

# PPA-SiO<sub>2</sub> catalyzed efficient synthesis of polyhydroquinoline derivatives through Hantzsch multicomponent condensation under solvent-free conditions

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## Abstract

Silica gel-supported polyphosphoric acid (PPA-SiO<sub>2</sub>) was found to be an efficient catalyst for the one-pot four-component Hantzsch condensation reaction of aryl aldehydes, dimedone, ethyl acetoacetate and ammonium acetate to afford the corresponding polyhydroquinoline derivatives in high yields. The main advantages of the present approach are short reaction times, clean reaction profiles, simple experimental and workup procedures.

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**Keywords:** Multicomponent reaction; One-pot synthesis; Solvent-free; Polyhydroquinoline derivatives; Silica-supported polyphosphoric acid (PPA-SiO<sub>2</sub>)

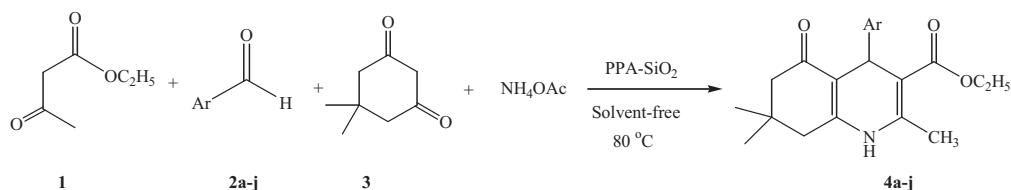
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1,4-Dihydropyridyl compounds are well known as calcium channel modulators. Cardiovascular agents such as nifedipine, nicardipine, amlodipine and other related derivatives are dihydropyridyl compounds, which are effective in treatment of hypertension [1]. 1,4-Dihydropyridine derivatives possess a variety of biological activities such as vasodilator, antitumour, bronchodilator, antiatherosclerotic, geroprotective and hepatoprotective activity [2]. Furthermore, these compounds exhibit diverse medicinal utility such as neuroprotectant, platelet anti-aggregatory activity, and cerebral antischaemic activity in the treatment of Alzheimer's disease and chemosensitiser behavior in tumour therapy [3]. Thus, the development of a new methodology for the efficient synthesis of these compounds which does not use large quantity of volatile organic solvents with stoichiometric amount of highly reactive catalyst and can be carried out under mild conditions would be highly desirable. For this reason, recently some studies have been devoted to the preparation of polyhydroquinoline derivatives [4–10]. Recently, solid-supported reagents, such as silica gel-supported acids, have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, low toxicity, greater selectivity and ease of handling [11–13]. For these reasons, in the present study, silica-supported polyphosphoric acid (PPA-SiO<sub>2</sub>) was introduced as a heterogeneous and reusable catalyst for synthesis of the polyhydroquinoline

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Scheme 1.

derivatives by one-pot four-component Hantzsch condensation reaction of aryl aldehydes, dimedone, ethyl acetoacetate and ammonium acetate (Scheme 1).

## 1. Experimental

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. The products were characterized by comparing of their physical data with those of known samples or by their spectral data. IR spectra were recorded on a4300 Shimadzu spectrophotometer as KBr disks. Melting points were recorded on an electrothermal type 9100 melting point apparatus.  $^1\text{H}$  NMR spectra were recorded on a Bruker DRX500 500-MHz spectrometer in  $\text{CDCl}_3$  as the solvent relative to TMS. The catalyst was synthesized according to the literature [14].

### 1.1. General procedure to synthesis of polyhydroquinoline derivatives using PPA-SiO<sub>2</sub> as catalyst

A mixture of ethyl acetoacetate **1** (1 mmol), aromatic aldehyde **2a-j** (1 mmol), dimedone **3** (1 mmol), ammonium acetate (1 mmol) and PPA-SiO<sub>2</sub> (0.03 g, 0.0150 mmol H<sup>+</sup>) [14] was heated on the oil bath at 80 °C for 40–60 min. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature and hot ethanol was added. The solid residue was dissolved in hot ethanol and filtered off. The crude product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give compounds **4a-j** in high yields. All of the polyhydroquinoline derivatives are known and were identified by comparison of their physical and spectroscopic data (IR, NMR) with those of authentic samples [8,10].

Representative  $^1\text{H}$  NMR spectral data for the selected products:

2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (entry **1**):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.27–7.32 (m, 2H), 7.17–7.22 (m, 2H), 7.07–7.12 (m, 1H), 6.63 (brs, 1H, NH), 5.06 (s, 1H), 4.05 (q, 2H,  $J = 7.1$  Hz), 2.34 (s, 3H), 2.12–2.28 (m, 4H), 1.20 (t, 3H,  $J = 7.1$  Hz), 1.06 (s, 3H), 0.93 (s, 3H).

2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (entry **3**):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.94 (s, 3H), 1.08 (s, 3H), 1.18 (t,  $J = 7.1$  Hz, 3H), 2.12–2.34 (m, 4H), 2.37 (s, 3H), 4.06 (q,  $J = 7.1$  Hz, 2H), 5.04 (s, 1H), 6.46 (brs, 1H, NH), 7.15–7.19 (d,  $J = 8$  Hz, 2H), 7.24–7.26 (d,  $J = 8$  Hz, 2H).

2,7,7-Trimethyl-5-oxo-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (entry **7**):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.89 (s, 3H), 1.09 (s, 3H), 1.2 (t, 3H,  $J = 7.3$  Hz), 2.2–2.4 (m, 4H), 2.5 (s, 3H), 4.00 (q, 2H,  $J = 7.3$  Hz), 5.05 (s, 1H), 6.01 (br s, 1 H, NH), 7.5 (d, 2H,  $J = 9.2$  Hz), 8.1 (d, 2H,  $J = 9.2$  Hz).

## 2. Result and discussion

To optimize the reaction conditions, the reaction of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), dimedone (1 mmol) and ammonium acetate (1 mmol) in the presence of PPA-SiO<sub>2</sub> (0.03 g, 0.0150 mmol H<sup>+</sup>) [11] was selected as a model. The reaction was carried out in various solvents and under solvent-free conditions. As shown in Table 1, in comparison to conventional methods, the yields of the reaction under solvent-free conditions are greater and the reaction time is shorter. The shortest time and best yield were achieved at 80 °C. Next, to found the optimum quantity of PPA-SiO<sub>2</sub>, the reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate was carried out under the previously mentioned conditions using different quantities of catalyst at 80 °C. The use of 0.03 g of catalyst resulted in the highest yield in 40 min.

Table 1

Synthesis of polyhydroquinoline derivative **4a** in the presence of PPA-SiO<sub>2</sub> (0.03 g, 0.0150 mmol H<sup>+</sup>) [14] in different solvents and optimization of temperature in solvent-free conditions<sup>a</sup>.

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%) <sup>a</sup>
1	MeOH	64	300	Trace
2	EtOH	78	300	75
3	CH <sub>3</sub> CN	81	300	80
4	H <sub>2</sub> O	100	300	72
5	Solvent-free	70	130	80
7	Solvent-free	80	40	91
8	Solvent-free	100	40	91
9	Solvent-free	120	40	92

<sup>a</sup> The yields were calculated based on benzaldehyde and refer to the pure isolated product.

Table 2

Preparation of polyhydroquinoline derivatives using PPA-SiO<sub>2</sub> (0.03 g) as catalyst<sup>a</sup>.

Entry	Ar	Products <sup>b</sup>	Time (min)	Yield <sup>c</sup>	M.p. (°C)	
					Found	Reported
1	C <sub>6</sub> H <sub>5</sub>	<b>4a</b>	40	91	202–204	(202–204) [10]
2	4-BrC <sub>6</sub> H <sub>4</sub>	<b>4b</b>	55	90	252–254	(252–253) [10]
3	4-ClC <sub>6</sub> H <sub>4</sub>	<b>4c</b>	45	92	244–246	(245–247) [10]
4	4-OHC <sub>6</sub> H <sub>4</sub>	<b>4d</b>	45	85	230–232	(231–233) [10]
5	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>4e</b>	60	86	255–258	(255–257) [10]
6	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>4f</b>	60	90	260–263	(261–263) [10]
7	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>4g</b>	55	90	176–178	(174–176) [10]
8	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>4h</b>	40	88	244–246	(244–246) [10]
9	3-OHC <sub>6</sub> H <sub>4</sub>	<b>4i</b>	50	88	218–221	(218–220) [10]
10	4-FC <sub>6</sub> H <sub>4</sub>	<b>4j</b>	60	85	184–186	(184–186) [8]

<sup>a</sup> The amount of PPA-SiO<sub>2</sub> as a catalyst was chosen (0.030 g, 0.0150 mmol H<sup>+</sup>) [14].

<sup>b</sup> All products were characterized by use of <sup>1</sup>H NMR and IR spectral data, and comparison of their melting points with those of authentic samples.

<sup>c</sup> Isolated yields.

Thus, we prepared a range of polyhydroquinoline derivatives under the optimized reaction conditions. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in excellent yields and short reaction times. The kind of aldehyde has no significant effect on the reaction. The results are shown in Table 2. It was indicated that both electron rich and electron deficient aldehydes reacted well, mostly leading to high yields of products.

The recyclability of the catalyst in the reaction of benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), dimedone (10 mmol) and ammonium acetate (10 mmol) in the presence of PPA-SiO<sub>2</sub> (0.3 g) was also checked. After the completion of the reaction, the reaction mixture was cooled to room temperature and hot ethanol was added. The catalyst was separated by simple filtration, dried at 100 °C under vacuum for 2 h and reused for the similar reaction. The catalyst was recovered in excellent yields (91, 89 and 87%) and used in the reaction three times; it showed the same activity as fresh catalyst without any significant loss of its activity.

### 3. Conclusion

In conclusion, we have reported a new simple catalytic method for the synthesis of polyhydroquinoline derivatives by one-pot condensation reaction of ethyl acetoacetate, aryl aldehydes, dimedone and ammonium acetate using PPA-SiO<sub>2</sub> as an efficient, reusable, and green heterogeneous catalyst under solvent-free conditions. High yields, short reaction times, easy work-up and absence of any volatile and hazardous organic solvents are some advantages of this protocol.

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