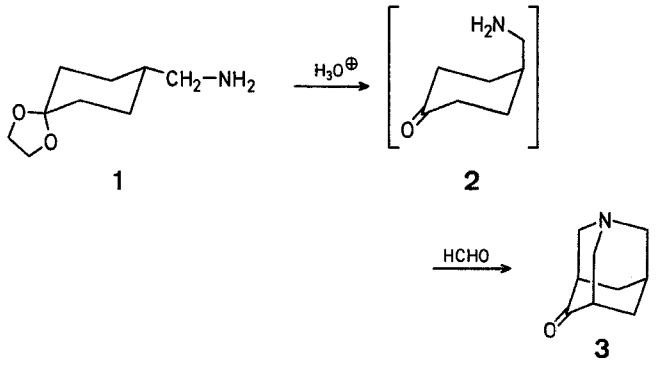
A Simple Synthesis of 1-Azaadamantan-4-one

R. M. BLACK

Chemical Defence Establishment, Porton Down, Salisbury, Wilts, SP4 OJQ, U.K.

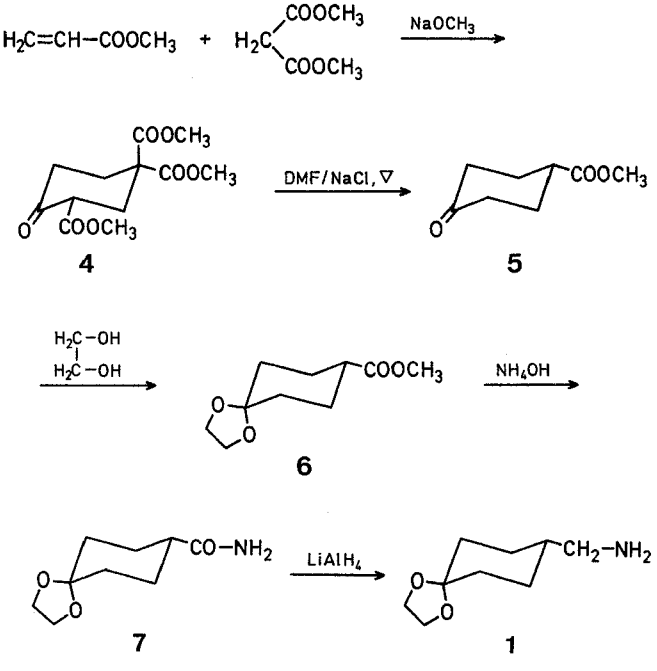
For part of a study of adamantane derivatives as conformationally rigid analogues of pharmacologically active molecules, a moderate amount of 1-azaadamantan-4-one (**3**), an important intermediate for the preparation of 4-substituted 1-azaadamantanes, was required. The published synthesis[1,2] of **3**, although an excellent route to some 1-azaadamantanes[3], required nine stages in all from simple starting materials and the use of an expensive oxidant in the final stage. A more direct synthesis from inexpensive starting materials was therefore sought.

The simplest route to **3** (Scheme **A**) appeared to be by a double intramolecular Mannich reaction[4] of the aminoketone **(2)**, which although requiring an unfavourable conformation should nevertheless proceed under conditions of high dilution and thermodynamic control. In practice, the more stable ethylene acetal derivative **(1)** was chosen as a preferred reactant, the ketone **(2)** then being formed *in situ* under acidic Mannich conditions. Thus heating a dilute solution of **1** and paraformaldehyde in 2% sulphuric acid for 24 h afforded **3** in 53–56% yield after a rapid chromatographic separation and sublimation.



Scheme **A**

Acetal **1** was readily obtained by the five stage sequence shown in Scheme **B**. Triester **(4)**, obtained from dimethyl malonate and methyl acrylate in high yield following the published procedure[5], was decarboxylated to methyl 4-oxocyclohexane-1-carboxylate **(5)** by heating in dimethylformamide/sodium chloride solution[6]. [An alternative preparation of **5** involves oxidation of methyl 4-hydroxycyclohexane-1-carboxylate obtained from hydrogenation of methyl *p*-hydroxybenzoate[7].] Protection of the keto function as its ethylene acetal **(6)** allowed a facile conversion into **(1)** by treatment with ammonia and reduction of amide **(7)** with lithium aluminium hydride. This procedure thus provided a simple six stage synthesis of **3** from dimethyl malonate and methyl acrylate.



Scheme **B**

0039-7881/81/1032-0829 $ 03.00

Methyl 4-Oxocyclohexane-1-carboxylate (5):
A solution of trimethyl 4-oxocyclohexane-1,1,3-tricarboxylate[5] (**4**; 136 g, 0.5 mol), sodium chloride (64 g, 1.1 mol), and water (40 ml, 2.22 mol) in dimethylformamide (600 ml) is gently heated under reflux under nitrogen for 48 h. Most of the solvent is then removed under reduced pressure, the residue diluted with water (100 ml), and extracted with dichloromethane (3 × 100 ml). The combined extracts are dried with magnesium sulphate, concentrated, and fractionated under reduced pressure to give **5**; yield: 49.1 g (64%); b.p. 78–80 °C/0.2 torr; Lit.[7], b.p. 127 °C/12 torr.

I.R. (film): $\nu = 1739, 1724\ cm^{-1}$.

Methyl 1,4-Dioxaspiro[4,5]decane-8-carboxylate (6):
Prepared following the literature method[7]; yield: 91%.

1,4-Dioxaspiro[4,5]decane-8-carboxamide (7):
A suspension of **6** (46 g) in 0.880 molar ammonia solution (350 ml) is rapidly stirred for 24 h at room temperature. Refrigeration overnight gives **7** as white crystals; yield: 27.1 g; m.p. 171–174 °C (after vac. drying). Concentration of the mother liquors and further refrigeration affords a second crop (7.0 g); m.p. 168–172 °C; total yield: 80%.

$C_9H_{15}NO_3$	calc.	C 58.36	H 8.16	N 7.56
(185.2)	found	58.66	8.07	7.84

I.R. (KBr): $\nu = 3425, 3226, 1667, 1639, 1105\ cm^{-1}$.

^{1}H-N.M.R. (CD_3OD): $\delta = 3.93$ (s, 4H, CH_2O); 2.4–1.3 ppm (m, 9H).

8-Aminomethyl-1,4-dioxaspiro[4,5]decane (1):
The amide **7** (34.7 g) is added portionwise over 30 min to a mechanically stirred suspension of lithium aluminium hydride (10 g) in dry tetrahydrofuran (500 ml). The mixture is heated under reflux for 2 h, cooled, and water (22 ml) carefully added dropwise with rapid stirring. After a further 15 min, the mixture is diluted with dichloromethane (200 ml), filtered, and the residue washed well with dichloromethane. The combined filtrates are dried with magnesium sulphate, concentrated, and fractionated under reduced pressure to give the amine **1**; yield: 23.8 g (74%); b.p. 88–90 °C/1 torr.

$C_9H_{17}NO_2$	calc.	C 63.13	H 10.01	N 8.18
(171.2)	found	63.09	9.87	7.94

I.R. (film): $\nu = 3356, 3311, 1600, 1098\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.92$ (s, 4H, CH_2O); 2.54 (d, 2H, CH_2N); 1.9–1.04 (m, 9H); 1.38 ppm (s, 2H, NH_2).

1-Azaadamantan-4-one (3):
A solution of **1** (8.55 g, 0.05 mol) in ethanol (20 ml) is slowly added dropwise over 4 h to a gently boiling solution of paraformaldehyde (or trioxan) (7.0 g) in 2% v/v sulphuric acid (1 l). After heating under reflux for a further 24 h, the solution is cooled, extracted twice with dichloromethane (2 × 50 ml), basified with 10 normal sodium hydroxide solution (80 ml), and finally extracted with dichloromethane (5 × 100 ml). The combined extracts are dried with magnesium sulphate, concentrated, and chromatographed on a short silica column using chloroform plus 2% ammonia saturated methanol as eluent. The white crystalline solid thus obtained is sublimed at 120–140 °C/9 torr to give pure **3**; yield: 4.0–4.21 g (53–56%). The spectral data were similar to those published[1].

$C_9H_{13}NO$	calc.	C 71.49	H 8.67	N 9.26
(151.2)	found	71.47	8.88	9.09

Received: May 4, 1981

[1] A. W. J. D. Dekkers, J. W. Verhoeven, W. N. Speckamp, *Tetrahedron* **29**, 1691 (1973).
[2] W. N. Speckamp, J. Dijkink, H. O. Huisman, *J. Chem. Soc. Chem. Commun.* **1970**, 196; 197.
[3] For a similar route to 1-azaadamantanes, see H. Stetter, W. Reinartz, *Chem. Ber.* **105**, 2773 (1972).
[4] For a review, see M. Tramontini, *Synthesis* **1973**, 703.
[5] P. Rosenmund, W. H. Haase, J. Bauer, R. Frische, *Chem. Ber.* **108**, 1871 (1975).
[6] A. P. Krapcho, A. J. Lovey, *Tetrahedron Lett.* **1973**, 957.
[7] F. Leyendecker, G. Mandville, J.-M. Conia, *Bull. Soc. Chim. Fr.* **1970**, 556.

0039-7881/81/1032-0830 $ 03.00