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ADDITION OF HYDROGEN FLUORIDE ON AZIRINECARBOXYLATES, A NOVEL METHOD FOR SYNTHESIS OF ALIPHATIC β,β-DIFLUORO-α-AMINOACID ALKYL ESTERS

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Summary: 3-Carbethoxy-2-methyl-I-azirine (IIa) and 3-carbomethoxy-2-phenyl-I-azirine (IIb) react with hydrogen fluoride under mild conditions, to give respectively the corresponding alkyl β-alkyl and β-aryl β,β-difluoro-α-aminopropionates (IIIa) and (IIIb).

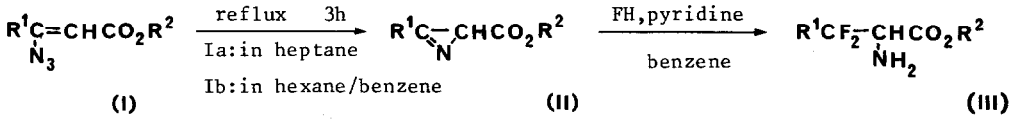
A new and elegant approach to specific irreversible enzyme inactivation is to design inhibitors possessing latent reactive groupings which are unmasked at the enzyme's active site as a result of the normal catalytic turnover[1]. Thus several aminoacid analogues such as β,γ-unsaturated α-aminoacids, α-fluoromethyl α-aminoacids and α-difluoromethyl α-aminoacids have recently been synthesized as specific irreversible inhibitors of pyridoxal phosphate dependent enzymes[1-3].

In view of the interest in such compounds, we have sought methods of preparing derivatives of β,β-difluoro-α-aminoacids, these compounds being potential irreversible inhibitors of various enzymes including aminoacid ammonia lyases and pyridoxal-phosphate dependent-aminoacid decarboxylase and aminotransferase enzymes.

In spite of numerous synthetic studies aiming at the preparation of various fluorinated aliphatic aminoacids[2-5], we have noted no direct procedure leading to these β,β-difluorinated aliphatic aminoacids or to their ester derivatives. Sulfur tetrafluoride[6] (SF_4) is the most commonly used reagent for direct synthesis of gem-difluorinated compounds. Unfortunately this reagent can also attack carboxylic ester functions and furthermore it demands special conditions of handling as a consequence of its high toxicity (comparable to phosgen).

This communication shows that azirinecarboxylates are valuable synthons for the preparation of β,β-difluoro-α-aminoacid alkyl esters.

The azirinecarboxylates (IIa) and (IIb) were obtained by refluxing azidoalkenoates (Ia) and (Ib)[7,8] for 2 hours in heptane and for 3.5 hours in hexane-benzene (I:I v/v) respectively.



(I) (II) (III)

Ia, IIa, IIIa : $R^1=CH_3$, $R^2=C_2H_5$
Ib, IIb, IIIb : $R^1=C_6H_5$, $R^2=CH_3$

IIIa = 32% yield from IIa
IIIb = 43% yield from IIb

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The 3-carbomethoxy-2-phenyl-1-azirine (IIb) was purified by precipitation in pentane at -20°C, whereas the azirinecarboxylate (IIa) (65% of the reaction mixture after pyrolysis) was used without separation for the last critical step.

A solution of crude azirine (IIa) (∿10 mmol) or 3-carbomethoxy-2-phenyl-1-azirine (IIb) (10 mmol) in a minimal amount of benzene (∿3 ml) was added to a 70% solution of hydrogen fluoride in pyridine (20 ml) cooled to 5°C; after stirring for 10 minutes at 5°C, the mixture was left at room temperature for 3 hours. Work up using an acid-base extraction procedure followed by silica gel column liquid chromatography (eluent : benzene-ethyl acetate (4:6 v/v) gave ethyl 3,3-difluoro-2-aminobutanoate (IIIa) and methyl 3,3-difluoro-2-aminophenylpropionate (IIIb) in 43% and 32% yield respectively.

IR and NMR spectral data[9] : IR ($CHCl_3$), νcm^{-1}; ^1H NMR ($CDCl_3$, TMS), δppm; ^{19}F NMR ($CDCl_3$, CCl_3F), ϕppm.

IIIa : νNH_2: 3320 and 3390, $\nu C{=}O$: 1725; δ1.29 (t, 3H, J = 7 Hz, $\underline{CH_3}CH_2$), 1.68 (t, 3H, J = 19 Hz, $\underline{CH_3}CF_2$), 1.75 (s, 2H, $\underline{NH_2}$), 3.72 (t, 1H, J = 11 Hz, $CF_2\underline{CH}NH_2$), 4.23 (q, 2H, J = 7 Hz, $O\underline{CH_2}CH_3$; ϕ: 99.0(m).

IIIb : νNH_2 : 3350 and 3310, $\nu C{=}O$: 1730 ; δ2.29 (s, broad, 2H, $\underline{NH_2}$), 3.63 (s, 3H, $\underline{CH_3}O$), 4.01 (t, 1H, J = 11.5 Hz, $CF_2\underline{CH}{-}NH_2$), 7.42 (s, 5H, $C_6\underline{H_5}$); ϕ = 105.4(m, ABX pattern).

Melting-points, elemental analysis and mass spectral data of the hydrochlorides :

IIIa : 156°C ; found : C, 34.84 ; H, 5.92 ; F, 18.13 ; calculated for $C_6H_{12}ClF_2NO_2$: C, 35.39 ; H, 5.90 ; F, 18.68 % ; MS for $(C_6H_{12}F_2NO_2)^+$, m/e (%) 168 (M^+, 16), 102 (M^+-H-CH_3CF_2, 83), 94 (95), 74 (100).

IIIb : 168-170°C ; found : C, 47.95 ; H, 4.59 ; F, 15.26 ; calculated for $C_{10}H_{12}ClF_2NO_2$: C, 47.72 ; H, 4.77 ; F, 15.11 % ; MS for $(C_{10}H_{12}F_2NO_2)^+$, m/e (%) 216 (M^+, 2), 88(M^+-H-$PhCF_2$, 100). This clearly indicates that the fluorines are benzylic.

Details concerning spectroscopic properties will be given in a full paper.

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9 ^{19}F NMR on a Bruker Spectrospin (84, 67 MHz) ; ^1H NMR on a Varian A-60 ; IR on a Leitz III G. M.p. (crystallisation solvent : ether-alcohol).