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

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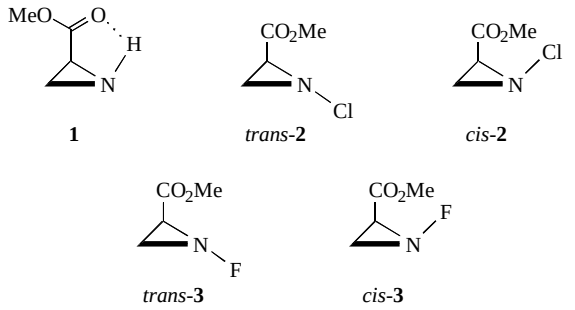
N-Fluorination and N-chlorination of methyl 2-trifluoromethylaziridine-2-carboxylate occurs predominantly from the more hindered side owing to the fixed orientation of the lone electron pair of the N atom caused by the formation of an intramolecular H-bond.

Chlorination of aziridine **1** with chlorosuccinimide or Bu$^t$OCl 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]




**1** *trans*-**2** *cis*-**2** *trans*-**3** *cis*-**3**

In the present study, we have obtained for the first time methyl 2-trifluoromethylaziridine-2-carboxylate **4** by alcoholysis of its 1-trifluoroacetyl derivative[4] (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:

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

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 $CF_3$ and $CO_2Me$ groups are 2.1 and 1.27 kcal mol$^{-1}$, respectively[6]).

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 $CF_3$ group) markedly predominates.

The *cis*- and *trans*-orientations of the fluorine atom were confirmed unambiguously by NMR data: $^3J^{trans}_{aF}$ (28.2 Hz) < < $^3J^{cis}_{bF}$ (40.6 Hz) and $^3J^{cis}_{aF}$ (40.0 Hz) > $^3J^{trans}_{bF}$ (28.7 Hz) for **5s** and **5a** [$^3J_{aF}$ (18.9 Hz) < $^3J_{cF}$ (33.6 Hz) for the aziridine **7s**;[7] $^3J^{trans}_{H–NF}$ (29.3 Hz) < $^3J^{cis}_{H–NF}$ (40.9 Hz) for derivatives of 1-fluoroaziridine-2,2-dicarboxylic acids[8]]; $^4J^{cis}_{FNCCF}$ (22.4 Hz) for **5s** > > $^4J^{trans}_{FNCCF}$ (9.2 Hz) for **5a** [$^4J_{FNCCF}$ = 19.0 Hz for **7s**,[7] $^4J^{cis}_{FNCCF}$ = 23.1 Hz and $^4J^{trans}_{FNCCF}$ = 2.2 for 1-fluoro-2,2-bistrifluoromethylaziridine[8]]. 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).

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

| Compound | $\delta = \delta_{CDCl_3} - \delta_{[^2H_8]toluene}$(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 |

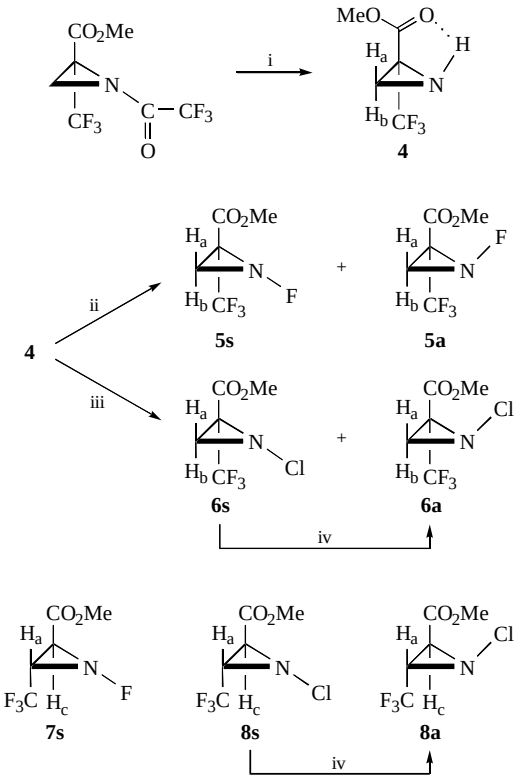
Chlorination of **4** with a bulky reagent, Bu$^t$OCl, is accompanied by partial destruction of the intramolecular H-bond under the action of the Bu$^t$OH formed; nevertheless, it affords a mixture of isomers **6s** and **6a** (in the ratio 1.5:1) in

† *Characteristics and spectral data*. $^1$H NMR (400.13 MHz), $^{13}$C NMR (50.32 MHz), with respect to TMS, $^{19}$F NMR (376.48 MHz), with respect to $CF_3CO_2H$.

**4**, yield 95%, bp 42–44 °C (8 Torr); $^1$H NMR ($CDCl_3$) $\delta$: 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); $^1$H NMR ([$^2H_8$]toluene) $\delta$: 1.36 (br. m, NH), 1.59 (ddq, $H_a$), 1.65 (dd, $H_b$), 3.18 (s, MeO); $^{19}$F NMR ([$^2H_8$]toluene) $\delta$: 10.9 (dd).

**5**, yield 69.5%, bp 74–76 °C (50 Torr); **5s**, $^1$H NMR ($CDCl_3$) $\delta$: 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); $^1$H NMR ([$^2H_8$]toluene) $\delta$: 2.34 (ddq, $H_a$, $^3J_{aNF}$ 27.9), 2.49 (dd, $H_b$, $^3J_{bNF}$ 41.5 Hz), 3.09 (s, MeO); $^{13}$C NMR ($CDCl_3$) $\delta$: 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); $^{19}$F NMR ($CDCl_3$) $\delta$: 14.13 (dd, $CF_3$, $^4J_{FCCNF}$ 22.4 Hz), 16.72 (br. m, NF). **5a**, $^1$H NMR ($CDCl_3$) $\delta$: 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); $^1$H NMR ([$^2H_8$]toluene) $\delta$: 2.00 (dd, $H_b$, $^3J_{bNF}$ 27.9 Hz), 2.44 (ddq, $H_a$, $^3J_{aNF}$ 41.5 Hz), 3.15 (s, MeO); $^{19}$F NMR ($CDCl_3$) $\delta$: 8.44 (dd, $CF_3$, $^4J_{FCCNF}$ 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**, $^1$H NMR ($CDCl_3$) $\delta$: 2.90 (d, $H_b$, $^2J_{ba}$ –3.1 Hz), 3.05 (dq, $H_a$, $^3J_{aF}$ 1.6 Hz), 3.97 (s, MeO); $^1$H NMR ($C_6D_6$) $\delta$: 2.08 (d, $H_b$), 2.49 (dq, $H_a$), 3.21 (MeO); $^{13}$C NMR ($CDCl_3$) $\delta$: 43.05 (s, 3-C), 49.55 (q, 2-C, $^2J_{CCF}$ 37.5 Hz), 54.04 (s, MeO), 121.13 (q, $CF_3$, $^1J_{CF}$ 275.6 Hz), 161.25 (s, CO); $^{19}$F NMR ($CDCl_3$) $\delta$: 6.39 (d). **6s**; $^1$H NMR ($CDCl_3$): 2.78 (d, $H_b$, $^2J_{ba}$ –3.1 Hz), 3.11 (dq, $H_a$, $^4J_{aCCF}$ 2.4 Hz), 3.84 (s, MeO); $^{13}$C NMR ($CDCl_3$) $\delta$: 42.93 (s, 3-C), 46.58 (q, 2-C, $^2J_{CCF}$ 34.4 Hz), 53.85 (s, MeO), 121.44 (q, $CF_3$, $^1J_{CF}$ 228.9 Hz), 163.47 (s, CO); $^{19}$F NMR ($CDCl_3$): 13.65 (d).



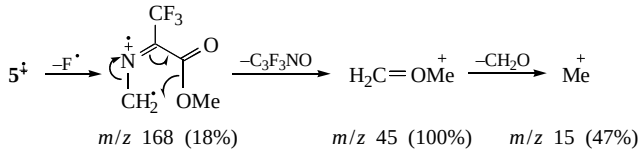

**Scheme 1** *Reagents and conditions*: i, anhydrous MeOH containing traces of MeONa, refluxing for 3 h; ii, $F_2/N_2$, a 4-fold excess of NaF, in Freon-113, 2.5 h at –5 °C; iii, a 4-fold excess of $Bu^tOCl$, in $CH_2Cl_2$, 30 min at –80 °C, iv, **6s**/**6a** changes from 1.5 to 0.1 and **8s**/**8a** from 1 to 0.1 over 0.5 h at 25 °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 $^4J^{trans}_{HCF_3}$ 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 $^4J^{trans}_{H_aCF_3}$ (2.4 Hz) for **6s** is greater than $^4J^{trans}_{H_aCF_3}$ (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** → **6a**, like **8s** → **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 ( $G^{\neq}$ = 24–25.5 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 | $\delta = \delta_{CDCl_3} - \delta_{C_6D_6}$(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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