Organic Process Research & Development **2007**, *11*, 268–269

Technical Notes

An Improved Synthesis of Memantine Hydrochloride: Anti-Alzheimer's Drug†

Jambula Mukunda Reddy,‡ Ganji Prasad,‡ Veeramalla Raju,‡ Mylavarapu Ravikumar,‡ Vurumidi Himabindu,§ and Ghanta Mahesh Reddy*,‡

Department of Research and Development, Dr. Reddy's Laboratories Ltd., Integrated Product Development, Unit-III, Plot No. 116, S.V. Co-Op. Industrial Estate, Bollaram, Jinnaram, Medak District 502 325, A.P., India, and Institute of Science and Technology, Center for Environmental Science, J. N. T. University, Kukatpally, Hyderabad 500 072, India

Abstract:

An economical new process route has been developed for the large-scale synthesis of memantine hydrochloride (1) an anti-Alzheimer's drug. The procedure involves the conversion of 1,3-dimethyl adamantane (2) to formamide intermediate 8 as a key step, followed by hydrolysis to (1-amino-3,5-dimethyl adamantane) hydrochloride (1) in good yield.

Introduction

Alzheimer's disease is a progressive brain disorder that gradually destroys a person's memory. Alzheimer's is the most common form of dementia, a group of conditions that gradually destroy brain cells and lead to progressive decline in mental function. Compounds such as Donepezil, Galanthamine, Rivastigmine, and Memantine have dual acetylcholine esterase inhibitory and monoamine oxidase inhibitory activities; therefore, they are expected to have potential activity for the treatment of Alzheimer's disease and other neurodegenerative disorders.[1] (1-Amino-3,5-dimethyl adamantane)hydrochloride (**1**) is one of a small group of tricyclic antiviral drugs (TAV).[2] It also provides good and persistent activation of central nervous *N*-methyl-D-aspartate (NMDA) receptors and thus can be used in the treatment of Parkinson's and Alzheimers diseases. Memantine was approved by FDA in 2003 for Alzheimer's treatment.

Several groups have reported[3] the synthesis of **1** with an overall low yield, whereby bromination of 1,3-dimethyl-adamantane (**2**), yields 1-bromo-3,5-dimethyl-adamantane (**3**). Conversion of **3** to *N*-(3,5-dimethyl-adamantan-1-yl)-acetamide (**4**) in the presence of sulfuric acid in acetonitrile, and treatment of **4** at reflux conditions followed by salt formation produces the memantine hydrochloride **1** (Scheme 1).[4] This procedure results in relatively low yield and for large scale has an additional safety concern of a step run at high temperature (200−250 °C). Several other syntheses of **1** have been reported which are either too long or contain unacceptable operations and are therefore less suitable for large-scale synthesis.

Results and Discussion

In this report **8** is identified as a suitable intermediate to prepare **1** via bromination of 1,3-dimethyl-adamantane **2** in aqueous medium to afford 3,5-dimethyl-adamantan-1-ol (**6**), which on treatment with aq HCl gives 1-chloro-3,5-dimethyl-adamantane (**7**). Conversion of **7** to *N*-(3,5-dimethyl-adamantan-1-yl)-formamide (**8**) is a key step in the synthesis of **1**.

In summary, Scheme 2 represents a safe, economically competitive synthesis of **1**, which may be obtained from **2** in four steps with an overall yield of 55% using inexpensive, commercially available, raw materials and reagents. To the best of our knowledge, this protocol is economically advantageous over the earlier reported synthesis owing to high yields and the use of less expensive raw materials.

Experimental Section

The ^{1}H NMR spectra were measured in $CDCl_3$ using 200 MHz on a Varian Gemini FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989A LC/MS spectrometer. The CHN analysis was carried out on a Perkin-Elmer model 2400S analyzer. The solvents and reagents were used without further purification.

3,5-Dimethyl-adamantan-1-ol (6). Bromine (390.0 mL, 7.31 mol) was slowly added to 1,3-dimethyl-adamantane (**2**, 250.0 g, 1.52 mol) for 10−15 min, and the reaction mass was maintained at reflux temperature for 4−5 h, then cooled to room temperature, and diethyl ether (100.0 mL) was added

† Dr. Reddy's Communication #-IPDO-IPM-00043.

* Corresponding author. E-mail: reddyghanta@yahoo.com. Telephone: +91 9849250324. Fax: +91 40 2373 1955.

‡ Dr. Reddy's Laboratories Ltd.

§ J. N. T. University.

(1) (a) Altman, H. J. *Alzheimer's Disease Problems, Prospects and Prospectives*; Plenium Press: New York, 1987. (b) Durnett, S. B.; Fibiger, H. C. *Prog. Brain Res.* **1993**, *98*, 413−420.

(2) (a) Reicova, N.; Pazourek, J.; Polaskova, P.; Havel, J. *Electrophoresis.* **2002**, *23*(2), 259−262. (b) Suckow, R. F. *J. Chromatogr., B* **2001**, *764*, 313−325.

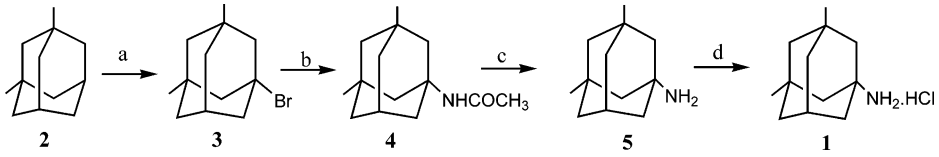
(3) (a) Sasaki, T.; Eguchi, S.; Katada, T.; Hiroaki, O. *J. Org. Chem.* **1977**, *42*, 3741−3743. (b) Kovacic, P.; Roskos, P. D. *J. Am. Chem. Soc.* **1969**, *91*, 6457−6460.

(4) (a) Mills, J.; Krumkalns, E. U.S. Patent 3,391,142, 1968. (b) Gerzon, K.; Krumkalns, E. V.; Brindle, R. L.; Marshall, F. J.; Root, M. A. *J. Med. Chem.* **1963**, 6, 760−763. (c) Scherin, A.; Homburg, B.; Peteri, D.; Markobel, H. U.S. Patent 4,122,193, 1978.

Published on Web 02/15/2007

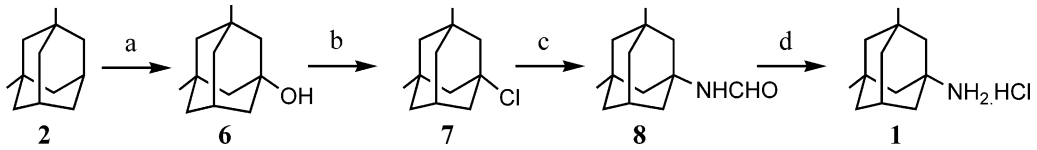
10.1021/op060246+ CCC: $37.00

Scheme 1[a]



[a] Reagents and conditions: a) Br_2/acetonitrile/25−30 °C/25−27 h; b) acetonitrile/H_2SO_4; c) diethylene glycol/KOH/200−250 °C/10−12 h; d) dry HCl gas/ethyl acetate/0−5 °C.

Scheme 2[a]



[a] Reagents and conditions: a) Br_2/H_2O/30 min/25−35 °C,95%; b) aq HCl (36%)/25−30 °C/15 h, 80%; c) formamide/95−100 °C/6−7 h, 98%; d) aq HCl (36%)/H_2O, 74%.

followed by washing with 15% sodium bisulphate solution (4.0 L); the separated organic layer was evaporated under vacuum which has yielded a white solid, triturated in petroleum ether: yield 260.0 g (95%), GC purity 99.99%. ^{1}H NMR: δ 4.5 (s, 1H), 1.4 (s, 2H), 1.25 (m, 10H), 0.85 (s, 6H); IR: 3322 cm^{-1} (OH); MS: *m*/*e* 181(M + 1); Anal. calcd for $C_{12}H_{20}O$: C 79.94, H 11.18. Found: C 79.83, H 11.11.

1-Chloro-3,5-dimethyl-adamantane (7). To a mixture 3,5-dimethyl-adamantan-1-ol (**6**, 250.0 g, 1.39 mol) and dichloromethane (2.0 L) was added concentrated hydrochloric acid (1300.0 mL) at ambient temperature; the resulting mixture was maintained for 12−15 h, the aqueous layer was separated from the organic layer, and the solvent was evaporated under vacuum which yielded oily liquid: yield 216.6 g (80%), GC purity 99.99%. ^{1}H NMR: δ 2.2 (m, 1H), 1.6−1.8 (m, 6H), 1.2−1.3 (m, 6H), 0.84 (s, 6H); IR: 750 cm^{-1} (C−Cl); MS: *m*/*e* 191(M + 1); Anal. calcd for $C_{12}H_{19}$-Cl: C 72.52, H 9.64. Found: C 72.43, H 9.45.

***N*-(3,5-Dimethyl-adamantan-1-yl)formamide (8)**. A mixture of 1-chloro-3,5-dimethyl-adamantane (**7**, 100.0 g, 0.50 mol) and formamide (500.0 mL) was heated to 150 °C for 8 h, to which was added ice-cold water; the reaction mass was extracted with methylene chloride (70.0 mL), the separated organic layer was concentrated, and a white solid was isolated and dried under vacuum: yield 101 g (98%), GC purity 99.85%. ^{1}H NMR: δ 8.2 (d, 1H), 7.8 (s, 1H), 2.15 (m, 1H), 1.68 (m, 2H), 1.45 (s, 4H), 1.2−1.3 (m, 6H), 0.80 (s, 6H); IR: 3347 cm^{-1} (NH), 1690 cm^{-1} (C═O); MS: *m*/*z* 208 (M + 1); Anal. calcd for $C_{13}H_{21}NO$: C 75.32, H 10.21, N 6.76. Found: C 75.16, H 10.16, N 6.86.

Memantine Hydrochloride (1). A mixture of *N*-(3,5-dimethyl-adamantan-1-yl)formamide (**8**, 75.0 g, 0.36 mol) and concentrated HCl (750.0 mL) was heated at reflux temperature (100−105 °C) for 6−7 h, the reaction mass was then cooled and stirred for 2 h, and a white solid was separated, filtered, and dried under vacuum: yield 58.0 g (74%), GC purity 99.99%. ^{1}H NMR: δ 1.45 (q, 2H), 1.12 (q, 2H),1.45 (q, 2H), 1.29 (s, 2H), 2.15 (m, 1H), 1.29 (s, 2H),1.65 (s, 2H), 0.85 (s, 3H), 0.85 (s, 3H).

Acknowledgment

We thank the management of Dr. Reddy's laboratories Ltd., for supporting this work. Cooperation from the project colleagues is highly appreciated.

Received for review November 24, 2006.

OP060246+