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Synthesis of 1,3,5-Triazabicyclo[3.1.0]hexanes and the New Heterocyclic System 1,3,6-Triazabicyclo[3.1.0]hexane

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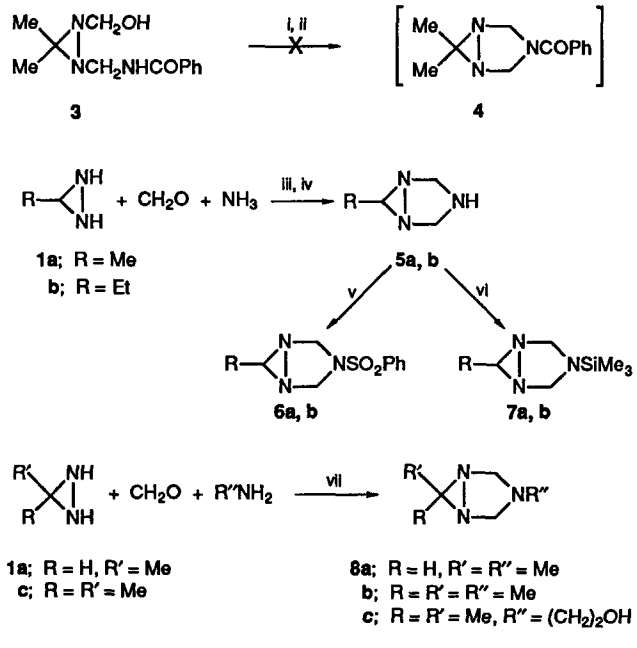
The conditions necessary for the condensation of 1,2-unsubstituted diaziridines **1** with CH_2O and NH_3, and also with CH_2O and $AlkNH_2$, into the corresponding 1,3,5-triazabicyclo[3.1.0]hexanes have been found; 1,3,6-triazabicyclo[3.1.0]hexanes, the primary representatives of the new heterocyclic system, were obtained by intermolecular α-aminomethylation of **1** and 1-alkyldiaziridines **2**.

The Mannich reaction of 1,2-unsubstituted diaziridines **1** and 1-alkyldiaziridines **2** is realised successfully only through α-aminomethylation in their capacity as NH-acids.[1–3] Compounds **2** do not enter into this reaction either with each other or with aziridine.[2] It has been shown[4] that alkoxymethyldiaziridines remain unchanged during attempts to react them with compounds having a mobile hydrogen atom (imidazole) and no deuterium exchange with CD_3OD is observed in the presence of CD_3CO_2D. The authors of ref. 4 believe that this absence of aminomethylation ability is a general property of saturated three-membered nitrogen heterocycles, since analogous compounds such as aziridine[5–7] and oxaziridine[4] behave similarly.

We could not overcome this problem, even using an intramolecular example: 1-benzamidomethyl-2-hydroxymethyl-3,3-dimethyldiaziridine **3** did not cyclize into 3-benzoyl-6,6-dimethyl-1,3,5-triazabicyclo[3.1.0]hexane **4** (Scheme 1).

Hence, in order to obtain compounds of type **4**, we attempted to prepare first the unknown 1,3,5-triazabicyclo[3.1.0]hexanes **5**, which are unsubstituted at C-2, C-3 and C-4, *via* Mannich condensation of **1** with the more basic ammonia, followed by substitution at N-3 of the products **5**. The N-3-unsubstituted 1,3,5-triazabicyclo[3.1.0]hexanes are described simply as 2,4,6-trialkyl derivatives.[2,5]

The best conditions for the synthesis of **5a,b** are as follows. The primary condensation of **1a,b** with CH_2O and NH_3 is carried out in water with subsequent transfer of the reaction into an organic solvent, where it is held over basic dehydrating agents. Under such conditions, the formation of the alternative product urotropin did not exceed 5%.† As expected, **5a,b** easily formed *N*″-benzenesulfonate **6a,b** and *N*″-trimethylsilyl **7a,b** derivatives (Scheme 1). Condensation of 3,3-dimethyldiaziridine **1c** with NH_3 and CH_2O led to a complicated mixture of compounds. However, condensation of **1c** with CH_2O and primary aliphatic amines more basic than ammonia in an organic solvent led to the formation of **8b,c** only. Under analogous conditions 3-methyldiaziridine also underwent the condensation with CH_2O and $MeNH_2$ to give **8a** (Scheme 1). Previously, structures such as **8b,c** were obtained by the interaction of **1c** with bis(alkoxymethyl)amines.[3]



Scheme 1 *Reagents and conditions*: i, $CHCl_3$, K_2CO_3 (BaO, zeolites), 20–60°C; ii, benzene, reflux; iii, H_2O, 25°C; K_2CO_3, 60°C; iv, K_2CO_3 (BaO), CH_2Cl_2 ($CHCl_3$), 20°C, 72 h; v, $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0–20°C; vi, Me_3SiCl, Et_3N, CH_2Cl_2–diethyl ether, −20 to −10°C, 15 h; vii, K_2CO_3, CH_2Cl_2 ($CHCl_3$), 20–40°C, 20–72 h. **5a** (85%), m.p. 92°C; **5b** (91%), oil; **6a** (80%), m.p. 65°C; **6b** (85%), m.p. 66°C; **7a** (50%), b.p. 42°C (1 mm Hg); **7b** (70%), b.p. 50°C (1 mm Hg); **8a** (42%), b.p. 53°C (10 mm Hg); **8b** (89%), b.p. 120°C (1 mm Hg); **8c** (71%), b.p. 117°C (2 mm Hg).

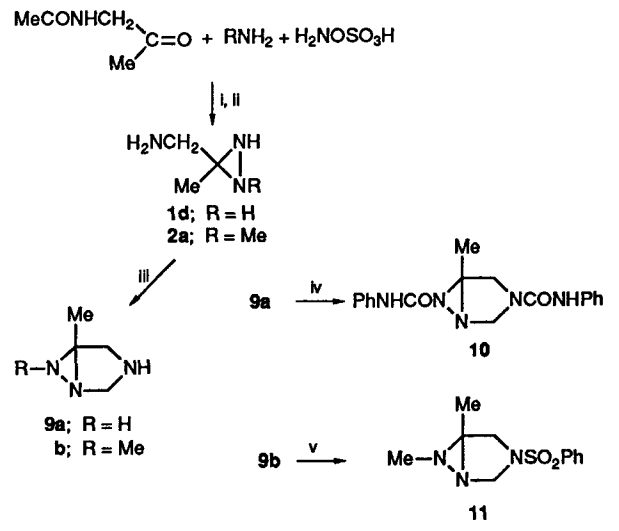
The observed regularity of the behaviour of diaziridines in the Mannich reaction indicates that intramolecular α-aminomethylation of the diaziridine nitrogen atoms should be

† Yields of **5a,b** were determined by means of ^1H NMR spectra. Compound **5a** was recrystallized from hexane.

possible if an amino group more basic than ammonia was introduced into the ring structure as a C-substituent. Indeed, the interaction of 3-aminomethyldiaziridines **1d** and **2a** with CH_2O led to the production of the primary representatives **9a,b** of the new heterocyclic system 1,3,6-triazabicyclo[3.1.0]hexane. The structures of **9a,b** were identified by the formation of derivatives **10** and **11** by substitution at the nitrogen atoms (Scheme 2).

Such intramolecular α-aminomethylation may be general for saturated three-membered nitrogen heterocycles: an example is provided by the condensation of *C*-aminomethylaziridines with carbonyl compounds to give 1,6-diazabicyclo[3.1.0] hexanes.[10–12]

All the new compounds have been characterized satisfactorily by elemental and spectroscopic analysis.‡



Scheme 2 *Reagents and conditions*: i, MeOH, −50°C, 2 h→−10 to −5°C, 2 h (**1d**), −10 to −5°C, 6 h (**2a**); ii, KOH, H_2O, 60–80°C, 7 h; iii, CH_2O, K_2CO_3 (BaO) $CHCl_3$, 60°C, 3 h (**a**), 20°C, 240 h (**b**); iv, PhNCO, CH_2Cl_2, 20°C, 8 h; v, $PhSO_2Cl$, Et_3N, $CHCl_3$, 60°C, 2 h. **1d** (44%), b.p. 76°C (17 mm Hg); **2a** (58%), b.p. 63°C (12 mm Hg), **9a** (97%); **9b** (95%); **10** (94%), m.p. 212°C; **11** (58%), undistilled oil.

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‡ *Spectroscopic data* for **3**: ^{1}H NMR [250 MHz, $(CD_3)_2SO$, standard $SiMe_4$] δ 1.25 (s) and 1.37 (s) (Me); 3.88 and 4.24 (NCH_2N, $^2J_{AB}$ − 12 Hz, ^3J 6.0 and 7.0 Hz), 3.96 and 3.99 (NCH_2O), $^2J_{A'B'}$ − 8.5 Hz, ^3J 0.8 and 1.0 Hz), 5.6 (t, OH), 7.48 (m, 3H, Ph), 7.90 (m, 2H, Ph), 8.85 (t, NH).

5a: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.15 (d, Me, ^3J 5.0 Hz); 2.18 (q, CH diaz. ring, ^3J 5.0 Hz), 2.54 (ex s, NH), 3.39 and 4.12 (NCH_2N, $^2J_{AB}$ − 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ 16.1 (Me), 46.5 (C diaz. ring, ^1J 166.0, ^2J 4.0 Hz), 66.9 [CH_2, ^1J 156.0 (*cis*), 148.0 (*trans*), ^3J 5.2 Hz].

5b: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.85 (t, Me), 1.35 (CCH_2), 2.05 (t, CH diaz. ring), 2.64 (ex s, NH), 3.82 and 4.10 (NCH_2N, $^2J_{AB}$ − 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 12.7 (Me), 23.6 (CH_2), 51.7 (C diaz. ring), 67.0 (NCH_2N).

6a: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.20 (d, Me), 2.55 (q, CH diaz. ring), 4.68 and 4.72 (NCH_2N, $^2J_{AB}$ − 7.20 Hz), 7.62 (m, Ph); ^{13}C NMR ($CDCl_3$) δ 15.9 (Me), 51.3 (C diaz. ring, ^1J 168.0, ^2J 5.0 Hz), 66.8 [NCH_2N, ^1J 159.0 (*cis*), ^1J 148.0 (*trans*), ^3J 5.4 Hz], 113.5 116.0, 119.9, 125.4 (*o*, *m*, *p*, *i*-Ph).

7a: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.1 (s, Me_3Si), 1.56 (d, MeC), 2.82 (d, CH diaz. ring), 4.04 and 4.64 (NCH_2N, $^2J_{AB}$ − 7.20 Hz); ^{13}C NMR ($CDCl_3$) δ 1.1 (Me_3Si), 16.4 (Me), 47.1 (C diaz. ring, ^1J 167.0, ^2J 7.50 Hz), 66.3 [NCH_2N, ^1J 157.0 (*cis*), 143.0 (*trans*), ^3J 4.9, 6.4 Hz].

8a: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.14 (d, MeC, ^3J 5.5 Hz), 2.23 (s, MeN), 3.24 (q, CH diaz. ring, ^3J 5.5 Hz), 3.03 and 4.07 (NCH_2N, $^2J_{AB}$ − 8.20 Hz); ^{13}C NMR ($CDCl_3$) δ 17.23 (Me), 35.61 (MeN), 51.67 (C diaz. ring), 73.40 [NCH_2N].

1d: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.27 (s, MeC), 2.20 (ex s, NH, NH_2), 2.75 (s, CH_2).

9a: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.5 (s, MeC), 2.51 and 3.15 (CCH_2N, $^2J_{AB}$ − 14.4 Hz), 2.62 (ex s, NH), 3.55 and 3.88 (NCH_2N, $^2J_{AB}$ − 13.2 Hz).

9b: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.45 (s, MeC), 2.30 (ex s, NH), 2.35 (s, MeN), 2.70 and 3.25 (CCH_2N, $^2J_{AB}$ − 12.0 Hz), 3.55 and 4.0 (NCH_2N, $^2J_{AB}$ − 12.0 Hz).

10: ^{1}H NMR [250 MHz, $(CD_3)_2SO$] δ 1.50 (s, MeC), 3.27 and 4.34 (CCH_2N, $^2J_{AB}$ − 12.0 Hz), 4.16 and 4.90 (NCH_2N, $^2J_{AB}$ − 10.5 Hz), 7.0, 7.25, 7.52 (m, *p*, *o*, *m*-Ph), 8.5 (s, NH), 9.66 (s, NH); ^{13}C NMR [$(CD_3)_2SO$] δ 14.39 (MeC), 48.85 (CCH_2N), 66.97 (C diaz. ring), 70.43 (NCH_2N), 119.91, 120.03, 128.89 and 129.12 ($C_{o,m}$ in Ph), 122.64 and 123.92 (C_p in Ph), 138.67 and 140.31 (C_i in Ph), 155.0 and 160.04 (C=O).

11: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.28 (s, MeC), 2.08 (s, MeN), 3.05 and 3.70 (CCH_2N, $^2J_{AB}$ − 12.0 Hz), 3.98 and 4.41 (NCH_2N, $^2J_{AB}$ − 11.4 Hz), 7.65 (m, Ph); ^{13}C NMR ($CDCl_3$) δ 10.72 (MeC, ^1J 128.17 Hz), 36.16 (MeN, ^1J 136.4 Hz), 52.13 (CCH_2N, ^1J 146.5 Hz), 66.09 (C diaz. ring), 70.58 (NCH_2N, ^1J 155.6, ^3J 3.7 Hz), 127.14, 128.56, 123.39, 136.03 (Ph).

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