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New Synthetic Approach to Memantine Hydrochloride starting from 1,3-Dimethyl-adamantane

Mukesh K. Madhra,* Mukesh Sharma, and C. H. Khanduri

Chemical Research Division, Ranbaxy Research Laboratories, Gurgaon, Haryana 122 001, India

Abstract:

A short and practical method for the synthesis of 1-amino-3,5-dimethyl-adamantane (Memantine hydrochloride) was established by using tertiary butyl alcohol under Ritter conditions to give 1-acetamido-3,5-dimethyl-adamantane. The 1-acetamido-3,5-dimethyl-adamantane is hydrolyzed using alkali to give free base which was then converted into its hydrochloride acid.

Introduction

In the field of Alzheimer's disease, Donepezil, Galanthamine, Rivastigmine, and Memantine are the most commonly used APIs. Memantine hydrochloride is an orally active *N*-methyl D-aspartate (NMDA) receptor antagonist. There is increasing evidence that memory loss and dementia in Alzheimer's disease are related to malfunctioning of the signals that pass messages between the nerve cells in the brain. Memantine works by blocking the NMDA receptors in the brain. This blocks the excessive activity of glutamate but still allows the normal activation of these receptors that occurs when the brain forms a memory. Memantine can therefore improve brain function in Alzheimer's disease and also blocks the glutamate activity that may further damage the brain cells. Memantine is used to treat moderately severe to severe Alzheimer's disease.[1]

An early method for synthesis of Memantine hydrochloride (**1**) discloses a process in which 1,3-dimethyl-adamantane (**2**) is brominated to give 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 (Ritter reaction)[2a,4,5] and treatment of **4** in diethylene glycol (DEG) at reflux conditions (245–250 °C) followed by salt formation produces Memantine hydrochloride **1** (Scheme 1).[2] This procedure has several disadvantages. The bromination is carried out under reflux, which can lead to the emission of toxic bromine vapour. The tertiary bromide **3** should not be stored for long periods due to issues with stability.[4] DEG, used as solvent, is toxic and poisonous; when heated to 230 °C with NaOH, it decomposes exothermally to release explosive hydrogen gas and also emits acid smoke and irritating fumes.[4] Ether was used both as a solvent for acidification of the free base and its recrystallization.[2a,3a] However, the use of ethers can constitute a hazard because of their highly inflammable nature and tendency to form peroxides. This process is unsafe for scale-up and environmentally hazardous, along with producing low yields. Several other syntheses of **1** have been reported that are either too long or contain unacceptable operations and are therefore less suitable for large-scale synthesis.[3] A recent reported method for synthesizing **1** through a key formamide intermediate also uses bromine as the initiating step.[5]

Results and Discussion

In this report, **4** is prepared directly from 1,3-dimethyl-adamantane (**2**) in the presence of *tert*-butyl alcohol, acetonitrile, and sulphuric acid. The reaction is carried out at 60–65 °C. Quenching is done by charging slowly the precooled reaction mass into a biphasic water/water-immiscible organic solvent, from which the strongly acid aqueous phase is discarded. The organic phase is washed with water and concentrated under vacuum to give **4**. Compound **4** is hydrolyzed using alkali in PEG-400 to give in situ **5**, which is converted into its hydrochloride salt **1** using IPA-HCl. Conversion of **2** directly into **4** is a key step in the synthesis of **1**.

In summary, the process described in Scheme 2 has the advantage of a safe and economically competitive synthesis of **1**. This process, with a reduced number of stages, an overall yield of 75%, and no use of bromine has been easily scaled up and is thus industrially feasible. 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 solvents and reagents were used as such without further purification. ^{1}H NMR spectra are recorded in DMSO/$CDCl_3$ using 300 MHz on a Bruker 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 Spectrum One spectrophotometer. The mass spectrum (70 eV) was recorded on an Applied Biosystem API-2000 LC/MS/MS spectrometer. Gas chromatography was carried out with a Hewlett Packard instrument (6890 series or

* To whom correspondence should be addressed. Tel: (91-124) 4011832. Fax: (91-124) 4011832. E-mail: mukesh.madhra@ranbaxy.com.

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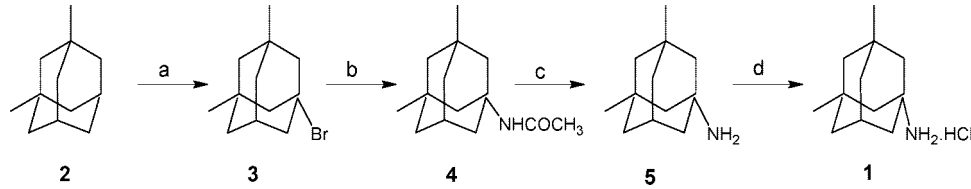
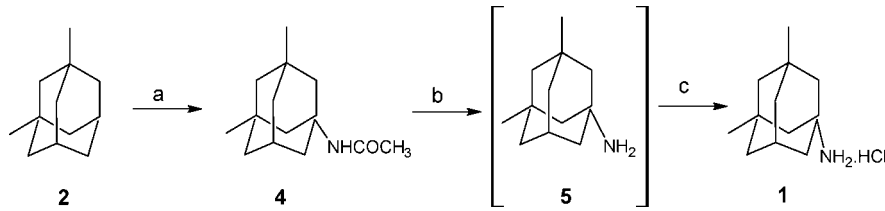
Scheme 1[a]



[a] Reagents and conditions: (a) Br_2/reflux/6 h; (b) acetonitrile/H_2SO_4; (c) diethylene glycol/NaOH/200–250 °C/6 h; (d) dry HCl gas/ether/0–5 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) H_2SO_4/*tert*-butyl alcohol/acetonitrile/60–65 °C/15–18h; (b) poly(ethylene glycol)/NaOH/130–135 °C/6–8 h; (c) IPA-HCl/acetone/15–25 °C.

equivalent) equipped with a flame ionization detector. The indicated columns were employed: fused silica column, 30 m long; 0.53 mm internal diameter; coated with 5% phenyl/95% dimethyl polysiloxane as stationay phase of 2.65 μm film thickness.

1-Acetamido-3,5-dimethyl-adamantane (4). Sulphuric acid (8.95 kg, 91.25 mol) was slowly added to a mixture of 1,3-dimethyl-adamantane (500 g, 3.04 mol), acetonitrile (2.54 L), and *tert*-butyl alcohol (282 g, 3.8 mol) at 60–65 °C in 2.0–2.5 h. The reaction mass was maintained for 18 h at 60–65 °C, then cooled to 5 °C, quenched with water, and extracted with dichloromethane (7.0 L). The organic layer was washed with water, evaporated, and finally crystallized with hexanes (3.0 L) to give a cream white solid: yield 605.0 g (90 %), GC purity 98.93 %. ^{1}H NMR (δ): 0.844 (s, 6H), 1.19−1.1 (q, 2H), 1.26–129 (s, 2H), 1.36–1.39 (q, 2H), 1.66–1.59 (q, 4H), 1.826–1.822 (q, 2H), 1.9 (s, 3H), 2.12–2.14 (m, 1H) 5.24 (s, 1H, NH). IR (cm^{-1}): 3435.98 N-H (s), 2899.88 CH_3 (s), 1512.91 N-H (b), 1521 CH_2 (s), 1384 C-H (s). MS (*m*/*e*): 222.1 (M + 1), 163.2 (M – C_2H_5NO).

Memantine Hydrochloride (1). A mixture of 1-acetamido-3,5-dimethyl-adamantane (**4**, 500.0 g, 2.26 mol) in poly(ethylene glycol) (PEG-400) (2.5 L) and pulverized sodium hydroxide (725 g, 18.12 mol) was heated at 130–135 °C for 6–8 h, quenched with water, and extracted with toluene (5.0 L). The toluene layer was washed with water and evaporated to give an oil of Memantine free base **5**. The free base was dissolved in acetone (1.25 L) and converted into the hydrochloride using IPA-HCl (325 mL; 22 % w/w strength) to give a white solid, which was filtered and dried under vacuum: yield 420 g (84 %), GC purity 99.87 %. ^{1}H NMR (δ): 0.848 (s, 6H), 1.14 (q, 2H) 1.29 (s, 2H); 1.29 (s, 2H); 1.44 (q, 2H); 1.48 (q, 2H); 1.636 (s, 2H); 2.15 (m, 1H); 8.09 (2H, NH_2, broad peak). IR (cm^{-1}): 3435.98 N-H (s), 2899.88 CH_3 (s), 1512.91 N-H (b), 1455.67 CH_2 (s). MS (*m*/*e*): 180.1 (M – Cl), 163.2 [M – ($NH_3^+Cl^-$)].

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