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SYNTHESIS OF SIDE-CHAIN MONOFLUORINATED AMPHETAMINES

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SUMMARY

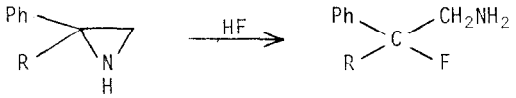
R- and S-2-Amino-3-fluoro-1-phenylpropane were prepared in approximately 50% yields by the action of HF-pyridine on R- and S-2-benzylaziridine. (±)-2-Amino-3-fluoro-1-(4-chlorophenyl)propane was similarly prepared from (±)-2-(4-chlorobenzyl)aziridine. Structures of products were confirmed by n.m.r. and mass spectroscopy. In contrast, when 2-benzyl-N-tosylaziridine was reacted with HF in pyridine, the C_2 atom of the aziridine ring was the site of fluorination and the N-tosylated derivative of 3-amino-2-fluoro-1-phenylpropane was obtained in excellent yield.

INTRODUCTION

The monofluorinated amphetamines, 2-amino-3-fluoro-1-phenylpropane (IIa) and the p-chloro analog (IIb), were required for pharmacological evaluation [1]. Several synthetic methods, including fluorodehydroxylation [2], photofluorination [2], and α-alkylation of amino acids with CH_2ClF and $CHClF_2$ [3,4] have been developed for the introduction of a fluorine atom or atoms on the carbon beta to an amino group. We decided to investigate the possibility of opening the aziridine ring with a fluoride ion source to give the desired compounds (IIa and b) since such an approach would be expected to give products which retained the same optical properties as those possessed by the precursor aziridines.

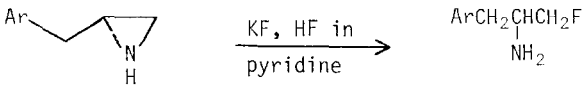
RESULTS AND DISCUSSION

While our study was in progress, other investigators reported that the action of liquid HF [5] or HF-pyridine [6] converted 2-phenylaziridine and 2,2-disubstituted aziridines to β-fluoroamines (Scheme 1). With our



Scheme 1

substrates [2-(2-aryl)methylaziridines Ia and Ib], however, ring opening involved the 1-3 bond (Scheme 2) in contrast to the 1,2-addition of HF illustrated in Scheme 1. Initially, the 2-aralkylaziridine (I) was reacted



I II

a) Ar = Ph; b) Ar = p-Cl-Ph.

Scheme 2

with HF in pyridine but the rate of this reaction was slow at 20-65°. After 7 days, 50% of IIa was obtained together with a 17.5% recovery of starting material. The reaction temperature could not be raised; at temperatures higher than 65°, HF-pyridine underwent extensive decomposition [7]. Other attempts were made to increase the rate of this reaction and improve the yield of the desired product (II). Alternative sources of F^- were investigated (pyridine solutions of KF, NaF, LiF and KF/HF mixtures) but none of these procedures improved the yield of IIa from Ia, and the rate of the reaction was not altered significantly. When the HF-pyridine reagent was replaced by an aqueous or methanolic solution of HF, the aziridine (Ia) underwent mainly solvolysis reactions producing 2-amino-3-phenyl-1-propanol or 3-methoxy-1-phenyl-2-aminopropane, respectively, in 85-90% yields and only 5-10% of the desired product (IIa).

Since two modes of ring opening were theoretically possible when the aziridine ring of I was treated with HF, it was imperative to confirm that the only fluorinated product was the desired one (II) and not the isomeric 3-aryl-2-fluoro-n-propylamine ($ArCH_2CHFCH_2NH_2$). Confirmation of structure IIa was obtained by interpretation of its mass spectrum and its 200 MHz n.m.r. spectrum (Fig. 1).

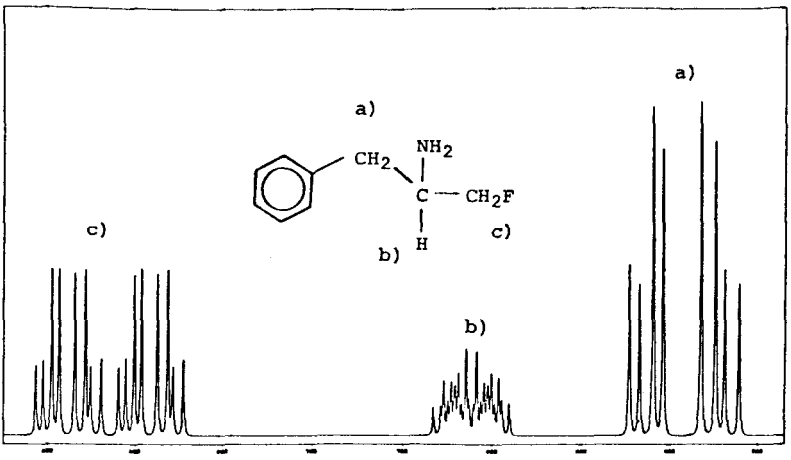
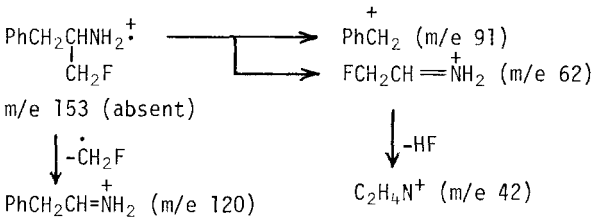


Fig. 1. 200 MHz n m.r. spectrum of 2-amino-3-fluoro-1-phenylpropane (IIa).

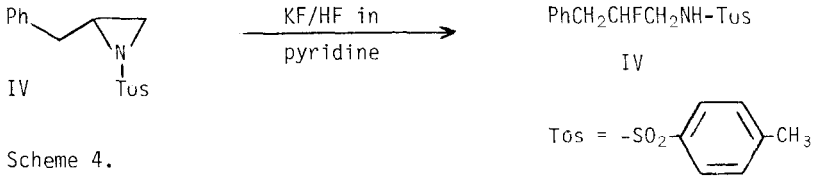
The major ions in the mass spectrum of IIa and plausible mechanisms for their formation [8] are identified in Scheme 3.



Scheme 3.

It has also been established that the opening of the aziridine ring of I to yield II proceeds without affecting the chiral centre. When R- and S-benzylaziridine (Ia) (prepared via the Wenker synthesis [9] from R- and S-phenylalanine, respectively) were converted to fluorinated amphetamines (IIa), the products were optically active with virtually identical but opposite specific rotation values.

2-Benzyl-N-tosylaziridine (III) was also reacted with HF-pyridine at 20° for 30 min. In this instance, the more substituted C atom (C_2) of the aziridine ring was the site of attack by F^- and the N-tosylated derivative of 1-amino-2-fluoro-3-phenylpropane (IV) was obtained in quantitative yield (Scheme 4). The structure of this product was confirmed by interpretation of its mass spectrum and its 200 MHz n.m.r. spectrum.



Scheme 4.

EXPERIMENTAL

The n.m.r. spectra were taken in $CDCl_3$ on a Bruker Spectrospin 200 MHz spectrometer with TMS as internal standard. ^{19}F n.m.r. spectra were run on a Bruker HFX-90 spectrometer in $CDCl_3$ using C_6F_6 and $CFCl_3$ as external standards. Specific rotation measurements were obtained with a Zeiss Circle Polarimeter (0.01 model), using a Na lamp source (589 nm). Samples were dissolved in distilled water in a 10 cm tube. Mass spectra were obtained with a Hewlett Packard 5981A mass spectrometer. Melting points are uncorrected.

R-(+)-2-Benzylaziridine (+)-Ia

This compound was prepared by reducing (+)-phenylalanine to the corresponding aminoalcohol [10] and converting the crude aminoalcohol to R-(+)-2-benzylaziridine using the Wenker synthesis [9]. $[\alpha]_D^{24}$ of (+)-Ia = +26.68° (c=0.152; 95% EtoH). N.m.r. spectrum was identical to that reported by Hassner [11] for the racemate.

S-(-)-2-Benzylaziridine (-)-Ia

This was prepared from (-)-phenylalanine in a manner similar to that described immediately above. $[\alpha]_D^{24}$= -26.64° (c=0.186; 95% EtoH).

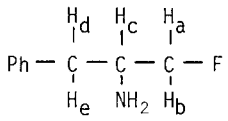
(±)-p-Chlorobenzylaziridine Ib

This compound was similarly prepared from (±)-p-chlorophenylalanine. M.p. of maleate: 94-98° (EtOH-Et_2O); lit. [12] 94-95°.

R-(+)-2-Amino-3-fluoro-1-phenylpropane (+)-IIa

One ml (50 mmol) of 100% w/v HF-pyridine (Aldrich) in a dry polyethylene bottle was cooled under N_2 to -78°. Anhydrous KF (174 mg; 3 mmol) was added in one portion. The bath was then removed and (+)-Ia (210 mg; 1.58 mmol)

was added and the mixture was stirred at 60° for 120 h. The reaction mixture was then quenched with a cold solution of 2N NaOH (20 ml) and extracted with diethyl ether (4 x 20 ml). The combined extracts were washed with brine and dried ($MgSO_4$). After distilling off the solvent (60°/0.02 mm Hg using a 12 cm Vigreux column) the residue was chromatographed on silica gel plates DF-5 (Kisselgel) using Et_2O-MeOH (9:1) as the developing solvent. The product (R_f 0.5) was extracted from the silica with diethyl ether and the solution was treated with dry HCl. Evaporation of the solvent gave 130 mg (45%) of (+)-IIa HCl salt, m.p. 143-144° (from CH_3CN); $[\alpha]_D^{22}$ = +20.42° (c= 0.715; H_2O). ^{1}H-n.m.r.: δ 1.70 (2H, NH, s); 2.30 and 2.82 [2H, $PhCH_eH_d$-CH_c, two d of d, $J(H_d-H_c)$ 5.69 Hz, $J(H_e-H_c)$ 8.60 Hz, $J(H_e-H_d)$ 13.55 Hz; 3.32 (1H, H_c, m) 4.23 and 4.29 [2H, $CH_c-CH_bH_a$, two d of d of d $J(H_a-H_b)$



IIa

4.00 Hz, $J(H_a-H_c)$ 4.10 Hz, $J(H_a-F)$ 47.10 Hz, $J(H_b-H_c)$ 6.10 Hz, $J(H_b-F)$ 47.40 Hz], 7.25 (5H, C_6H_5, m).

Mass spectrum, m/e (% relative abundance) 120(2), 92(2), 91(10), 72(2), 65(6), 63(5), 62(100). Analysis: Found: C, 56.82; H, 6.84; N, 7.90%. $C_9H_{13}ClFN$ requires C, 56.99; H, 6.91; N, 7.73%.

S-(-)-2-Amino-3-fluoro-1-phenylpropane (-)-IIa

This compound was prepared from (-)-Ia using the method described for the preparation of (+)-IIa. The HCl salt of (-)-IIa had m.p. 143-144°C (from CH_3CN). $[\alpha]_D^{22}$ + -19.89° (c=0.525; H_2O). The n.m.r. and mass spectra were identical to those of (+)-IIa. Analysis: Found: C, 56.70; H, 6.76; N, 7.43%. $C_9H_{13}ClFN$ requires C, 56.99; H, 6.91; N, 7.39%.

(±)-2-Amino-3-fluoro-1-phenylpropane IIa

This compound was similarly prepared from (±)-Ia; its HCl salt had m.p. 124-125°C (From CH_3CN). N.m.r. and mass spectra were identical to those of (+)-IIa.

(±)-2-Amino-3-fluoro-1-(4-chlorophenyl)propane IIb

This was prepared from Ib in 55% yield by the method used to prepare (+)-IIa. M.p. of IIb HCl was 186°C (from CH_3CN). Mass spectrum, m/e (% relative abundance): 127(1), 125(3), 119(1), 118(1), 89(5), 63(5), 42(10), 62(100), 42(10). Analysis: Found: C, 47.95; H, 5.41; N, 6.10%. $C_9H_{12}Cl_2FN$ requires C, 48.24; H, 5.40; N, 6.25%.

(±)-2-Benzyl-1-tosylaziridine III

III, m.p. 70-71°C, was prepared by a literature [13] method.

N-Tosyl-2-fluoro-3-phenylpropylamine IV

To a solution of 100% w/v HF-pyridine (4 ml) at 25° in a polyethylene bottle was added in one portion, the tosylaziridine III (200 mg; 0.7 mmol) and the mixture was stirred under N_2 for 30 min. The reaction mixture was then quenched with cold water (15 ml) and extracted with diethyl ether (3 x 15 ml). The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was then removed (rotatory evaporator) and the residue was crystallized from CH_2Cl_2-hexanes. This gave the title compound (207 mg) m.p. 112-114°C. ^{19}F-n.m.r. complex multiplet at - 24.06 (C_6F_6). Mass spectrum, m/e (% relative abundance): 287(19) $[M-HF]^+$, 184(10), 155(47), 133(10), 132(100), 131(5), 130(25), 122(6), 105(12), 103(9), 92(10), 91(80), 80(5), 77(10), 65(20), 57(4). ^{1}H-n.m.r.: δ 2.35(3H, CH_3, s); 2.75 to 3.50 (4H, two methylene protons, complex 2nd order multiplets); 4.00 to 5.50 [1H, CHF, m of d, J(H-F) 49.0 Hz]; 5.71 (1H, NH, br.t.); 7.00 to 7.80 (9H, C_6H_5, C_6H_4, m). Analysis: Found: C, 62.35; H, 5.97; N, 4.32%. $C_{16}H_{18}FNO_2S$ requires C, 62.52; H, 5.90; N, 4.56%.

ACKNOWLEDGEMENTS

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