Stereospecific synthesis of bicyclic diaziridines: 4a-chloro-; 4e,6a- and 4a,6e-dichloro-5-methoxycarbonyl-1,6-diazabicyclo[3.1.0]hexanes

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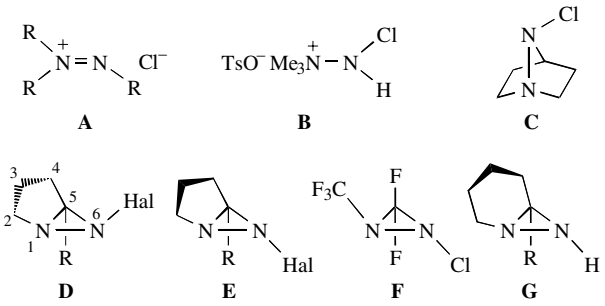
Amination of 2-methoxycarbonyl-3-chloro-1-pyrroline **1** with H_2NOSO_3H occurs predominantly from the *anti* side with respect to chlorine to afford the bicyclic diaziridine **2** with axial orientation of the 4-chloro substituent. Chlorination of **2** takes place exclusively in the 6-*endo* position to give **3a**. 4,6-Dichlorodiaziridine is transformed from chair **3a** into boat **3b** as a result of *endo–exo* isomerization.

Similarly to -chloroalkylamines, *N*-chlorohydrazines have an ionic state and exist in the form of diazenium salts **A**.[1–5] This can be explained by kinetic destabilizing n(N) → *(NCl) and n(N)-n(N) interactions.[3-5] These interactions can be eliminated by: i, quaternization of the donor N atom to give a stable *N*-chlorohydrazinium salt **B**;[4] ii, transformation of the nitrogen atom into a bridgehead position of bicyclic *N*-chlorohydrazine **C**[4,6] or *N*-chlorodiaziridines **D** and **E**,[7–16] or iii, attaching a strong electron-withdrawing group to the N atom to form a stable monocyclic *N*-chlorodiaziridine **F**.[17]



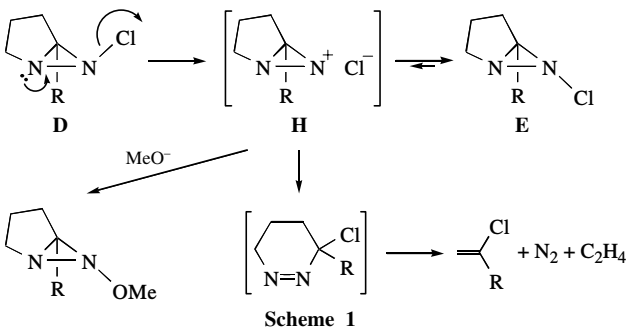
A **B** **C**

D **E** **F** **G**

R = CONHMe, CO_2Me, CF_3 R = CONHMe, CO_2Me, CF_3, Me, H

In the strained bicyclic compounds the nitrogen atom in the bridgehead position is forced to re-hybridize to accommodate bond angle variations. For example, the donor capacity of the bridgehead nitrogen in bicyclic compounds **D**,**E** is greatly reduced due to the decrease of p-character of the lone-pair. Therefore, the contribution of destabilizing n(N) → *(NCl) interactions is less pronounced.[5] In contrast, the geometry of the donor nitrogen atom in bicyclic diaziridine **G** is 'flattened'. Therefore, n(N) → *(NCl) interaction is still significant, and N-chloro derivatives of this type cannot be obtained.[11] Additional stabilization of structures **D**,**E** by electron-withdrawing substituents R[16] in position 5 allows the isolation of *endo*-6-Cl isomers **D** in quantitative yield.

The properties, including molecular and electronic structures,



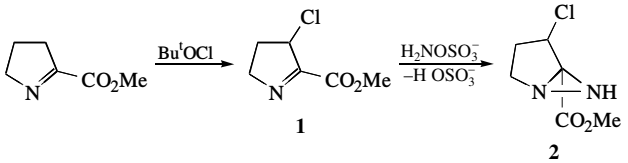
Scheme 1

Table 1 Spin coupling constants $^3J_{HH}$/Hz of diaziridine **2** and calculated values for **2b**,**2c**.

Coupled protons	Experiment **2**	Calculated by PCMODEL	
		2b (axial 4-Cl)	**2c** (equatorial 4-Cl)
2a3a	10.9	11.8	11.9
2a3e	6.3	6.1	6.2
2e3a	7.8	7.0	6.9
2e3e	1.0	0.5	0.5
3a4	5.4	6.0	10.1
3e4	0.0	1.3	7.3

of bicyclic 6-chlorodiaziridines **D**,**E**[7–16] and their 6-H-precursors[7–16,18–25] have been studied in detail. The boat conformation of 6-*exo* isomers of type **E**, *e.g.* 6-bromodiaziridine (R = CONHMe)[9] and the ephedrinium salt of 6-H-derivative (R = CO_2^-), was confirmed using X-ray diffraction.[23] Reliable ^1H, ^{13}C and ^{15}N NMR criteria for the conformational analysis of **D**,**E** have been developed, *e.g.*, the downfield chemical shift of the C(3) atom with a conformational change from boat **E** to chair **D** (*i.e.* 21 to 28 ppm).[11] A quadrant rule for the N–Hal chromophore of optically active 6-chlorodiaziridines **D**,**E** and 6-bromo derivatives of type **E** has been proposed.[14]

Although the vicinal interaction n(N) → *(N-Hal) is diminished it is still sufficient to ensure N-Hal bond ionization. Therefore, the isomerization of **D** to **E** occurs *via* an intermediate ion pair **H** (Scheme 1). In our opinion, this intermediate **H** is also involved in other chemical transformations of **D** such as nucleophilic substitution of the chlorine atom and thermal decomposition at $T \geq 40$ °C, *etc.* (Scheme 1).

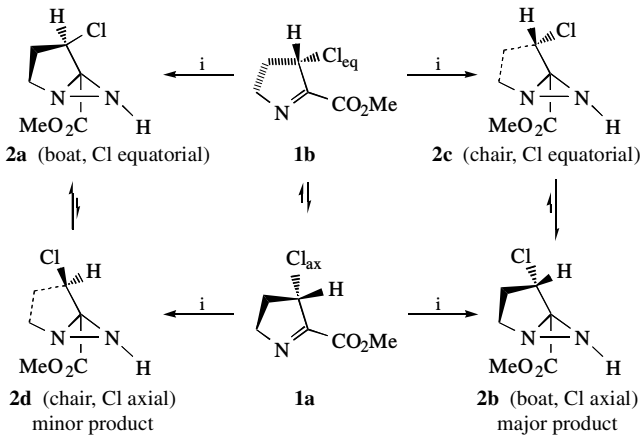


Scheme 2

We believe that introducing an additional electronegative substituent into position 4 of bicyclic diaziridines **2** will further inhibit the formation of ion pair **H**. For example, 1-fluoro-2-*tert*-butyl-3,3-pentamethylenediaziridine rearranges spontaneously into the corresponding -fluoroalkyldiazene[26] whereas perfluorinated *N*-fluoro diaziridines are quite stable.[27,28] Thus, we have prepared a new bicyclic diaziridine **2** from 2-methoxycarbonyl-3-chloro-1-pyrroline (Scheme 2). The intermediate **1** was obtained by a known chlorination procedure.[29]

Surprisingly, the amination of pyrroline **1** by treatment with H_2NOSO_3H in the presence of a phase-transfer catalyst according to a previously developed methodology[15] gave almost exclusively only one isomer of diaziridine **2** (Scheme 2).

The stereospecificity of amination of pyrroline **1** can be explained as follows (Scheme 3). Two conformers with an



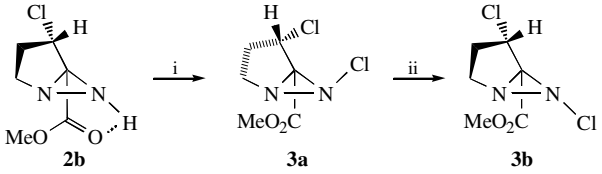
Scheme 3 *Reagents and conditions*: i, H_2NOSO_3H/K_2CO_3 as described.[22]

axial (**1a**) or equatorial (**1b**) 3-Cl atom are possible. Molecular mechanics calculations by the MMX method predict a slight preference of axial conformer **1a** compared to **1b**. The calculated dihedral angle of the -bond fragment N=C-C=O is 180° for **1a**. At the same time, steric 1,2-repulsion between the equatorial Cl atom and the CO_2Me group in conformer **1b** changes the N=C-C =O dihedral angle to 155°. Comparison of experimental and calculated coupling constants $^3J_{HH}$ for both conformers confirms the predomination of the envelope conformation **1a** with an axial chlorine atom.† However, the energy difference of the conformers is rather small, and therefore both of them might undergo amination (Scheme 3). Nevertheless, the approach of the aminating agent to the C=N bond of **1** from the opposite side of the chlorine atom seems to be preferable owing to steric and dipole-d ipole interactions. This leads to the formation of a single isomer **2**, which assumes the boat conformation **2b**. Comparison of ^{13}C, ^1H chemical shifts and spin coupling constants $^3J_{HH}$ with those described earlier[19] unambiguously confirmed the axial orientation of the 4-Cl substituent in boat **2b**.‡ The axial orientation of the 4-Cl atom in **2b** is also convincingly confirmed by comparison of experimental and calculated values of $^3J_{HH}$ for isomers with axial or equatorial 4-Cl substituents (PCMODEL molecular mechanics program, QCPE 395) (Table 1). Hence, equatorial orientation of the hydrogen and accordingly axial orientation of the Cl-atom follow.

The 4-Cl substituent in diaziridine **2b** leads to a reduction of the energies of the two highest occupied MOs, but is not however, as efficient as a CF_3 group in the 5-position.[16] Therefore, the configurational and thermal stabilities of 4,6-dichlorodiaziridines **3a**,**b**, derived from **2b**, are similar to those of 6-chlorodiaziridines **D**,**E** (R = CO_2Me). Like in cases reported earlier,[11,15] chlorination of **2** with Bu^tOCl occurs stereospecifically to form the 6-*endo* isomer **3a** in quantitative yield.

† **1**, yield 77%, yellowish oil, bp 40–48 °C (0.1 torr) (chromatographic purity 98%); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.32 (m, 4-H_e, ^2J = -14 .8 Hz, ^3J = 5.7, 3.6, 2.2 Hz), 2.47 (m, 4-H_a, ^2J = –14.8 Hz, ^3J = 7.6, 7.2 Hz), 3.94 (s, MeO), 4.0–4.45 (m, 5-CH_2), 5.12 (m, 3-H, ^3J = 7.6, 2.2 Hz, ^4J = 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.6 (t, 4-C), 53.0 (q, MeO), 58.7 (d, 3-C), 60.8 (t, 5-C), 161.3 (s, 2-C), 165.7 (s, CO); MS, *m/z* (%): 163, 164 (4) [M^+], 133, 131 (48), 126 (30), 105, 103 (100), 99 (36), 94 (26), 78, 76 (90), 67 (31), 66 (38), 59 (37), 54 (37), 45 (29), 41 (95).

‡ **2**, yield 56%, bp 74.8 °C (0.5 torr); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.9 (ddd, 3-H_e, ^2J = –14.0 Hz, $^3J_{3e2a}$ = 6.3 Hz, $^3J_{3e2e}$ = 1.0 Hz), 2.3 [m, 3-H_a, ^2J = –14.0 Hz, $^3J_{3a2a}$ = 10.9 Hz, $^3J_{3a2e}$ = 7.8 Hz, $^3J_{3a4e}$ = 5.4 Hz, $^5J_{3a6H}$ = 0.8 Hz, spin-s pin coupling constants ^5J were observed earlier only in similar systems with a boat conformation, such as 1,5-diazabicyclo[3.1.0]hexanes ($^5J_{3a6e}$ = 0.7 Hz, $^5J_{3e6e}$ = 0.5 Hz)[19]], 2.51 (br. m, NH), 3.2 (m, 2-H_e, ^2J = –12.8 Hz, $^3J_{2e3a}$ = 7.8 Hz, $^3J_{2e3e}$ = 1.0 Hz), 3.3 (m, 2-H_a, ^2J = –12.8 Hz, $^3J_{2a3a}$ = 10.9 Hz, $^3J_{2a3e}$ = 6.3 Hz), 3.86 (s, MeO), 4.82 (d, 4-H_e, $^3J_{4e3a}$ = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.1 (t, 3-C), 51.9 (t, 2-C), 53.1 (q, MeO), 57.4 (d, 4-C), 67.9 (s, 5-C), 167.2 (s, CO); MS, *m/z* (%): 147, 145 (4) [M–MeO], 141 (100), 114 (13), 109 (17), 85 (43), 81 (38), 59 (26), 54 (24), 53 (80).



Scheme 4 *Reagents and conditions*: i, Bu^tOCl in Et_2O at 20 °C; ii, 6 h at 20 °C in $CDCl_3$ or 15-20 min in pure form.

The chair conformation of **3a** is sterically inconvenient,[19] therefore, **3a** transforms quantitatively to the boat conformer **3b** within a few hours at room temperature in $CDCl_3$ solution. Conformational change from boat **2b** to chair **3a** and to boat **3b** (Scheme 4) was confirmed by the characteristic chemical shifts of C(3).§

It is noteworthy that the new diaziridines **2** and **3** are of interest as potential inhibitors of monoaminooxidase.[30]

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§ **3a**, obtained from **2** under the action of Bu^tOCl in Et_2O followed by evaporation *in vacuo* (0.5 torr, 0 °C), in quantitative yield; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.46 (m, 3-H_e, ^2J = –14.7 Hz, ^3J = 10.7, 3.0, 2.1 Hz), 2.76 (m, 3-H_a, ^2J = –14.7 Hz, ^3J = 9.2, 7.9, 7.6 Hz), 3.38 (m, 2-H_e, ^2J = = –15.3 Hz, ^3J = 9.2, 3.7 Hz), 4.1 (m, 2-H_a, ^2J = –15.3 Hz, ^3J = 10.7, 7.6 Hz), 3.89 (s, MeO), 4.9 (dd, 4-H_e, ^3J = 7.9, 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.1 (t, 3-C), 53.7 (q, MeO), 53.8 (t, 2-C), 56.9 (d, 4-C), 76.3 (s, 5-C), 162.6 (s, CO).

3b, obtained from **3a** by keeping its solution in $CDCl_3$ (6 hrs, 20 °C), in quantitative yield; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.97 (m, 3-H_e, ^2J = = –14.1 Hz, ^3J = 7.3, 1.0 Hz), 2.21 (m, 3-H_a, ^2J = –14.1 Hz, ^3J = 11.3, 8.0, 5.9 Hz), 3.43 (ddd, 2-H_a, ^2J = –13.3 Hz, ^3J = 11.3, 7.3 Hz), 3.66 (ddd, 2-H_e, ^2J = –13.3 Hz, ^3J = 8.0, 1.0 Hz), 3.99 (s, MeO), 4.96 (d, 4-H_e, ^3J = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.6 (t, 3-C), 53.5 (q, MeO), 54.0 (t, 2-C), 57.4 (t, 4-C), 78.8 (s, 5-C), 164.3 (s, CO).

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