

Synthesis of Novel Methyl-substituted 1-Azaadamantanes from 1-Boraadamantane Derivatives

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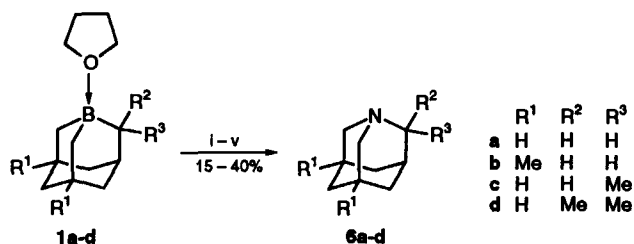
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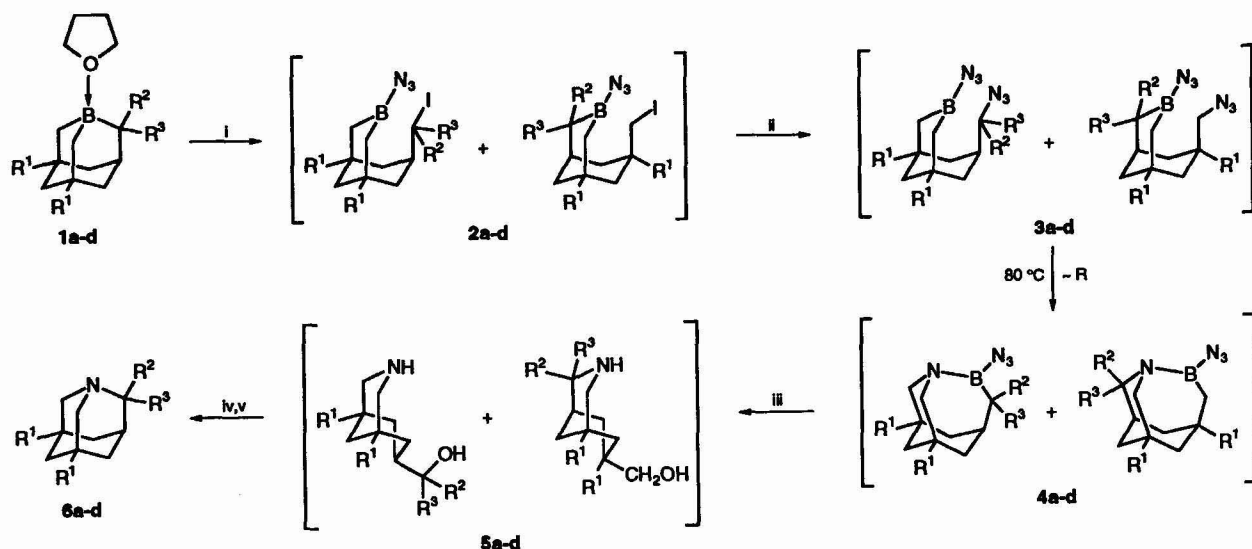
Three new homologues of 1-azaadamantane (2-Me, 2,2- and 3,5-Me₂) have been prepared from the corresponding 1-boraadamantane compounds; the key stage in the transformation is an intramolecular 1,2-anionotropic rearrangement of the ω -azidoalkylborane intermediate.

1-Azaadamantane is attracting much attention due to the high symmetry of the molecule^{1,2} as well as to the biological activity of its derivatives.^{3–5} However, these studies have been hampered by the difficulties in assembling the 1-azaadamantane framework (6–8 stages in a 5–7% overall yield^{6,7}).

Recently we have elaborated the most effective route so far to 1-azaadamantane from its 'electronic antagonist'—1-boraadamantane.⁸ The key stage in the method is a thermal intramolecular 1,2-anionotropic rearrangement (transfer of an organic moiety from boron to nitrogen) in 3-azido-7 α -azidomethyl-3-borabicyclo[3.3.1]nonane, which is readily generated by iodination of 1-boraadamantane in the presence of sodium or lithium azide (2.5–3M). The subsequent oxidation and



Scheme 1 Reagents and conditions: i, NaN₃ (1M), I₂ (1M), diglyme 80 °C; ii, NaN₃ (1.5–2M), diglyme, 80 °C, 1 h; iii, NaOH, H₂O₂, Et₂O/H₂O, 0–5 °C, then 35 °C, 0.5 h; iv, SOCl₂, C₆H₆, 80 °C, 0.5 h; v, NaOH, H₂O/Et₂O, 20 °C.



Scheme 2 Reagents and conditions: i, NaN_3 (1M), I_2 (1M), diglyme, 80 °C; ii, NaN_3 (1.5–2M), diglyme, 80 °C, 1 h; iii, NaOH , H_2O_2 , $\text{Et}_2\text{O}/\text{H}_2\text{O}$, 0–5 °C, then 35 °C, 0.5 h; iv, SOCl_2 , C_6H_6 , 80 °C, 0.5 h; v, NaOH , $\text{H}_2\text{O}/\text{Et}_2\text{O}$, 20 °C.

Table 1 Synthesis and properties of 1-azaadamantanes **6a–d**.

Starting organoborane	1-Azaadamantane	Yield (%), from 1a–d	M.p. /°C	HRMS, $[\text{M}]^+$ Found/calc.	Formula
 1a	 6a [1,2]	40	260–262	$\frac{137.12038}{137.12043}$	$\text{C}_9\text{H}_{15}\text{N}$
 1b	 6b	15	<i>a</i>	$\frac{165.15148}{165.15173}$	$\text{C}_{11}\text{H}_{19}\text{N}$
 1c	 6c	36	98–101	$\frac{151.13579}{151.13608}$	$\text{C}_{10}\text{H}_{17}\text{N}$
 1d	 6d	30	67–70	$\frac{165.15137}{165.15173}$	$\text{C}_{11}\text{H}_{19}\text{N}$

^a Liquid, b.p. 55–57 °C/15 mmHg, n_D^{20} 1.4893.

transannular cyclization lead to 1-azaadamantane in 40% overall yield.

We have now expanded upon and demonstrated the generality of the methodology⁸ for the transformation of 2-methyl-2,2-

and 3,5-dimethyl-1-boraadamantane **1b–d** into the corresponding 1-azaadamantane derivatives **6b–d** (Scheme 1, Table 1). The starting methylated 1-boraadamantanes **1b–d** were obtained from triallyl- and trimethallylborane according to literature

procedures^{9,10} (three stages, 50–70% overall yields).

The reaction pathway from **1** to **6** is presented in Scheme 2.^{††}

[†] *General details.* All manipulations with organoboron compounds were performed in dry argon. ¹H and ¹³C NMR spectra were recorded on a Bruker WM-250 spectrometer (68.69 MHz carbon). ¹¹B NMR spectra were obtained on a Bruker AC-200P spectrometer (Standard BF₃·Et₂O). High resolution mass-spectra were recorded on a Varian-MAT instrument.

Typical experimental procedure for the synthesis of the 1-azaadamantanes 6b–d. From two dropping funnels, a solution of 12 g (54.5 mmol) of **1c** in 30 ml of diglyme and 13.8 g (54.5 mmol) of iodine in 60 ml of diglyme were simultaneously added dropwise to a stirred suspension of 10.9 g (168 mmol) of NaN₃ in 90 ml of diglyme at 70–80 °C for 1 h. The mixture was stirred at 80 °C for 0.5 h. Nitrogen (985 ml, 72%) was evolved. The resulting white solid was filtered off and diglyme was distilled off *in vacuo* (35–37 °C/1 mmHg). The solid residue was extracted with diethyl ether (3 × 120 ml) and the organic phase was concentrated to 150 ml. A solution of 6.6 g (165 mmol) NaOH in 80 ml of water (at 20 °C) and 21 ml of 30% H₂O₂ (over 1 h at 0 °C) were added with stirring. The reaction mixture was refluxed over a period of 0.5 h. The ether layer was separated while the aqueous layer was saturated with potassium carbonate and extracted with ether (2 × 100 ml). The combined ether extracts were dried (Na₂SO₄) and ether was distilled off *in vacuo* (12 mmHg). Judging from TLC SiO₂ (100/160μ, MeOH–aqueous NH₃, 8:1), 4.0 g (43.5%) of an isomeric mixture of aminoalcohols **6c** was isolated.

A solution of 4.0 g (23.7 mmol) of a mixture of azabicyclononanes **5c** in 55 ml of benzene was added to 6.5 ml of SOCl₂ in 90 ml of benzene. The mixture was refluxed for 0.5 h. Benzene and an excess of SOCl₂ were distilled off *in vacuo*, then the solid residue was suspended in 100 ml of ether, filtered, washed with ether (2 × 40 ml) and dried *in vacuo* to give 3.8 g of the hydrochloride of **6c** (86% from **5c** or 37% from **1c**). To a solution of the hydrochloride in 30 ml of water, 10 ml of 10% NaOH was added and the product was extracted with ether. The ether was distilled off and drying *in vacuo* (9 mmHg) gave 3.0 g **6c** (84% from **5c** or 36% from **1c**), m.p. 98–101 °C.

^{††} *Selected spectral data for:*

5a: ¹H and ¹³C NMR data are identical with that presented in ref. 2.
5b: ¹H NMR (CDCl₃) 0.70 (s, 6H, Me), 1.29 (s, 2H, C⁴H), 1.44–1.60 (AB system, 4H, C⁶, ¹⁰H, J_{AB} 25.8 Hz), 1.86 (m, 1H, C⁷H), 2.58–2.76 (AB system, 4H, C^{2,9}H, J_{AB} 24.4 Hz), 2.91 (s, 2H, C⁸H); ¹³C NMR (CDCl₃) 27.6 (Me), 28.2 (C⁵), 28.6 (C^{3,7}), 42.6 (C^{4,6}), 50.5 (C¹⁰), 57.2 (C⁹), 64.1 (C^{2,8}).

5c: ¹H NMR (CDCl₃) 1.09 (d, 3H, Me, J 7.4 Hz), 2.71 (d, 1H, C⁹H^B, J 12.4 Hz), 3.05 [m, 4H, C(2,8)H, C⁹H^A]; ¹³C NMR (CDCl₃) 18.0 (Me), 26.4 (C⁵), 26.85 (C⁷), 29.85 (C⁴), 30.7 (C³), 37.2 (C⁶), 38.1 (C¹⁰), 50.5 (C⁹), 58.6 (C²), 60.6 (C⁸).

5d: ¹H NMR (CDCl₃) 1.20 (s, 6H, Me), 1.34 (w.s., 1H, C³H), 2.87 (d, 2H, NCH₂^A, J 12.6 Hz), 3.46 (d, 2H, NCH₂^B, J 12.6 Hz); ¹³C NMR (CDCl₃) 26.2 (C^{5,7}), 27.0 (Me), 32.3 (C^{4,10}), 33.5 (C³), 38.4 (C⁶), 53.35 (C^{8,9}), 54.9 (C²).

Iodination of tetrahydrofuran complexes **1b–d** in the presence of sodium azide (2.5–3M) in diglyme at 80 °C proceeds with cleavage of one B–C bond to give a mixture of the corresponding intermediate diazido compounds **3b–d**. Under these reaction conditions (80 °C), the latter undergo rearrangement to produce a mixture of cage azidoboranes **4b–d**. Treatment of mixtures **4b–d** with sodium hydroxide and hydrogen peroxide leads to mixtures of aminoalcohols **5b–d**, treatment of which with SOCl₂ followed by treatment with sodium hydroxide solution yields the target 1-azaadamantanes **6b–d**.

Solid **6c** and **6d** readily sublime *in vacuo*; 3,5-dimethyl-1-azaadamantane **6b** is a liquid.

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