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Simple and Economical Process for Producing Amantadine Hydrochloride

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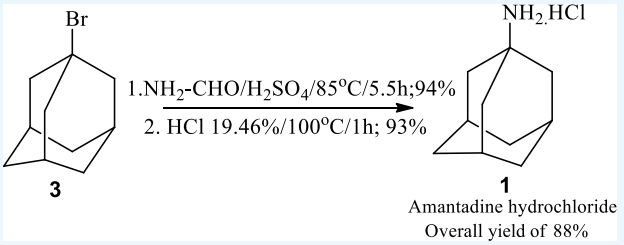
ABSTRACT: A simple and economical process for producing amantadine hydrochloride (**1**) on a 250 g scale, an antiviral and anti-Parkinson drug, has been developed. Several methods for the preparation of **1** through intermediate *N*-(1-adamantyl)-acetamide (**4**) in four or three steps were reported. These procedures started with adamantine (**2**) or 1-bromoadamantane (**3**), acetonitrile, and sulfuric acid by using the Ritter-type reaction to obtain *N*-(1-adamantyl)-acetamide, which was deacetylated to afford 1-amino-adamantane (**5**) and then the salt formed with anhydrous HCl gives **1** with the overall yield of **1** being 50−58%. In this article, a two-step procedure for the synthesis of **1** from 1-bromadamantane (**3**) and formamide via *N*-(1-adamantyl)-formamide (**6**) in two steps with an overall yield of 88% was reported. In this procedure, the preparation of **6** from **3** is a key step with a yield of 94%, followed by the hydrolysis of **6** with an aq. solution of HCl to give **1** in high yield (93%). The procedure was also carried out under optimal conditions established to reduce the use of toxic reagents or solvents and was carried out in one pot to make it more environmentally friendly. The procedure can be considered as more suitable for the large-scale production of **1**. The structures of product **1** and intermediate **6** were confirmed by IR, MS, ^{1}H NMR, ^{13}C NMR.



INTRODUCTION

Amantadine hydrochloride is an antiviral drug, which was used to treat certain type-A influenza infections. This compound is also used as an antidyskinetic agent to treat Parkinson's disease. The antiviral activity of amantadine hydrochloride was first reported in 1964 by Davies et al.[1] This article found that amantadine inhibited almost every influenza virus, especially influenza A. On October 1966, the Food and Drug Administration approved its use in the prevention of respiratory infections caused by influenza A virus strains.[2] Amantadine was also used to treat type A influenza viruses in the Asian influenza epidemic.[3]

There are many publications reporting the synthesis of amantadine (**5**) or amantadine hydrochloride (**1**), using different raw materials such as adamantine,[4−18] 1-adamantanol,[19−21] 1-bromoadamantane,[22−26] 1-adamantyl-magesium-bromide,[27−29] 1-adamantane-carboxylic-acid,[30−32] and tetrahydro-dicyclopentadiene.[33]

Several groups have reported the synthesis of amantadine (**5**) and amantadine hydrochloride (**1**) from **2**[4−6] or **3**[22] via four or three steps with relatively low yields. First, adamantane (**2**) was brominated with liquid bromine to yield 1-bromoadamantane (**3**),[3] respectively. In the next step, **3** was converted to **4** in the presence of sulfuric acid and acetonitrile,[3,22] followed by treatment with a mixture of sodium hydroxide and diethylene glycol (DEG) at reflux conditions (240−250 °C) to give **5**. Also, then **5** was salt formatted into **1** with anhydrous HCl in the ether solution. The overall yield of these procedures varies from 50 to 58% (Figure 1).[4,5,22]

This procedure has several disadvantages: (a) multisteps (four or three steps), that is, the cause of producing a low

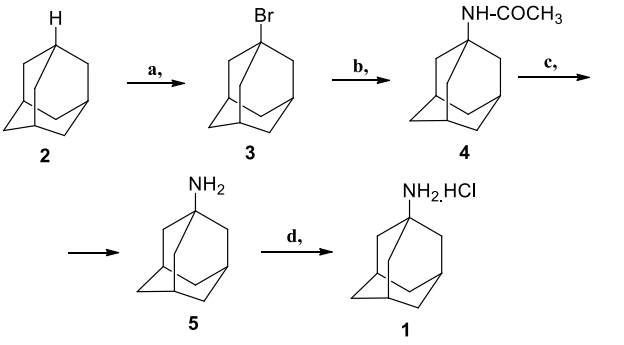


Figure 1. Four-step synthesis of 1 from 2[4,5] or three-step synthesis from 3.[22] [a] Reagents and conditions: (a) liquid Br_2 reflux; (b) CH_3CN/H_2SO_4/40 °C/12 h/benzene extraction; (c) NaOH, DEG, reflux, and 5 h/ether extraction; and (d) anhydrous HCl/ether.

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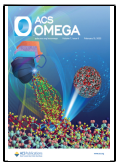

overall yield; (b) the bromination of **2**, with liquid bromine at reflux conditions can lead to the release of bromine vapor; (c) in the separation of **4** from the reaction mixture, benzene was used as a solvent for the extraction of compound **4**[4,5] (i.e., toxic); (d) in deacetylation, DEG, used as a solvent, is poisonous, when heated to 240−250 °C with sodium hydroxide, it decomposes to release explosive hydrogen gas and also emits acid smoke and irritating fumes;[33] and (e) in steps (**c**,**d**): Ether was used both as a solvent for the extraction of **5** and acidification of it into **1** with anhydrous HCl.[4−6,22] However, the use of ethers can constitute a hazard because of their highly inflammable nature and tendency to form peroxides. These procedures involved a lot of steps, due to which they resulted **1** in a relatively low overall yield (50−58%) and required additional safety concerns in the step run at a high temperature for a long time (at 240−250 °C for 5 h in an oil bath[4]), therefore this process is unsafe for scale-up and is environmentally hazardous. Several other syntheses of **1** have been reported that are either too long or contain unacceptable operations and therefore are less suitable for large-scale synthesis. A recent reported method for synthesizing **1** in only two steps through a *N*-(1-adamantyl)-formamide (**6**) from **3** and formamide in sulfuric acid as a key reaction, then **6** was de-formylated with a solution of HCl 19.46% to give **1**.

In the last year, we published two convenient methods for the synthesis of amantadine hydrochloride (**1**) from 1-bromoadamantane (**3**) and urea by the direct amination of **3** with urea in diphenyl ether at 175 °C for 1 h to give amantadine, which was treated with a solution of aq. 5 N hydrochloride to obtain **1**.[25]

This article gives another method for the synthesis of **1** from 1-bromoadamantane (**3**) and formamide, which focuses on setting a two-step procedure go through a key intermediate substance *N*-(adamantane-1-yl)-formamide (**6**), with the purpose of rejecting the abovementioned disadvantages and saving time, reagents, and solvents and giving a high yield for the synthesis in the industry scale. With many modifications as compared to previous reported procedures,[4,6] the method in this study is safer, more efficient, and more economical.

RESULTS AND DISCUSSION

In this report, **1** was synthesized from **3** in only two steps. The compound **6** is identified as a suitable intermediate to prepare **1**, which was prepared from **3**, formamide, and sulfuric acid in one step to afford *N*-(1-adamantyl)-formamide (**6**) (on the basis of the Ritter-type reaction). The reaction is carried out at 85 °C for 5.5 h. After the reaction was finished off, the reaction mixture was added to ice-cold water, then the white solid was precipitated, filtered, and washed with cool water. The obtained product **6** was hydrolyzed by using a solution of aq. HCl 19.46% to receive **1** (Figure 2).

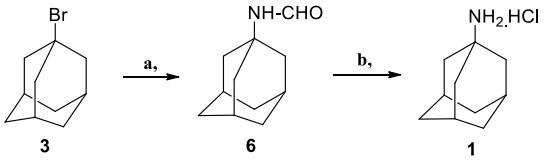

Figure 2. Two-step synthesis of 1 from 3.[a] Reagents and conditions: (a) /NH_2CHO/H_2SO_4/85 °C/5.5 h; 94% and (b) aq. HCl 19.46%/ref./1 h; 93%. An overall yield of 88%.

The process described above has advantages such as the following: (a) reduced number of steps of the procedure (only two steps instead of three or four steps); (b) the key step is adopting formamide instead of acetonitrile; (c) in addition, the molar ratio between reactants was optimized to reduce the use of sulfuric acid and formamide, resulting in the receipt of compound **6** in a high yield (94% and with purity by gas chromatography (GC): 98.834%), which could be easily hydrolyzed to **1** with aq. solution of HCl 19.46% to give a very good yield (93.17%); (d) in this key step for the preparation of **6** from **3**, no unnecessary amount of fuming sulfuric acid (oleum) or nitric acid is used, which decreases the population of the environment; (e) without the use of benzene or ether as a solvent for extraction of intermediate **4**,[3,4,22] so it reduced the toxicity level of the described procedure; (f) the parameters of reaction efficacy on the yield of compound **6** such as reaction temperature and time (see Table 1 in the Supporting Information), the molar ratio of reagents (see Tables 2 and 3 in the Supporting Information) were optimized. The results pointed out that using the optimal molar ratio (formamide: sulfuric acid: 1-bromoadamantane (**3**) = 10:5.6:1); reaction temperature = 85 °C; and reaction time = 5.5 h will help achieve the highest yield of **6** (94.44%); (g) the hydrolysis of **6** into **1** step with an aq. solution of hydrochloride 19.46% in reflux for only 1 h avoids the hydrolysis method using NaOH in DEG at reflux conditions for a high temperature and long time[4−6,22] (on 240−250 °C for 5−15 h), so that no poisonous and explosive substances are used; (h) without the use of ether and anhydrous HCl in the formed salt of **1** from **5**, this way cannot constitute a hazard because of their highly inflammable nature; and (I) furthermore, the parameters used to measure the conversion of compound **6** into **1** such as the concentration of HCl and reaction time (see Table 4 in the Supporting Information), the molar ratio of HCl: *N*-(1-adamantyl)-formamide (**6**) (see Table 5 in the Supporting Information) were optimized. The total yield of the procedure for the preparation of **1** from **3** is a high overall yield (88%) instead of 50−58%.[4,6,22] To the best of our knowledge, this protocol is economically advantageous over the earlier reported synthesis owing to its high yield and the use of less expensive raw materials.

CONCLUSIONS

A simple and economical process for producing amantadine hydrochloride (**1**) from 1-bromoadamantane (**3**) via *N*-(1-adamantyl)-formamide (**6**) using a two-step procedure in one pot has been provided. The synthesis of **6** from **3** was successfully accomplished in one step via the reaction between **3** and formamide in the presence of sulfuric acid 96% at 85 °C. This method does not require oleum as a reactant. The subsequent conversion of **6** to **1** was carried out under milder reaction conditions with an aq. solution of hydrochloride 19.46% at reflux for 1 h. Each parameter of the reaction steps was optimized to reduce or eliminate the use of toxic reagents and solvents. This process saves time, reagents, and solvents and gives a high yield of product **1**. Our results suggest that this method is economically advantageous over the earlier reported approaches owing to its high overall yields (88%, a purity of 99.221%) and the use of less expensive raw materials. These advantages facilitate the efficient, cost-effective, and industrially convenient production of **1**.

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EXPERIMENTAL SECTION

General Procedure. The reagents and solvents were used without further purification. Analytical thin layer chromatography (TLC) was carried out on Merck precoated aluminum silica gel sheets (Kieselgel 60F-254). The mass spectrum (70 eV) was recorded using an AutoSpec Primer spectrometer. The infrared (IR) spectra were recorded in the solid state as KBr dispersion using a GX-PerkinElmer 1650 FT-IR spectrophotometer (USA). The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were measured in $CDCl_3$ using a Bruker-AV500 spectrometer; the chemical shifts are reported in ppm relative to Tetramethylsilane (TMS). The melting points were measured on Stuart, SMP-10 apparatus and were uncorrected.

Synthesis of *N*-(1-adamantyl)-Formamide (6). At 75 °C, 1-bromoadamantane (66.0 g; 0.3 mol) was added to formamide (122 mL; 2.7 mol) with stirring. To this mixture, H_2SO_4 96% (90 mL, 1.65 mol) was added dropwise, then it was heated to 85 °C and maintained until the finished reaction (5.5h, the compound **2** disappeared), which was indicated by TLC: solvents/methanol: $CHCl_3$/aq. NH_3 25% = 1:6:1 (v/v); visualization: iodine. After the reaction mixture cooled to room temperature, it was slowly added to ice-cold water (350 mL) and stirred at 0−5 °C for 1 h. The white solid was precipitated, filtered, and washed with cool water. Finally, the recrystallization of raw *N*-(1-adamantyl)-formamide from methanol−water gave 50.81 (94.44%) compound **6**, purity (GC): 98.834%. mp 130−133 °C; **IR** (KBr, cm^{-1}): 3333−3084 (N−H); 2897, 2851 (C−H); 1688 (C═O); 1362 (C−N); MS, *m*/*z*: 180,35 $[M + 1]^+$; 152.30 $[M - CHO + 1]^+$; 136.35 $[M - NHCHO + 1]^+$; ^{1}H NMR(500 MHz, $CDCl_3$): δ (ppm): 8.31 (d, J = 12.3 Hz, 0.67H): 8,07 (d, J = 1.7 Hz, 0.33H); 6.26 (s, 0.65H); 5.35 (s, 0.35H); 2.16 (d, J = 18,6 Hz, 3H), 1,88 (d, J = 2.4 Hz, 2H),; 1,70 (d, J = 2.2 Hz, 4H), 1,69−1,65 (m, 6H); ^{13}C NMR(125 MHz, $CDCl_3$): δ (ppm): 162.33; 160.42; 52.24; 50.79; 44.16; 41.85; 38.88; 35.26; 29.41; 29.31.

Preparation of 1-Adamantylamine Hydrochloride (1). The mixture of solution hydrochloride 19.46% (180 mL, 1.05 mol) and *N*-formyl-1-amino-adamantane (**6**) (53.79 g, 0.3 mol) was stirred at room temperature for 10 min, and then it was heated to reflux until the compound **6** disappeared (1 h), which was indicated by TLC (solvents/$CHCl_3$: methanol/25% NH_3 aq. = 6:1:1; visualization: Dragendorff reagent). After the reaction was finished, the reaction mixture was extracted with dichloromethane (100 mL). The separated aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (35 mL), stirred at 50 °C for 1 h, and then at 0−5 °C for additional 1 h. The white solid was precipitated, filtered, and washed with cooled acetone (30 mL) and dried under vacuum to give 52.48 g amantadine hydrochloride (**1**), (93.17%); R_f = 0,5 ($CHCl_3$/methanol/25% NH_3 aq. = 6:1:1), did not melt up to 360 °C (from ethanol as described previously[6]); **MS**, *m*/*z*: 152.22 $[M + 1]^+$; 135.20 $[M - NH_2]^+$;**^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm): 8.31 (br, s, 3H, NH_2·HCl), 2.17 (s, 3H, C_3−H, C_5−H, C_7−H); 2.06 (s, 6H, C_4−H_2,C_6−H_2 và C_9−H_2); 1.70 (s, 6H, C_2−H_2, C_8−H_2 và C_{10}−H_2); **^{13}C NMR** (125 MHz, $CDCl_3$), δ (ppm): 52.9 (C_1); 40.6 (C_3 + C_5 và C_7); 35.4 (C_2 + C_8 và C_{10}); 28.9 (C_4 + C_6 và C_9) (PL 20).

One − pot procedure for preparation of

1 − adamantylamine hydrochloride (1) from

1 − bromo − adamantane

In the two abovementioned subsections, we carried out two separate steps (synthesis of **6** from **3** and **1** from **6**) to determine the characteristics of the key intermediate substance **6** and evaluate the yield of each step. However, on an industrial scale, the key intermediate substance does not need to be separated. Therefore, in this subsection, a two-step procedure in one pot was presented for the production of **1** on a 250 g scale.

At 75 °C, 1-bromoadamantane (330 g; 1.5 mol) was added to formamide (610 mL; 13.5 mol) with stirring. To this mixture, H_2SO_4 96% (450 mL, 8.25 mol) was added dropwise, then it was heated to 85 °C and maintained until the compound **2** disappeared (5.5 h), which was indicated by TLC: solvents: methanol/$CHCl_3$/aq. NH_3 25% = 1:6:1 (v/v); visualization: iodine. After the reaction was finished, the mixture was cooled to 20−25 °C and then slowly added to ice-cold water (1750 mL) and stirred at 0−5 °C for 1 h. The white solid was precipitated, filtered, and washed with cool water, then filtered by suction until achieved dryness. The obtained crude product **6** was added to a solution of hydrochloride 19.46% (990 mL, 5.25 mol) and stirred at room temperature for 10 min, and then it was heated to reflux until the compound **6** disappeared (1 h), which was indicated by TLC (solvents/$CHCl_3$/methanol/25% NH_3 aq. = 6:1:1; visualization: Dragendorff reagent).After the reaction was finished, the reaction mixture was cooled to 15−20 °C and then extracted with dichloromethane (450 mL). The separated aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (150 mL), stirred at 50 °C for 1 h, and then at 0−5 °C for an additional 1 h. The white solid was precipitated, filtered, and washed with cooled acetone (50 mL) and dried under vacuum to give 247.67 g amantadine hydrochloride (**1**), (87.94%); purity (GC): 99.221%; R_f = 0,5 ($CHCl_3$/methanol/25%NH_3 aq. = 6:1:1); did not melt up to 360 °C.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04652.

Experimental procedures and analytical data (NMR, IR, mass spectroscopy (MS), and GC) for compounds **6** and **1** (PDF)

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Author Contributions

The manuscript was written with contributions from all the authors. All the authors have given approval to the final version of the manuscript. The authors declare no competing financial interest.

Notes

The authors declare no competing financial interest.

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