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# One-Pot Synthesis of Papaverine Hydrochloride and Identification of Impurities

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**Abstract**—A one-pot synthesis of papaverine hydrochloride with 99.6% purity was performed using xylene as solvent for the entire process. The critical parameters of each step, as well as the impurities generated, were identified. The overall yield was improved to 63%. The proposed synthetic procedure is suitable for industrial production.

**Keywords:** papaverine hydrochloride, one-pot synthesis, impurities, efficiency

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## INTRODUCTION

In 1978, papaverine hydrochloride (**1**), promoted under the trade name Oxadilene, was marketed in France for the treatment of ischemia, as well as kidney, gallbladder, and gastrointestinal visceral fistulae caused by brain, heart, and peripheral vasospasms [1].

There are many ways to synthesize papaverine hydrochloride [2], and the general route [3–5] used for its synthesis is shown in Scheme 1. First, 3,4-dimethoxyphenylacetic acid (**2**) was reacted with $SOCl_2$ in toluene to form 3,4-dimethoxyphenylacetyl chloride. The reaction of 3,4-dimethoxyphenylacetyl chloride with 2-(3,4-dimethoxyphenyl)ethanamine (**3**) in dichloromethane at room temperature for 3 h gave amide **4**. The latter was treated with $POCl_3$ in acetonitrile at 80°C to generate dihydroisoquinoline derivative **5**, and the latter was dehydrogenated in toluene over Pd/C at 230°C to yield papaverine (**6**). Finally, papaverine (**6**) was converted to papaverine hydrochloride (**1**) by treatment with a solution of hydrogen chloride in ethanol.

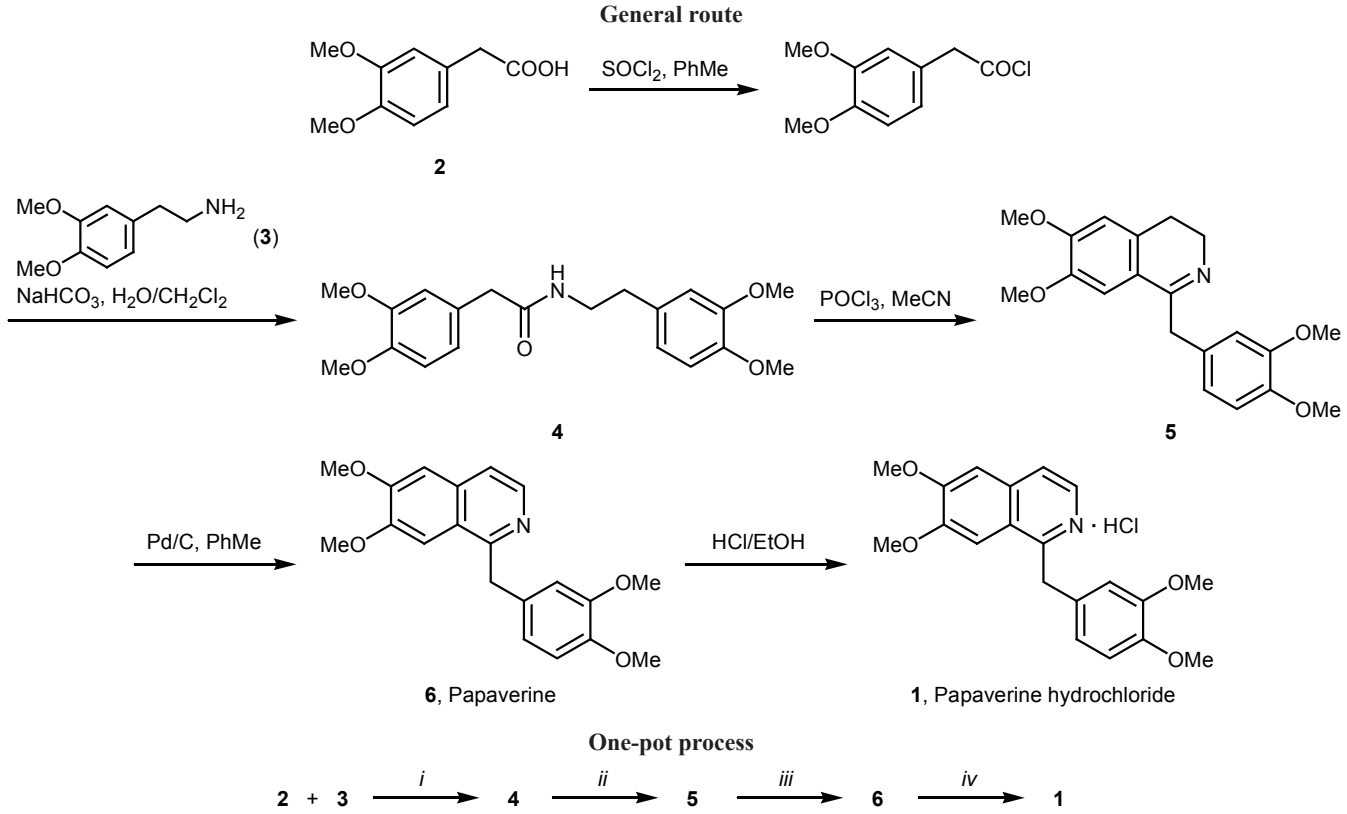
The process shown in Scheme 1 would first generate acid waste, which is contrary to the requirements of green environmental protection. In addition, frequent solvent changes makes solvent recycling impossible, which results in increased production costs and reduced atom economy. Finally, the use of Pd/C as a dehydrogenation catalyst requires a high temperature. Therefore, development of an economical, efficient, practical, and robust synthetic route for industrial production is highly desired, and such process is described in the present article.

## RESULTS AND DISCUSSION

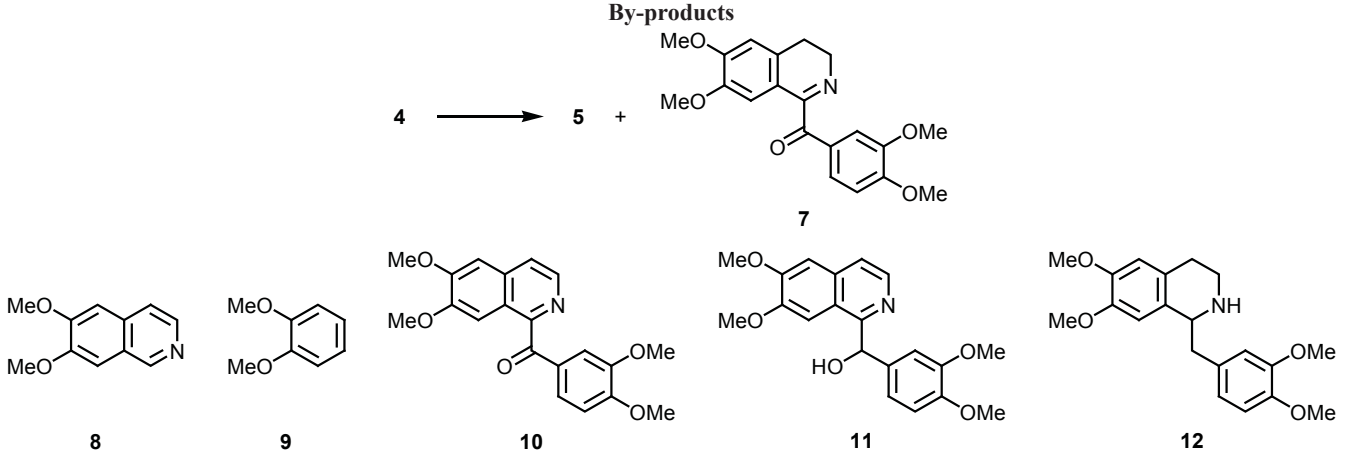
The proposed synthetic process involves the following four steps. First, 3,4-dimethoxyphenylacetic acid (**2**) and 2-(3,4-dimethoxyphenyl)ethanamine (**3**) reacted at high temperature [6]. Amide **4** reacted with $POCl_3$ to yield imine **5** [7]. Imine **5** was dehydrogenated with Raney nickel at high temperature [8] to form papaverine **6**, which was treated with hydrochloric acid to yield papaverine hydrochloride (**1**) (Scheme 1; *i*–*iv*).

2-(3,4-Dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (**4**) was prepared by the condensation of 3,4-dimethoxyphenylacetic acid (**2**) and 2-(3,4-dimethoxyphenyl)ethanamine (**3**) in xylene with azeotropic removal of water at different temperatures (acid **2** is insoluble in xylene at temperatures below 130°C) [6]. The obtained results are shown in Table 1.

**Scheme 1.**




Reagents and conditions: *i*: xylene, 150°C, 17 h; purity 95.03%; *ii*: $POCl_3$, xylene, 80°C, 1.5 h; purity 98%; *iii*: Raney nickel, xylene, 130°C, 20 h; purity 92.56%; *iv*: hydrochloric acid, ethanol, $H_2O$, followed by recrystallization; purity 99.6%; overall yield 63%.




The reaction required 17 h, and the conversion was 95% at 150°C (entry no. 2); the remaining 3.91% of **2** and 1.07% of **3** did not change over time.

In the next step, phosphoryl chloride was added to the reaction mixture obtained in the previous step, and the mixture was heated at 80°C [7]. Apart from targeted 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (**5**), the mixture contained (6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)-(3,4-dimethoxyphenyl)methanone (**7**) as oxidation by-product. According to the HPLC data, the amount of ketone **7** can be reduced to 0.8% by controlling the amount of phosphoryl chloride (Table 2, entry no. 3). The optimal amount of phosphoryl chloride was found to be 0.75 equiv.

Dihydroisoquinoline **5** and a dehydrogenation catalyst were reacted at high temperature to form papaverine **6** [8]. We tested several dehydrogenation

**Table 1.** Condensation of 3,4-dimethoxyphenylacetic acid (**2**) and 2-(3,4-dimethoxyphenyl)ethanamine (**3**) in xylene at different temperatures

| Entry no. | Temperature, °C | Reaction time, h | Yield, % (HPLC) | | |
|---|---|---|---|---|---|
| | | | **2** | **3** | **4** |
| 1 | 130 | 27 | 3.72 | 1.32 | 94.96 |
| 2 | 150 | 17 | 3.91 | 1.07 | 95.03 |
| 3 | 170 | 17 | 3.93 | 1.12 | 94.95 |

**Table 2.** Determination of the stoichiometry of the cyclization reaction **4** → **5** (+**7**)

| Entry no. | Amount of $POCl_3$, equiv | Reaction time, h | Yield, % (HPLC) | | |
|---|---|---|---|---|---|
| | | | **4** | **5** | **7** |
| 1 | 0.5 | 6 | 10 | 78 | 3.2 |
| 2 | 0.6 | 3.5 | 2.73 | 91.81 | 2.5 |
| 3 | 0.75 | 1.5 | ND[a] | 98 | 0.8 |
| 4 | 1 | 1 | ND | 97.2 | 1.2 |
| 5 | 2 | 1 | ND | 95 | 10 |

[a] Not detected.

**Table 3.** Effect of different catalysts on the dehydrogenation of **5** to form **6**

| Entry no. | Catalyst | Yield, % (HPLC) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **5** | **6** | **8** | **9** | **10** | **11** | **12** |
| 1[a] | Pd/C | ND | 67.4 | 0.9 | 0.9 | 12 | 3.5 | 15.3 |
| 2[a] | Cobalt | 13.3 | 21 | 0.7 | 0.7 | 30.6 | 11 | 22.7 |
| 3[a] | Nickel | ND | 92.56 | 1.2 | 1.2 | 0.7 | 0.7 | 3.64 |
| 4[b] | Nickel | ND | 76.2 | 5.8 | 5.8 | 4.8 | 3.2 | 4.2 |
| 5[a] | Cobalt oxide | 5.8 | 27.8 | 0.5 | 0.5 | 35.6 | 5.2 | 24.6 |

[a] Temperature 130°C, light-proof reaction.
[b] Temperature 130°C, exposure to light.

**Table 4.** Temperature effect on the dehydrogenation of **5** to form **6**[a]

| Entry no. | Temperature, °C | Reaction time, h | Yield of **6**,[b] % (HPLC) |
|---|---|---|---|
| 1 | 100 | 25 | 68.75 |
| 2 | 110 | 23 | 73.35 |
| 3 | 130 | 20 | 92.56 |
| 4 | 150 | 20 | 78.82 |

[a] Raney nickel-to-**5** weight ratio (0.4–0.6):1.
[b] Only the HPLC peaks for **5** and **6** were integrated.

catalysts, such as Pd/C [9], Raney cobalt, Raney nickel, and cobalt oxide and found that Raney nickel was ideal as the dehydrogenation catalyst (Table 3, entry no. 3). Therefore, we continued to optimize the reaction conditions by using Raney nickel. In the absence of light, the major impurities were compounds **8** (5.8%), **9** (5.8%), **10** (4.8%), **11** (3.2%), and **12** (9.3%) (Table 3, entry no. 4). Compounds **8** and **9** are likely to result from photodegradation of **10** [10]. To verify this assumption, ketone **10** was added to xylene and Raney nickel, and the mixture was irradiated with strong light with stirring at a high temperature [10]. In fact, compound **10** was found to decompose to **8** and **9**. The amounts of the latter could be reduced from 5.8 to 1.2% by protection from light (Table 3, entry nos. 3, 4). Ketone **10** was formed via dehydrogenation of **7**.

**Table 5.** Effect of the amount of Raney nickel on the dehydrogenation of **5** to form **6**[a]

| Entry no. | Weight ratio Raney Ni/**5**[b] | Reaction time, h | Yield,[c] % (HPLC) | |
|---|---|---|---|---|
| | | | **5** | **6** |
| 1 | (0.1–0.3):1 | 25 | 30 | 51 |
| 2 | (0.4–0.6):1 | 20 | 0 | 92.56 |
| 3 | (0.7–1.0):1 | 20 | 0 | 87.52 |

[a] Reaction temperature 130°C.
[b] The weight of nickel was the wet weight.
[c] Only the HPLC peaks for **5** and **6** were integrated.

Impurities **11** and **12** were produced by the reduction of **10** and **5**, respectively, by the generated hydrogen. When the reaction time was prolonged, compound **12** was partially converted to papaverine **6** and eventually reduced to 3.64% (Table 3, entry no. 3). Therefore, we used nitrogen to remove hydrogen and minimize this side reaction. The effect of the dehydrogenation temperature is shown in Table 4. The optimal temperature was 130°C (Table 4, entry no. 3). The amounts of Raney nickel used for the reaction are shown in Table 5. The conversion was the highest when the catalyst-to-**5** ratio was (0.4–0.6):1 (entry no. 3).

Finally, papaverine **6** and concentrated hydrochloric acid (36%) were reacted in ethanol to obtain papaverine hydrochloride (**1**); ethanol and water were maintained at a ratio of 7.7:1 ratio to obtain a good yield (63%) of highly pure (99.6%, single impurity less than 0.1%) papaverine hydrochloride of ICH-grade quality.

For the entire process, we used only two solvents, xylene and ethanol. The number of solvents was reduced from the previous four (toluene, dichloromethane, acetonitrile, and ethanol) to two, and the solvent amount was reduced from the previous 13.5 L to 5.04 L (Table 6).

In conclusion, we have developed a recoverable and cost-effective one-pot route to generate papaverine hydrochloride that is suitable for industrial production. The proposed synthetic route utilizes only commercial and inexpensive reagents and only one solvent (xylene), and the one-pot method reduces loss of intermediates. Compared to the general route, the total yield was significantly increased (to 63%).

**Table 6.** Amounts of solvents (L) used in the general and new synthetic routes

| General route | | New one-pot route | |
|---|---|---|---|
| Dichloromethane | 3 | Ethanol | 2.04 |
| Toluene | 4.5 | Xylene | 3 |
| Acetonitrile | 3 | | |
| Ethanol | 3 | | |
| Total | 13.5 | Total | 5.04 |

## EXPERIMENTAL

All solvents and reagents were purchased from suppliers and were used without further purification. NMR spectra were recorded on a Bruker Avance III 400/600 MHz spectrometer in $CDCl_3$. Mass spectra were recorded on an Agilent 6210 series single quadrupole LC/MS. The reactions were monitored by HPLC, and the purity was calculated according to the HPLC peak areas. The HPLC analyses were performed using the standard method on a Dionex UltiMate 3000 HPLC instrument using a Syncronis C18 column (250 mm×4.6 mm, 5 μm) at 40°C, flow rate 1 mL/min; UV detector (λ 245 nm); duration 45 min; mobile phases: A: 0.2% sodium heptanesulfonate and 0.2% potassium dihydrogen phosphate in water, $H_2O$/MeOH 7:3, pH 3.2; gradient elution program, time (min)/% B: 0/5, 30/50, 20/15, 35/60, 40/60, 40/5, 45/5.

**2-(3,4-Dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (4).** A mixture of 3,4-dimethoxyphenylacetic acid (**2**, 300 g, 1.66 mol) and 2-(3,4-dimethoxyphenyl)ethanamine (**3**, 325 g, 1.66 mol) in xylene (3 L) was stirred at 150°C for 17 h with azeotropic removal of water [5]. The reaction was monitored by HPLC until initial compounds **2** and **3** comprised less than 5% in total or until 95% conversion to amide **4** was attained.

**1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (5).** Phosphoryl chloride (175.8 g, 1.15 mol) was added to the reaction solution obtained in the previous step, and the solution was heated at 80°C for 2 h; the HPLC peaks were integrated to confirm that the conversion was complete.

An aqueous solution of sodium hydroxide (276 g, 6.9 mol, 0.02 M) was then added, and the mixture was stirred for 30 min and allowed to settle down, the organic phase was separated, and the aqueous phase was extracted once with xylene and combined with the organic phase. The purity of **5** was 98%.

**1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline (6).** The organic phase obtained in the previous step was transferred to a 5-L reaction flask, Raney nickel (260 g, 3.04 mol) was added, and the mixture was heated at 130°C for 8 h; compound **5** was completely converted (according to HPLC). The amount of by-product **12** was approximately 30%; when the mixture was further heated at that temperature for 20 h, the amount of **12** decreased to 3.64%. The purity of **6** was 92.56%. Finally, the catalyst was filtered off.

**1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline hydrochloride (1).** The organic phase obtained in the previous step was evaporated to dryness. Absolute ethanol (2.04 L) was added, 36% hydrochloric acid (121.94 g, 1.2 mol) was then added at room temperature, and the mixture was stirred for 1 h. The solid product was filtered off; it had a purity of 99%. Crude **1** and pure water (0.265 L) were placed in a 3-L reactor and heated under reflux for 20 min. Absolute ethanol (2.04 L) was slowly added over a period of 30 min to the clear solution. Crystal seeds (0.1 g) were added to the solution, and the solution was stirred at 70°C for 1 h. The mixture was allowed to cool to room temperature over 2 h. The product was formed as a white needle-like crystalline solid (361 g, yield 63%, HPLC purity 99.6%; single impurity less than 0.1%). mp 223.7–224.4°C [11]. $^1$H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm: 8.26 d (1H, $J$ = 6.5 Hz), 7.88 d (1H, $J$ = 6.5 Hz), 7.63 s (1H), 7.24 d (1H, $J$ = 2.0 Hz), 6.93 d.d (1H, $J$ = 8.2, 2.0 Hz), 6.75 d (1H, $J$ = 8.3 Hz), 4.99 s (2H), 4.11 s (3H), 4.04 s (3H), 3.85 s (3H), 3.80 s (3H). $^{13}$C NMR spectrum (151 MHz, $CDCl_3$), $\delta_C$, ppm: 157.00, 154.09, 152.59, 149.52, 148.38, 136.92, 129.33, 128.04, 122.52, 121.54, 120.81, 112.54, 111.33, 106.02, 104.96, 56.88, 56.55, 56.31, 55.87, 36.52. Mass spectrum: $m/z$ 339.1 $[M + H]^+$. $C_{20}H_{21}NO_4$. Calculated: $M$ + H 339.15.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1070428020070258 and are accessible for authorized users.

## REFERENCES

1. Leslie, A., Mulinos, M.G., and Scott, W.S., Jr., *Proc. Soc. Exp. Biol. Med*., 1940, vol. 44, p. 625. https://doi.org/10.3181/00379727-44-11550
2. Galat, A., *J. Am. Chem. Soc*., 1951, vol. 73, p. 3654. https://doi.org/10.1021/ja01152a027
3. Kadam, H.K. and Tilve, S., *Arkivoc*, 2018, vol. 2018, part (iii), p. 184. https://doi.org/10.24820/ark.5550190.p010.433
4. Yu, R., Zhou, Y., Huan, Y., Liu, Q., Shen, Z., Liu, Z., *Yaoxue Xuebao*, 2011, vol. 46, p. 311.
5. Ivanova, B. and Spiteller, M., *Nat. Prod. Commun*., 2012, vol. 7, p. 581. https://doi.org/10.1177/1934578x1200700508
6. Yamamoto, Y., Tabuchi, Y., Baba, A., Hideshima, K., Nakano, M., Miyawaki, A., and Tomioka, K., *Heterocycles*, 2014, vol. 88, p. 1311. https://doi.org/10.3987/COM-13-S(S)101
7. Kakhki, S., Shahosseini, S., and Zarghi, A., *Iran. J. Pharm. Res*., 2014, vol. 13 (suppl.), p. 71.
8. Zhang, K., Zhang, J., Guo, W., Zhu, H., and Guo, Z., CN Patent no. 105541714A, 2016.
9. Minachev, Kh.M., Kharlamov, V.V., and Ryashentseva, M.A., *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1988, vol. 37, p. 2405. https://doi.org/10.1007/BF00952605
10. Stermitz, F.R., Pua, R., and Vyas, H., *J. Chem. Soc., Chem. Commun*., 1967, no. 7, p. 326. https://doi.org/10.1039/c1967000326a
11. Solodukhina, L.A. and Abrosimova, L.A., RU Patent no. 2647583C2, 2018.