Hydrochloride 7r: mp 204–205 °C; δ_F (D_2O) 179.0 (septet of d, ^3J = 10.7 Hz, ^3J = 23 Hz); *m/e* 120 [3.39 $(M - Cl)^+$], 58 [100, $(EtCHNH_2)^+$].

Registry No. **1a**, 1499-00-9; **1b**, 22596-57-2; **1c**, 768-82-1; **1d**, 25564-63-0; **1e**, 4164-24-3; **1f**, 1485-13-8; **1g**, 20993-60-6; **1h**, 1605-06-7; **1i**, 25125-72-8; *cis*-**1j**, 51626-61-0; *trans*-**1j**, 75197-96-5; **1k**, 25022-23-5; **1l**, 23040-89-3; **1m**, 7764-13-8; **1n**, 26162-53-8; **1o**, 25865-52-5; **1p**, 25865-63-8; **1q**, 286-18-0; **1r**, 25022-28-0; **6a**, 55601-20-2; **6b**, 75197-97-6; **6c**, 69681-76-1; **6d**, 69681-77-2; **6e**, 69681-82-9; **6fT**, 74275-07-3; **6fE**, 75197-98-7; **6hT**, 71057-09-5; **6hE**, 71057-08-4; **6jT**, 75197-99-8; **6jE**, 75198-00-4; **6k**, 75213-92-2; **6l**, 69681-78-3; **6m**, 71057-03-9; **6n**, 75198-01-5; **6oT**, 71057-05-1; **6oE**, 71057-06-2; **6pT**, 75198-02-6; **6pE**, 75198-03-7; **6q**, 75198-04-8; **6r**, 75198-05-9; **7a**, 64068-24-2; **7b**, 75198-06-0; **7c**, 75198-07-1; **7d**, 75198-08-2; **7e**, 75198-09-3; **7fT**, 75198-10-6; **7hT**, 75198-11-7; **7jT**, 75198-12-8; **7k**, 75213-93-3; **7l**, 75198-13-9; **7m**, 75198-14-0; **7n**, 75198-15-1; **7q**, 75198-16-2; **7r**, 75198-17-3; **8l**, 69681-79-4; HF, 7664-39-3.

New Convenient Synthesis of β,β-Difluoro Amines and β,β-Difluoro-α-amino Acid Alkyl Esters by the Addition of Hydrogen Fluoride to 1-Azirines[1]

Tamsir N. Wade*[2] and Rabia Khéribet

Laboratoire de Chimie Structurale Organique, Université de Nice, Parc Valrose, 06034 Nice, France

Received June 4, 1980

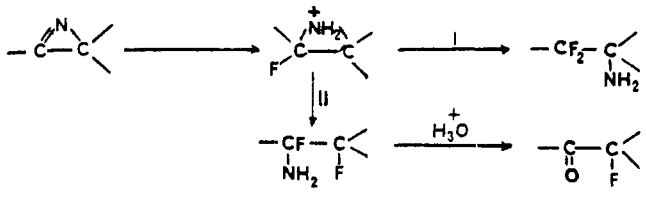
The reaction of hydrogen fluoride in pyridine solution with a series of substituted 1-azirines (**1**) was investigated. β,β-Difluoro amines (**4**) were obtained in good yields. The exceptions are the cases of 2-phenyl-3-methyl-1-azirine (**1b**) and 2,3-diphenyl-1-azirine (**1c**) for which the direct formation of a stabilized carbocation (**6**) from the azirinium ion **2** is probable. The former gave 54% of a pyrazine (**11b**) and 5% of α-fluoropropiophenone (**9b**) along with 20% of difluoro amine **4b**, while the latter afforded only the corresponding α-fluoro ketone (**9c**). A mechanism is suggested.

β-Fluorinated amines and amino acids are important targets in the search for new drugs by the application of the principle of isogeometric modification of metabolites with maximal shift of electron distribution in the design of antimetabolites and drugs.[3] The lack of general methods of synthesizing β,β-difluoro amines and β,β-difluoro-α-amino acids led us to examine the reactivity of the now easily accessible 1-azirines **1** with hydrogen fluoride.[4] This idea was supported by the fact that 1-azirines add smoothly 1 mol of such reagents as methanol, acyl chloride, and hydrogen to give aziridines, which can undergo ring opening if reacted with a second mole of reagent.[5,6]

Thus, it seemed to us of interest to evaluate whether or not the addition of hydrogen fluoride to these unsaturated rings will be a convenient synthetic route to β,β-difluoro amines.

Presumably, following the probable formation of fluoroaziridines in a first step, according to the above-mentioned reactions, two ring-opening pathways would be possible, yielding after hydrolysis either β,β-difluoro amines or α-fluoro ketones as described in Scheme I.

Scheme I



Results

The reactivity of hydrogen fluoride in pyridine solution with 1-azirines was tested on a series of substituted substrates, prepared by pyrolysis of the azidoalkene obtained from dehydrohalogenation of the corresponding iodo or bromo azide adducts of the olefin.[5,7]

1-Azirines **1g** and **1i** were reacted immediately after their preparation with hydrogen fluoride (in pyridine solution) to avoid any polymerization. For substrates **1e,f,i**, the reactions were run with a mixture containing, respectively, 44%, 65%, and 71% of 1-azirine. (The other components were minor nonseparated products such as iodo azide, azide, and iodoalkene arising from the preceding reactions.) The results are summarized in Table I.

All the products obtained were identified by their ^1H and ^{19}F NMR, IR, and mass spectra and also by elemental analyses for new compounds.

The 1-azirines **1** reacted under mild conditions (more easily than their aziridine homologues)[8] with hydrogen fluoride to give the corresponding β,β-difluoro amines **4** in convenient yields; exceptions, however, were 2-phenyl-3-methyl-1-azirine (**1b**), which gave 54% of 2,5-dimethyl-3,6-diphenylpyrazine (**11b**) and 5% of α-fluoro ketone **9b** along with a 20% yield of the difluoro amine **4b**, and 2,3-diphenyl-1-azirine (**1c**), which afforded only the corresponding α-fluoro ketone **9c**. From the azirine **1h**, only a trace amount of α-fluoro ketone **9h** was detected.

In order to avoid or diminish the dimerization observed on azirine **1b** in the HF–pyridine solution, hoping thus to improve the difluoro amine **4b** yield relative to that of

(1) Presented at the 9th International Symposium on Fluorine Chemistry, Avignon, France, Sept 1979, and at the 1st European Symposium on Organic Chemistry, Cologne, Federal Republic of Germany, Aug 1979.

(2) Present address: Département de Chimie, Faculté des Sciences, Dakar-Fann, Sénégal.

(3) J. Kollonitsch, *Isr. J. Chem.*, **17**, 53 (1978); R. W. Fuller and B. B. Molloy, "Biochemistry Involving Carbon–Fluorine Bonds" American Chemical Society, Washington, DC, 1976; J. J. M. Hageman, M. J. Wanner, G. J. Koomen, and U. K. Pandit, *J. Med. Chem.*, **20**, 1677 (1977).

(4) T. N. Wade and R. Guedj, *Tetrahedron Lett.*, 3247 (1978); *ibid.*, 3953 (1979).

(5) A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, **90**, 2869 (1968).

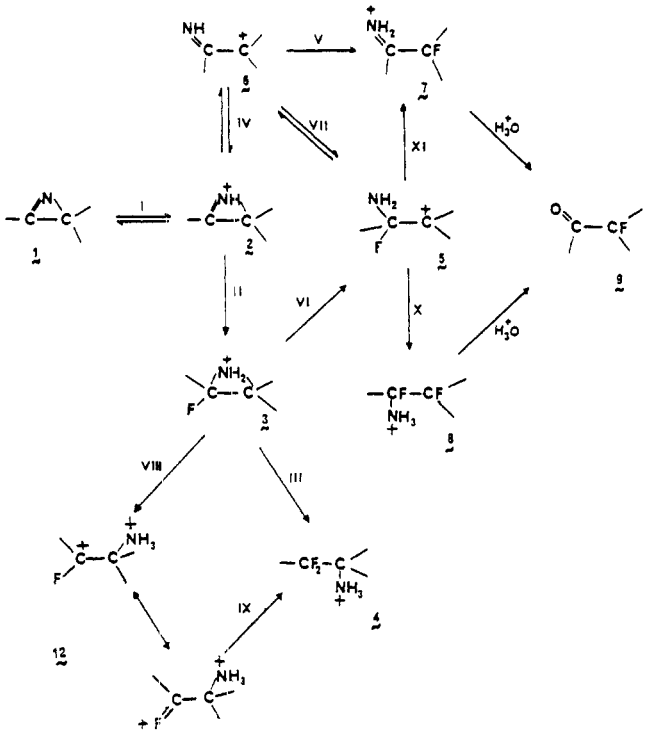
(6) F. W. Fowler and A. Hassner, *J. Am. Chem. Soc.*, **90**, 2875 (1968).

(7) A. G. Hortmann, D. A. Robertson, and B. K. Gillard, *J. Org. Chem.*, **37**, 322 (1972); A. Hassner and F. W. Fowler, *ibid.*, **33**, 2686 (1968); Chung-Gi Shin, Y. Yonezawa, and J. Yoshimura, *Chem. Lett.*, 1062 (1976).

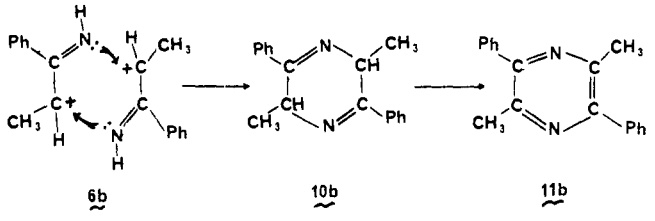
(8) T. N. Wade, *J. Org. Chem.*, accompanying paper in this issue.

0022-3263/80/1945-5333$01.00/0

Scheme II



Scheme III



pyrazine **11b**, we carried out the reaction with a more dilute solution of azirine in benzene, and in a second experiment, we used a 40% solution of HF in pyridine on this diluted azirine solution. In both cases, the product distribution did not seem to be much influenced; moreover, in the second case, some unreacted 1-azirine was recovered after 12 h of reaction.

Discussion

The study of the mechanism of addition of hydrogen fluoride to 1-azirine certainly needs more investigation. However, our results can probably be rationalized as indicated in Scheme II, and the following comments can be made.

1-Azirines are known to add easily a proton on their nitrogen in the presence of an acid, thus giving azirinium ions of type **2**. From such intermediates, two main pathways are possible. The first can lead to the formation of either β,β-difluoro amines **4** via steps II and III or steps II, VIII, and IX or to α-fluoro ketones **9** and pyrazines **11**, via steps VI, VII, etc. The second path (IV), which first involves the formation of a carbonium ion (intermediate **6**), can only give α-fluoro ketone and pyrazines (Scheme III). The intervention of such a carbonium ion was suggested by Leonard and Zwanenburg[9] for the reaction of 2-phenyl-3,3-dimethyl-1-azirine with acetone in the presence of anhydrous perchloric acid.

(9) N. S. Leonard and B. Zwanenburg, *J. Am. Chem. Soc.*, **89**, 4456 (1967).

In point of fact, the obtainment of α-fluoro ketone **9c** and pyrazine **11b** is likely to proceed along path IV, rather than along II, VI, etc. The reason is as follows. Since intermediates **12** are expected to be more stable than intermediate **5**, owing to the stabilization effect of the p electrons[10] of the fluorine, the major products arising from aziridines **3b** and **3c** should be the corresponding difluoro amines **4** and not the fluoro ketones or pyrazine; but this was not the case.

Concerning the other azirines, the presence of a fluorine on the aziridinic ring of intermediates **3** would have for an effect the considerable increase of the positive charge of the aziridinyl carbon and, consequently, an increase of the cycle bond-breaking rate. That is what was observed since 1-azirines appeared to be more reactive toward HF–pyridine than their aziridine homologues.[8] It is, however, noteworthy that the ring opening of these intermediates **3** can proceed either via the stabilized carbonium ion **12** (paths VIII and IX) or by the direct replacement of the amine group by a fluoride ion (path III).

The fact that the deuterated difluoroamino ester **4e** was obtained from **1e** excludes a mechanism involving an HF addition on a fluoro enaminium ion intermediate formed from **3** or **12**.[11]

In conclusion, the reaction of 1-azirines with HF–pyridine is likely to proceed by following two main pathways (which may be competing). The first path (II, III, VIII, and IX) leads to β,β-difluoro amines, while the second (IV, etc.) affords α-fluoro ketones and pyrazines. Although the yields of the reaction of hydrogen fluoride with 1-azirines were lower than those of the reaction of this reagent with their aziridine homologues,[8] 1-azirines can be considered as valuable synthons for the preparation of β,β-difluoro amines.

Experimental Section

General Methods. See accompanying paper.[8]

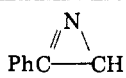
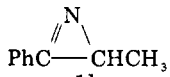
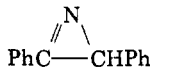
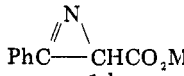
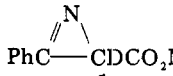
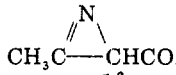
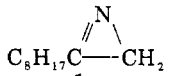
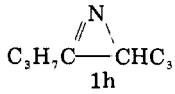
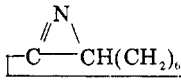
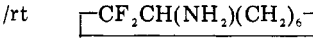
General Procedure for the Reaction of Hydrogen Fluoride with the 1-Azirines. A solution of crude or pure azirine **1** (0.01 mol) in a minimal amount of benzene (3–5 mL) was added dropwise to a 70% solution of hydrogen fluoride in pyridine (20 mL) cooled to 5 °C; after being stirred for 10 min at 5 °C, the mixture was left at room temperature for the time indicated in Table I and then poured into an Erlenmeyer flask containing 20 mL of water. For compounds **1a,d–e,f,i** the water solution was washed with three portions of 20 mL of ether, neutralized with 30% ammonia solution, and extracted with three portions of 20 mL of ether; for compounds **1b,c,g,h** the above acidic water solution was directly neutralized with a 30% ammonia solution and extracted with three portions of 20 mL of ether. The ether solution was dried ($MgSO_4$) and evaporated in vacuo; the products were separated by silica gel column chromatography (eluent benzene–ethyl acetate, 4:1 v/v). Further purifications were made by crystallization of their hydrochloride according to the following procedure. The fluoro amine hydrochloride was dissolved in a minimal amount of warm absolute ethanol (ca. 35 °C), anhydrous ether was then added until near saturation, and the solution was left at 5–10 °C for a time which depended on the products. Filtration gave the pure hydrochloride.

The yields and ^{19}F NMR data of the fluoro amines are indicated in Table I. The IR spectra ($CHCl_3$) show two weak bands at ca. 3300–3380 cm^{-1} corresponding to the stretching of the NH_2 group. We give here below the other physical characteristics of the obtained products: ^1H NMR, δ_H, $CDCl_3$ solvent, Me_4Si internal standard, s = singlet, d = doublet, t = triplet, q = quartet, m =

(10) G. A. Olah, R. D. Chambers, and M. B. Comisarow, *J. Am. Chem. Soc.*, **89**, 1268 (1967); D. T. Clarke and D. M. J. Lilley, *J. Chem. Soc., Chem. Commun.*, 603 (1970).

(11) For 70% addition of HF–pyridine to double bonds, see G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 779 (1973); S. Hamman and C. G. Beguin, *J. Fluorine Chem.*, **13**, 163 (1979).

Table I. Reaction of 1-Azirines 1 with HF-Pyridine

azirine 1	conditions[d]	products	yields,[a] %	^{19}F NMR spectral data[b] δ	$^2J_{FF}$, Hz	$^3J_{FH}$, Hz
 1a	1 h/rt	$PhCF_2CH_2NH_2$ (4a)	67	106.5		14.9
 1b	1 h/rt	$PhCF_2CH(NH_2)CH_3$ (4b) $PhC(O)CHFCH_3$ (9b) pyrazine (11b)	20 5 54	106.4 (δ_1), 113.3 (δ_2)	243.7	J_1 = 10.1, J_2 = 12.7
 1c	1 h/rt	PhCOCHFPh (9c)	37	176.7		
 1d	1 h/rt	$PhCF_2CH(NH_2)CO_2Me$ (4d)	32	105.46 (δ_1), 105.53 (δ_2)		J_1 = 11.4, J_2 = 11.7
 1e	1 h/rt	$PhCF_2CD(NH_2)CO_2Me$ (4e)	40	108.3		
 1f	3 h/rt	$CH_3CF_2CH(NH_2)CO_2Et$ (4f)	43	97.6 (δ_1), 100.6 (δ_2)	247.0	J_1 = 11.0, J_2 = 11.8
 1g	3 h/rt	$C_8H_{17}CF_2CH_2NH_2$ (4g)	58	107.8		14.9
 1h	10 h/rt	$C_3H_7CF_2CH(NH_2)C_3H_7$ (4h) $C_3H_7C(O)CHFC_3H_7$ (9h)	43 4	110.3 (δ_1), 110.5 (δ_2) 193	243.0	
 1i	10 h/rt	 4i	35	96.2 (δ_1), 113.0 (δ_2)	239.7	J_1 = 20.0

[a] Yield based on azirine and after silica gel column chromatography (eluent benzene–ethyl acetate, 4:1 v/v). [b] In $CDCl_3$ solution with $CFCl_3$ as internal standard; positive shifts are to high field; $^3J_{FH}$ = J between F and $CHNH_2$. [c] The reaction was run on a mixture containing 44% of azirine for **1e**, 65% for **1f**, and 71% for **1i**. [d] rt = room temperature.

multiplet; melting point (uncorrected); mass spectrum, *m/e* (relative intensity); satisfactory elemental analyses (±0.4% of theory) were obtained for C, H, and F for all new fluoro amine hydrochlorides.

2,2-Difluoro-2-phenylethylamine (4a): δ_H 1.71 (s, 2 H, NH_2), 3.17 (t, 2 H, ^3J = 14.5 Hz, CH_2NH_2), 7.46 (s, 5 H, C_6H_5). **Hydrochloride**: mp 169–172 °C; *m/e* 158 [88.25, $(M - Cl)^+$], 127 (86.77, $PhCF_2^+$).

2,2-Difluoro-2-phenyl-1-methylethylamine (4b): δ_H 1.09 (d, 3 H, ^3J = 7 Hz, CH_3CHNH_2), 1.93 (s, 2 H, NH_2), 3.33 (m, 1 H, $CHNH_2$), 7.42 (s, 5 H, C_6H_5). **Hydrochloride**: mp 201 °C; *m/e* 172 [0.24, $(M - Cl)^+$], 44 (100.00, $CH_3CHNH_2^+$).

α-Fluoropropiophenone (9b): δ_H 1.67 (dd, 3 H, ^3J = 24.5 Hz, ^3J = 7 Hz, CH_3CHF), 5.29 and 6.09 (qd, ^3J = 7 Hz, ^2J = 48.2 Hz, $CHFCH_3$), 7.2–8.1 (m, 5 H, C_6H_5).

2,5-Dimethyl-3,6-diphenyl pyrazine (11b): mp 126 °C; δ_H 2.64 (s, 6 H, 2 CH_3), 7.27–7.87 (m, 10 H, 2 C_6H_5); *m/e* 260 (95.47, M^+), 259 (100.00), 116 (45.48), 115.1 (80.94). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19. Found: C, 82.36; H, 6.11.

α-Fluoro-α-phenylacetophenone (9c): mp 47–48 °C; ν (C=O) 1670, 1680 cm^{-1}; δ_H 6.53 (d, 1 H, ^2J = 49 Hz, CHF), 7.20, 7.70, and 7.88–8.2 (2m, 10 H, 2 C_6H_5); δ_F = 176.7 (d, ^2J = 49.7 Hz); *m/e* 214 (0.55, $M^{+\cdot}$), 109 (25.82, $PhCHF^+$), 105 (100.00, $PhCO^+$), 77 (87.31). Anal. Calcd for $C_{14}H_{11}FO$: C, 78.49; H, 5.17; F, 8.87. Found: C, 78.36; H, 5.03; F, 8.29.

Methyl 3,3-difluoro-2-amino-3-phenylpropionate (4d): ν 3350, 3310, 1730 cm^{-1}; δ_H 2.29 (br s, 2 H, NH_2), 3.63 (s, 3 H, CH_3O), 4.01 (t, 1 H, ^3J = 11.5 Hz, CF_2CHNH_2), 7.42 (s, 5 H, C_6H_5). **Hydrochloride**: mp 168–170 °C; *m/e* 216 [2.35, $(M - Cl)^+$], 88 (100.00, $CHNH_2CO_2CH_3^+$).

Methyl 3,3-difluoro-2-amino-2-deuterio-3-phenylpropionate (4e): ν 3320, 3380, 1725 cm^{-1}; δ_H 2.23 (br s, 2 H, NH_2), 3.60 (s, 3 H, CH_3O), 7.46 (s, 5 H, C_6H_5). **Hydrochloride**: mp 176–177 °C; *m/e* 217 [2.03, $(M - Cl)^+$], 89 (100.00, $CDNH_2CO_2CH_3^+$).

Ethyl 3,3-difluoro-2-aminobutanoate (4f): ν 3320, 3390, 1725 cm^{-1}; δ_H 1.29 (t, 3 H, ^3J = 7 Hz, CH_3CH_2), 1.68 (t, 3 H, ^3J = 19 Hz, CH_3CF_2), 1.75 (s, 2 H, NH_2), 3.72 (t, 1 H, ^3J = 11 Hz, CF_2CHNH_2), 4.23 (q, 2 H, ^3J = 7 Hz, OCH_2CH_3). **Hydrochloride**: mp 156 °C; *m/e* 168 [15.58, $(M - Cl)^+$], 94 (94.67, $CH_3CF_2CHNH_2^+$).

2,2-Difluorodecylamine (4g): δ_H 0.7–2.1 (m, 19 H, C_8H_{17} and NH_2), 2.93 (quintet, 2 H, ^3J = 15 Hz, $CF_2CH_2NH_2$). **Hydrochloride**: mp 208–210 °C; *m/e* 194 [8.59, $(M - Cl)^+$], 41 (92.38).

2,2-Difluoro-1-propylpentylamine (4h): δ 0.7–2.1 (m, 16 H, 2 C_3H_7 and NH_2), 2.75 (m, 1 H, $CHNH_2$). **Hydrochloride**: mp 192 °C; *m/e* 166 [0.49, $(M - Cl)^+$], 122 (10.96, $C_3H_7CF_2CHNH_2^+$), 72 (100.00, $C_3H_7CHNH_2^+$).

5-Fluorooctan-4-one (9h): δ_H 0.93 (t, 6 H, ^3J = 7 Hz, 2 CH_3), 1.1–2 (m, 8 H, 2 $CH_3H_2CH_2$), 4.3 and 5.16 (md, K of ABKX pattern, 1 H, $^2J \simeq$ 51 Hz, CH_2CHFCO); δ_F 192.8 (m).

2,2-Difluorocyclooctylamine (4i): δ_H 1.6 and 2.1 [2 m, 14 H, $(CH_2)_6$ and NH_2], 3.02 and 3.27 (md, 1 H, ^3J = 22 Hz, $W_{1/2}$ = 8.5 Hz, CF_2CHNH_2). **Hydrochloride**: mp 218–220 °C; *m/e* 164 [0.43, $(M - Cl)^+$], 56 (100.00).

Registry No. **1a**, 7654-06-0; **1b**, 16205-14-4; **1c**, 16483-98-0; **1d**, 18709-45-0; **1e**, 75149-41-6; **1f**, 14369-88-1; **1g**, 75149-42-7; **1h**, 54902-93-1; **1i**, 14747-97-8; **4a**, 55601-21-3; **4a**·HCl, 39625-10-0; **4b**, 39038-72-7; **4b**·HCl, 39038-72-7; **4d**, 73757-44-5; **4d**·HCl, 75149-43-8; **4e**, 75149-44-9; **4e**·HCl, 75149-45-0; **4f**, 73757-45-6; **4f**·HCl, 75149-46-1; **4g**, 75149-47-2; **4g**·HCl, 75149-48-3; **4h**, 75149-49-4; **4h**·HCl, 75149-49-4; **4i**, 75149-50-7; **4i**·HCl, 75149-51-8; **9b**, 21120-36-5; **9c**, 720-43-4; **9h**, 75149-52-9; **11b**, 290-37-9; HF, 7664-39-3.