Organic Preparations and Procedures International: The New Journal for Organic Synthesis
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

IMPROVED SYNTHESIS OF 1,3-DIAZA-6-ADAMANTANONE

Timothy A. Lewis [a] & Gurmit Grewal [a]

[a] UCB Research, Inc., 840 Memorial Drive, Cambridge, MA, 02139

To cite this article: Timothy A. Lewis & Gurmit Grewal (2003): IMPROVED SYNTHESIS OF 1,3-DIAZA-6-ADAMANTANONE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 35:5, 524-525

To link to this article: http://dx.doi.org/10.1080/00304940309355865

5. It should be noted that both procedures (Chow *et al.*[2d] and Matsuoka *et al.*[3a]) are identical.

6. A. Adeeko, D. Li, D. S. Forsyth, V. Cassey, G. M. Cooke, J. Barthelemy, D. G. Cyr, J. M. Trasler, B. Robaire and B. F. Hales, *Toxicol. Sci.*, **74**, 407 (2003).

7. H. Wojahn and I. Lerch, *Arzneim. Forsch.*, **2**, 455 (1952).

****

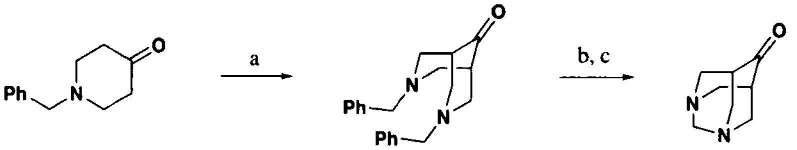
IMPROVED SYNTHESIS OF 1,3-DIAZA-6-ADAMANTANONE

Submitted by (08/11/03)

Timothy A. Lewis* and Gurmit Grewal

UCB Research, Inc.
840 Memorial Drive, Cambridge, MA 02139

1,3-Diaza-6-adamantanone was first synthesized by oxidation of 1,3-diaza-6-adamantanol.[1] The alcohol synthesis[2] (6 steps, 10%) was later shortened (3 steps, 8%) and the oxidation yield improved.[3] We have synthesized the ketone directly, improving the overall yield (3 steps, 35%) while avoiding the lachrymators and thiols used previously.



a) Benzylamine, $(CH_2O)_n$, HOAc/HCl/MeOH (69%), ref. 4; b) H_2, $Pd(OH)_2/C$, HOAc/MeOH; (c) CH_2O (aq) (51%, two steps)

Mannich condensation of benzylamine, paraformaldehyde, and *N*-benzyl-4-piperidone was performed using a literature procedure.[4] Hydrogenolysis of the *bis*-benzylamine product proceeded slowly under atmospheric pressure. Cyclization of the crude product with aqueous formaldehyde gave 1,3-diaza-6-adamantanone, which was isolated by hot filtration.

EXPERIMENTAL SECTION

Mps were determined on a Mel-temp apparatus and are uncorrected. All reactions were run under an argon atmosphere except where noted. All solvents and reagents were purchased from Aldrich or VWR and used without purification, except for benzylamine and *N*-benzyl-4-piperidone which were distilled before use.[4] NMR spectra were obtained on a 300 MHz Varian instrument using $CDCl_3$ as solvent with TMS as an internal standard. Infrared spectra were determined on a Mattson Galaxy Series FTIR 5000 spectrometer.

1,3-Diaza-6-adamantanone.- Dried (60°C, 1 mm Hg, 1 h) 20% $Pd(OH)_2/C$ catalyst, 350 mg, was added to 2.01 g (6.25 mmol) of 3,7-dibenzyl-3,7-diaza-bicyclo[3.3.1]nonan-9-one,[4] in 5 mL of acetic acid and 90 mL of MeOH. The reaction mixture was charged with hydrogen (balloon) and stirred overnight. An additional 100 mg of catalyst (wetted with MeOH) was added and stirring was continued under hydrogen another 24 h before filtering, followed by the addition of 0.47 mL (6.3 mmol) of 30% aq. formaldehyde. After 24 h, the mixture was made basic with 10% aq. NaOH, concentrated and partitioned between CH_2Cl_2 and water. The water was extracted four times with CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, and concentrated to give 1.15 g of an orange solid which was heated in 100 mL of hexane at reflux temperature for 10 min and gravity filtered while hot. The procedure was repeated twice with the residual solids and the hexane extracts were saved each time. After cooling overnight, white crystals formed from the first hexane extraction, and filtration provided 302 mg of the product, mp. 253°C (dec.) *lit*[3] mp. 253°C. The spectral data matched those of the literature.[1a,3] Concentration of all the hexane extracts yielded another 187 mg of product sufficiently pure for further use (489 mg, 51%).

REFERENCES

1. (a) J. Kuthan, J. Palecek, and L. Musil, *Collect. Czech. Chem. Commun.*, **38**, 3491 (1973). (b) J. Kuthan, J. Palecek, and L. Musil, *Z. Chem.*, **8**, 229 (1968).

2. H. Stetter, K. Dieminger, and E. Rauscher, *Chem. Ber.*, **92**, 2057 (1959).

3. E. M. Gonikberg and W. J. le Noble, *J. Org. Chem.*, **60**, 7751 (1995).

4. G. L. Garrison, K. D. Berlin, B. J. Scherlag, R. Lazzara, E. Patterson, S. Sangiah, C-L. Chen, F. Schubot, J. Siripitayananon, M. B. Hossain, and D. van der Helm, *J. Org. Chem.*, **58**, 7670 (1993).