SUPPORTING INFORMATION

A Simple Two-Step Procedure for Synthesis of Memantine Hydrochloride from 1,3-Dimethyladamantane

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1. GENERAL PROCEDURE THE SYNTHESIS OF N-FORMYL-1-AMINO—3,5-DIMETHYLADAMANTANE (6)

1.1. Investigation for the effect of reaction parameters on the yield of N-formyl-1-amino-3,5-dimethyladamantane (6)

1.1.1. Effect of reaction temperature on the yield of 6

In a round-bottom flask, at 20-25 °C 1,3-dimethyl-adamantane (2 mL, 0.01 mol) was slowly added to nitric acid (10.65 mL, 0.25 mol) over 20 min with stirring at this temperature over 1 h, then formamide (11 mL, 0.27 mol) was slowly added within 0.5 h followed by heating the mixture to 75 °C for 3.5 h. After the reaction was finished, the solution was cooled to 5-10 °C and added to ice-cold water (20 mL), the reaction mixture was extracted with dichloromethane (40 mL). The separated organic layer was adjusted to pH 8-9 with 10% NaOH solution and then washed with chilled water, the organic layer was dried over Na₂SO₄, and then the solvent was evaporated to dryness in vacuum to give N-formyl-1-amino-3,5-dimethyladamantane (1.54 g, 77.4%) as an oil, which crystallized to a white solid at 10-15 °C, m.p. 60-64 °C. The reaction above preparation of 6 was performed the same operation as 2.1.1, but reaction temperature 75 °C instead of 60, 70, 75, 80, 85, 90 °C, respectively. (Table S1)

| No. | Temperature (°C) | Reaction Time (h) | Compound 6 |
|-----|-----------------|-----------------|------------|
|     |                 |                 | Weight (g) | Mp (°C)  | Yield (%) |
| 1   | 60              | 7               | 1.24       | 60-65    | 59.64     |
| 2   | 70              | 5               | 1.45       | 61-66    | 69.76     |
| 3   | 75              | 3.5             | 1.54       | 62-66    | 77.44     |
| 4   | 80              | 3.0             | 1.78       | 60-67    | 85.65     |
| 5   | 85              | 2.0             | 1.82       | 63-65    | 87.58     |
| 6   | 90              | 2               | 1.81       | 60-66    | 87.13     |

Other reaction parameters. 1,3-Dimethyl-adamantane (2) = 0.01 mol; Reaction temperature: 60 °C, 70 °C, 75 °C, 80 °C, 85 °C, 90 °C; molar ratio of (compound 2: nitric acid : formamide) = (1:12.5:13.5).

Conclusion: The reaction temperature gives the best yield of 6 was 85 °C for 2.5 h (the yield 87.58%) (No.5, Table S1).

1.1.2. Effect of molar ratio between nitric acid and compound 2 on the yield of 6

Experiment: The reaction preparation of 6 was performed the same operation as 1.1.1, but the molar ratio between nitric acid and compound 6 was 7.5:1; 9:1; 10:1; 11.5:1, respectively. (Table S2)
Table S2. Effect of molar ratio between nitric acid and compound 2 on the yield of N-formyl-1-amino-3,5-dimethyladamantane (6)

| No. | HNO₃ ml (mol) | Molar ratio of HNO₃: 2 | Compound 6 |
|-----|---------------|------------------------|------------|
|     |               |                        | Weight (g) | Mp (°C) | Yield (%) |
| 1   | 3.2 (0.075)   | 7.5:1                  | 1.73       | 60-64   | 83.65     |
| 2   | 3.7 (0.09)    | 9:1                    | 1.81       | 62-66   | 87.56     |
| 3   | 4.2 (0.10)    | 10:1                   | 1.91       | 63-66   | 92.10     |
| 4   | 4.8 (0.113)   | 11.5:1                 | 1.90       | 62-67   | 91.74     |

Other reaction parameters. Reaction temperature = 85 °C; Reaction time = 2.5 h;

Conclusion: The result found that using molar ratio of nitric acid:compound 2 was 10:1 got the highest yield of 6 was 92.10% (No.3, Table S2)

1.1.3. Effect of molar ratio between formamide and compound 2 on the yield of 6

Experiment: The reaction preparation of 6 was performed the same operation as 1.1.2, but the molar ratio between nitric acid and compound 6 was 20:1 and molar ratio between formamide and compound 2 was 5:1; 7.5:1; 9:1; 10:1, respectively. (Table S3)

Table S3. Effect of molar ratio between formamide and compound 2 on the yield of N-formyl-1-amino-3,5-dimethyladamantane (6)

| No. | Formamide ml (mol) | Molar ratio of Formamide:2 | Compound 6 |
|-----|--------------------|----------------------------|------------|
|     |                    |                            | Weight (g) | Mp (°C) | Yield (%) |
| 1   | 2.10 (0.05)        | 5:1                        | 1.80       | 60-64   | 86.96     |
| 2   | 3.15 (0.075)       | 7.5:1                      | 1.95       | 62-66   | 94.20     |
| 3   | 3.65 (0.09)        | 9:1                        | 2.02       | 63-66   | 97.58     |
| 4   | 4.25 (0.10)        | 10:1                       | 1.99       | 62-67   | 96.14     |

Other reaction parameters. Reaction temperature = 85 °C; Reaction time = 2.5 h;

Conclusion: The result found that using molar ratio of formamide:compound 2 was 9:1 got the highest yield = 97.58% (No.3, Table S3)

⇒ Results. The combination of reaction parameters found that the highest yield of N-formyl-1-amino-3,5-dimethyl adamantane were followed: 1,3-Dimethyladamantane (2) = 0.01 mol; Reaction condition: Reaction temperature = 85°C; Reaction time = 2.0 h; Molar ratio of (nitric acid:formamide:1,3-dimethyladamantane) = (10:9:1); Yield = 97.58%.
1.2. Experimental section

*Synthesis of N-formyl-1-amino-3,5-dimethyladamantane (6)*

In a round-bottom flask, at 20-25 °C 1,3-dimethyladamantane (11.13 mL, 9.86 g, 0.06 mol) was slowly added to nitric acid (25.25 mL, 0.6 mol) over 20 min with stirring at this temperature for 1 h, then formamide (22.5 mL, 0.54 mol) was added within 0.5 h followed by heating the mixture to 85 °C for 2 h. After reaction completion, the solution was cooled to 5-10 °C and added to ice-cold water (120 mL), the reaction mixture was extracted with dichloromethane (150 mL). The separated organic layer was adjusted to pH 8-9 with 10% NaOH solution and then washed with chilled water, the organic layer was dried over Na$_2$SO$_4$, and the solvent was evaporated to dryness in vacuum to give N-formyl-1-amino-3,5-dimethyladamantane (12.18 g, 97.91%) as an oil, which crystallized into white solid 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, CDC$_3$), $\delta$ (ppm): 8.23 (d, J=12.5 Hz, 1H, NH) 7.99 (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); 0.85-0.83 (m, 6H, 2CH$_3$). $^{13}$C-NMR (125 MHz, CDC$_3$), $\delta$ (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$_{12}$).
1.3. Analytical data (IR, MS, NMR) of N-formyl-1-amino-3,5-dimethyladamantane (6)

1.3.1. IR spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

IR (KBr), (cm$^{-1}$): 3450-3199 (N-H); 2947-2847 (C-H); 1693,50 (C=O).

**Figure S1.** IR spectrum 6.
1.3.2. MS spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

MS (m/z): 208.16 [M+1]^+ 

Figure S2. MS spectrum of 6.
1.3.3. $^1$H-NMR spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

$^1$H-NMR (500 MHz, CDCl$_3$), δ (ppm): 8.23 (d, J=12.5 Hz, 1H, NH) 7.99 (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$_3$).
Figure S3. $^1$H-NMR spectrum of 6.
1.3.4. $^{13}$C-NMR spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

$^{13}$C-NMR (125 MHz, CDCl$_3$), $\delta$ (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$_{12}$).

Figure S4. $^1$H-NMR spectrum of 6.
2. GENERAL PROCEDURE FOR THE SYNTHESIS OF MEMANTINE HYDROCHLORIDE (1)

2.1. Effect of reaction parameters on the synthesis of memantine hydrochloride (1) from N-formyl-1-amino-3,5-dimethyladamantane (6)

2.1.1. Effect of solvent type on the yield of memantine hydrochloride (1)

Experiment: In a round-bottom flask, a mixture 18 mL water, 36% hydrochloride solutions (21 mL, 0.24 mol) and N-formyl-1-amino-3,5-dimethyladamantane (6) (6.55 g, 0.03 mol) was stirred for 10 min, and then was heated to reflux until the reaction was finished off (the compound 6 was consumed). The reaction mixture was concentrated to a half volume of solvent under vacuum. To this solution, n-hexane (10 mL) was added, the reaction mixture was heated to reflux for 0.5 h. The reaction was cooled to 5-10 °C for 1 h, whereupon a white solid was separated. The solid was filtered and washed with cooled ethyl acetate to obtain a white solid, which was further recrystallized from a mixture of ethanol and ethyl acetate and dried under vacuum to give memantine hydrochloride (1), which was melted at 290 °C and sublimated at 300 °C (Table S4)

Table S4. Effect of solvent type on the yield of memantine hydrochloride (1)

| No. | Solvent type (ml) | Reaction Temperature/reaction time (°C/h) | Memantine hydrochloride (1) | Yield (%) |
|-----|-------------------|------------------------------------------|-----------------------------|-----------|
|     |                   |                                          | Weight (g)                  | Mp & Sp (°C) |         |
| 1   | H2O (18)          | 100-103/1                                | 5.19                        | 290-300    | 80.45    |
| 2   | 95% C2H5OH (18)   | 80-85/3                                  | 4.83                        | 290-300    | 74.56    |
| 3   | CH3OH (18)        | 70-75/2.5                                | 4.68                        | 290-300    | 72.47    |

Other reaction parameters. 36% HCl; Molar ratio of (HCl:compound 6) = (8:1).

Conclusion: The result found that using water as a solvent got the highest yield (No.1, Table S4)
2.1.2. Effect of reaction time on the yield of memantine hydrochloride (I)

**Experiment:** The reaction preparation of 1 was performed the same operation as 2.1.1, but reaction temperature 75, 80, 90, 100, and reaction time was 2.5, 2, 1.5, 1 h, respectively. (Table S5)

**Table S5. Effect of reaction time on the yield of memantine hydrochloride (I)**

| No. | Reaction time (°C) | Reaction time (h) | Memantine hydrochloride(1) | Weight (g) | Mp & Sp (°C) | Yield (%) |
|-----|-------------------|------------------|---------------------------|------------|--------------|-----------|
| 1   | 75                | 2.5              | 5.10                      | 290-300    |              | 78.81     |
| 2   | 80                | 2.0              | 5.13                      | 290-300    |              | 79.15     |
| 3   | 90                | 1.5              | 5.16                      | 290-300    |              | 79.93     |
| 4   | 100               | 1.0              | 5.22                      | 290-301    |              | 80.58     |

**Other reaction parameters.** Solvent = water. Molar ratio of (HCl:compound 6) = (8:1).

**Conclusion:** The reaction temperature gives the best yield of 1 was 100 °C for 1 h (No.4, Table S5).

2.1.3. Effect of molar ratio between HCl and compound 6 on the yield of memantine hydrochloride (I)

**Experiment:** The reaction preparation of 1 was performed the same operation as 2.1.2, but molar ratio between HCl and compound 6 was 6:1, 7.2:1, 8.4:1, 9.6:1, 10.8:1, respectively. (Table S6)

**Table S6. Effect of molar ratio between HCl and compound 6 on the yield of memantine hydrochloride (I)**

| No. | HCl 36% ml (mol) | Molar ratio of HCl:6 | Memantine hydrochloride(1) | Weight (g) | Mp & Sp (°C) | Yield (%) |
|-----|-----------------|----------------------|-----------------------------|------------|--------------|-----------|
| 1   | 15(0.180)       | 6.0:1                | 5.22                        | 290-300    |              | 80.45     |
| 2   | 18(0.216)       | 7.2:1                | 5.37                        | 290-300    |              | 82.98     |
Other reaction parameters. Solvent = water. Molar ratio of (HCl:compound 6) = (6:1, 7.2:1, 8.4:1, 9.6:1 and 10.8:1).

Conclusion: The molar ratio between HCl and compound 6 gives the best yield of 1 was 8.4:1 (see No.4 in Table S6).

2.1.4. Effect of solvent volume on the yield of memantine hydrochloride(1)

Experiment: The reaction preparation of 1 was performed the same operation as 2.1.3, but solvent (water) volume was 6, 9, 12, 15, 18, 21, 24 mL, respectively. (Table S7)

Table S7. Effect of solvent volume on the yield of memantine hydrochloride (1)

| No. | Water volume (ml) | HCl concentration N | Memantine hydrochloride(1) |   |   |
|-----|------------------|---------------------|-----------------------------|---|---|
|     |                  |                     | Weight (g)                  | Mp & Sp (°C) | Yield (%) |
| 1   | 6                | 10.50               | 5.22                        | 290-300 | 80.25     |
| 2   | 9                | 9.33                | 5.30                        | 290-300 | 81.86     |
| 3   | 12               | 8.40                | 5.37                        | 290-300 | 82.98     |
| 4   | 15               | 7.64                | 5.43                        | 290-300 | 83.87     |
| 5   | 18               | 6.46                | 5.49                        | 290-300 | 84.85     |
| 6   | 21               | 6.0                 | 5.47                        | 290-300 | 84.46     |
| 7   | 24               | 5.5                 | 5.36                        | 290-300 | 82.75     |

Other reaction parameters. Solvent = water. Reaction time = 1h. Molar ratio of (HCl: compound 6) = (8.4:1).

Conclusion: The solvent (water) volume gives the best yield of 1 was 18 ml (No.5, Table S7)
Results. The optimal parameters of reaction for the highest yield of memantine hydrochloride were followed: Compound 6 (0.03 mol); 36% HCl (25 ml, 0.288 mol); Molar ratio of (HCl:compound 6) = (8.4:1); water (18 mL); Temperature = 100-104 °C; Reaction time = 1.0 h.
2.2. Experimental section

In a round-bottom flask, a mixture of water (36 mL), solution of 36% hydrochloride (45 mL, 0.51 mol) and N-formyl-1-amino-3,5-dimethyladamantane (12.44 g, 0.06 mol) were stirred for 10 min, followed by heating to reflux for 1 h. The reaction mixture was concentrated to half volume of the solvent under vacuum. To this solution, n-hexane (20 mL) was added, the reaction mixture was heated to reflux for 0.5 h. The reaction was cooled to 5-10 °C for 1 h, whereupon a white solid was separated. The solid was filtered and washed with cooled ethyl acetate to obtain a white solid, which was further recrystallized from a mixture of ethanol and ethyl acetate (5:4, v/v) and dried under vacuum to give memantine hydrochloride (1) (10.97 g, 84.74%), which was melted at 290 °C and sublimated at 300 °C (literature17 m.p. 290-295 °C). IR (KBr), (cm⁻¹): 3441 (N-H); 2943, 2901 (CH); 1364 (C-N); MS, m/z: 180.17 [M-HCl+1]+. ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 8.34 (s, 3H, NH₂.HCl); 2.20 (m, 1H); 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, IH); 1.16 (d, J=12.5Hz, IH); 0.86 (s, 6H, 2CH₃. ¹³C-NMR (125 MHz, CDCl₃), δ (ppm): 54.4 (C₁); 49.8 (2C, C₂ and C₉); 46.4 (C₄); 41.8 (2C, C₆ and C₁₀); 39.2 (C₇); 32.6 (C₃ and C₅); 29.8 (C₈); 29.6 (2C, C₁₁ and C₁₂).
2.3. Analytical data (IR, MS, NMR) of Memantine Hydrochloride

2.3.1. IR spectrum of Memantine Hydrochloride

**IR** (KBr), (cm$^{-1}$): 3406 (N-H); 2988, 2901 (CH); 1361 (C-N);

![IR spectrum of Memantine Hydrochloride](image)

**Figure S5.** IR spectrum of Memantine Hydrochloride.
2.3.2. MS spectrum of Memantine Hydrochloride

MS, m/z: 180.17 [M-HCl+1]+

Figure S6. MS spectrum of Memantine Hydrochloride.
2.3.3. $^1$H-NMR spectrum of Memantine Hydrochloride

$^1$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$_3$)

Figure S7. $^1$H-NMR spectrum of Memantine Hydrochloride
2.3.4. $^{13}$C-NMR spectrum of Memantine Hydrochloride

$^{13}$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$_{12}$).

Figure S8. $^{13}$C-NMR spectrum of Memantine Hydrochloride
3. THE SAFETY STUDIES

Sample preparation:
Sample 1. 1 mL 1,3-dimethyl-adamantane
Sample A. 1.24 ml 1-3 dimethyl-adamantane and 2.25 ml formamide
Sample B. 1.24 mL 1-3 dimethyl-adamantane and 2.52 mL acid nitric
Sample C. 1.24 ml 1-3 dimethyl-adamantane, 2.25 ml formamide and 2.52 mL acid nitric

![Figure S9. The DSC measurement result of sample 1](image-url)
Figure S10. The DSC measurement result of sample A

Figure S11. The DSC measurement result of sample B
**Figure S12.** The DSC measurement result of sample C

**Figure S13.** The ARC study of sample C
Conclusion:

The DSC results showed that, when heating in the area from room temperature to 300 °C, only the endothermic effect corresponding to the evaporation of the liquid is accompanied by decomposition at high temperature, no effect appears exothermic decomposition.

The ARC study of sample C also illustrated that this reaction still has an exothermic effect at 150 °C but decomposes more smoothly.

Therefore, it can be concluded that it is safe and not explosive.