Asian Journal of Chemistry; Vol. 34, No. 2 (2022), 251-255

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2022.23447

Two Step Cost-Saving Process for Industrial Scale Production of 1-Amino-3,5-dimethyladamantane Hydrochloride (An Anti-Alzheimer's Drug)

THI HONG THAM NGUYEN[1], VIET DUC LE[2], SY THINH NGO[3], THI HONG THANH NGUYEN[4], DINH CHAU PHAN[5] and BINH DUONG VU[1,*]

[1]Vietnam Military Medical University, No. 160, Phung Hung Str., Phuc La Ward, Ha Dong District, Hanoi 100000, Vietnam
[2]Military Institute of Drug, Medical Equipment Quality Control and Research, Km 15, Lien Ninh Ward, Thanh Tri District, Hanoi, Vietnam
[3]354 Military Hospital, 120 Doc Ngu, Ba Dinh, Hanoi, Vietnam
[4]Vinh Medical University, 161 Nguyen Phong Sac, Vinh, Nghe An, Vietnam
[5]School of Chemical Engineering, Hanoi University of Science and Technology, No.1, Dai Co Viet Str., Bach Khoa Ward, Hai Ba Trung District, Hanoi, Vietnam

*Corresponding author: Tel: +84 983425460; E-mail: vbduong2978@gmail.com

Received: 28 July 2021; *Accepted*: 16 September 2021; *Published online*: 11 January 2022; AJC-20644

This work presents a predominant cost-saving process for the industrial scale synthesis of memantine hydrochloride (**1**) from 1,3-dimethyladamantane (**2**) by a two-step method in which both steps were carried out in one-pot. The conversion of **2** to *N*-(3,5-dimethyladamantane-1-yl)acetylamide (**3**) was synthesized first in mixture of sulfuric acid 96-98% and nitric acid 64-65% at 25 ºC for 2.5 h and then in acetonitrile at 40 ºC for 3.5 h as a key step. The yield of this process reached to 98%. Next, the deacetylation of **3** with potasium hydroxide in mixture of water-ethylene glycol at 140 ºC for 15 h to get memantine base which was then converted into memantine hydrochloride (**1**) by aq. HCl 14% (yield of 93%). Overall yield of this synthetic route was 91.65%. The advantages of this process is saving time, solvents, reagents and giving a higher yield as compared to reported procedures.

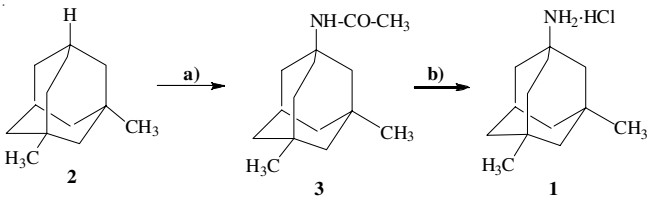
Keywords: 1,3-Dimethyladamantane, Acetonitrile, Memantine hydrochloride, *N*-Acetyl-1-amino-3,5-dimethyladamantane.

INTRODUCTION

Dementia is a disease that damages cognitive function of the human brain especially elderly people, in which the most universal type is Alzheimer's. Researchers believed that the main reason to chronic neurodegeneration gradually is the persistent activation of *N*-methyl-D-aspartate (NMDA) receptor [1-3]. Several drugs are used for the treatment of Alzheimer, among them memantine hydrochloride is able to block the NMDA receptor and the excessive activity of glutamate, thus it can improve brain functions *i.e.* thinking, learning, *etc*. Hence, the official approval of using memantin in symptomatic treatment of this disease by FDA in 2003 has led to high hopes for many patients.

Despite a large body of researches regarding synthesis of memantine hydrochloride (**1**), generally these procedures involved many steps [4-9] and the overall yield of processes was low [10-19]. Schreiner & Wanka [12] synthesized compound **1** from 1,3-dimethyladamantane (**2**) in two steps: firstly, compound **2** in a mixture of sulfuric acid 97-98%, nitric acid 60-65% and oleum (30% SO_3) were stirred at 0 ºC for 1 h and then 3 h at room temperature. After cooling to 0 ºC, acetonitrile was introduced in this mixture and then stirred for 10 min at 10 ºC and 3 h at ambient temperature to form *N*-acetyl-1-amino-3,5-dimethyladamantane (**3**). The separation and isolation of compound **3** from the mixture was carried out by ether extraction and the purification was done with chromatography on basic Al_2O_3 to give **3** with the yield of 60%. Next, the deacetylation of compound **3** was performed with HCl 36-38% at reflux for 20 h to afford compound **1** with yield of 65% (overall yield of 39%) [12] (**Scheme-I**).

Although the process of Schreiner & Wanka [12] has some advantages with only two steps as compared to previous processes, but has many limitations in industrial scale including



Scheme-I: Two-step procedure for synthesis of **1** from **2** [Ref. 12]; Reagents, conditions and yields: a) i, HNO_3//H_2SO_4/SO_3/0 °C/1 h and room temperature for 3 h; ii, acetonitrile/0 ºC/10 min + RT ºC/3 h; iii, Ether extraction; iv, chromatography; 60%; b) aq. 36-38% HCl/ reflux/20 h; 65%. Overall yield: 39%

(i) reaction was carried out at low temperature (0 ºC), which requires that the manufacturing equipment must be industrial fridge (oven cooler) to maintain reaction in long time; (ii) this procedure used the mixture of acids and oleum 30%, in which oleum is a toxic solvent; (iii) molar ratio of reagents between 1,3-dimethyladamantane (**2**): HNO_3:H_2SO_4:oleum 30%: acetonitrile (1:17.4:44.7:9.3:19.5), this implies the amount of reaction agents were used large, causing the prodigality of chemicals and environmental pollution; (iv) the use of ether as solvent for extraction of compound **3** is an important consideration because of its high flammability and it tends to form peroxides; (v) chromatography (Al_2O_3, $CHCl_3$) used in purification of compound **3** drives up the cost in industrial scale; (vi) the reaction time was too long (about 40-50 h) which can raise many difficulties in control of the reaction conditions.

Two convenient methods for the synthesis of **1** *via* N-formyl-1-amino-3,5-dimethyladamantane from **2** and formamide in the presence of mixture of acid nitric and acid sulfuric [20] or acid nitric [21] were also reported. This intermediate compound was converted to **1** by aq. HCl (overall yields 83-85%).

The present work reports another alternative method for the synthesis of **1** from **2** and acetonitrile, which focuses on setting a two-step procedure go through a key intermediate substance *N*-(3,5-dimethyladamantane-1-yl)acetylamide (**3**) with the purpose of better conditions and saving time, solvents, reagents as well as giving a high yield for the synthesis at the industrial scale. With several modifications as compared to procedure reported by Schreiner & Wanka [12], the current method in this study is safer, more effecient and economical.

EXPERIMENTAL

The reagents and solvents were of analytical chemicals and procured from the reputed commercial sources. Thin layer chromatography was carried out on a Kiesel gel $60F_{254}$ plate. The melting point of investigated substances were measured on a SMP-10 apparatus (Stuart) and are uncorrected. The IR spectra of substances were recorded on a GX-Perkin Elmer 1650 FT-IR spectrophotometer (USA). The mass spectra of substances were performed on an AutoSpec Primer spectrometer at a voltage of 70 eV. The ^{1}H NMR and ^{13}C NMR spectra of substances were measured in $CDCl_3$ on a Bruker-AV500 spectrometer; the chemical shifts were calculated in ppm relative to tetramethylsilane (TMS).

Synthesis of *N*-acetyl-1-amino-3,5-dimethyladamantane (3) from 1,3-dimethyladamantane (2): Compound **2** (9.3 mL, 0.05 mol) was added slowly to sulfuric acid 96-98% (19.2 mL, 0.35 mol) in a round-bottom flask at 5-10 ºC for 20 min and then over 10 min, HNO_3 64-65% (2.2 mL, 0.0315 mol) was introduced to this mixture at 20-25 ºC with stirring. The suspension mixture was maintained for 2.5 h, then acetonitrile (10.5 mL, 0.2 mol) was added slowly within 15 min and after that the mixture was heated to 40 ºC and maintained for 3.5 h. After the completion of reaction, it was cooled to 5-10 °C and added to ice-cold water (100 mL) before extracting with dichloromethane (120 mL). The separated organic was washed with ice-cold water, the organic layer was dried over Na_2SO_4 and the solvent was then evaporated in a vacuum to obtain a pale yellow solid, which was further recrystallized from *n*-hexane (25 mL) to give **3** (10.81 g, 97.74%) in white solid with m.p.: 111-112 ºC (Ref. [7] m.p.: 113-114 ºC); R_f = 0.51 (acetone:*n*-hexane = 2:4). IR (KBr, ν_{max}, cm^{-1}): 3294-3204 (N-H), 2945-2862 (C-H), 1655 (C=O). MS (*m/e*): 221.9 $[M + 1]^+$; 177.8 $[M-(CH_3CO)]^+$; 162.9 $[M-(CH_3CONH)]^+$. ^{1}H NMR (500 MHz, $CDCl_3$), (δ): 0.84 (s. 6H), 1.11-1.19 (q. 2H), 1.27-1.29 (d, 2H), 1.36-1.39 (q, 2H), 1.61-1.67 (q. 4H), 1.83 (s, 2H), 1.90 (s, 3H), 2.12-2.14 (m, 1H), 5.35 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 169.4 (C=O); 53.5 (C_1) 50.6 (2C, C_2 and C_9); 47.6 (C_4); 42.7 (C_{10}); 40.1 (C7); 32.3 (2C, C_3 and C_5); 30.1 (C_8); 30.1 (2C, C_{11} and C_{12}); 24.6 (CH_3-CO) [3].

Synthesis of memantine hydrochloride (1) from *N*-acetyl-1-amino-3,5-dimethyladamantane (3): A mixture of KOH 85% (23.62 g, 0.36 mol), water (15 mL) and ethylene glycol (69 mL) was stirred at room temperature for 0.5 h before **3** (11.12 g; 0.05 mol) was added. Next, the mixture was heated to 130 ºC and maintained at 140 ºC for 15 h (as indicated by TLC until compound **3** completely was disappeared (solvent: mixture of acetone:*n*-hexane = 2:4, visualization: Dragendorff reagent). After the completion of reaction, it was cooled to room temperature and ice-cold water (200 mL) was added. Then, the reaction mixture was extracted with dichloromethane (200 mL) for three times. The separated organic layer was concentrated to 50 mL and aq. 14% HCl (63 mL) was added before heating to 55-60 ºC for 1 h. Ethyl acetate (15 mL) was added following the mixture was evaporated in a vacuum until to remaining one-third volume of mixture. The mixture was stirred and heated to 60 ºC for 20 min and then at 0-5 ºC for 1 h. White solid portion was filtered and washed with cooled ethyl acetate, then dried in the vacuum to give **1** (10.05 g, 93.23%) with m.p. 290-295 ºC [22]; R_f = 0.5 (acetone:hexane = 2:4, visualization: Dragendorff reagent); Purity (GC): 99.91%; IR (KBr, ν_{max}, cm^{-1}): 3209-3115 (N-H); 2981-2706 (C-H); 1358 (C-N); MS, *m/z*: 221.9 $[M+1]^+$; 179.9 $[M-(HCl)]^+$; 162.9 $[M-(NH_2{\cdot}HCl)]^+$; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm) 8.32 (s, 3H); 2.21-2.20 (m, 1H); 1.89 (s, 2H); 1.75-1.72 (d, *J* = 11.5, 2H); 1.69-1.67 (d, *J* = 11.5, 2H); 1.41-1.39 (d, *J* = 12.5, 2H); 1.32-1.29 (d, *J* = 12.5 2H); 1.22-1.20 (d, *J* = 12.5 Hz, 1H); 1.16-1.14 (d, *J* = 12.5 Hz, 1H); 0.86 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 29.6 (2C, C_{11} and C_{12}); 29.8 (C_8); 32.6 (C_3 and C_5); 39.2 (C_7); 41.8 (2C, C_6 and C_{10}); 46.4 (C_4); 49.8 (2C, C_2 and C_9); 54.4 (C_1) [3,20,21].

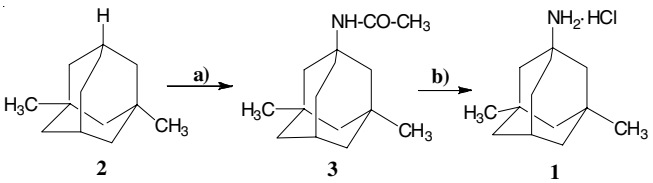
Synthesis of memantine hydrochloride (1) from 1,3-dimethyladamantane (2) in one pot: In two above subsections,

we carried out 2 separated steps (synthesis **3** from **2** and; **1** from **3**) to determine the characteristics of the key intermediate substance **3** and evaluate the yield of each step. However, in industrial scale, the key intermediate substance does not need to separate. Therefore, in this subsection, a two-step procedure in one pot was presented for the production of **1**.

Compound **2** (186 mL, 1.0 mol) was slowly added to conc. sulfuric acid 96-98% (385 mL, 7.0 mol) in a round-bottom flask at 5-10 ºC for 0.5 h and then within 0.5 h, HNO_3 64-65% (44 mL, 0.63 mol) was introduced to this mixture at 20-25 ºC with constant stirring. The suspension mixture was maintained for 2.5 h, then acetonitrile (210 mL, 4.0 mol) was added within 15 min before heating to 40 ºC for 3.5 h. Then, it was cooled to 5-10 ºC and added to ice-cold water (1200 mL), the reaction mixture was then extracted with dichloromethane (1500 mL). The separated organic layer was washed with chilled water, the organic layer was then dried over Na_2SO_4 and next, solvent was evaporated in a vacuum to give **3** (pale yellow solid). The solid part was introduced into a mixture of 85% KOH (470 g, 7.2 mol), water (300 mL) and ethylene glycol (1400 mL), which was stirred at room temperature for 0.5 h and then the reaction mixture was heated to 140 ºC for 15 h. When the reaction was terminated, the mixture was cooled to room temperature before adding ice-cold water (3000 mL); and finally the reaction mixture was extracted with dichloromethane (3000 mL). The separated organic layer was concentrated to 400 mL of volume and then the concentrate aq. 14% HCl (1200 mL) was added. The mixture was stirred at 55-60 ºC for 1 h and the solvent was evaporated in a vacuum to give a white solid before ethyl acetate (200 mL) was added. The mixture was stirred and heated to 60 ºC for 0.5 h and then at 0-5 ºC for 1 h and white solid part was filtered and washed with cooled ethyl acetate, then dried in a vacuum to give **1** (197.8 g, 91.65%) with m.p. 289-294 ºC; purity (GC): 99.91%; R_f = 0.5 (acetone: hexane = 2:4, visualization: Dragendorff reagent).

RESULTS AND DISCUSSION

Scheme-II is the two-step procedure for the synthesis of memantine hydrochloride (**1**) from 1,3-dimethyladamantane (**2**) in one pot, which is suitable for production of **1** in industrial scale.



Scheme-II: A two-step procedure for synthesis of **1** from **2**; [a]Reagents, conditions and yields: a) i, 96-98% H_2SO_4 + 64-65% HNO_3/ 25 °C/2.5 h; ii, CH_3CN/40 °C/3.5 h; 98%; b) i, KOH, H_2O+PG, 140 °C/15 h; ii, aq. HCl; 93%. Overall Yield: 91%

In the first step, *N*-(3,5-dimethyladamantane-1-yl)acetylamide (**3**) was synthesized from **2** in the presence of conc. sulfuric acid (96-98%), nitric acid 64-65% and acetonitrile. The nature of this reaction is the amidation of *ter*-C-H link in compound **2** into **3** by Ritter-type reaction, mixture of sulfuric acid and nitric acid as well as acetonitrile play the role of both reagent and solvent of reaction afforded compound **3**. This reaction was occured through two small steps: (i) oxidation of **2** to generate "the complex" between compound **2** and a mixture of H_2SO_4 and HNO_3 in the investigated optimal condition at 25 ºC for 2.5 h; (ii) synthesis of **3** by the reaction between "the complex" and acetonitrile at 40 ºC for 3.5 h (Tables 1 and 2). The optimized molar ratio of reagents (**2**:sulfuric acid: nitric acid:acetonitrile) was 1:7:0.63:4 (Tables 3-5). Finally, dichloromethane was used as the solvent for isolation and purification

TABLE-1
EFFECT OF TEMPERATURE IN THE FIRST STEP ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE

Temp. (°C)	M-NHCOCH$_3$ (**3**)		
	Weight (g)	Yield (%)	m.p. (°C)
15	1.45	65.61	110-112
20	1.51	68.32	111-113
25	1.56	70.58	110-112
30	1.49	67.42	112-113
35	1.42	64.25	110-112

TABLE-2
EFFECT OF TEMPERATURE IN THE SECOND STEP (RITTER-TYPE REACTION) ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE

Temp. (°C)	M-NHCOCH$_3$		
	Weight (g)	Yield (%)	m.p. (°C)
20	1.51	68.32	110-112
40	1.94	87.78	111-113
50	1.88	85.08	110-112
60	1.86	84.16	110-112
80	1.58	71.48	112-113
100	1.55	70.13	110-112

TABLE-3
EFFECT OF REACTION TIME ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE IN THE "COMPLEX" STAGE

Reaction time (h)	M-NHCOCH$_3$ (**3**)		
	Weight (g)	Yield (%)	m.p. (°C)
1.5	1.83	82,80	111-112
2.5	1.98	89.59	111-113
3.5	1.97	89.14	111-112
4.5	1.95	88.23	112-113
5.5	1.93	87.33	110-112
1.5	1.83	82,80	111-112

TABLE-4
EFFECT OF REACTION TIME ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE IN THE RITTER TYPE REACTION

Reaction time (h)	M-NHCOCH$_3$ (**3**)		
	Weight (g)	Yield (%)	m.p. (°C)
2.5	1.85	83.71	111-113
3.0	1.97	89.14	111-112
3.3	2.02	91.40	110-112
3.5	2.09	94.57	112-113
4.0	2.05	92.76	110-112

TABLE-5
EFFECT OF MOLAR RATIO BETWEEN NITRIC ACID 65% AND 1,3-DIMETHYLADAMANTAN ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE

Molar ratio between nitric acid 65% and 1,3-dimethyl adamantan	M-NHCOCH$_3$		
	Weight (g)	Yield (%)	m.p. (°C)
1.11:1	2.01	90.95	111-112
0.85:1	2.07	94.09	111-113
0.63:1	2.10	95.02	110-112
0.56:1	1.99	90.04	111-113
0.46:1	1.86	84.21	110-111
0.33:1	1.60	72.40	111-113

of **3** instead of using ethyl ether for extraction of crude **3** and then purification **3** with chromatography on basic Al_2O_3 in dichloromethane. The yield of first step in this procedure (obtain **3**) is high, 98% as compared to yield of 60% is report [12].

In second step, the hydrolysis of compound **3** with KOH in a mixture of ethylene glycol-water on 140 ºC leads to form memantine base. Finally, memantine base was converted into memantine hydrochloride (**1**) by aq. 14% HCl. The nature of this reaction is hydrolysis of **3** into memantine base and salt foramtion of its into memantine hydrochloride (**1**). The deacetylation of compound **3** into memantine base can be carried out under base or acid catalysis conditions, but in alkali hydroxide was used more conveniently leads to memantine base.

The parameters of the hydrolysis process were examined and optimized, including hydroxide type, solvent choice, reaction temperature and time, molar ratio between (hydroxide and compound **3**), (HCl and compound **3**), saw that memantine base was best prepared from compound **3** by treatment with KOH in mixture of water-ethylene glycol (EG) on 140 ºC for 15 h and weight ratio of KOH:EG:H_2O:**3** is 2.2:6.3:1.4:1 (molar ratio of 8:25:17.2:1 relatively) (Tables 6-12) instead of using

TABLE-6
EFFECT OF MOLAR RATIO BETWEEN SULFURIC ACID 98% AND 1,3-DIMETHYLADAMANTAN ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE

Molar ratio between sulfuric acid 98% and 1,3-dimethyladamantane	M-NHCOCH$_3$		
	Weight (g)	Yield (%)	m.p. (°C)
12:1	2.05	92.76	111-112
9:1	2.11	95.48	111-113
7:1	2.14	96.83	110-112
6:1	2.04	92.31	111-113
5:1	1.92	86.87	110-111
3:1	1.56	70.59	111-113

TABLE-7
EFFECT OF MOLAR RATIO BETWEEN ACETONITRILE AND 1,3-DIMETHYLADAMANTAN ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE

Molar ratio between acetonitrile and 1,3-dimethyladamantane	M-NHCOCH$_3$		
	Weight (g)	Yield (%)	m.p. (°C)
6:1	2.13	96.38	111-112
5:1	2.14	96.83	111-113
4:1	2.15	97.28	110-112
3:1	2.04	92.31	110-111
2:1	1.98	89.59	111-113

TABLE-8
EFFECT OF SOLVENT IN THE HYDROLYSIS REACTION

Solvent	Time (h)	Compound:memantin.HCl		
		Weight (g)	Yield (%)	m.p. (°C)
Water	0	0	0	0
Ethanol 96%	0	0	0	0
Glycerol	25	1.46	67.91	290-295
Ethylene glycol	12	1.74	80.93	291-293
PEG 400	29	1.53	69.23	292-295

TABLE-9
EFFECT OF ALKALINE ENVIRONMENT ON THE YIELD OF MEMANTINE HYDROCHLORIDE

Alkali	Time (h)	Compound:memantine.HCl		
		Weight (g)	Yield (%)	m.p. (°C)
NaOH	12	1.75	81.39	293-295
KOH	13	1.82	82.35	292-294

TABLE-10
EFFECT OF TEMPERATURE ON THE YIELD OF MEMANTINE HYDROCHLORIDE

Temp. (°C)	Time (h)	Compound:memantine.HCl		
		Weight (g)	Yield (%)	m.p. (°C)
120	24	1.74	80.93	290-295
130	18	1.78	82.79	291-293
135	17	1.81	84.19	292-295
140	15	1.91	88.83	293-295
145	14	1.87	86.98	292-294

TABLE-11
EFFECT OF MOLAR RATIO BETWEEN ETHYLENE GLYCOL AND 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE ON THE YIELD OF MEMANTINE HYDROCHLORIDE

Molar ratio of EG and 1-acetmido-3,5-dimethyladamantane	Compound:memantine.HCl		
	Weight (g)	Yield (%)	m.p. (°C)
12.5:1	1.63	75/81	291-293
18:1	1.87	86.97	292-295
22:1	1.93	89.77	292-294
25:1	1.97	91.62	291-293
27:1	1.95	90.70	292-295
30:1	1.90	88.37	290-295
40:1	1.89	87.91	291-293

TABLE-12
EFFECT OF MOLAR RATIO BETWEEN POTASSIUM HYDROXIDE AND 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE ON THE YIELD OF MEMANTINE HYDROCHLORIDE

Molar ratio between KOH and 1-acetamido-3,5-dimethyladamantane	Compound:memantine.HCl		
	Weight (g)	Yield (%)	m.p. (°C)
8.5:1	1.96	91.16	292-295
7.7:1	1.98	92.09	290-295
6.8:1	1.99	92.55	291-293
6:1	1.85	86.05	291-293
5.1:1	1.76	81.86	292-295
3.4:1	1.52	70.69	292-294

conc. HCl (36-38%) on reflux for 20 h, with molar ratio of (HCl:**3**) = 17.9:1 as reported by Schreiner & Wanka [12]. The overall yield of **1** from **2** is 91.65%, 2.35 times higher than that of Schreiner & Wanka [12] (overall yield of 39%).

As compared to other procedures, the present procedure is highly suitable for the production of memantine hydrochloride at the industrial scale with many advantages. The raw materials and reagents used in this procedure are inexpensive and commercially available. In step 1, in compound **3** synthesis, it is not necessary to use oleum SO_3 30% (a toxic reagent) and the volume of used sulfuric acid and nitric acid was decreased remarably, which helps in the reduction of secondary pollution. The use of dichloromethane solvent replacing ether solvent in the extraction of **3** and the non-requirement to use the chromatography with basic Al_2O_3 in purification of **3** [12] limits the flamability and cost saving in the processing. Also in step 2, the conversion of **1** from memantine base using aq. HCl 14% requires only 1 h helps to save time in production. The overall yield of this procedure is very high, 91.65% and the purity of **1** is also remarkable high, 99.91%.

Conclusion

In summary, **Scheme-II** presents a two-step method in one pot for synthesis of memantine hydrochloride (**1**) from *N*-(3,5-dimethyladamantane-1-yl)acetylamide (**3**). Compound **1** was obtained with a high purity of 99.91% and the overall yield for the reaction is very high, 91.65%. The solvent volume and reaction time have been limited many times as compared to the reported procedure. This procedure is more facile, cost-effective, friendly environment and safer. It is very suitable for industrially convenient production of memantine hydrochloride.

ACKNOWLEDGEMENTS

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

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. J. Liu, L. Chang, Y. Song, H. Li and Y. Wu, *Front. Neurosci*., **13**, 43 (2019); https://doi.org/10.3389/fnins.2019.00043
2. R. Crupi, D. Impellizzeri and S. Cuzzocrea, *Front. Mol. Neurosci*., **12**, 20 (2019); https://doi.org/10.3389/fnmol.2019.00020
3. M.K. Madhra, M. Sharma and C.H. Khanduri, *Org. Process Res. Dev.*, **11**, 922 (2007); https://doi.org/10.1021/op700138p
4. M. McLaughlin, S.G. Rubio, U. Tilstam, O.A.C. Antunes, T. Laird, G.D. Yadav and A. Zlota, *Org. Process Res. Dev.*, **11**, 2 (2007); https://doi.org/10.1021/op600268a
5. O.P. Tyagi, G.S. Ramanjaneyulu, B. Mohan, I.V.S. Kumar and K.N.A. Rao, WO Patent 132476A2 (2007).
6. R.U. Roy, P. Chan, R. Kumar and D.S. Dhar, WO Patent 062472 A2 (2008).
7. E. Vigano, M. Arrighi, R. Molteni, S. Lanfranconi and E. Landonio, New Process for the Synthesis of Moguisteine, EP2231627A2 (2006).
8. M.R. Gold, H. Koller and M. Pyerin, Process for Manufacturing Adamantane Derivatives with High Yield, US Patent 8796491B2 (2014).
9. E.A. Ivleva and Y.N. Klimochkin, *Org. Prep. Proced. Int.*, **49**, 155 (2017); https://doi.org/10.1080/00304948.2017.1291004
10. R. Ponnaiah, A. Prasad, P.M. Rana, K.S. Kanzariya and M.B. Dolia, WO Patent 067252 A1 (2010).
11. K.A. Ovchnikov, E.A. Ivleva and J.N. Klimmochkin, RU Patent 2541545 C2 (2015).
12. P.R. Schreiner and L. Wanka, WO Patent 010362 A1 (2006).
13. P.K. Jauhari, WO Patent 153806A2 (2009).
14. F.A.M., Huber, G. Gallo and D.F. Carla, WO Patent 115334 A2 (2009).
15. M.S. Reddy, S. Eswaraiah, G.V. Reddy and C. Suresh, WO Patent 057140 A2 (2009).
16. G. Quack and M.R. Gold, Process for Preparing Memantine, US Patent 0282100A1 (2011).
17. S.L. Pathi and R.N. Kankan, WO Patent 007351A1 (2010).
18. P.R. Schreiner, A.A. Fokin, L. Wanka and D.M. Wolfe, Method for Producing 1-Formamido-3,5-dimethyladamantane, US Patent 8138375 B2 (2012).
19. S. Wang, J. Li, J. Du, L. Wang and L. Huang, Method of Synthesizing Amantadine Hydrochloride, CN Patent 1556094A (2004).
20. B.D. Vu, B.N.M. Ho, V.H. Tran, V.H. Pham and D.C. Phan, *Org. Prep. Proced. Int.*, **52**, 463 (2020); https://doi.org/10.1080/00304948.2020.1785807
21. B.D. Vu, B.N.M. Ho, V.H. Pham and D.C. Phan, *ACS Omega*, **5**, 16085 (2020); https://doi.org/10.1021/acsomega.0c01589
22. F. Zhang, M. Hu, L. Zhao and M. Ge, Method of Preparing Memantine Hydrochloride, US Patent 7355080B2 (2008).