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SYNTHESIS OF 3-FLUOROPYRUVATES FROM GLYCIDIC-α-CYANOESTERS

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ABSTRACT: The decyanation of α-cyano-β-fluoro-α-hydroxyesters is achieved , at room temperature , by action of $Ni(OAc)_2$. The corresponding 3-fluoropyruvates are obtained in good yields.

3-Fluoropyruvates are known to act as inhibitors of enzymes more efficiently than their non-fluorinated homologous series[1]. Two methods have been reported for their synthesis. The first one corresponds to the action of fluorine on the enolic form of ketoesters[2]. The second is the oxidation, with Jones reagent, of β-fluoro-α-hydroxyesters[3].

In the present work we describe an other simple method where the preparation of 3-fluoropyruvates is carried out by decyanation of α-cyano-β-fluoro-α-hydroxyesters. The synthesis of these starting materials, via opening ring reaction by action of HF/pyridine on glycidic-α-cyanoesters, has been reported in a previous work[4].

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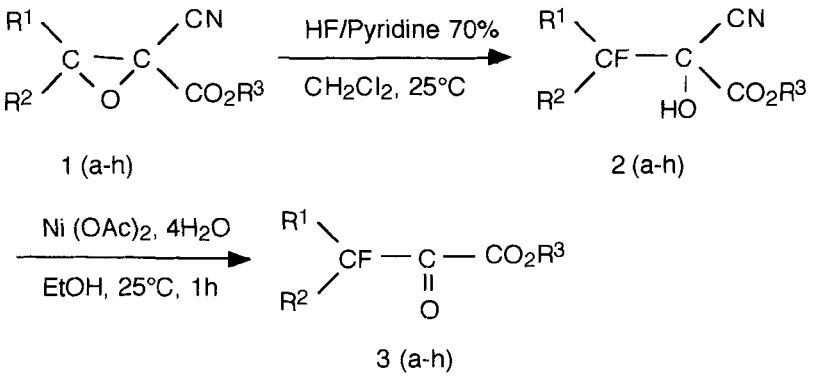
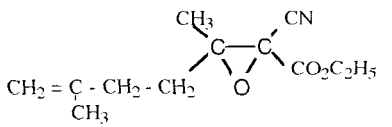


The prepared 3-fluoropyruvates are grouped in table 1

Table 1: 3-fluoropyruvates prepared.

Fluoropyruvate	R1	R2	R3	Yield(%)	bp°C/Torr
3a	CH3	CH3	C2H5	70	58/15
3b	C2H5	CH3	C2H5	58	71/15
3c	Ph	CH3	C2H5	69	82/0,2
3d	Ph	H	C2H5	67	98/0,2
3e	Ph	H	CH3	56	104/0,4
3f	C2H5	C2H5	C2H5	59	85/15
3g	Ph	Ph	C2H5	47	139/0,4
3h	(CH2)5		C2H5	61	107/15

In order to highlight the advantage of this method, when an oxidable group such as carbon-carbon double bond is present in the starting glycidic-α-cyanoester molecule, the procedure reported in the scheme is conducted on



Unfortunately, in this case, both opening ring reaction and HF addition on the double bond take place by action of pyridine polyhydrofluoride[5] .

Other glycidic-α-cyanoesters in which hydroxylated group is present are under study.

Experimental:

^1H spectra were obtained on a Jeol NMR-PMX apparatus (60MHz) using TMS as internal standard and ^{19}F NMR spectra on a Bruker WH 90 DS (84,6MHz) using $CFCl_3$ as internal standard. Mass spectra were obtained on a Nermag R 10-10C spectrometer. Infrared spectra were recorded on a Perkin-Elmer 681 instruments.The α-cyano-β-fluoro-α-hydroxyesters[4] **2(a-h)** were obtained by action of pyridine polyhydrofluoride on glycidic-α-cyanoesters.

Synthesis of 3-fluoropyruvates

General procedure: To a solution of α-cyano-β-fluoro-α-hydroxyester (5mmol) in ethanol (20ml), $Ni(OAc)_2,4H_2O$(10mmol) was added. The reaction mixture was stirred at room temperature for 1 hour and then filtered. The filtrate was diluted with water (100ml) and extracted with diethylether. The organic layer was then washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was distilled.

Ethyl-3,3-dimethyl-3-fluoropyruvate (3a) :

bp: 58°C/15torr. IR($CHCl_3$,vcm^{-1}): 1727(C=O); 1751(CO_2Et). ^1H NMR(CCl_4 , δppm): 1,34 (t, 3H, J= 7,0Hz) ; 1,56(d, 6H, J = 21,0Hz); 4,28(q, 2H, J = 7,0Hz). NMR ^{19}F($CFCl_3$, δppm): -152,9 (heptuplet, J =22,0Hz).Mass m/z (%) : 162 ($M^{+\cdot}$, 1,4); 61($C_3H_6F^+$, 100) ; 41(16).

Ethyl-3-ethyl-3-methyl -3-fluoropyruvate (3b) :

bp: 71°C/15torr. IR ($CHCl_3$,vcm^{-1}): 1727(C=O); 1748(CO_2Et). ^1H NMR(CCl_4 , δppm): 0,93(t, 3H, J=7,0Hz); 1,35(t, 3H , J=7,0Hz); 1,52(d, 3H, J=21,0Hz); 4,33 (q, 2H, J=7,0Hz). NMR ^{19}F ($CFCl_3$, δppm): -162,7(sextuplet, J=22,0Hz). Mass m/z (%): 176 ($M^{+\cdot}$, 2,45); 75 ($C_4H_8F^+$, 100); 74 (11) ; 55 (37); 47 (31) .

Ethyl-3-methyl-3-phenyl-3-fluoropyruvate (3c):

bp: 82°C/0,2torr. IR ($CHCl_3$,vcm^{-1}): 1730(C=O); 1751(CO_2Et) . ^1H NMR (CCl_4 . δppm): 1,23(t, 3H, J=7,0Hz); 1,86(d, 3H, J=22,4Hz); 4,20 (q, 2H, J=7,0Hz);

7,34 (m, 5H). NMR $^{19}F(CFCl_3$, δppm): -158,3 (q, J=22,4Hz). Mass m/z (%) : 224 ($M^{+\cdot}$, 5) ;123 ($C_8H_8F^+$, 100) ; 103(19) ; 77(18) .

Ethyl-3-phenyl-3-fluoropyruvate (3d) :

bp: 98°C/0,2torr. IR ($CHCl_3$,νcm^{-1}) : 1728(C=O); 1750(CO_2Et). ^1H NMR(CCl_4, δppm):1,20(t, 3H, J=7,0Hz); 4,15(q, 2H, J=7,0Hz); 6,28 (d, 1H, J=46,0Hz); 7,35(s, 5H). NMR $^{19}F(CFCl_3$, δppm) : -184,5(d, J=45,0Hz). Mass m/z (%): 210($M^{+\cdot}$, 7,8); 109($C_7H_6F^+$, 100); 110(8,7); 89($C_7H_6F^+$-HF, 4,5); 83(14,4).

Methyl-3-phenyl-3-fluoropyruvate (3e) :

bp: 104°C/0,4torr. IR($CHCl_3$,νcm^{-1}): 1727(C=O); 1750(CO_2Me). ^1H NMR(CCl_4 , δppm): 3,68 (s, 3H); 6,30(d, 1H, J=47,0Hz); 7,63(s, 5H). NMR ^{19}F ($CFCl_3$, δppm) : -184,6(d, J=47,0Hz). Mass m/z (%): 196($M^{+\cdot}$, 11,7);110(16,4); 109 ($C_7H_6F^+$, 100); 89(8,6); 83 (32,7); 59(17,1).

Ethyl-3,3-diethyl-3-fluoropyruvate (3f) :

bp: 105°C/15torr. IR ($CHCl_3$,νcm^{-1}): 1724(C=O); 1751(CO_2Et) . ^1H NMR(CCl_4, δppm): 0,93 (t, 6H, J=7,0Hz); 1,35(t, 3H, J=7,0Hz); 4,28(q, 2H, J=7,0Hz). NMR ^{19}F ($CFCl_3$, δppm): -162,3(m). Mass m/z (%) : 190($M^{+\cdot}$, 1,6); 89($C_5H_{10}F^+$,100); 88 (13); 69(33); 47(15); 43(22); 41(24) .

Ethyl-3,3-diphenyl-3-fluoropyruvate (3g) :

bp: 139°C/0,4torr. IR($CHCl_3$,νcm^{-1}): 1727(C=O); 1745(CO_2Et). ^1H NMR(CCl_4, δppm): 1,28(t, 3H, J=7,0Hz); 4,32 (q, 2H , J=7,0Hz); 7,45 (m,10H).NMR $^{19}F(CFCl_3$, δppm): -147,0(s). Mass m/z (%) :186(17,8); 185($C_{13}H_{10}F^+$, 100) ; 165(26,5).

Ethyl-2-(1-fluorocyclohexyl)pyruvate (3h) :

bp: 107°C/15torr. IR($CHCl_3$,νcm^{-1}) : 1727(C=O); 1748(CO_2Et). ^1H NMR(CCl_4,

δppm): 1,36(t, 3H, J=7,0Hz); (1,53 - 2,33) (m,10H); 4,28 (q,2H, J=7,0Hz). NMR $^{19}F(CFCl_3$, δppm): -159,0(m). Mass m/z (%): 202($M^{+\cdot}$,0,5); 101 ($C_6H_{10}F^+$, 60,5); 81(100); 59(13,3); 55(11,2); 41(13).

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