

Derivatives of 1-fluoroaziridine-2,2-dicarboxylic acid

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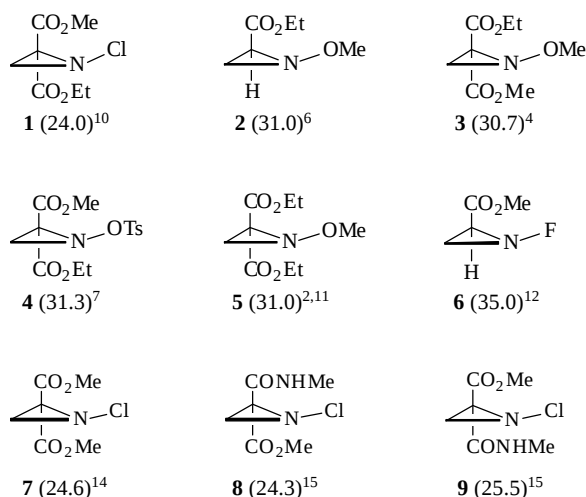
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Derivatives of 1-fluoroaziridine-2,2-dicarboxylic acid **10–14** have been synthesized for the first time and characterized by spectroscopic methods; nucleophilic reactions of dimethyl 1-fluoroaziridine-2,2-dicarboxylate, such as transesterification and amidation, occur predominantly at the carboxy group *trans*-oriented with respect to the N-substituent.

Synthesis of derivatives of aziridinecarboxylic acids with electronegative N-substituents,^{1–12} such as **1–6** ($\Delta G_{\text{inv}}^{\ddagger}$ kcal mol^{–1} in parentheses) has been developed in our laboratory in connection with the investigation of asymmetric nitrogen.



In the case of 1-alkoxyaziridines the chemistry and configurational stability were studied first on monoesters of type **2**, then diesters, *e.g.* **3** and **4**, were examined (compounds of type **4** were studied later¹³), and, finally, using diester **5**, the optical activation, complete resolution into antipodes, determination of their absolute configuration as well as reactions with retention of nitrogen atom configuration were carried out. Similarly, 1-chloro- and 1-bromoaziridinecarboxylates were investigated.^{3,4,9,10,14–19} The structure of compounds **7**,¹⁶ **8**¹⁷ and **9**,¹⁵ as well as configurational stability of **10** and **7–9**^{14,15} were established; enzymatic resolution of 1-chloroaziridine **7**¹⁴ was achieved, and the chiroptical properties of these types of compounds were studied.^{15,18,19}

The same strategy was used for the investigation of 1-fluoroaziridinecarboxylates. Stable *cis*- and *trans*-isomers of methyl 1-fluoroaziridine-2-carboxylate were obtained recently. It was shown that aziridine **6** has a record high configurational stability.¹²

In this work, for the first time derivatives of 1-fluoroaziridine-2,2-dicarboxylic acid **10–14** have been synthesized and studied (Scheme 1).[†] Compound **10** was prepared by fluorination of dimethylaziridine-2,2-dicarboxylate. 1-Fluoro-2,2-bistrifluoromethylaziridine **15** was obtained in a similar manner from 2,2-bistrifluoromethylaziridine.²⁰ It was synthesized earlier by another method²¹ but no ¹³C NMR spectra were reported.²² We managed to obtain the corresponding *N*-fluoroaziridine **16** by fluorination of diisopropyl aziridine-2,3-dicarboxylate¹⁹ but the yield was as

low as 5.5%.

Fluoroaziridine **10** is quite stable; it can be distilled *in vacuo* without decomposition and does not change under boiling in a CF₃CO₂H–H₂SO₄ mixture with removal of CF₃CO₂H by distillation (under the same conditions aziridine **4** undergoes *trans*-deesterification⁷). Under prolonged boiling of **10** in [²H₄]methanol stereospecific transesterification into **11** is observed, and after 10 h the ratio of signal intensities is as follows: B-MeO : A-MeO : MeOH = 2 : 1 : 1. Upon treatment with equimolar quantities of NH₃ or MeNH₂ *trans*-monoamidation of **10** and formation of amides **12** and **13**, respectively, occurs on cooling. When treated with excess MeNH₂, diester **10** transforms into bismethylamide **14**. Therefore, in spite of the small size of the N-substituent, fluoroaziridine **10** is similar to 1-alkoxyaziridinecarboxylates^{1–11} and 1-chloro analogue **7**,^{14,15–17} in terms of its behaviour in nucleophilic reactions.

[†] ¹H NMR (400.13 MHz), ¹³C (100.62 MHz), standard TMS, ¹⁹F (376.48 MHz), standard CF₃CO₂H, δ /ppm, J/Hz.

10, yield 75%, bp 86–88°C (3 torr); ¹H NMR (CDCl₃): 2.80 dd (H_a, ²J_{ab} = –5.5, ³J_{aF} = 29.3), 3.32 dd (H_b, ³J_{bF} = 40.9), 3.80 s and 3.87 s (MeO); ¹³C NMR (CDCl₃): 43.51 ddd (3-C, ¹J_{Ca} = 180.2, ¹J_{Cb} = 176.6, ²J_{CF} = 2.9), 51.0 dt (2-C, ²J_{CF} = 7.3, ²J_{Ca} = ²J_{Cb} = 3.6), 53.08 q and 53.41 q (MeO, ¹J_{CH} = 149.0), 161.1 m (B-CO, ³J_{CF} = 8.7, ³J_{CH} ~ 4.4), 164.3 hept (A-CO, ³J_{CF} = ³J_{Ca} = ³J_{Cb} = 4.4); ¹⁹F NMR (CD₃OD): 29.1 dd; mass spectrum (EI, 70 eV), *m/z* (%): 158 (4.6) [M–F]⁺, 146 (4.6) [M–MeO]⁺, 130 (2.9), 99 (2.6), 70 (2.5), 68 (3.2), 59 (29.4), 54 (11.0), 45 (100), 40 (6.4), 33 (3.6), 29 (6.1), 15 (46.0).

11 was characterized without isolation, ¹H NMR (CD₃OD): 2.89 dd (H_a, ²J_{ab} = –5.8, ³J_{aF} = 30.0), 3.35 dd (H_b, ³J_{bF} = 42.0), 3.35 s (MeOH), 3.78 s (B-MeO), 3.84 s (A-MeO); ratio of the intensities of signals of MeO at 3.35, 3.78 and 3.84 ppm = 1 : 2 : 1.

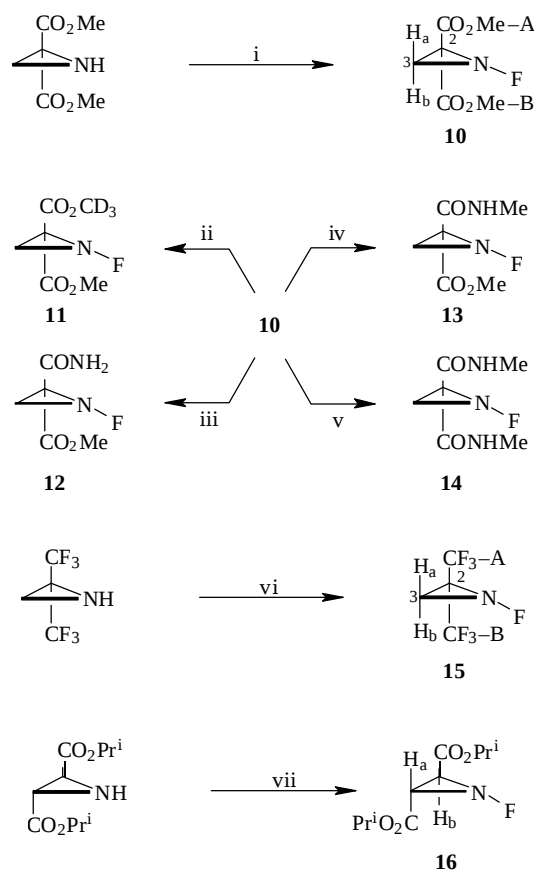
12, yield ~ 70%, oil contaminated with starting **10**; ¹H NMR (CDCl₃): 2.88 dd (H_a, ²J_{ab} = –5.0, ³J_{aF} = 26.5), 3.47 dd (H_b, ³J_{bF} = 40.0), 3.9 s (MeO), 6.81 br. s (HN).

13, yield ~ 70%, oil contaminated with starting **10**; ¹H NMR (CDCl₃): 2.81 dd (H_a, ²J_{ab} = –5.8, ³J_{aF} = 26.6), 2.87 d (MeN, ³J = 5.8), 3.42 dd (H_b, ³J_{bF} = 40.0), 3.87 s (MeO), 6.83 br. s (HN).

14, yield 80%, mp 148–150°C; ¹H NMR (CDCl₃): 2.76 dd (H_a, ²J_{ab} = –5.0, ³J_{aF} = 26.6), 2.83 d and 2.91 d (MeN, ³J = 4.9), 3.45 dd (H_b, ³J_{bF} = 39.7), 6.75 br. m and 6.97 br. m (HN); ¹³C NMR (CD₃OD): 26.51 q and 26.97 q (MeN, ¹J_{CH} = 139.5), 43.54 ddd (3-C, ¹J_{Ca} = 178.8, ¹J_{Cb} = 174.4, ²J_{CF} = 4.4), 54.75 dt (2-C, ²J_{CF} = 6.5, ²J_{CH} = 3.2), 163.2 m (B-CO, ³J_{CF} = 8.0), 166.94 m (A-CO, ³J_{CF} = 3.6); ¹⁹F NMR (CD₃OD): 24.34 dd.

15, yield 50%, bp 65°C; ¹H NMR (CDCl₃): 2.85 ddq (H_a, ²J_{ab} = –6.6, ³J_{aF} = 27.2, ⁴J_{B-CF₃-a} = 2.3), 3.33 ddq (H_b, ³J_{bF} = 38.9, ⁴J_{A-CF₃-b} = 1.1); ¹³C NMR (CDCl₃): 39.06 td (3-C, ¹J_{CH} = 180.2, ²J_{CF} = 3.0), 47.65 hept. dt (2-C, ²J_{CF} = 37.1, ²J_{CNF} = 5.8, ²J_{CH} = 2.9), 120.3 q (CF₃, ¹J_{CF} = 277.6) (Commonly, chemical shifts of CF₃ group carbons in the ¹³C NMR spectra of 2,2-bistrifluoromethylaziridines either coincide or differ slightly.²²); ¹⁹F NMR (CDCl₃): 6.05 ddq (A-CF₃, ⁴J_{FCCNF} = 7.4, ⁴J_{FCCNF} = 2.2), 8.64 br. m (FN), 13.43 ddq (B-CF₃, ⁴J_{FCCNF} = 23.1).

16, yield 5.5%, bp 85°C (0.6 Torr), ¹H NMR (CDCl₃): 1.24 m and 1.28 m (Me, ³J = 6.1), 3.34 dd (H_a, ³J_{HH} = 6.7, ³J_{aF} = 20.1), 3.72 dd (H_b, ³J_{bF} = 33.6), 5.01 hept and 5.08 hept (HC).



Scheme 1 Reagents and conditions: i, F_2/N_2 , 4–10 fold excess of NaF, in a mixture of freon-113– CHCl_3 (1:1), 3 h at 0°C ; ii, CD_3OD , boiling 10 h; iii, equimol. quantity of dry NH_3 in abs. MeOH, 3 days at 0°C ; iv, equimol. quantity of dry MeNH_2 in abs. MeOH, 1 day at 0°C ; v, excess of dry MeNH_2 in abs. MeOH, 0.5 h at 0°C ; vi, F_2/N_2 , excess of NaF in $\{\text{CF}_3\text{O}[\text{CF}(\text{CF}_3)\text{CF}_2\text{O}]_2\text{CF}_2\}_2$ (bp 215°C); vii, under conditions i, 1.5 h at -50°C .

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