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N-Fluorination of aziridinecarboxylates *via* fluorolysis of their *N*-aminomethyl derivatives

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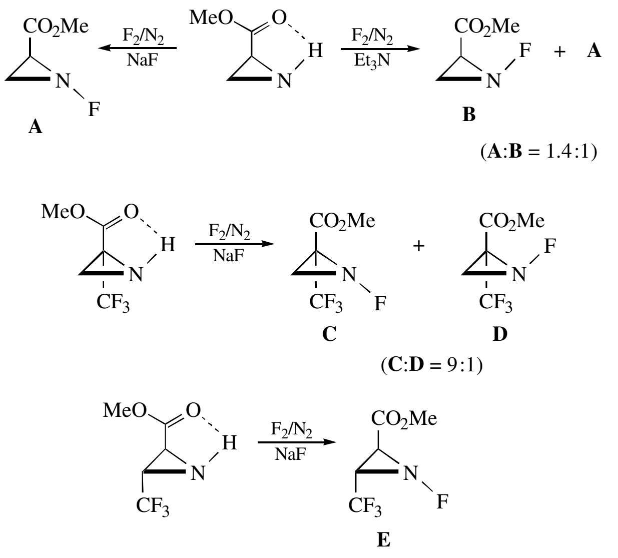
A new and convenient method for the synthesis of 1-fluoroaziridinecarboxylates through the fluorolysis of *N*-aminomethylaziridinecarboxylates is revealed.

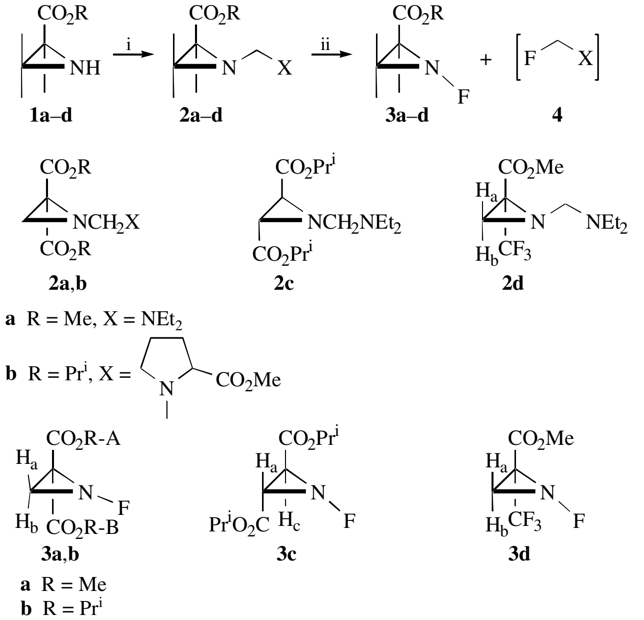
1-Fluoroaziridines show an extraordinarily high configurational stability of the nitrogen atom (G_{inv} = 35 kcal mol^{-1})[1] but only a few of these scarcely available compounds have been reported.[1–3] They are obtained by addition of CH_2N_2 to the *N*-fluoroimine of hexafluoroacetone followed by acidolysis of the resulting ^{2}-1,2,3-triazoline (yield 38%).[2,3] Later, 1-fluoro-2,2-bis(trifluoromethyl)aziridine was obtained by direct fluorination of 2,2-bis(trifluoromethyl)aziridine (F_2/NaF) in 50% yield and its NMR parameters were refined.[4] Also, 1-fluoro-2-aryl(alkyl)aziridines were detected spectroscopically (NMR, IR) following the interaction of 2-aryl(alkyl)aziridines with CF_3OF.[5]

Recently, by direct fluorination of NH-aziridines, some stable *N*-fluoroaziridinecarboxylates **A**–**E** were synthesised and isolated in pure form (Scheme 1).[4,6,7] N-Fluorination in the presence of NaF proceeds *trans*-stereospecifically due to the fixed orientation of the nitrogen lone pair through the intramolecular H-bond. When this H-bond is broken in the presence of Et_3N both isomers **A** and **B** are formed.[1] In the case of unsymmetrically-substituted aziridinecarboxylates this leads to fluorine attack from the more sterically hindered side with the formation of mostly *N*-fluoroaziridine **C**[6] or exclusively **E**.[7] However, fluorination of aziridines in the presence of NaF is difficult to reproduce and yields strongly depend on the reaction conditions (dispersivity of NaF, mixing conditions, dilution extent, rate of F_2 feed), and fluorination in the presence of Et_3N is limited. Thus, methyl *trans*-2-trifluoromethylaziridine-3-carboxylate is far less nucleophilic than methyl aziridine-2-carboxylate and in the presence of Et_3N it does not undergo fluorination because of the concurrent and easier fluorination of Et_3N itself.[7]

In this connection, we have evolved a more convenient method for the synthesis of *N*-fluoroaziridines by fluorolysis of aminomethyl derivatives. Chlorolysis of symmetric bis(dialkylamino)methanes is well known to give *N*-chloroamines.[8] 1-Aminomethylaziridines[9–11] and methyl 1-aminomethylaziridine-2-carboxylate[12] were obtained for the first time in our laboratory. It was shown that these compounds are attacked by electrophilic reagents at the aziridine nitrogen with C–N bond breakage,[10] whereupon the 1-aminomethyl derivative of 2,2-dimethylaziridine containing the residue of a chiral secondary amine gives an optically active 1-chloro-2,2-dimethylaziridine under the action of Bu^{t}OCl or *N*-chlorosuccinimide.[13]



Scheme 1

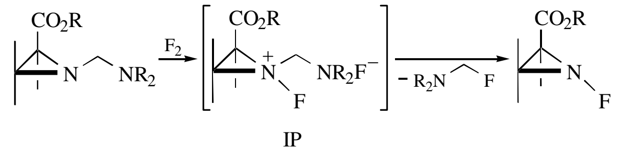


Scheme 2 *Reagents and conditions*: i, equimolar quantity of $MeOCH_2NEt_2$ or methyl ester of *N*-methoxymethylproline, 48 h in the presence of 4Å molecular sieves, 20–25 °C; ii, F_2/N_2, freon-11, –78 °C.

In this work we have synthesized new aminomethyl derivatives of aziridinecarboxylates and showed that they smoothly undergo fluorolysis forming the corresponding *N*-fluoroaziridines (Scheme 2).

In our opinion the reaction can be explained by formation of the ion pair IP as intermediate (Scheme 3). A stable immonium ion eliminates this ion pair to form the final NF-aziridine. Recently, the existence of a similar ion pair between Me_3N and fluorine was confirmed by rotational spectroscopy in the gas phase.[14]

It should be noted that aziridinecarboxylate **2d** as its *N*-unsubstituted analogue (Scheme 1)[7] forms only one isomer



Scheme 3

3d under these conditions. The cause of such stereospecificity is the high population of the *trans*-form (with respect to the CF_3 group) of the aminomethyl derivative due to the significantly greater bulk of the CF_3 substituent in comparison with CO_2Me. So, fluorine attack occurs from the more hindered side too. The configuration of **2d** (Scheme 2) was assigned on the basis of the NMR data,† based on the presence of $^4J_{HCCF}$ for H_a and its value (1.5 Hz).[2,15]

1-Fluoroaziridine **3c** was obtained in an optically active form from optically active aminomethylaziridine (2*S*,3*S*)-**2c**.

Product **4** was precipitated under the conditions of the reaction and at 20 °C is a viscous oil of indefinite structure and insoluble in CCl_4 or $CHCl_3$, but very soluble in MeOH and acetone. Most likely, this is the fluorohydrate of the product of subsequent fluorination of fluoromethyldialkylamine.

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† ^1H and ^{19}F NMR spectra were recorded on a Bruker WM-400 (at 400.13 MHz for ^1H and 376.48 MHz for ^{19}F), ^{13}C NMR spectra were recorded on a Bruker AC 200 and WM-400 (at 50.32 MHz and 100 MHz). Chemical shifts are expressed in ppm downfield of tetramethylsilane for ^1H and ^{13}C; for ^{19}F, relative external CF_3CO_2H.

Methoxymethylamine and *N*-methoxymethylproline methyl ester were obtained according to refs. 16 and 17, aziridines **1a–d** according to refs. 18,19 and 6.

2a: ^1H NMR ($CDCl_3$) δ: 1.06 (t, 6H, $2CH_3CH_2$, $^3J = 7.3$ Hz), 2.7 (q, 4H, $2CH_3CH_2$, $^3J = 7.3$ Hz), 2.3 (br. s, 2H, CH_2-aziridine ring), 3.54 (br. s, 2H, NCH_2N), 3.84 (br. s, 6H, MeO); ^{13}C NMR ($CDCl_3$) δ: 11.48 (q, CH_3CH_2, $^1J = 125.0$ Hz), 38.00 (t, CH_2-aziridine ring, $^1J = 173.0$ Hz), 43.38 (t, C-aziridine ring, $^2J = 2.9$ Hz), 44.11 (t, CH_3CH_2, $^1J = 133.0$ Hz), 51.39 (q, MeO, $^1J = 147.5$ Hz), 69.55 (t, NCH_2N, $^1J = 146.1$ Hz), 165.48 and 166.45 (m, CO).

2b: $[\alpha]_D^{15}$ –2 2.33° (*c* 0.1, MeOH). ^1H NMR ($CDCl_3$) δ: 1.24 and 1.26 [m, 12H, $2(CH_3)_2CH$, $^3J = 6.4$ Hz], 1.79 and 1.85 (m, 2H, -CH_2), 1.93 and 2.23 (m, 2H, -CH_2), 2.23 (br. s, 2H, CH_2-aziridine ring), 2.97 and 3.06 (m, 2H, -CH_2), 3.70 (s, 3H, MeO), 3.72 (m, 1H, -CH), 4.43 (dd, 2H, NCH_2N, AB spectrum, $\nu = 100$ Hz, $^2J_{AB} = -9.8$ Hz), 5.08 (hept, 2H, $2CHMe_2$, $^3J = 6.4$ Hz).

2c: $[\alpha]_D^{15}$ +7.23° (*c* 9, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.05 (t, 6H, $2CH_3CH_2$, $^3J = 7.3$ Hz), 1.26 and 1.29 [m, 12H, $2(CH_3)_2CH$, $^3J = 6.4$ Hz], 2.71 (m, 4H, $2MeCH_2$, ABX_3 spectrum, $\nu = 12$ Hz, $^2J_{AB} = -12.6$ Hz, $^3J_{AX} = {}^3J_{BX} = 7.3$ Hz), 2.29 and 2.82 (d, 2H, 2H-ring, $^3J = 6.1$ Hz), 3.76 (q, 2H, NCH_2N, AB spectrum, $\nu = 24$ Hz, $^2J_{AB} = -12.6$ Hz), 5.04 (hept, 2H, $2CHMe_2$, $^3J = 6.4$ Hz).

2d: ^1H NMR ($CDCl_3$) δ: 1.06 (t, 6H, $2CH_3CH_2$, $^3J = 7.3$ Hz), 2.43 (dq, 1H, H_a, $^2J_{ab} = -1.5$ Hz, $^4J_{aCCCF_3} = 1.5$ Hz), 2.45 (d, 1H, H_b, $^2J_{ab} = -1.5$ Hz), 2.68 (m, 4H, $2CH_2Me$, ABX_3 spectrum, $\nu = 24$ Hz, $^2J_{AB} = -12.8$ Hz, $^3J_{AX} = {}^3J_{BX} = 7.3$ Hz), 3.57 (dd, 2H, NCH_2N, AB spectrum, $\nu = 52$ Hz, $^2J_{AB} = -11.6$ Hz), 3.84 (s, 3H, MeO).

3a: yield 91%, bp 61–63 °C (1 torr). ^1H NMR ($CDCl_3$) δ: 2.81 (dd, 1H, H_a, $^2J_{ab} = -5.5$ Hz, $^3J_{aF} = 29.3$ Hz), 3.32 (dd, 1H, H_b, $^2J_{ab} = -5.5$ Hz, $^3J_{bF} = 40.9$ Hz), 3.80 (s, 3H, A-MeO), 3.87 (s, 3H, B-MeO), *cf.* ref. 4.

3b: yield 90%, bp 71–72 °C (1 torr). ^1H NMR ($CDCl_3$) δ: 1.30 and 1.34 [m, 12H, $2(CH_3)_2CH$, $^3J = 6.4$ Hz], 2.74 (dd, 1H, H_a, $^2J_{ab} = -5.5$ Hz, $^3J_{AF} = 29.3$ Hz), 3.27 (dd, 1H, H_b, $^2J_{ab} = -5.5$ Hz, $^3J_{bF} = 40.9$ Hz), 5.11 (hept, 1H, A-$CHMe_2$, $^3J = 6.4$ Hz), 5.13 (hept, 1H, B-$CHMe_2$, $^3J = 6.4$ Hz). ^{19}F NMR ($CDCl_3$) δ: 16.32 (dd, FN, $^3J_{aF} = 29.3$ Hz, $^3J_{bF} = 40.9$ Hz).

3c: yield 90%, bp 82–85° (0.5 torr), $[\alpha]_D^{15}$ +34.45° (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.24 and 1.28 [m, 12H, $2(CH_3)_2CH$, $^3J = 6.1$ Hz], 3.36 (dd, 1H, H_a, $^3J_{ac} = 6.7$ Hz, $^3J_{aF} = 20.1$ Hz), 3.75 (dd, 1H, H_c, $^3J_{ac} = 6.7$ Hz, $^3J_{cF} = 33.6$ Hz), 5.01 (hept, 1H, A-$CHMe_2$, $^3J = 6.1$ Hz), 5.08 (hept, 1H, B-$CHMe_2$, $^3J = 6.1$ Hz). ^{19}F NMR ($CDCl_3$) δ: 18.36 (dd, FN, $^3J_{aF} = 20.1$ Hz, $^3J_{cF} = 33.6$ Hz), *cf.* ref. 4.

3d: yield 52%, bp 72–75 °C (70 torr). ^1H NMR ($CDCl_3$) δ: 3.10 (ddq, 1H, H_a, $^2J_{ab} = -5.8$ Hz, $^3J_{aNF} = 28.7$ Hz, $^4J_{aCCF} = 2.4$ Hz), 3.29 (dd, 1H, H_b, $^2J_{ab} = -5.8$ Hz, $^3J_{bNF} = 41.5$ Hz), 3.87 (s, 3H, MeO). ^{19}F NMR ($CDCl_3$) δ: 14.13 (dd, CF_3, $^4J_{FCCa} = 2.4$ Hz, $^4J_{FCCNF} = 22.4$ Hz). ^{13}C NMR ($CDCl_3$) δ: 41.50 (dd, 3-C, $^1J_{Ca} = 172.1$ Hz, $^1J_{Cb} = 171.8$ Hz), 47.91 (qdt, 2-C, $^2J_{CCF} = 35.4$ Hz, $^2J_{CNF} = 7.0$ Hz, $^2J_{CCH} = 3.5$ Hz), 53.87 (q, MeO, $^1J_{CH} = 149.2$ Hz), 120.84 (q, CF_3, $^1J_{CF} = 277.4$ Hz), 162.21 (dq, CO, $^3J = 5.1$ Hz).