

Methyl 2-trifluoromethylaziridine-2-carboxylate: stereodirected N-halogenation from the sterically more hindered side

Vladimir V. Rozhkov,^a Kirill N. Makarov,^b Sergey N. Osipov,^b Ivan I. Chervin,^c Anatolii V. Ignatenko^d and Remir G. Kostyanovsky*^c

^a Ukrainian State University of Chemistry and Technology, 320005 Dnepropetrovsk, Ukraine. Fax: +7 0562 477 478

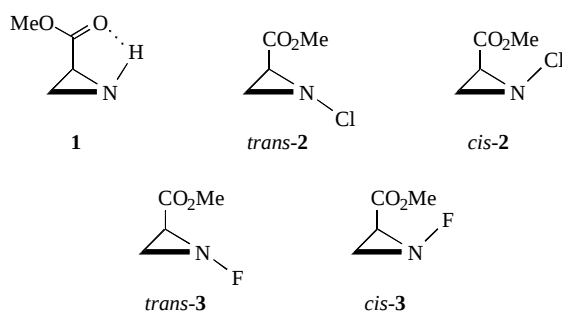
^b A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow, Russian Federation. Fax: +7 095 135 5085

^c N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 117977 Moscow, Russian Federation. Fax: +7 095 938 2156; e-mail: kost@center.chph.ras.ru

^d N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation. Fax: +7 095 135 5328

N-Fluorination and N-chlorination of methyl 2-trifluoromethylaziridine-2-carboxylate occurs predominantly from the more hindered side owing to the fixed orientation of the lone electron pair of the N atom caused by the formation of an intramolecular H-bond.

Chlorination of aziridine **1** with chlorosuccinimide or Bu^tOCl yields only the *trans*-isomer of compound **2**.¹ Only recently, a mixture of *cis*- and *trans*-**2** was obtained by the reaction with KOCl in the toluene–water system.² Fluorination of aziridine **1** also yields only the *trans*-isomer of product **3**, despite the fact that the fluorine atom is small. This stereospecificity is due to the fixed *trans*-orientation of the lone electron pair (LEP) of nitrogen caused by the formation of an intramolecular H-bond, the presence of which has been unambiguously proved by NMR spectroscopy.³ If this H-bond is cleaved during the reaction, a mixture of *cis*- and *trans*-isomers of **3** is formed in the ratio of ~1:1.5.²



In the present study, we have obtained for the first time methyl 2-trifluoromethylaziridine-2-carboxylate **4** by alcoholysis of its 1-trifluoroacetyl derivative⁴ (Scheme 1).[†] Based on the NMR criteria developed previously,^{3,5} the occurrence of an intramolecular H-bond in the aziridine **4** is confirmed unambiguously:

$$^3J_{\text{aNH}}^{\text{cis}} (10.6 \text{ Hz}) > ^3J_{\text{bNH}}^{\text{trans}} (9.5 \text{ Hz}) \gg ^2J_{\text{ab}}^{\text{gem}} (1.4 \text{ Hz})$$

Therefore, one should expect that its N-halogenation would be highly stereospecific and occur from the sterically more hindered side (the conformational energies of the CF₃ and CO₂Me groups are 2.1 and 1.27 kcal mol⁻¹, respectively⁶).

In fact, fluorination of the aziridine **4** carried out under conditions retaining the intramolecular H-bond yields two isomers **5s** and **5a** in the ratio 9:1, i.e. the *syn*-isomer (with respect to the CF₃ group) markedly predominates.

The *cis*- and *trans*-orientations of the fluorine atom were confirmed unambiguously by NMR data: $^3J_{\text{aF}}^{\text{trans}}$ (28.2 Hz) < $^3J_{\text{bF}}^{\text{cis}}$ (40.6 Hz) and $^3J_{\text{aF}}^{\text{cis}}$ (40.0 Hz) > $^3J_{\text{bF}}^{\text{trans}}$ (28.7 Hz) for **5s** and **5a** [$^3J_{\text{aF}}$ (18.9 Hz) < $^3J_{\text{bF}}$ (33.6 Hz) for the aziridine **7s**; $^3J_{\text{H-NF}}^{\text{trans}}$ (29.3 Hz) < $^3J_{\text{H-NF}}^{\text{cis}}$ (40.9 Hz) for derivatives of 1-fluoroaziridine-2,2-dicarboxylic acids⁸]; $^4J_{\text{FNCCF}}^{\text{cis}}$ (22.4 Hz) for **5s** > $^4J_{\text{FNCCF}}^{\text{trans}}$ (9.2 Hz) for **5a** [$^4J_{\text{FNCCF}}^{\text{cis}}$ = 19.0 Hz for **7s**,⁷

Table 1 ASIS effect for *N*-fluoroaziridines **5s**, **5a** and **7s**.

Compound	$\Delta\delta = \delta_{\text{CDCl}_3} - \delta_{[\text{2-H}_8]\text{toluene}} (\text{ppm})$			
	H _a	H _b	H _c	MeO
5s	0.76	0.8	–	0.78
5a	0.88	1.08	–	0.79
7s	0.57	–	0.44	0.82

$^4J_{\text{FNCCF}}^{\text{cis}} = 23.1 \text{ Hz}$ and $^4J_{\text{FNCCF}}^{\text{trans}} = 2.2$ for 1-fluoro-2,2-bis(trifluoromethyl)aziridine⁸). The similarity of the ASIS effects of the H_a and H_b protons in the aziridine **5s** and their dissimilarity from the ASIS effect of the protons in the aziridine **7s**⁷ become obvious from the consideration of the geometries of the molecules (Table 1).

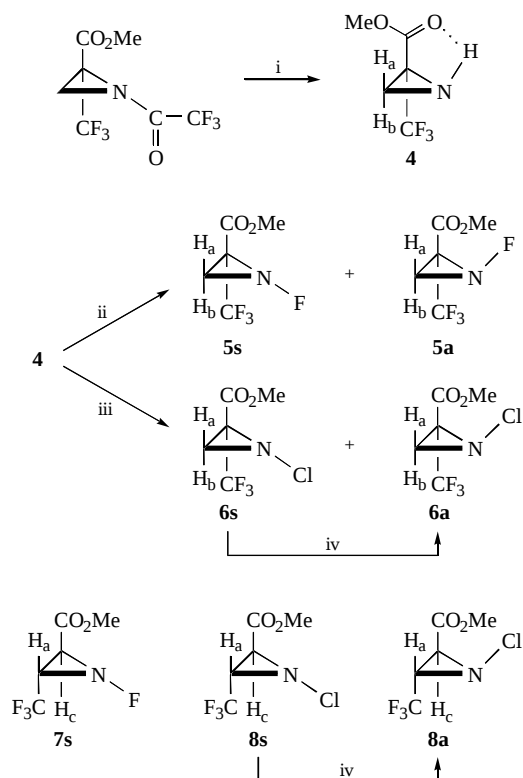
Chlorination of **4** with a bulky reagent, Bu^tOCl, is accompanied by partial destruction of the intramolecular H-bond under the action of the Bu^tOH formed; nevertheless, it affords a mixture of isomers **6s** and **6a** (in the ratio 1.5:1) in

[†] Characteristics and spectral data. ¹H NMR (400.13 MHz), ¹³C NMR (50.32 MHz), with respect to TMS, ¹⁹F NMR (376.48 MHz), with respect to CF₃CO₂H.

4, yield 95%, bp 42–44 °C (8 Torr); ¹H NMR (CDCl₃) δ: 1.8 (br. m, NH), 2.2 (dd, H_b, ²J_{ba} –1.4 Hz, ³J_{bNH} 9.5 Hz), 2.36 (ddq, H_a, ³J_{aNH} 10.6 Hz, ⁴J_{aCCF} 1.3 Hz), 3.9 (s, MeO); ¹H NMR ([²H₈]toluene) δ: 1.36 (br. m, NH), 1.59 (ddq, H_a), 1.65 (dd, H_b), 3.18 (s, MeO); ¹⁹F NMR ([²H₈]toluene) δ: 10.9 (dd).

5, yield 69.5%, bp 74–76 °C (50 Torr); **5s**, ¹H NMR (CDCl₃) δ: 3.1 (ddq, H_a, ²J_{ab} –5.8 Hz, ³J_{aNF} 28.7 Hz, ⁴J_{aCCF} 2.4 Hz), 3.29 (dd, H_b, ³J_{bNF} 40.6 Hz), 3.87 (s, MeO); ¹H NMR ([²H₈]toluene) δ: 2.34 (ddq, H_a, ³J_{aNF} 27.9), 2.49 (dd, H_b, ³J_{bNF} 41.5 Hz), 3.09 (s, MeO); ¹³C NMR (CDCl₃) 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, CF₃, ¹J_{CF} 277.4 Hz), 162.21 (dq, CO, ³J 5.1 Hz); ¹⁹F NMR (CDCl₃) δ: 14.13 (dd, CF₃, ⁴J_{FCCNF} 22.4 Hz), 16.72 (br. m, NF). **5a**, ¹H NMR (CDCl₃) δ: 2.87 (dd, H_b, ²J_{ba} –5.8 Hz, ³J_{bNF} 28.7 Hz), 3.52 (ddq, H_a, ³J_{aNF} 40.0 Hz, ⁴J_{aCCF} 1.8 Hz), 3.94 (s, MeO); ¹H NMR ([²H₈]toluene) δ: 2.00 (dd, H_b, ³J_{bNF} 27.9 Hz), 2.44 (ddq, H_a, ³J_{aNF} 41.5 Hz), 3.15 (s, MeO); ¹⁹F NMR (CDCl₃) δ: 8.44 (dd, CF₃, ⁴J_{FCCNF} 9.2 Hz), 17.71 (br. m, NF); MS (EI, 70 eV) *m/z* (%): 168 (18) [M–F]⁺, 109 (12), 69 (35), 59 (38), 45 (100), 33 (28), 32 (10), 28 (43), 15 (47).

6, yield 98%, bp 40 °C (1 Torr); **6a**, ¹H NMR (CDCl₃) δ: 2.90 (d, H_b, ²J_{ba} –3.1 Hz), 3.05 (dq, H_a, ³J_{aF} 1.6 Hz), 3.97 (s, MeO); ¹H NMR (C₆D₆) δ: 2.08 (d, H_b), 2.49 (dq, H_a), 3.21 (MeO); ¹³C NMR (CDCl₃) δ: 43.05 (s, 3-C), 49.55 (q, 2-C, ²J_{CCF} 37.5 Hz), 54.04 (s, MeO), 121.13 (q, CF₃, ¹J_{CF} 275.6 Hz), 161.25 (s, CO); ¹⁹F NMR (CDCl₃) δ: 6.39 (d). **6s**, ¹H NMR (CDCl₃) δ: 2.78 (d, H_b, ²J_{ba} –3.1 Hz), 3.11 (dq, H_a, ⁴J_{aCCF} 2.4 Hz), 3.84 (s, MeO); ¹³C NMR (CDCl₃) δ: 42.93 (s, 3-C), 46.58 (q, 2-C, ²J_{CCF} 34.4 Hz), 53.85 (s, MeO), 121.44 (q, CF₃, ¹J_{CF} 228.9 Hz), 163.47 (s, CO); ¹⁹F NMR (CDCl₃) δ: 13.65 (d).



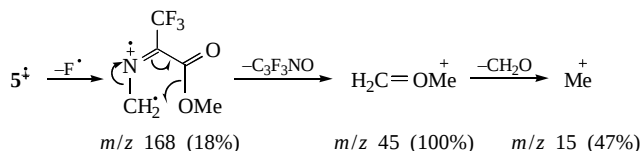
Scheme 1 Reagents and conditions: i, anhydrous MeOH containing traces of MeONa, refluxing for 3 h; ii, F_2/N_2 , a 4-fold excess of NaF, in Freon-113, 2.5 h at $-5^\circ C$; iii, a 4-fold excess of Bu^tOCl , in CH_2Cl_2 , 30 min at $-80^\circ C$; iv, **6s/6a** changes from 1.5 to 0.1 and **8s/8a** from 1 to 0.1 over 0.5 h at $25^\circ C$.

which the *syn*-isomer **6s** predominates. Configurations of the chloroaziridines were established based on the following data. The long-range spin-spin coupling constant $^4J_{H_aCF_3}^{trans}$ for the H_a proton with a *cis*-orientation with respect to the LEP of the ring nitrogen atom is always greater.^{8,9} The spin-spin coupling constant $^4J_{H_aCF_3}^{trans}$ (2.4 Hz) for **6s** is greater than $^4J_{H_aCF_3}^{trans}$ (1.5 Hz) for **6a**; hence, the chlorine atom in the aziridine **6s** has a *syn*-arrangement relative to the CF_3 group, whereas in the aziridine **6a**, this atom has the *anti*-orientation. In addition, greater ASIS effects for the H_b protons in **6a** and for H_c in **8a** are observed (Table 2).

Spontaneous epimerisation, **6s** $\rightarrow$ **6a**, like **8s** $\rightarrow$ **8a**,⁷ occurs in line with the difference between the conformational energies of the substituents;⁶ this also confirms the configurations of these molecules. The barriers to inversion for known 1-chloroaziridine-2-carboxylic acid derivatives are relatively low ($\Delta G^\ddagger = 24\text{--}25.5 \text{ kcal mol}^{-1}$).^{7,10} In the presence of the bulky CF_3 substituent, this barrier should decrease as is actually observed for **6s**.

Table 2 ASIS effect for *N*-chloroaziridines **6a** and **8a**.

Compound	$\Delta\delta = \delta_{CDCl_3} - \delta_{C_6D_6}(\text{ppm})$			
	H_a	H_b	H_c	MeO
6a	0.56	0.82	—	0.76
8a	0.32	—	0.55	0.80



Scheme 2

The most intense peak in the mass spectra of **5**, as in the case of **7**,⁷ corresponds to a fragmentation, accompanied by rearrangement, of the open form of the $[M-Hal]^+$ ion (Scheme 2), which is typical of esters of *N*-halogenoaziridinecarboxylic acids.^{11,12}

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