Journal of Fluorine Chemistry, 18 (1981) 93–96

Received: January 2, 1981

PRELIMINARY NOTE

A NOVEL SYNTHESIS OF 3-FLUOROPHENYLALANINE and SOME of ITS DERIVATIVES

A.I. AYI, M. REMLI and R. GUEDJ

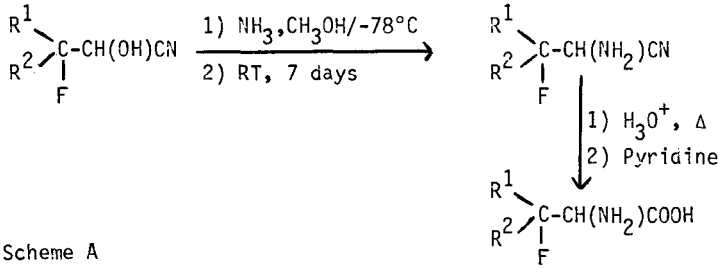
Laboratoire de Chimie Structurale Organique, U.E.R. I.M.S.P., Université de Nice, Parc Valrose, 06034 Nice Cédex (France).

SUMMARY

Ring opening of 2-cyano-3-phenylaziridine and 2-amido-3-phenylaziridine by HF/pyridine was found to give 2-amino-3-fluorophenylpropionitrile (IV) and 2-amino-3-fluorophenylalanamide (VII) respectively. 3-fluorophenylalanine (V) could be obtained by an acidic hydrolysis of (IV) or (VII) whereas isopropyl-3 fluorophenylalanate (VI) was isolated by esterification of (V) or by heating (IV) with iso-propanal-12 NHCl under reflux.

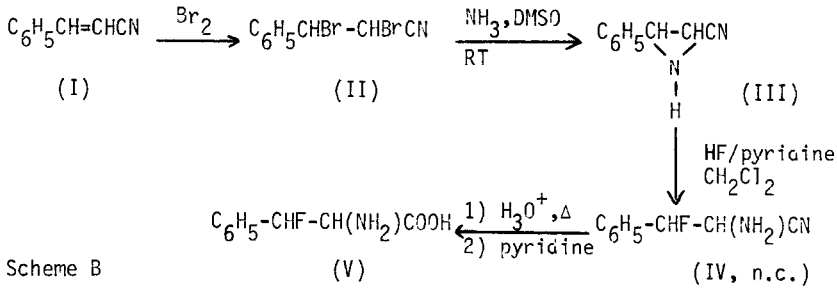
Increasing interest in the bioactivity and the pharmacological properties of fluorinated aminoacids [1,2], prompted recent new synthetic studies using SF_4 in liquid HF [3] on β-hydroxy-α-aminoacids, reductive amination of 3-fluoro-phenylpyruvic acid [4] and an aziridine ring opening reaction with HF/pyridine [5,6,7]. The lastnamed method which was developed in our Laboratory, enabled us to obtain β-fluoro-α-aminoesters, but any attempted ester cleavage of these products failed due to facile elimination of hydrogen fluoride.

We have recently reported [8] a facile synthesis, with good yields, of some β-fluoro-α-aminoacids via a Strecker-type reaction between fluorocyanohydrins and ammonia followed by an acidic hydrolysis of the fluoroaminonitriles by the route given in the scheme A.



Scheme A

We now wish to describe a convenient synthesis of 3-fluorophenylalanine (V) and two of its derivatives which makes use of readily available commercial cinnamonitrile (I) and employs HF/pyridine as the fluorinating agent [9], by the route given in the scheme B.



(I) (II) (III) (V) (IV, n.c.)

Scheme B

Bromination of cinnamonitrile (I) proceeds normally and treatment of a solution of the 2,3-dibromo-2,3-dihydrocinnamonitrile (II) in DMSO with gaseous ammonia [10] at room temperature led to the 2-cyano-3-phenylaziridine (III) as crystalline solid in about 70-80 % yield. When (III) was reacted with HF/pyridine in anhydrous methylene dichloride a quantitative yield of 2-amino-3-fluoro-3-phenylpropionitrile (IV) was obtained as a white crystalline solid. To our knowledge, this synthesis represents the first reported example of 3-fluoroaminonitrile obtained by aziridine ring opening.

$C_6H_5CHFCH(NH_2)CN$ (IV) : m.p. 97-97,5°C (benzene).

^1H NMR ($CDCl_3$, int. TMS) δ 1.7 (s, 2H, NH_2), 4.12 (dd, $J_{H_\alpha H_\beta}$ = 5.0 Hz, J_{FH_α} = 21.0 Hz, H_α threo), 4.30 (dd, $J_{H_\alpha H_\beta}$ = 4.1 Hz, J_{FH_α} = 15 Hz, H_α erythro), 5.56 (dd, $J_{H_\alpha H_\beta}$ = 5.0 Hz, J_{FH_β} = 46.5, H_β threo) 5.50 (dd, $J_{H_\alpha H_\beta}$ = 4.1 Hz, J_{FH_β} = 45.1 Hz, H_β erythro), 7.30-7.4 (m, 5H, C_6H_5).

^{19}F ($CDCl_3$, int. CCl_3F) ϕ - 188.73 (dd, J_{FH_α} = 21.3 Hz, J_{FH_β} = 46.5 Hz) -184.10 (dd, J'_{FH_α} = 15.1 Hz, J'_{FH_β} = 45.1 Hz) threo and erythro.

I.R. ($CHCl_3$, cm^{-1}) 2230 (CN), 3330 (NH).

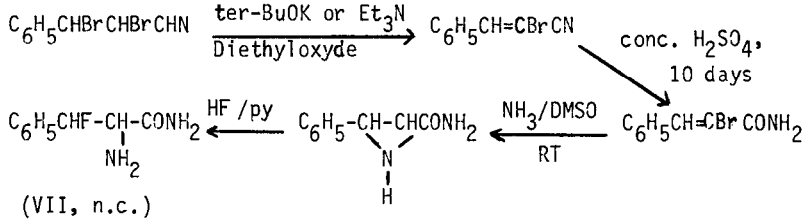
The acidic (H_2O-conc. HCl) hydrolysis of (IV) to (V) was obtained by heating under reflux for 2-5 hr. and the 3-fluorophenylalanine was isolated in 55-60 % yield. Isopropyl 3-fluorophenylalanate (VI)* could be obtained by esterification of (V) with an iso-propanol 3NHCl solution or by heating (IV) with iso-propanol-12NHCl under reflux for 10-12 h.

* These compounds have identical properties (mp, IR, ^1H, ^{19}F NMR and MS) with those obtained by other methods previously described [3,4,5].

(V) $\xrightarrow{i\text{-}C_3H_7OH,3NHCl,\Delta}$ $C_6H_5CHFCH(NH_2)CO_2\text{-}i\text{-}C_3H_7$ (VI)

(IV) $\xrightarrow{i\text{-}C_3H_7OH\text{-}12NHCl,\Delta}$ (VI)

Finally, the amide (VII) has been obtained starting from (II) by the route given in scheme C.



$C_6H_5CHFCH(NH_2)CONH_2$ (VII) : m.p. 112-113°C

^1H NMR (DMSOd_6, ext. TMS) δ 4,15 (dd, $J_{H_\alpha H_\beta}$ = 4.5 Hz, J_{FH_α} = 26 Hz, H_α threo) 4.31 (dd, $J_{H_\alpha H_\beta}$ = 2.8 Hz J_{FH_α} = 16 Hz, H_α threo), 5.65 (dd, $J_{H_\alpha H_\beta}$ = 4.5 Hz, J_{FH_β} = 45.7 H_β threo). 5.85 (dd, $J_{H_\alpha H_\beta}$ = 2.8 Hz, J_{FH_β} = 45.2 Hz, H_β erythro) 7.35-7.40 (m, 5H, C_6H_5).

I.R. ($CHCl_3$, cm^{-1}) 1670 ($CONH_2$), 3335 and 3500 (NH_2)

In summary, these results clearly indicate that the reaction of HF/pyridine with 2-cyano-3-phenylaziridine is a good method of preparing 2-amino-3-fluoro-3-phenyl propionitrile which can be converted into the 3-fluorophenylalanine. We are continuing to explore these 2-cyanoaziridines as well as the fluoroaminonitriles for the synthesis of the other β-fluoro-α-aminoacids and their derivatives.

1 D.F. Loncrini and R. Filler, Adv. Fluorine Chem., Butterworths, London, 6, (1972), p. 43.

2 J. Kollonitsch, Israel J. chem., 17, (1978), 53.

3 J. Kollonitsch, S. Marburg and L.M. Perkins, J. Org. Chem., 44, (1979), 771.

4 T. Tsuschima, J. Nishikawa, T. Sato, H. Tanida, K. Tori, T. Tsuji, S. Misaki and M. Suefuji, Tetrahedron Lett., 21, (1980), 3593.

5 T.N. Wade, F. Gaymard and R. Guedj, Tetrahedron Lett., 29, (1979), 2681.

6 A. Barama, R. Condom and R. Guedj, J. Fluorine Chem., 16, (1980), 183.

7 T.N. Wade and R. Guedj, Tetrahedron Lett., 41, (1978), 3247 ; G. Alvernhe, E. Kozlowska-Gramsz, S. Lacombe-Bar and A. Laurent, ibid, 52, (1978), 5203.

8a A.I. Ayi, M. Remli and R. Guedj, in 'Abstracts of 7th European Symposium on Fluorine Chemistry, Venice, Sept. 1980', J. of Fluorine Chem., 16,(1980) 540-541.

8b A.I. Ayi, M. Remli and R. Guedj, Tetrahedron Lett., (to be published).

9 G. Olah, N. Nojima and I. Kerekes, Synthesis, (1973), 779.

10 A number of 2-alkoxycarbonylaziridine have been prepared by the same method. J.W. Lown, T. Itoh and N. Ono, Can. J. Chem., 51, (1973), 856 ; E.P. Styngach and A.A. Semenov, Ser. Biol. Khim. Nauk., 4, (1975), 62.