

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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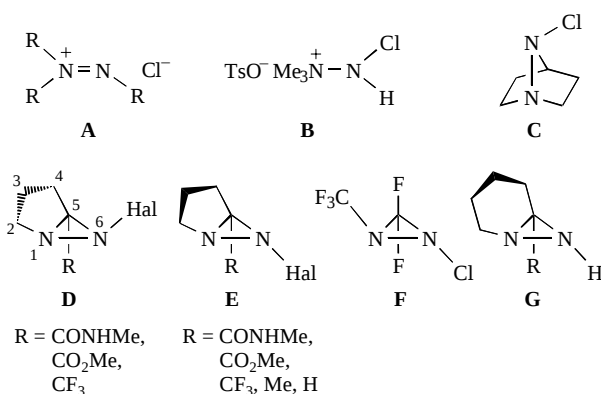
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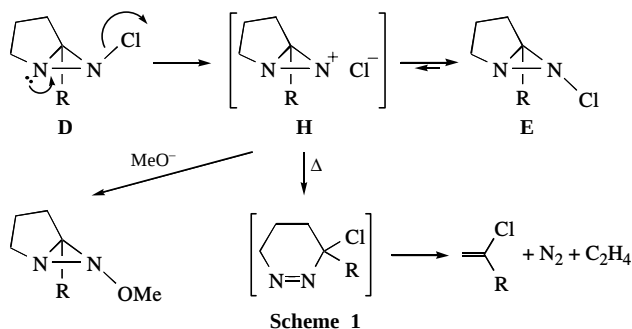
Amination of 2-methoxycarbonyl-3-chloro-1-pyrroline **1** with H₂NOSO₃H occurs predominantly from the *anti* side with respect to chlorine to afford the bicyclic diaziridine **2** with axial orientation of the 4-chloro substituent. Chlorination of **2** takes place exclusively in the 6-*endo* position to give **3a**. 4,6-Dichlorodiaziridine is transformed from chair **3a** into boat **3b** as a result of *endo-exo* isomerization.

Similarly to α -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 $n(N) \rightarrow \sigma^*(NCl)$ 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



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 $n(N) \rightarrow \sigma^*(NCl)$ interactions is less pronounced.⁵ In contrast, the geometry of the donor nitrogen atom in bicyclic diaziridine **G** is 'flattened'. Therefore, $n(N) \rightarrow \sigma^*(NCl)$ 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 R¹⁶ in position 5 allows the isolation of *endo*-6-Cl isomers **D** in quantitative yield.

The properties, including molecular and electronic structures,



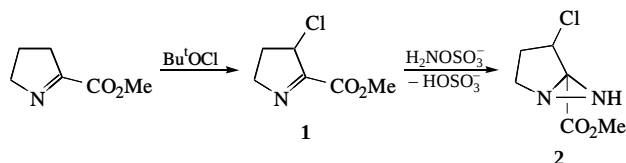
Scheme 1

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 = CO₂), was confirmed using X-ray diffraction.²³ Reliable ¹H, ¹³C and ¹⁵N 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 $n(N) \rightarrow \sigma^*(N-Hal)$ 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 ≥ 40 °C, etc. (Scheme 1).

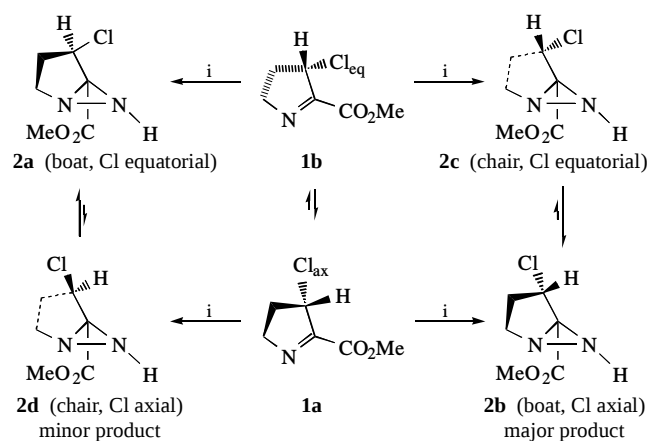


Scheme 2

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 α -fluoroalkyldiazene²⁶ 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 H₂NOSO₃H in the presence of a phase-transfer catalyst according to a previously developed methodology¹⁵ 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



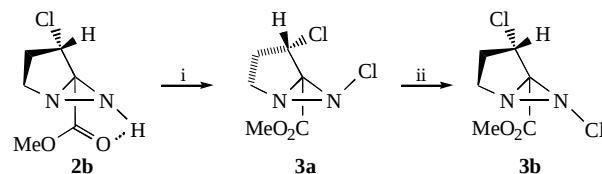
Scheme 3 Reagents and conditions: *i*, $\text{H}_2\text{NOSO}_3\text{H}/\text{K}_2\text{CO}_3$ as described.²²

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 π -bond fragment $\text{N}=\text{C}-\text{C}=\text{O}$ 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 $\text{N}=\text{C}-\text{C}=\text{O}$ dihedral angle to 155° . Comparison of experimental and calculated coupling constants $^3J_{\text{HH}}$ 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 $\text{C}=\text{N}$ bond of **1** from the opposite side of the chlorine atom seems to be preferable owing to steric and dipole-dipole 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 $^3J_{\text{HH}}$ with those described earlier¹⁹ 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 $^3J_{\text{HH}}$ 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** ($\text{R} = \text{CO}_2\text{Me}$). 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 $40\text{--}48^\circ\text{C}$ (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-spin 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) [$\text{M}-\text{MeO}$], 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 , $^2J = 7.9, 2.1$ 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_a , $^3J = 5.9$ 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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