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THE SYNTHESIS OF DERIVATIVES OF 3-FLUORO-2-KETOACIDS

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SUMMARY

3-Fluoro-2-hydroxynitriles I_{a-h} were found to be versatile intermediates to the 3-fluoropyruvic acids II_{a-h} via a new method for the synthesis of these important compounds. Treatment of II_{a-h} with diazomethane in anhydrous ether led to the corresponding methyl pyruvates. According to previously described routes we have obtained one 3-fluoro-2-aminoacid.

INTRODUCTION

In our search for biologically active fluorinated organic compounds, we directed our attention to mono or difluorinated aminoacids. Although many methods of fluoroaminoacids synthesis have been recently reported [1,6], there is a need for an operationally simple procedure which avoids the use of a highly toxic reagent (eg SF_4 ; F_2). We synthesized some 3-fluoro-2-aminoacids [6] via a Strecker type reaction and ring-opening of 2-cyano-3-phenylaziridine with HF in pyridine solution followed by an acidic hydrolysis of the fluoroaminonitrile allowed us to obtain 3-fluorophenylalanine [4].

Dolling and coworkers [2] have obtained fluoroalanine and more recently Tsushima and coworkers [3] synthesized 3-fluorophenylalanine by reductive amination of fluoropyruvic acid sodium salt and 2-fluoro-2 phenylpyruvic acid sodium salt, respectively.

In one of our publications [7], we showed that epoxynitriles react under mild conditions with HF in pyridine affording fluorocyanhydrins quantitatively.

We tried a route which included as the first step the reaction of 2-epoxynitriles with Olah's reagent (Scheme I).

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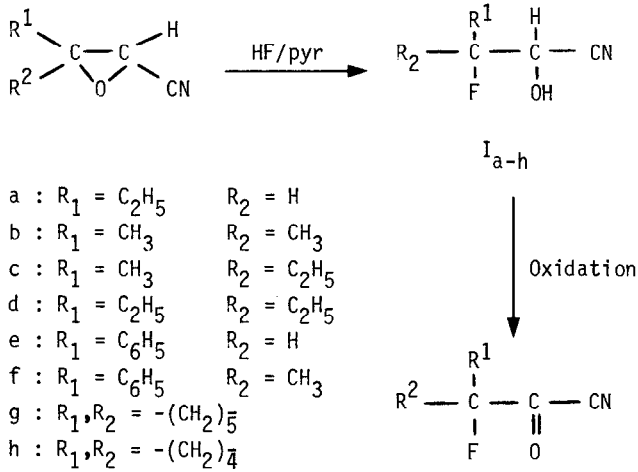
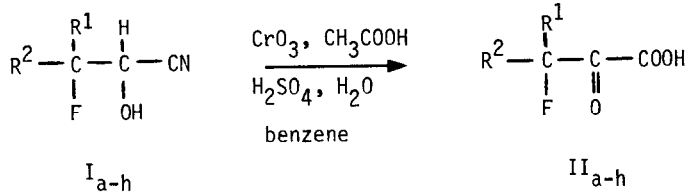


a : $R_1 = C_2H_5$ $R_2 = H$
b : $R_1 = CH_3$ $R_2 = CH_3$
c : $R_1 = CH_3$ $R_2 = C_2H_5$
d : $R_1 = C_2H_5$ $R_2 = C_2H_5$
e : $R_1 = C_6H_5$ $R_2 = H$
f : $R_1 = C_6H_5$ $R_2 = CH_3$
g : $R_1, R_2 = -(CH_2)_5-$
h : $R_1, R_2 = -(CH_2)_4-$

SCHEME I

In a second step, we attempted to obtain the corresponding 3-fluoro-2-ketonitriles, but all conventional approaches failed :

- Oppenauer's oxidation led to defluorination of the products.
- Potassium permanganate in aqueous ethanol solution in the presence of catalytic quantities of sulfuric acid gave only a small amount of 3-fluoro-2-ketoacid after three days reaction.
- When the fluorocyanhydrins were treated with potassium dichromate in acetone or water solution, the reactants were recovered.
- However, if the reaction was conducted in benzene, and the potassium dichromate replaced by anhydrous chromic anhydride dissolved in acetic acid-sulfuric acid mixture, 3-fluoro-2 ketoacids could be obtained in good yield (Scheme II).



SCHEME II

Thus, these products which are of great interest and an important point of departure for the synthesis of 3-fluoro-2-aminoacids [2], could be prepared by a simple method.

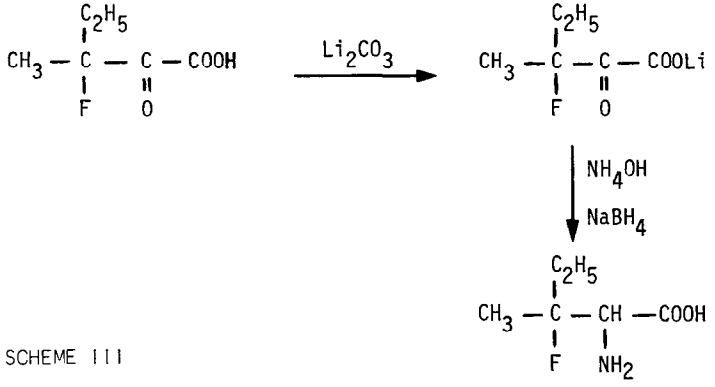
RESULTS and DISCUSSION

The reaction of epoxynitriles with HF in pyridine solution has been already discussed [7]. It provided 3-fluoro-2 hydroxynitriles in quantitative yield.

Slow addition of the reagent (CrO_3, CH_3COOH, H_2SO_4, H_2O) to I_{a-h} in benzene at 0°C, followed by variable reaction times at room temperature led to 3-fluoro-2-ketoacids II_{a-h} in 60-70 % yield.

No 3-fluoro-2-ketonitrile was isolated, so the IR spectrum of the crude product showed no obsorption band at 2200 cm^{-1} which is generally assigned to the C ≡ N streching mode; in the ^{19}F NMR spectrum only a multiplet, which became a singlet when the protons were decoupled, was observed.

At this time, the sodium or lithium salt could be obtained by treating one equivalent of II_{a-h} in ethanol at 0°C with one equivalent of sodium or lithium carbonate in water. The reductive amination procedure could be applied, as in case of the 3-fluoro-2-keto-3-methylpentanoïc acid which allowed us to obtain 3-fluoroisoleucine (Scheme III).



SCHEME III

EXPERIMENTAL

Melting points are uncorrected. IR spectra were taken on a Lietz Wetzlar M III G using sodium chloride cells. NMR spectra were recorded at 60 MHz and 84,67 MHz for ^1H and ^{19}F respectively on a Varian EM 360 NMR spectrometer and Bruker Spectrospin ($CDCl_3$). The chemical shifts are in ppm from TMS and CCl_3F

Materials

All the 3-fluoro-2-hydroxynitriles I_{a-h} were prepared by our previously described method [7]. They have been purified by distillation under reduced pressure.

Reagent

The reagent was prepared by dissolving 39 g of chromic anhydride in 28 ml of acetic acid and 51 ml of sulfuric acid. The mixture was diluted with 170 ml of distilled water giving a 1,56 M solution. One equivalent of II_{a-h} was treated by two equivalents of the reagent.

General procedure for the synthesis of 3-fluoro-2-ketoacids

A solution of II_{a-h} in dry benzene was added with stirring to the reagent cooled at 0°C. Thirty minutes after the end of the addition, the mixture was allowed to stir at room temperature for two or three days. The reaction mixture was poured in water and extracted with ether. The organic layers were washed with water in four portions and dried over $MgSO_4$. After the evaporation of the solvent, the product was isolated as liquid or solid, which were further purified by chromatography or recrystallisation.

3-fluoro-2-ketopentanoïc acid (nc) (IIa)

From 20 mmoles of I_a , II_a was obtained after 96 h of reaction time.
Yield 60 %.
IR ($CHCl_3$) 3500 - 2900 cm^{-1} (broad peak), 1720 cm^{-1}
^1H NMR : 11,2 (s broad, 1H, COO<u>H</u>) 4,9 (m, 1H, $^2J_{FH}$ = 47,5 Hz, J_{HH} = 6,5 Hz) 2,5 - 1,4 (m, 2H, C<u>H</u>$_2$) 0,9 - 1,2 (m, 3H, C<u>H</u>$_3$).
^{19}F NMR : 178,4 (m, $^2J_{FH}$ = 47,6 Hz).

3-fluoro-2-keto-3-methylbutanoïc acid (nc) (IIb)

Was isolated (72 h) in the same manner as described above. Yield 65 %.
IR ($CHCl_3$) : 3500 - 3000 cm^{-1} (broad), 1730 cm^{-1}
^1H NMR : 10,7 (s, broad, 1H, COO<u>H</u>), 1,6 and 1,49 (d, 6H, 2C<u>H</u>$_3$, $^3J_{FH}$ = 20 Hz and $^3J'_{FH}$ = 22 Hz).
^{19}F NMR : 156 septet, J_{FCH_3} = 22 Hz).

3-fluoro-2-keto-3-methylpentanoïc acid (nc) (IIc)

Was prepared as above (72 h).Yield 68 %.
IR ($CHCl_3$) : 3500 - 2950 cm^{-1} (broad), 1730 cm^{-1}
^1H NMR : 11,0 (s, broad, 1H, COO<u>H</u>) 2,5 - 1,8 (m, C<u>H</u>$_2$CH$_3$) 1,60 (d, C<u>H</u>$_3$, $^3J_{FH}$ = 20 Hz) 1,05 (t, CH$_3$C<u>H</u>$_2$, ^3J = 7,1 Hz).
^{19}F NMR : 159,3 (apparent sextuplet, J = 21,3 Hz).

3-fluoro-3-ethyl-2-ketopentanoïc acid (nc) (IId)

Was isolated as above (72 h). Yield 65 %.
IR ($CHCl_3$) : 3500 - 2900 cm^{-1} (broad) 1720 cm^{-1}
^1H NMR : 10,8 (s, broad, 1H, COO$\underline{H}$) 2,4 - 1,5 (m, 4H, CH_2 - $\underset{\underset{CH_2}{|}}{CF}$-)
1,0 (triplet apparent, 6H, 2CH_3).
^{19}F NMR : 165,2 (m, $^3J_{FH}$ = 23,5 Hz).

3-fluoro-2-keto-3-phenylpropanoïc acid (IIe)

Was obtained as a crystalline solid (48 h), m.p. 67-70°C. Yield 70 %.
IR ($CHCl_3$) : 3500 - 3000 cm^{-1} (broad) 1725 cm^{-1}
^1H NMR : 12,7 (s, broad, 1H, COO$\underline{H}$) 7,3 (s, 5H, $C_6\underline{H}_5$) 5,73 (d, 1H, $\underline{CH}F$,
$^2J_{FH}$ = 46,0 Hz).
^{19}F NMR : 181,2 (1d, ^2J = 45,8 Hz).

3-fluoro-2-keto-3-phenylbutanoïc acid (nc) (IIf)

Was obtained as a crystalline solid (48 h), m.p. 85-87°C. Yield 65 %.
IR ($CHCl_3$) : 3500 - 2950 cm^{-1} (broad) 1720 cm^{-1}
^1H NMR : 10,5 (s, broad, 1$\underline{H}$, COOH) 7,3 - 7,4 (m, 5H, $C_6\underline{H}_5$)
1,8 (d, 3H, $\underline{CH}_3F$, J = 23 Hz)
^{19}F NMR : 156,2 (q, J = 23,2 Hz).

2 -(1-fluorocyclohexyl)-2-ketothanoïc acid (nc) (IIg)

The titled compound was prepared analogously from 20 mmoles of 1 g. The yield was 60 % and the reaction time was three days.
IR ($CHCl_3$) : 3500 - 3000 cm^{-1} (broad) 1725 cm^{-1}
^1H NMR : 10,9 (s, broad, 1H, COO$\underline{H}$) 2,5 - 1,8 (m, 10H, cyclohexyl).
^{19}F NMR : 168,2 (m).

2 -(1-fluorocyclopentyl)-2-ketoethanoïc acid (nc) (IIh)

Was obtained as above (72 h). Yield 65 %.
IR ($CHCl_3$) : 3500 - 3000 cm^{-1} (broad) 1720 cm^{-1}
^1H NMR : 10,5 (s, broad, 1H, COO$\underline{H}$) 2,5 - 1,8 (m, 8H, cyclopentyl).
^{19}F NMR : 155,1 (m).

General method for the preparation of the methyl-3-fluoro-2-ketoesters

The 3-fluoro-2-ketoacids obtained were treated with a solution of diazomethane in diethyl ether freshly prepared, at room temperature. After the evaporation of the solvent, the fluoro ester was isolated as a slight colored liquid. The ^{1}H NMR showed a singlet at 3,8 ppm assigned to the methylester protons. These spectra were identical with those of authentic samples obtained by oxidation of methyl 3-fluorolactates by Jones'reagent [8].

Reductive animation of 3-fluoro-2-keto-3-methylpentanoïc acid

According to the previously described methods [2] the lithium or sodium salt of 3-fluoro-2-keto-3-methylpentanoïc acid was treated with a solution of ammonia (13M) at 37°C for 2 h then with $NaBH_4$ (1,7 equivalent) and the mixture was allowed to stir at room temperature for 18 h. The product obtained gave positive test with ninhydrin. At this time no attention was made to isolate the fluorinated aminoacid. We intend to test this method as a general synthesis of these very interesting compounds.

CONCLUSION

We have showed in this paper that 3-fluoro-2-hydroxynitriles are goods points of departure for the synthesis of new organic fluorinated compounds of great interest. These products could allow us to obtain other organic compounds such as 3-fluoro-2-aminoacids.

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