	29	90
10	70	4	25	$C_6H_5C(CH_3)FC(CH_3)OHCO_2Me$	50 / 50	30	95
11	60	3	25	$(CH_2)_5CFCHOHCO_2Et$		31	90
12	60	3	25	$(CH_2)_4CFCHOHCO_2Et$		32	85

(continued on facing page)

Table II *(cont.)*

13a	70	1	20	$C_6H_5CHFCHOHCONH_2$ (n.c.) 35 65	33a	96
13b	70	1	20	$C_6H_5CHFCHOHCONH_2$ [e] (n.c.) 8 92	33b	94
14	70	24	25	$(CH_2)_4$ $CFCHOHCONH_2$ (n.c.)	34	85
15	70	1	25	$C_6H_5CHFCHOHCNH$ [f] (n.c.) OEt 42 58	35	90
16	70	1	25	$C_6H_5CHFCHOHCN$ 57 43	36	91
17	70	1	25	$C_6H_5C(CH_3)FCHOHCN$ 55 45	37	96
18	70	1	25	$C_6H_5CHFC(CH_3)OHCN$ 50 50	38	90
19	70	3	25	$(CH_2)_5$ $CFCHOHCN$	39	90
20	70	2	25	$(CH_2)_4$ $CFCHOHCN$	40	88

[a] The proportions of the threo and erythro isomers of the products have been determined by ^{19}F NMR.

[b] Yields refer to purified products.

[c] For starting materials (4,5 and 8) 5-15% of the isomeric 2-fluoro 3-hydroxy 3-phenyl propanoates have been detected by ^{19}F NMR.

[d] Four compounds have been detected by ^{19}F NMR: 32 (60% erythro and threo) methyl 4-fluoro 2-hydroxy 3-methyl 3-phenyl pentanoate (n.c.) Φ:145.6,148.8 (two multiplets).

[e] This epoxide has been obtained by the reaction of methyl trans-3-phenyl--glycidate with aqueous ammonia (sp. gr. 0.9).

[f] From the mixture of the epoxides 17 and the 18 and HF/Pyridine, 39 was obtained as its hydrofluoride salt, m.p. 135-136°C (uncorrected).

TABLE III a

$R\text{-}\overset{F}{\underset{|}{C}}R^1\text{-}\overset{OH}{\underset{|}{C}}R^2\text{-}Y$ - ^1H NMR properties ($CDCl_3$/ TMS, δ ppm, J Hz)

N°	R	R^1	R^2	Y	$\delta_{H\alpha}$ (F, T)	$\delta_{H\beta}$	$J_{\alpha\beta}$	$J_{FH\ gem}$	$J_{FH\ vic.}$	δ_{OH}	δ_R	Other signals
21	C_6H_5	H	H	$CO_2C_2H_5$	4.25(dd) 4.18(dd)	5.60 (dd) 5.65 (dd)	4.2 2.5	46.5 46.3	25.5 15.2	3.70 (s)	7.28 (s)	
22	C_6H_5	H	H	CO_2CH_3	4.48(dd) 4.30(dd)	5.54(dd) 5.62 (dd)	4.5 2.6	46.0 45.0	27.0 15.0	3.70(s)	7.25(s)	3.53 (s) OCH_3 3.65 (s) OCH_3
25	4-Cl-C_6H_4	H	H	$CO_2C_2H_5$	4.50(dd) 4.46(dd)	5.53(dd) 5.56(dd)	4.2 2.3	45.0 44.5	22.5 14.5	3.60(s)	7.28(m) 7.30(m)	1.30(t)CH_3CH_2,4.1(q)OCH_2CH_3 1.25(t)CH_3CH_2, 4.15(q)CH_2CH_3
26	C_6H_5	H	CH_3	CO_2CH_3		5.56(d) 5.55(d)		44.3 44.0		3.80(s)	7.36(m) 7.38(m)	3.65(s) OCH_3, 1.24(d) αCH_3 3.76(s) OCH_3, 1.26(d) αCH_3
27	C_6H_5	H	C_6H_5	CO_2CH_3	4.62(d) 4.50(d)			44.5 44.0		3.85(s)	7.25-7.5 (m)	3.70(s) OCH_3 3.75(s) OCH_3
28	C_6H_5	CH_3	H	CO_2CH_3	4.51(d) 4.38(d)				J_{FCCH_α}=20.5} J_{FCCH_β}=22.9} J_{FCCH_β}=18.5} J_{FCCH_α}=23.8}	5.60(s)	7.33(m)	3.48(s) OCH_3, 1.71(d) βCH_3 3.56(s) OCH_3, 1.78(d) βCH_3
29	C_6H_5	i-C_3H_7	H	CO_2CH_3	4.49(d) 4.27(d)				J_{FCCH_β}=19.0} J_{FCCH_α}=25.5} J_{FCCH_β}=18.5} J_{FCCH_α}=25.5}	3.76(s)	7.35(s)	3.32(s) OCH_3 3.45(s) OCH_3
30	C_6H_5	CH_3	CH_3	CO_2CH_3					23.0 23.5	3.65(s)	7.35(m)	3.50(s)OCH_3,1.70(d)βCH_3,1.48 (s)αCH_3 3.57(s)OCH_3,1.76(d) βCH_3,1.5(s)αCH_3

31	$-(CH_2)_5-$		H	$CO_2C_2H_5$	4.18(d)				J_{FH_α}=14.2	4.60(s)	2.43-1.50 (m)	4.25(q) $\underline{CH_2}CH_3$, 1.24(t) $\underline{CH_3}CH_2$ $J_{HH\ vic.}$=7.10
32	$-(CH_2)_4-$		H	$CO_2C_2H_5$	4.04(d)				$J_{FH\alpha}$=20.5	4.57(s)	2.50-1.45 (m)	4.20(q) CH_2CH_3, 1.23(t)CH_3CH_2 $J_{HH\ vic.}$=7.1
33+	C_6H_5	H	H	$CONH_2$	4.36(dd) 4.56(dd)	5.97(dd) 5.76(dd)	4.00 2.10	45.0 45.6	23.0 11.3	3.0(s)	7.55(m)	
34+	$-(CH_2)_5-$		H	$CONH_2$	4.16(d)				$J_{FH\alpha}$=22.0	4.61(s)	2.35-1.50 (m)	5.75(s broad) NH_2
35+	C_6H_5	H	H	CNH OC_2H_5	4.21(dd) 4.28(dd)	5.50(dd) 5.52(dd)	4.20 2.5	45.1 45.5	26.0 16.5	3.78(s)	7.28(s)	
36	C_6H_5	H	H	CN	4.58(dd) 4.76(dd)	5.44(dd) 5.65(dd)	6.00 4.2.	47.0 46.5	15.0 21.2	4.05(s)	7.32(s)	
37	C_6H_5	CH_3	H	CN	4.58(d)				J_{FCCH_α}=13.5 J_{FCCH_3}=23.2 J_{FCCH_α}=17.2 J_{FCCH_3}=23.2	4.10(s)	7.40(s)	1.78(d) αCH_3 J=23.2 1.76(d) αCH_3 J=23.2
38	C_6H_5	H	CH_3	CN		5.42(d) 5.56(d)		47.0 46.3		4.20(s)	7.30(s)	1.30(s) αCH_3 1.28(s) αCH_3
39	$-(CH_2)_5-$		H	CN	4.45(d)				$J_{FH\alpha}$=16.0	4.25(s)	2.35-1.25 (m)	
40	$-(CH_2)_4-$		H	CN	4.55(d)				$J_{FH\alpha}$=15.5	4.15(s)	2.50-1.70 (m)	

+ $(CD_3)_2SO$, external TMS

TABLE III b

$R\text{-}CR^1(F)\text{-}CR^2(OH)\text{-}Y$ - ^{19}F NMR ($CDCl_3$/ CCl_3F, δ ppm, Φ Hz)

N°	R	R^1	R^2	Y	Erythro / Threo Φ	J_{FH} gem	J_{FH} vic.
21	C_6H_5	H	H	$CO_2C_2H_5$	188.90(dd) 193.7 (dd)	45.0 45.3	25.5 15.2
22	C_6H_5	H	H	CO_2CH_3	189.0(dd) 194.9(dd)	45.6 45.5	26.0 15.8
25	4-Cl-C_6H_4	H	H	$CO_2C_2H_5$	186.7(dd) 192.1(dd)	45.0 44.5	18.5 16.0
26	C_6H_5	H	CH_3	CO_2CH_3	170.1(d) 182.8(d)	44.3 44.0	
27	C_6H_5	H	C_6H_5	CO_2CH_3	168.8(d) 171.0(d)	44.3 44.0	
28	C_6H_5	CH_3	H	CO_2CH_3	162.18(dd) 157.9(dd)		J_{FCCH_3} = 23.0 J_{FCCH} = 20.5
29	C_6H_5	i-C_3H_7	H	CO_2CH_3			$J_{FCCH(OH)}$=17.0; $J_{FCCH<}$=26.0 $J_{FCCH(OH)}$=19.0; $J_{FCCH<}$=25.0
30	C_6H_5	CH_3	CH_3	CO_2CH_3	156.1(dd) 157.8(dd)		23.0 23.5

31	$-(CH_2)_5-$		H	$CO_2C_2H_5$	158.8(m)		14.2
32	$-(CH_2)_4-$		H	$CO_2C_2H_5$	154.75(m)		14.50
33	C_6H_5	H	H	$CONH_2$	182.43(dd) 195.27	45.0 45.6	22.9 11.3
34	$-(CH_2)_5-$		H	$CONH_2$	167.1(m)		$J_{FH\alpha}$ =22.0
35	C_6H_5	H	H	CNH OC_2H_5	181.5(dd) 194.2(dd)	41.5 45.5	26.0 16.5
36	C_6H_5	H	H	CN	181.8(dd) 193.2(dd)	47.0 46.5	15.0 21.2
37	C_6H_5	CH_3	H	CN	155.92(dq) 157.25(dq)		$J_{FCCH\alpha}$= 13.0; J_{FCCH_3} = 22.9 $J_{FCCH\alpha}$= 17.2; J_{FCCH_3}= 23.0
38	C_6H_5	H	CH_3	CN	169.6(d) 172.41(d)	46.5 46.0	
39	$-(CH_2)_5-$		H	CN	168.25(m)		$J_{FH\alpha}$= 16.0
40	$-(CH_2)_4-$		H	CN	154.7(m)		$J_{FH\alpha}$= 15.5

3. The reaction, realized under the same conditions with the oxide 3b, which is the cis isomer of 3a, led to a mixture of methyl threo-3-fluoro-3-phenyllactate 23b (75 %), methyl 3-phenylpyruvate (10 %) and methyl threo-2-fluoro-3-phenyllactate (15 %).

All these results allow us to say that the mechanism of the reaction of HF/pyridine with the glycidates we have studied is probably a trans-addition. This trans-addition of HF on the epoxides is in agreement with the former works [15,16].

EXPERIMENTAL

NMR Spectra were taken on Varian EM 360 and A60 NMR Spectrometers at 60 MHz for ^{1}H and on Brucker Spectrospin at 84,67 MHz for ^{19}F.

1. General procedure for the synthesis of glycidic derivatives

a) Using Potassium t- Butoxide

To a mixture of one equivalent of ketone or aldehyde and one equivalent of α-bromoester, α-bromoacetamide or α-chloroacetonitrile was added with stirring under nitrogen a freshly prepared solution of one equivalent of potassium in dried t-butyl alcohol. The temperature was kept at 15° and the mixture was allowed to stir overnight at this temperature. The solvent was removed under vacuum and the residue was dissolved in 100 ml of water and extracted with ether. The ether layers were washed with water dried (Na_2SO_4) and evaporated and the product was then distilled under reduced pressure.

b) Oxidation of Alkylcimamates with metachloroperbenzoïc acid (MCPA)

Following the method of earlier workers [13], by refluxing a solution of α,β-unsaturated esters in methylene chloride with m-chloroperbenzoïc acid good yields of four glycidic esters (compounds 3a, 6, 7 and 8) have been obtained.

Preparation of ethyl-3-phenylglycidate

From 0.15 mole of benzaldehyde, 0,15 mole of ethyl α-bromoacetate and 0.15 mole of potassium in 100 ml of t-butylalcohol there was obtained 18.5 g (68 %) of glycidate (1) bp 118-119° at 1,5 mm - IR (CCl_4) 1750, 1730 cm^{-1} (C=O).

In this manner to that described above compounds 2, 4, 5, 9, 10, 11, 12, 13, 14 and 15 were obtained (see Table I).

Their spectrometric properties are summerized in the Table II.

Preparation of 3-phenylglycidonitrile

From 0.1 mole of benzaldehyde, 0.1 mole of chloroacetonitrile and 0.1 mole of potassium in 100 ml of dried t-butylalcohol, there was obtained 7.50 g (51 %) of glycidonitrile (16) bp at 86° 0.7 mm

IR (CCl_4) 3200-2950 cm^{-1} (C-H), 2250 cm^{-1} (sharp)(ν_{CN})

NMR (CCl_4/TMS) cis δppm 3.60 (d, αH, $J_{\alpha\beta}$=4.0 Hz), 4.08 (d, βH, $J_{\alpha\beta}$ = 4.0 Hz), 7.31 (m, $C_6\underline{H}_5$) ; trans δ 3.21 (d, αH, $J_{\alpha\beta}$=2.1 Hz), 4.15 (d, βH, $J_{\alpha\beta}$ = 2.1 Hz), 7.32 (m, $C_6\underline{H}_5$).

Compounds 16,17, 18, 19 and 20 have been prepared in a similar manner (Table I). They all have a sharp absorption band at 2250 cm^{-1} attributed to the C≡N vibration.

Preparation of methyl trans 3-phenylglycidate

A solution of 0.05 mole of distilled methyl trans-cinnamate was mixed with a solution 0.065 mole of m-chloroperbenzoïc acid in 100 ml of dried methylene chloride. The mixture was refluxed for 3 days, cooled and shaken with 10 % solution of sodium sulfite. The organic layer was isolated and the aqueous layer extracted with methylene chloride. The organic layers were washed with 5 % solution $NaHCO_3$, dried over sodium sulfate. The solvent was evaporated and the product was distilled to give 3.8 g of a coloress liquid (3a) bp 83° (0,5 mm)

IR (CCl_4) 1750 cm^{-1}, 1730 cm^{-1} (ν_{CO})

NMR (CCl_4/TMS) δppm 3.35 (d, 1H, αH, $J_{\alpha\beta}$= 2.1) 3.73 (s, 3H , $O\underline{CH}_3$) 4.01 (d, 1H, βH, $J_{\alpha\beta}$=2,1 Hz) 7.23 (S, 5H, $C_6\underline{H}_5$).

The epoxide cis 3b has been prepared from the chlorohydrin threo which was obtained from the trans isomer 3a and anhydrous hydrochloride acid in ether [18].

NMR (CCl_4/TMS) δppm 3.66 (S, 3H, $O\underline{CH}_3$), 3.74 (d, 1H, αH, $J_{\alpha\beta}$ = 2.5 Hz) 4.18 (d, 1H, βH, $J_{\alpha\beta}$=2,5 Hz), 7.23 (S, 5H, $C_6\underline{H}_5$).

2. General procedure for the preparation of the β-fluoro β-phenyllactic acid derivatives and fluorocyanohydrins

All the reactions were carried out in a polyethylene flask.

a) Preparation of ethyl 3-fluoro 3-phenyllactate (nc)

To a solution of 70 % HF/pyridine (w/w %) (10 ml) in 10 ml of CH_2Cl_2, ethyl 3-phenylglycidate (1.92 g, 10 m moles) dissolved in the same solvent was added dropwise at room temperature. The reaction mixture was stirred at this temperature for 1 H. The mixture was shaken with cold water, extracted with methylene chloride washed with a 5 % solution of bicarbonate and water, and finally dried ($MgSO_4$). After evaporating the solvent, thin layer chromatography (eluant : hexane - ethylacetate 8/2 v/v) shows one major product. This was isolated by column chromatography over neutral alumina (eluant : hexane-ethylacetate 6/4 v/v). Yield 95 %.

IR (CCl_4) 3610, 3560 cm^{-1} (ν_{OH}), 1750 cm^{-1} (ν_{CO}).

Anal. calcd for $C_{11}H_{13}FO_3$: C, 62. 26 ; H, 6.13 ; Found : C, 62. 39 ; H, 6.06.

In a similar manner to that described above compounds n° 21, 24, 26, 28, 29, 30, 36, 37, 38, 39 and 40 were obtained (see Table II).

b) Preparation of methyl erythro 3-fluoro 3-phenyllactate (nc)

To a cold solution of 70 % HF/pyridine (10 ml) was added slowly 2.5 g of freshly distilled pyridine to obtain a mixture of 45 % HF/pyridine. To this solution was added methylene dichloride (10 ml) and the resulting solution was stirred. Methyl trans-3-phenylglycidate (2.83 g, 15 mmoles) in CH_2Cl_2 (10 ml) was then added dropwise. The reaction mixture was allowed to stand at room temperature 5 days with continuous stirring. The reaction mixture was then worked up as described previously. The crude product has been chromatographed over neutral alumina. The colorless liquid isolated (Yield 90 %), containing methyl erythro-3-fluoro-3-phenyllactate (88 %) and the threo isomer (12 %).

A sample which had been obtained starting with 6 g of oxide gave after distillation under reduced pressure (85% of 25 - bp : 102-103° 10.5 mm).

Anal. calcd for $C_{10}H_{11}FO_3$: C, 48,00 ; H, 5,55 ; Found : C, 48,2 ; H : 5,31.

c) Preparation of ethyl 3-fluoro 3- [4-chlorophenyllactate] (nc)

To a solution of 45 % HF/pyridine (10 ml) in CH_2Cl_2 ethyl 3- [4-chlorophenyl] glycidate (2.26, 10 mmoles) was added. The mixture was then stirred à 50°C for 24 H and worked up as described above, followed by neutral alumina column chromatography (eluant : hexane - ethyl acetate 6/4 v/v) to give the pure slightly yellow-colored ethyl 3-fluoro-3- [4-chlorophenyllactate]. Yield 85 %.

d) Preparation of 3-fluoro 3-phenyllactamide (nc)

This product was obtained by the reaction of a 70 % HF/pyridine (10 ml) and 10 mmoles of 3-phenylglycidamide in 10 ml of dried CH_3CN. The product was recristallized from ethanol. Yield 95 %. mp : 86-87° (uncorrected).

Compounds 33b, 34 and 35 were prepared in a similar manner.

e) Preparation of 1-cyano 3-fluoro-2-phenylethanol

To a solution of 70 % HF/pyridine (25 ml) in 10 ml of 10 ml of CH_2Cl_2 was added 15.9 g (0.1 mole) in 20 ml of the same solvent during 45 minutes. The mixture was stirred 3 H at room temperature and worked up as described for previous reactions of HF/pyridine with oxides. After evaporating the solvent, distillation of the crude product gave 16.30 g (91 %) of the pure compound 36. bp : 93° (1.5 mm).

IR ($CHCl_3$) : ν_{CN} : 2250 cm^{-1} ; ν_{OH} : 3546 cm^{-1} (sharp), 3390 cm^{-1} (large)

Anal. calcd. for C_9H_8FNO : C, 65. 44 ; H, 4.88 ; Found : C, 65. 50 ; H, 4.83.

All the other fluorocyanohydrins have been obtained in this manner.

CONCLUSION

Now, the following conclusions can be drawn. Glycidic esters, amides, imidoesters and nitriles can be converted to the corresponding fluorohydrins ; the ring opening proceeds through a preferential stereospecific trans-addition. Furthemore it has been shown that the reaction is regioselective.

The β-fluorolactic acid derivatives reported herein are of particular interest because their hydrogenated analogues have been found recently to be enzyme inhibitors [17,18] and plant growth regulators [19], and it is generally known now that the introduction of fluorine exerts an important and useful influence on the bioreactivity of organic molecules, while the fluorocyanohydrins would be precious intermediates for β-fluoroamino acids synthesis [20].

The reaction of the above epoxides with both boron trifluoride ethyletherate and phenyltetrafluorophosphorane [21] are being studied in our laboratory.

We intend to test whether this method can be extended to other epoxides. The results will be reported in due course.

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