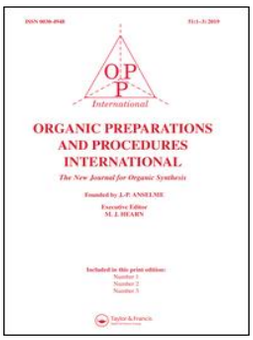

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The New Journal for Organic Synthesis

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uopp20

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To cite this article: Binh Duong Vu , Ngoc Minh Ho Ba , Hung Van Tran & Dinh Chau Phan (2020): An Improved Synthesis of Memantine Hydrochloride, Organic Preparations and Procedures International, DOI: 10.1080/00304948.2020.1785807

To link to this article: https://doi.org/10.1080/00304948.2020.1785807

Published online: 08 Sep 2020.

ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL
https://doi.org/10.1080/00304948.2020.1785807

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OPPI BRIEF

An Improved Synthesis of Memantine Hydrochloride

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ARTICLE HISTORY Received 25 September 2019; Accepted 24 March 2020

Memantine is an acetylcholine esterase and monoamine oxidase inhibitor used to treat Alzheimer's and Parkinson's diseases. Galanthamine, Rivastigmine, Donepezil, and Memantine are the most commonly used drugs for the treatment of Alzheimer's disease and other neurodegenerative disorders. Mechanisms of neuroprotection and clinical evidence for the effectiveness of Memantine have been provided[1]. The USFDA approved Memantine in 2003 for Alzheimer's treatment.

Prior synthesis methods for Memantine hydrochloride (**1**) have started from such materials as 1,3-dimethyladamantane, 1-halogeno-3,5-dimethyladamantane, and 1-hydroxy-3,5-dimethyladamantane; some of the most significant methods originated from 1,3-dimethyladamantane (**2**) and required two to four steps. Among the latter approaches, several groups have reported the synthesis of Memantine hydrochloride from **2** in three or four steps with an overall yield of 38-60%,[2–8] while other groups prepared **1** from **2** in two steps[9–16] with an overall yield of 65-75%. The method for the synthesis of Memantine hydrochloride from 1,3-dimethyladamantane via N-formyl-1-amino-3,5-dimethyl-adamantane (**3**) in two steps is noteworthy because of the cost of starting materials. Among these procedures, P. R. Schreiner's report[10] is a landmark for its simplicity and convenience: Schreiner and coworkers prepared Memantine hydrochloride (**1**) in two steps from 1,3-dimethyladamantane and formamide in a mixture of nitric acid and sulfuric acid via (**3**). The reaction was stirred at 0 °C for 15-20 h, and then for 1.5 h at room temperature. Following the reaction of **3** with 15% aq. HCl for 24 h one obtained **1** with an overall yield of 71% (Scheme 1).[10]

The above procedure is feasible for industrial production; however, there are some difficulties for this kind of scale-up. Among these we may note: a) the conversion of **2** to **3** is carried out at low temperature for 15-20 h, which requires that the manufacturing equipment must be even cooler for this prolonged length of time; b) the molar ratio of reagents among **2**:H_2SO_4:HNO_3:formamide (1:22.9:1.42:62.5) indicates that sulfuric acid and formamide are used lavishly; c) separation and purification of **3** from its reaction mixture must use chromatography (SiO_2, $CHCl_3$/acetone (20:1)), which becomes an expensive matter in industry; d) the time for hydrolysis of **3** into **1** is lengthy; e) the

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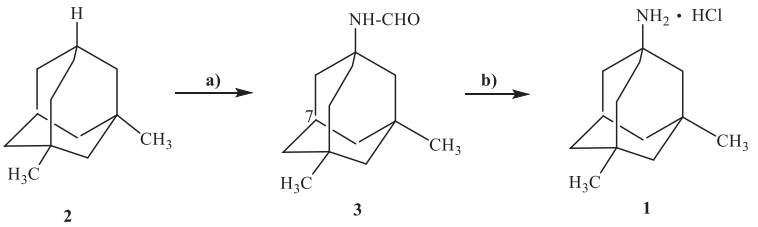


Reagents, conditions and yields: a) i, HNO_3/0 °C/3 h/H_2SO_4/0 °C/15-18 h; ii, formamide/ 0 °C/ 0.5 h +RT/1.5 h; iii, Chromatography, 89%; **b)** 15% HCl/reflux/24 h, 80%.

Scheme 1. Schreiner synthesis.

total preparation time of **1** from **2** is as much as 48 hrs. We chose this method[10] to optimize the preparation of Memantine hydrochloride. Our goal was to increase the effectiveness of the procedure and to keep costs down. We summarize our findings below, and complete details are provided in the Experimental section.

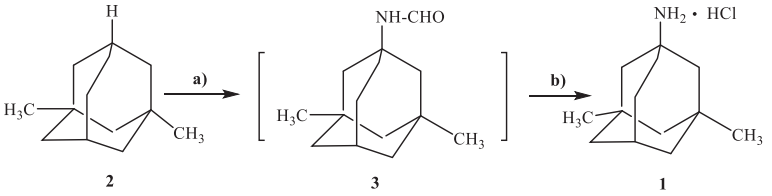
Synthesis of N-formyl-1-amino-3,5-dimethyladamantane (3)

Compound **3** was prepared in one step from 1,3-dimethyladamantane (**2**) and formamide in the presence of a mixture of sulfuric and nitric acids. This constitutes amidation of the tertiary C-H link in compound **2** by a Ritter reaction. We examined the effect of reaction temperature from 0 to 55 °C. Our study showed that the optimal temperature of this step (Scheme 2, i) is 20-25 °C over 6 h. For the subsequent reaction (ii) the optimum is 30-35 °C over 3 h. This eliminates the need for stirring at 0 °C for 15-20 h. We also optimized the molar ratio of reagents and saw that the best molar ratio of **2**:sulfuric acid:nitric acid:formamide was 1:9:0.67:2.67, a substantial decrease in the amount of sulfuric acid and formamide over the previous report.[10] We also found that **3** could be isolated without chromatography. The yield was high (97% compared to an overall yield of 89% in previous work[10]).

Synthesis of Memantine hydrochloride (1)

The nature of this reaction is deformylation of **3** into Memantine and formation of Memantine hydrochloride (**1**). The deformylation of **3** into Memantine can be carried out under base or acid catalysis, but if HCl is used, it conveniently leads directly to **1**. The parameters of the hydrolysis process were optimized, including solvent choice, deformylation time, the molar ratio between **3** and HCl, and the volume of solvent. We saw that **1** was best prepared from **3** by refluxing a mixture of 5N HCl and N-formyl-1-amino-3,5-dimethyladamantane in a molar ratio of 9:1 for 1 h. The yield of **1** is 82-85% (compared to the prior yield of 80%), and the deformylation reaction time is much shorter (1 h instead of 24 h).[10]

In summary, *Scheme 2* presents a facile and economically competitive synthesis of **1**. Compound **1** was obtained in two steps in one pot with a high overall yield of 82-85% (compared to overall yields of 38-60% in four steps[2–8] or 65-75% in two-steps[9–16]), with a purity (GC-MS) of 99.39%. Each reaction step was optimized to reduce the use of toxic reagents and solvents and avoid low temperatures and long reaction times. The



Reagents, conditions and yields: a) i, H_2SO_4 + HNO_3/20-25 ºC/6 h; ii, $OHCNH_2$, 30-35 ºC/3 h, 97%; **b)** HCl 5N/reflux/1 h, 85%.

Scheme 2. Present work.

total preparation time was significantly reduced compared to those methods described previously (about 10-12 h compared to 45-48 h[10]).

Experimental section

The reagents and solvents were obtained commercially and were used without further purification. Thin layer chromatography was performed on Kieselgel 60F-254 plates (Solvent: acetone/n-hexane 2/4). The melting points were measured on Stuart SMP-10 equipment. The IR spectra were obtained in the solid state (KBr dispersion) using a GX-Perkin Elmer 1650 FT-IR spectrophotometer (USA). The mass spectra (70 eV) were recorded on an AutoSpec Primer spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ on a Bruker-AV500 spectrometer; the chemical shifts are calculated in ppm relative to tetramethylsilane (TMS).

N-Formyl-1-amino-3,5-dimethyl-adamantane (3) from 1,3-dimethyladamantane (2)

1,3-Dimethyladamantane (11.13 mL, 9.86 g, 0.06 mol) was slowly added to 96% H_2SO_4 (30 mL, 55.13 g; 0.54 mol) over 20 min. Then 65% HNO_3 (2.8 mL, 3.86 g; 0.04 mol) was added to this reaction mixture at 20-25 °C over 0.5 h. The resulting suspension was maintained for 6 h, then formamide (6.4 mL, 7.2 g; 0.16 mol) was slowly added over 0.5 h, and after that the mixture was heated to 30-35 °C for 3 h. After the reaction was finished, which was indicated by TLC (as above), the reaction mass was cooled to 0-5 °C and added to ice-cold water (40 mL). The reaction mixture was extracted with dichloromethane (80 mL). The separated organic layer was treated with ammonia solution to pH 8-9 and then with chilled water. The organic layer was dried over Na_2SO_4, filtered, and then the solvent was evaporated to dryness under vacuum to give N-formyl-1-amino-3,5-dimethyladamantane (12.06 g, 96.96%) as an oil, which solidified at 10-15 °C, m.p. 60-64 °C. **IR** (KBr), (cm^{-1}): 3450-3199 (N-H); 2947-2847 (C-H); 1693,50 (C = O). **MS** (m/z): 208.16$[M+1]^+$. **^{1}H-NMR** (500 MHz, $CDCl_3$), δ (ppm): 8.23 (d, J = 12.5 Hz, 1H, NH) 7.90 (s, 1H, CHO); 6.23 and 5.25 (br, s, 1H); 2.12-2.17 (m, 1H); 1.83 (s, 1H); 1.67-1.61 (m, 2H); 1.48-1.40 (m, 2H); 1.37-1.25 (m, 4H); 1.17-1.12 (m, 2H); 0.85-0.83 (m, 6H, $2CH_3$). **^{13}C-NMR** (125 MHz, $CDCl_3$), δ (ppm): 162.3/160.3 (CHO); 53.7/52.3 (C_1) 50.5-50.3 (2C, C_2 and C_9); 47.8 (C_4); 42.7/42.5 (C_6); 42.2 (C_{10}); 40.4 (C_7); 32.5-32.4 (2C, C_3 and C_5); 30.1/30.0 (C_8); 29.9 (C_{11}); 29.8 (C_{12}).

Memantine hydrochloride (1) from N-formyl-1-amino-3,5-dimethyl-adamantane (3)

A mixture of water (44 mL), 36% HCl (48 mL) and N-formyl-1-amino-3,5-dimethyladamantane (12.65 g, 0.060 mol) was stirred for 10 min, and then heated to reflux for 1 h. The reaction mixture was concentrated to half volume, then to this reaction mass n-hexane (20 mL) was added, and the reaction mixture was heated to reflux for 0.5 h. The reaction mass was cooled to 5-10 °C for 1 h, the white solid was separated, filtered and washed with cold ethyl acetate to obtain a white solid, which was further recrystallized from a mixture of methanol and ethyl acetate, then dried under vacuum to give Memantine hydrochloride (**1**) (10.94 g; 84.65%), which did not melt up to 300 °C. Purity (GC-MS) 99.93%. **IR** (KBr), (cm^{-1}): 3441 (N-H); 2943, 2901 (CH); 1364,38 (C-N); **MS**, m/z: 180.17 $[M\text{-}HCl + 1]^+$. **^{1}H-NMR** (500 MHz, $CDCl_3$), δ (ppm): 8.34 (s, 3H, NH_2.HCl); 2.20 (m, 1H, C_7-H); 1.89 (s, 2H); 1.74 (d, J = 11.5, 2H); 1.68 (d, J = 11.5, 2H); 1.42 (d, J = 12.5, 2H); 1.31 (d, J = 12.5 2H); 1.22 (d, J = 12.5Hz, 1H,); 1.16 (d, J = 12.5Hz, 1H); 0.86 (s, 6H, $2CH_3$). **^{13}C-NMR** (125 MHz, $CDCl_3$), δ (ppm): 54.4 (C_1); 49.8 (2C, C_2 and C_9); 46.4 (C_4); 41.8 (2C, C_6 and C_{10}); 39.2 (C_7); 32.6 (C_3 and C_5); 29.8 (C_8); 29.6 (2C, C_{11} and C_{12}).

Memantine hydrochloride (1) from 1,3-dimethyladamantane (2)

At 20-25 °C, 1,3-dimethyladamantane (222.5 mL, 197.1 g, 1.2 mol) was slowly added to 96% sulfuric acid (600 mL, 1098 g; 10.8 mol) over 0.5 h. Then over 0.5 h, 65% HNO_3 (56 mL, 77.2 g; 0.8 mol) was added to this reaction mixture. The suspension was maintained for 6 h, then formamide (128 mL, 144 g; 3.2 mol) was slowly added over 1 h. After that, the mixture was heated to 30-35 °C for 3 h. After the reaction was finished, which was indicated by TLC (as above), the reaction mass was cooled to 0-5 °C and added to ice-cold water (800 mL). Then the reaction mixture was extracted with dichloromethane (1600 mL). The separated organic layer was treated with an ammonia solution to pH 8-9 and then with chilled water. The organic layer was dried over Na_2SO_4, filtered, and then the solvent was evaporated to dryness in vacuum to give N-formyl-1-amino-3,5-dimethyladamantane as an oil. To this oil, a solution of 5 N HCl (1800 mL) was added and stirred for 10 min, then heated to reflux for 1 h. The reaction mixture was concentrated to half volume. To this reaction mass n-hexane (300 mL) was added, the reaction mixture was heated to reflux for 0.5 h. The reaction mass was cooled to 5-10 °C for 1 h; the white solid was separated, filtered, and washed with cold ethyl acetate and dried under vacuum to give Memantine hydrochloride (**1**) (219.61 g, 84.87%) which did not melt up to 300 °C. The product has met United States Pharmacopoeia standard USP 38 with checklist number 1219/KNT-17 of the Preventive Medical Center, Hanoi Department of Health.

Acknowledgments

This research was financially supported by the Drug R&D Center, Vietnam Military Medical University.

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