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AN IMPROVED SYNTHESIS OF AMANTADINE HYDROCHLORIDE

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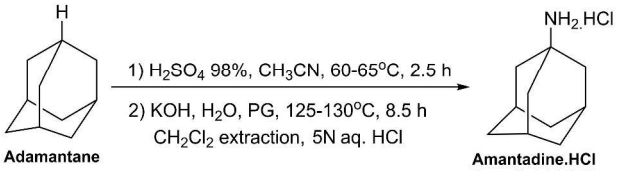
For Table of Contents Only

Simple and short synthesis of amantadine hydrochloride



Adamantane

Amantadine.HCl
Overall yield 67%

KEYWORDS: Amantadine hydrochloride, adamantane, *N*-(1-adamantyl)acetamide, Ritter, antiviral, antidyskinetic.

ABSTRACT: Amantadine hydrochloride **1** is an antiviral drug used in prevention and treatment of influenza A infections. It has also been used for alleviating early symptoms of Parkinson's disease. Several methods for the preparation of **1** have been reported. These procedures started with adamantane **2** using as many as four reaction steps to produce amantadine hydrochloride with overall yields ranging from 45% to 58%. In this article, we describe a two-step procedure for the synthesis of **1** from **2** via *N*-(1-adamantyl)acetamide **4** with an improved overall yield of 67%. The procedure was also optimized to reduce the use of toxic solvents and reagents, rendering it more environment-friendly. The procedure can be considered as suitable for large-scale production of amantadine hydrochloride. The structure of amantadine hydrochloride was confirmed by ^{1}H-NMR, ^{13}C-NMR, IR and MS.

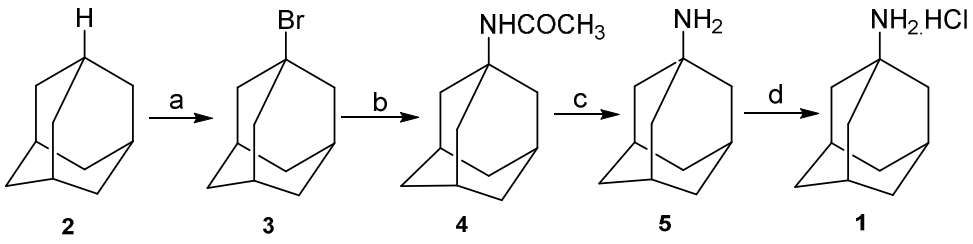
INTRODUCTION

Amantadine hydrochloride **1** is an antiviral drug used to treat influenza A infections. Its antiviral activity was first reported in 1964 by Davies W.L. *et al*.[1] A few years later, the drug received FDA approval as a preventative for Asian influenza and influenza A infections.[2] In addition to its use as an antiviral medication, amantadine hydrochloride has been utilized for alleviating early symptoms of Parkinson's disease and treating dyskinesia.[2]

There have been a number of publications about the synthesis of amantadine **5** and amantadine hydrochloride **1**[3a-o] using one of the following raw materials: adamantane **2**,[3a-e] 1-bromoadamantane **3**,[3f-h] 1-adamantanecarboxylic acid,[3i] 1-adamantanol,[3j-k] 1-adamantyl-magnesium-bromide[3l-n] and tetrahydrodicyclopentadiene.[3o]

Several groups have reported the synthesis of **1** from **2** via four steps with relatively low yields,[3a,3c,3f] whereby bromination or nitration of **2** produces **3** or 1-adamantyl nitrate, respectively. Conversion of **3** to **4** in the presence of concentrated sulfuric acid and acetonitrile followed by treatment with sodium hydroxide and polyethylene glycol (PEG) at reflux conditions (240-250^{o}C) yields **5**. Finally, salt formation between **5** and anhydrous HCl in ether solution produces **1** with overall yields varying from 45 to 58% (*Scheme 1*).[3a, 3c]

Scheme 1. Four-step synthesis of amantadine hydrochloride **1** from adamantane **2**



Reagents and conditions: (a) Br_2, $CHCl_3$, reflux; (b) CH_3CN, H_2SO_4, rt, 12 h, benzene extraction; (c) NaOH, DEG, reflux, 15 h; (d) anhydrous HCl, ether.

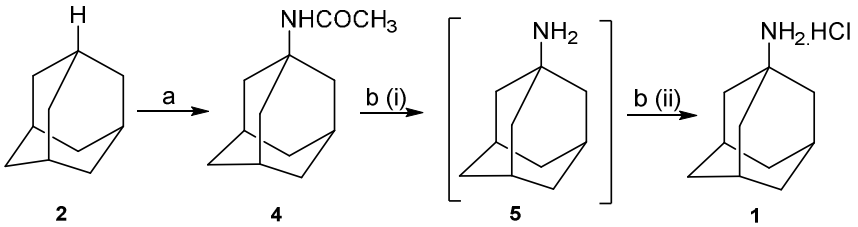
In order to make these procedures suitable for large-scale production of amantadine hydrochloride **1**, several issues should be addressed. First, the bromination step (a) carried out under reflux can lead to the emission of toxic bromine vapor. Second, 1-bromoadamantane **3** is sensitive to moisture, and thus not suitable for long-term storage.[4] Third, some solvents used in these procedures, such as benzene and diethylene glycol (DEG), are toxic.[3c, 4] DEG can also decompose exothermally when heated to 240-250°C, releasing explosive hydrogen gas and acid smoke.[4] Finally, using ether as a solvent for amantadine extraction and subsequent hydrochloride formation is a matter of concern because of its high flammability and tendency to form peroxides.[3a-c,3f]

Other groups have also described the synthesis of **1** from **2** via two steps, whereby **4** was prepared from **2** in one step using one of the following reactants: molybdenum hexacarbonyl, bromotrichloromethane,[5a] oleum or fuming H_2SO_4.[5b-f] However, these reagents are either expensive or toxic, rendering the described methods unfavorable for large-scale production of **1**. In this article, we report an improved method for the synthesis of **1** from **2** via two steps.

RESULTS AND DISCUSSION

In this report, compound **4** was identified as a suitable intermediate to prepare **1** via a one-step acetamidation of **2** in concentrated sulfuric acid and acetonitrile. Hydrolysis of **4** in a mixture of potassium hydroxide, propylene glycol (PG) and water at 125-130°C yields **5**, which on treatment with 5N aq. HCl produces **1**. Direct conversion of **2** to **4** is the key step in the synthesis of **1** (*Scheme 2*).

Scheme 2. Two-step synthesis of amantadine hydrochloride **1** from adamantane **2**



Reagents and conditions: (a) 98% H_2SO_4, 99.5% CH_3CN, 55-65^oC, 4.5 h; (b) (i) 82% KOH, water, PG, 125-130^oC, 7.5 h, CH_2Cl_2 extraction, (ii) 5N aq. HCl.

Synthesis of N-(1-adamantyl)acetamide **4.** Compound **4** was prepared from **2** in one step via the Ritter reaction. In this reaction, concentrated sulfuric acid induced the addition of a nitrile (−C≡N) to the carbenium ion of **2**, which on treatment with water produces **4**. This method bypassed the bromination or nitration of **2** (*Scheme 1*, step a), thus eliminating the need for liquid bromine or fuming nitric acid. In addition, the molar ratio between reactants was optimized to reduce the use of concentrated sulfuric acid (see **Table S1-4**). Finally, dichloromethane was used as the alternative solvent to benzene for isolation and separation of **4**. This change reduced the toxicity level of the described procedure.

Synthesis of amantadine hydrochloride **1.** Compound **5** was synthesized in a mixture of water, propylene glycol (PG) and potassium hydroxide instead of sodium hydroxide in diethylene glycol (DEG). The molar ratio between water, propylene glycol (PG), potassium hydroxide and **4** was also optimized for deacetylation (see **Table S5-8**), which resulted in a lower reaction temperature (125-130^oC) and a shorter reaction time (8.5 h) than described previously (i.e. 240-245^oC; 15 h).[3c] Finally, the synthesis of **1** from **5** utilized 5N aq. HCl in place of anhydrous HCl in ether solution to reduce the risk of explosion from ether.

In summary, *Scheme 2* presents a safe, economically competitive and environmentally friendly synthesis of **1**. Compound **1** was obtained in two steps with a high overall yield of 67% (compared to overall yields of 45-58% in four steps). Raw materials and reagents used in our procedure are inexpensive and commercially available. Each reaction step was optimized to reduce or eliminate the use of toxic reagents and solvents. Total preparation time was significantly reduced compared to those methods described previously. Our results suggest that this method is economically

advantageous over the earlier reported approaches owing to its high yields and the use of less expensive raw materials.

CONCLUSION

An improved synthesis for amantadine hydrochloride **1** has been provided. It produces a total yield of 67% over two steps and a purity of 99%. The synthesis of **4** from **2** was successfully accomplished in one step via the Ritter reaction. This method does not require liquid bromine or fuming nitric acid as reactants. The subsequent conversion of **4** to **5**, and then **5** to **1**, was carried out under milder reaction conditions without using hazardous solvents. These advantages facilitate the efficient, cost-effective and industrially convenient production of amantadine hydrochloride.

EXPERIMENTAL SECTION

General Procedures. All of the commercially available reagents and solvents were used without further purification. The ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ on Bruker-AV500 spectrometer; the chemical shifts are reported in ppm relative to TMS. The IR spectra were recorded in the solid state as KBr dispersion using a GX-Perkin Elmer spectrophotometer (USA). The mass spectra (70 *eV*) were recorded on AutoSpec Premier Spectrometer. The melting points were measured on Stuart SMP-10 apparatus. Analytical thin layer chromatography (TLC) was carried out on Merck pre-coated aluminum silica gel sheets (Kieselgel 60F-254).

N-(1-adamantyl)acetamide (**4**)**.** To a mixture of 99.5% acetonitrile (400 mL, 7.66 mol) and 98% adamantane **2** (277g, 2.0 mol) was added dropwise 98% sulfuric acid (1.56 L, 28.4 mol) with stirring at 25-30^{o}C for 2 h. The reaction mixture was stirred at 60-65^{o}C for an additional 2.5 h. At the end of the reaction, ice water (5.00 L) was added to the reaction mixture and stirred for 1.0 h at 0-5^{o}C. The resulting mixture was then extracted with dichloromethane (8.00 L); the separated organic layer was washed with cold water (0-5^{o}C) and dried over Na_2SO_4. The solvent was removed under vacuum to yield **4** as a white solid**.** Yield: 314 g (82%). Purity (GC): 99.20%, t_R 15.90 min;

mp 147-149°C. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 5.45 (s, 1H), 2.06 (s, 3H), 2.00 (s, 6H), 1.91 (s, 3H), 1.67 (s, 6H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 169.32, 51.78, 41.58, 36.35, 29.41, 24.59. IR (KBr): cm^{-1} 3277.04 (N-H); 2900.03-2849.76 (C-H); 1643.57 (C=O). MS: m/z = 194.0 $[M+1]^+$, 151.9 $[M-COCH_3+1]^+$, 135.0 $[M-NHCOCH_3]^+$.

Amantadine hydrochloride (**1**)**.** A mixture of 82% potassium hydroxide (600 g, 8.74 mol), water (100 mL) and propylene glycol (750 mL) was stirred at room temperature for 1 h, to which was added **4** (290 g, 1.5 mol). The mixture was maintained at 125°C-130°C for 8.5 h, then cooled to room temperature and followed by the addition of ice-cold water (2.00 L). The reaction mixture was extracted with dichloromethane (3 x 2.00 L). The separated organic layer was concentrated by three-fold. To the concentrate was added 5N aq. HCl (1.40 L), stirred at 55-60°C for 1 h, and then cooled to room temperature. The resulting aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (200 mL), stirred at 50°C for 1 h, and then at 0-5°C for additional 1 h. The obtained colorless precipitate was filtered off and dried under vacuum to give **1.** Yield: 232 g (82%). R_f = 0.5 ($CHCl_3$/MeOH/25% aqueous NH_3= 6:1:1). Purity (GC): 99.22%, t_R 10.10 min; mp 360°C. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.28 (br, s, 3H), 2.15 (s, 3H), 2.04 (s, 6H); 1.69 (s, 6H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 52.95, 40.56, 35.38, 28.97. IR (KBr): cm^{-1} 3331.73-3185.17 (N-H); 3054.60-2917.82 (C-H); 1363.50 (C-N). MS: m/z = 151.9 $[M+1]^+$, 135.0 $[M-NH_2-1]^+$.

Supporting Information Available: Experimental procedures and analytical data (NMR, IR, MS and GC) for compounds **4** and **1**. This material is available free of charge via ACS Publications website at http://pubs.acs.org.

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Author Contributions

The manuscript was written with contributions from all authors. All authors have given approval to the final version of the manuscript.

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