Aluminum Phosphate [$AlPO_4$(H)]: A Mild and Efficient Recyclable Catalyst for One-Pot Synthesis of Polyhydroquinoline *via* the Hantzsch Reaction Under Solvent-Free Conditions

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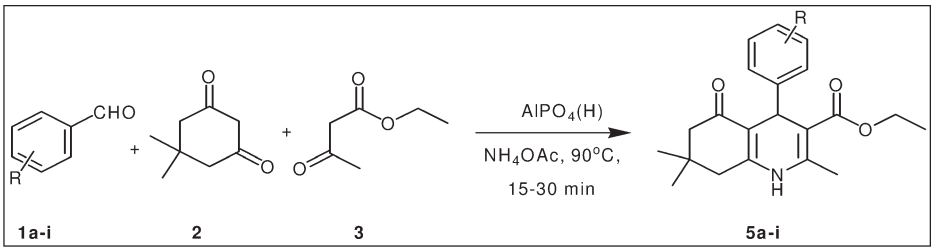

Polyhydroquinolines have been synthesized in good to excellent yields (80–90%) and short reaction times (15–30 min) in the presence of aluminum phosphate [$AlPO_4$] as heterogeneous catalyst at 90°C; the reaction workup is simple and the catalyst aluminum phosphate [$AlPO_4$] can be easily separated from the product and reused.

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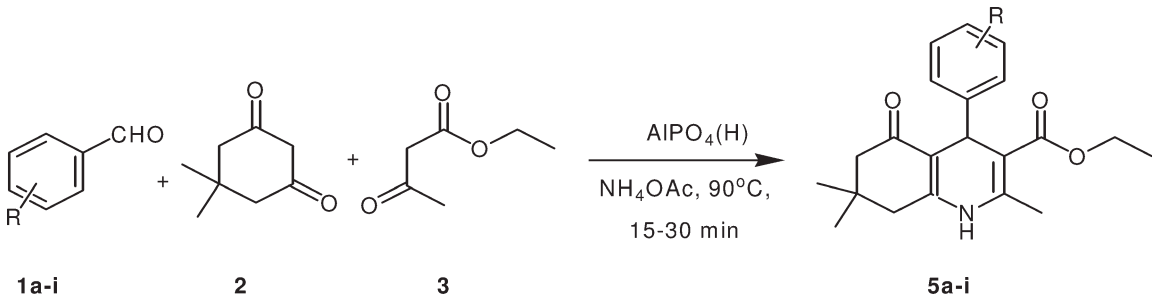
INTRODUCTION

The polyhydroquinolines are potent active compounds and these compounds have been receiving a lot of attention in the recent years owing to their excellent biological activities. The chemistry of dihydropyridines (DHPs) and their cyclic analogs polyhydroquinolines up to the year 2006 had been reviewed in several surveys of literature [1,2]. Among the polyhydroquinoline compounds, 1,4-dihydropyridines are more important as its application in medicine and industry and investigations along these lines include the synthesis of model compounds NAD (P) H-analogs of 1,4-dihydronicotinamide and their involvement in hydrogen transfer reactions is important task. Recently, several review papers have appeared on the subject [3] including the transfer of hydrogen and other groups by chiral DHP [4]. These compounds are chiefly obtained by using various modifications of Hantzsch synthesis. Most extensively studied are the calcium antagonists, whose synthesis [5] and properties [6] have been treated in a number of reviews. Several papers describe investigations of individual drug [7] such as vasodilators and antihypertensive remedies—nifedipine, nitrendipine. Calcium transport agonists have been also found among 1,4-DHP [8]. 1,4-DHP posses antioxidant [9] (diludine is routinely used [10]), hepatoprotective [11], antimutagenic [12], geroprotective [13], bronchodilating [14], antidiabetic [15], herbicidal [16], photosensitizing activities [17] and posses hypotension of long duration (more than 17 min) when administered intravenously to the anaesthetized animal [18]. More extensive studies indicate that these compounds exhibit different medical functions such as neuroprotectants, platelet antiaggregators, cerebral antiischemic agents, and chemosensitizers [19].

Generally, the basic skeleton of DHP was first discovered [20] by Hantzsch in 1882 and this classical method involves the three-component coupling of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol. Numerous methods have been reported [21–32] for the synthesis of polyhydroquinoline derivatives, because of the biological importance associated with 1,4-DHP ring and polyhydroquinoline derivatives. However, these methods suffer from drawbacks such as a long reaction time, an excess of organic solvent, lower product yields, and harsh refluxing conditions. Thus, chemists have developed several alternate and more efficient methods for the synthesis of polyhydroquinoline derivatives, which include the use of microwaves, ionic liquids, refluxing at high temperature,

Scheme 1. Synthesis of polyhydroquionoline derivatives.



tri methyl silyl chloride (TMSCI)-NaI, metal triflates, I_2, $HClO_4{\cdot}SiO_2$ and very recently ceric ammounium nitrate (CAN) was reported to be efficient for this transformation. However, the use of high temperatures, expensive metal precursors, catalyst that are harmful to the environment and long reaction times limits the use of these methods. Thus the development of a simple and efficient method for the preparation of plolyhydroquinoline derivatives is an active area of research and there is scope for further improvement involving milder reaction conditions and higher product yields.

In view of its inherent properties like environmental compatibility, reusability, greater selectivity, operational simplicity, noncorrosiveness, low cost and ease of isolation, we wish to describe our results on $AlPO_4$(H) [33–35] catalyzed four-component reactions of aldehydes, dimedones, ethyl acetoacetate, and ammonium acetate (Scheme 1). In addition, to the best of our knowledge, there are no reports on the use of $AlPO_4$(H) as a heterogeneous catalyst in a solvent-free media at 90°C for this conversion. This fact has prompted us to investigate $AlPO_4$(H) for the synthesis of polyhydroquinoline derivatives in a facile and practical manner.

Intially, *p*-chlorobenzaldehyde was selected as a representative aldehyde along with 5,5-dimethyl-1,3-cyclohexanedione, ethylacetoacetate, ammonium acetate, and $AlPO_4$(H) as catalyst to optimize the reaction conditions. As can be seen from Table 1, it was found that the reaction in the presence of catalytic amount of $AlPO_4$(H) needs shorter reaction time than that without any catalyst at room temperature (Table 1, entries 1 and 2).

But when the reaction was investigated at 90°C under solvent-free media, the reaction catalyzed by $AlPO_4$(H) was completed with higher yield and in shorter reaction time (Table 1, entries 3 and 4). Obviously, the temperature and the catalyst have important effect on the reaction. So the best condition was that the reaction was catalyzed by 10 mg, 0.813 mmol of $AlPO_4$(H) at 90°C.

Using the optimized conditions reported in Table 1 (entry 3), we continued to investigate the reaction at temperature of 90°C under solvent-free media with 10 mg of $AlPO_4$(H); the desired product was obtained in satisfactory yields. It was observed that the yield of the final product increases with increasing the temperature and amount of the catalyst in the reaction mixture. The yield of the final product increases from 25% to 90% with increasing the temperature from room temperature to 90°C.

Encouraged by these results, we examined several aromatic aldehydes under the optimized reaction conditions. Many aromatic aldehydes underwent smooth reaction with 5,5-dimethyl-1,3-cyclohexanedione, ethyl acetoacetate, and ammonium acetate to give high yields of products (Table 2). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked well in this reaction. Clearly, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because they were obtained in excellent yields. The catalyst also found to be very active for the preparation of polyhydroquinoline derivatives and substituted aldehydes have been used with similar success to provide the corresponding products in high yields, which are also of much interest with respect to biological activity.

We investigated the reusability of the $AlPO_4$ catalyst in this reaction, and we used *p*-chlorobenzaldehyde (10 mmol), 5,5-dimethyl-1,3-cyclohexanedione (10 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (15 mmol), and 4.06 mmol of $AlPO_4$(H) together, and then the

Table 1

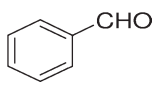
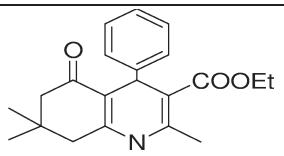
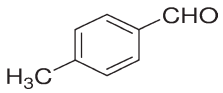
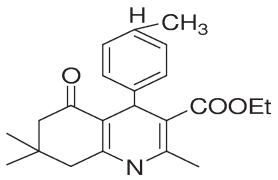
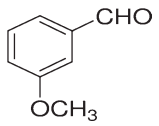
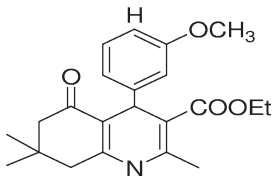
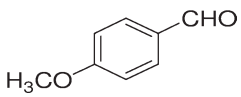
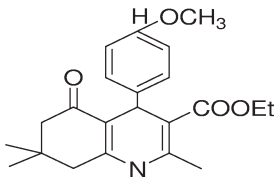
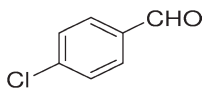
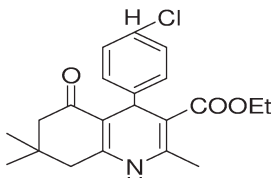
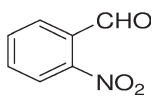
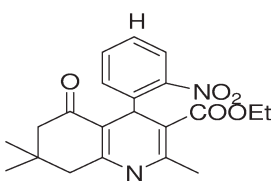
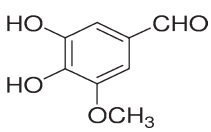
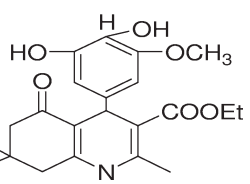
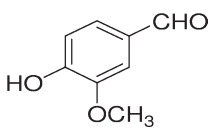
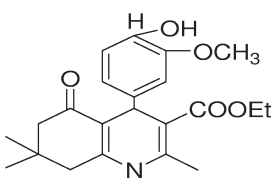
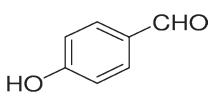
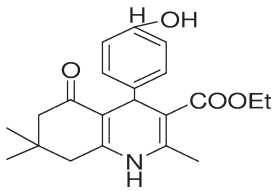
The effect of temperature and weight of the catalyst in the synthesis of polyhydroquinoline derivatives.

Entry	Temperature (°C)	$AlPO_4$(H) weight (mg)	Time (min)	Yield (%)[a]
1	RT	No catalyst	150	25
2	RT	10	150	60
3	90	10	15	90
4	90	15	15	90
5	90	20	15	90

Reaction conditions—substrates: *p*-chloro benzaldehyde; 5,5-dimethyl-1,3-cyclohexanedione; ethyl acetoacetate; ammonium acetate.(1:1:1:1.5).
[a] Isolated yields.

Table 2

$AlPO_4$(H) catalyzed synthesis of polyhydroquinoline derivatives with various aldehydes under solvent-free conditions.

Entry	Aldehyde (**1**)	Product (**5**)[a]	Time (min)	Yield (%)[b]
a			15	87
b			15	90
c			20	89
d			25	89
e			15	90
f			30	85
g			30	85
h			20	80
i			30	82

[a] All the products were characterized by IR, ^{1}H NMR, and mass spectroscopy.
[b] Isolated yields.

Table 3

Recyclability of the catalyst for synthesis of **5e** (Table 2).

Cycle No.	1	2	3	4	5	6	7
Time (min)	15	15	15	25	30	30	40
Yield (%)	90	90	87	85	80	75	60

mixture in round bottomed flask was stirred at 90°C for 15 min without any solvent. When the reaction was completed, the catalyst was separated by simple filtration by diluting with methanol and recovered $AlPO_4$(H) was reused in subsequent reactions, and the results are presented in Table 3.

In conclusion, the present study describes a convenient and efficient process for the synthesis of polyhydroquinoline derivatives through a four-component coupling of various aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione, ethyl acetoacetate, and ammonium acetate in a solvent-free media at 90°C using $AlPO_4$(H) as a heterogeneous catalyst. The catalyst is highly active, stable, and could be reused several times without much loss of its activity. Present methodology offers very attractive features such as reduced reaction times, higher yields, and has wide scope in organic synthesis. This simple procedure with ease of recovery makes this method economic, benign, and a waste-free chemical process for the synthesis of polyhydroquinoline derivatives. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of polyhydroquinoline derivatives. This catalyst is highly fascinating; this could also be used for several acid catalyzed organic transformations and could replace the existing homogenous catalysts which are currently being used in the industry.

TYPICAL PROCEDURE

Aldehyde (2 mmol), dimedone (2 mmol), ammonium acetate (3 mmol), ethyl acetoacetate (5 mL), and $AlPO_4$(H) (10 mg, 0.813 mmol) were successively charged in to a 50 mL round bottomed flask, equipped with a magnetic stirrer. Then the reaction mixture proceeded at 90°C for 15–30 min and a solid product was gradually formed. After completion of reaction as indicated by thin layer chromatography (TLC), the resulting solid product was diluted with methanol, filtered and catalyst was washed with methanol for reuse and filtrate was concentrated *in vaccuo* to afford the crude product. A pure product was obtained as a yellowish solid by further recrystallization in ethanol.

Compound (5a). m.p.: 251–253°C. IR (KBr): 3288 (N—H), 1699 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.85 (s, 3H, —CH_3), 1.50 (s, 3H, —CH_3), 1.20 (t, 3H, J = 7.5 Hz, —CH_3), 2.10 (dd, 2H, —CH—), 2.30 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 4.00 (q, 2H, J = 7.4 Hz, —OCH_2—), 4.88 (s, 1H, —CH_2—), 7.00–7.21 (m, 5H, ArH), 8.70 (brs, 1H, —NH—). electro spray ionisation-mass spectrometry (ESI-MS): m/z 340 [M^+].

Compound (5b). m.p.: 268–270°C. IR (KBr): 3275 (N—H), 1700 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 0.90 (s, 3H, —CH_3), 1.10 (s, 3H, —CH_3), 1.20 (t, 3H, J = 7.2 Hz, —CH_3), 2.09 (dd, 2H, —CH_2—), 2.20 (s, 3H, —CH_3), 3.33 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 4.00 (q, 2H, J = 6.4 Hz, —OCH_2—), 4.80 (s, 1H, —CH—), 6.90 (d, 2H, J = 8.2 Hz, ArH), 7.09 (d, 2H, J = 8.2 Hz, ArH), 8.62 (brs, 1H, —NH—). ESI-MS: m/z 354 [M^+].

Compound (5c). m.p.: 200–203°C. IR (KBr): 3395 (N—H), 1695 (C=O), cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 0.92 (s, 3H, —CH_3), 1.00 (s, 3H, —CH_3), 1.20 (t, 3H, J = 7.3 Hz, —CH_3), 2.10 (dd, 2H, —CH_2—), 2.30 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 3.73 (s, 3H, —OCH_3), 4.50 (q, 2H, J = 7.4 Hz, —OCH_2—), 4.79 (s, 1H, —CH—), 6.59 (d, 1H, J = 5.2 Hz, ArH), 6.72 (s, 1H, ArH), 6.78 (d, 1H, ArH) 7.05 (t, 1H, J = 7.4 Hz, ArH), 8.60 (brs, 1H, —NH—). ESI-MS: m/z 370 [M^+].

Compound (5d). m.p.: 243–245°C. IR (KBr): 3275 (N—H), 1644 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.90 (s, 3H, —CH_3), 1.00 (s, 3H, —CH_3), 1.15 (t, 3H, J = 7.3 Hz, —CH_3), 2.10 (dd, 2H, —CH_2—), 2.35 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 3.73 (s, 3H, —OCH_3), 4.00 (q, 2H, J = 7.2 Hz, —OCH_2—), 4.82 (s, 1H, —CH—), 6.70 (d, 2H, J = 9.0 Hz, ArH), 7.15 (d, 2H, J = 9.0 Hz, ArH), 8.80 (brs, 1H, —NH—).

Compound (5e). m.p: 250–253°C. IR (KBr): 3274 (N—H), 1706 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.89 (s, 3H, —CH_3), 1.10 (s, 3H, —CH_3), 1.19 (t, 3H, J = 7.2 Hz, —CH_3), 2.10 (dd, 2H, —CH_2—), 2.30 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 4.00 (q, 2H, —OCH_2—), 4.89 (s, 1H, —CH), 7.10 (d, 2H, J = 9.0 Hz, ArH), 8.62 (brs, 1H, —NH—). ESI-MS: m/z 374 [M^++H].

Compound (5f).

m.p.: 208–210°C. IR (KBr): 3292 (N—H), 1698 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 0.85 (s, 3H, —CH_3), 1.09 (s, 3H, —CH_3 and dd merged with triplet, 3H, J = 7.2 Hz, —CH_3), 2.00 (dd, 2H, —CH_2—), 2.25 (dd, 2H, —CH_2—), 2.43 (s, 3H, —CH_3), 4.00 (q, 2H, —OCH_2—), 5.72 (s, 1H, —CH—), 7.20 (t, 2H, J = 6.4 Hz, ArH), 7.45 (m, 2H, ArH), 7.65 (d, 1H, J = 8.0 Hz, ArH), 8.60 (brs, 1H, —NH—).

Compound (5g). m.p.: 278–280°C. IR (KBr): 3300 (N—H), 1695 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz,

$CDCl_3$ + DMSO-d_6): δ 0.95 (s, 3H, —CH_3), 1.09 (s, 3H, —CH_3), 1.25 (t, 3H, J = 7.2 Hz, —CH_3—), 2.10 (dd, 2H, —CH_2—), 2.30 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 3.75 (s, 3H, —OCH_3), 4.05 (q, 2H, J = 6.4 Hz, —OCH_2—), 4.79 (s, 1H, —CH—), 6.25 (s, 1H, Ar—H), 6.35 (s, 1H, Ar—H), 7.18 (brs, 1H, —OH), 7.85 (s, 1H, —OH), 8.49 (brs, 1H, —NH—). ESI-MS: m/z 402 [M^++H].

Compound (5h). m.p.: 230–233°C. IR (KBr): 3395 (N—H), 1690 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 0.92 (s, 3H, —CH_3), 1.00 (s, 3H, —CH_3), 1.25 (t, 3H, J = 15.4 Hz, —CH_3), 2.00 (dd, 2H, —CH_2—), 2.22 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 3.70 (s, 3H, —OCH_3), 4.05 (q, 2H, —OCH_2), 4.75 (s, 1H, —CH—), 6.50 (s, 2H, Ar—H), 6.70 (s,1H, ArH), 8.02 (s, 1H, —OH), 8.65 (brs, 1H, —NH—). ESI-MS: m/z 386 [M^++H].

Compound (5i). m.p.: 243–245°C. IR (KBr): 3415 (N—H), 1685 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 0.90 (s, 3H, —CH_3), 1.00 (s, 3H, —CH_3), 1.25 (t, 3H, J = 7.0 Hz, —CH_3), 2.12 (dd, 2H, —CH_2—), 2.30 (s, 3H, —CH_3 and dd merged with singlet, 2H, —CH_2—), 4.05 (q, 2H, J = 7.0 Hz, —OCH_2—), 4.82 (s, 1H, —CH—), 6.55 (d, 2H, J = 8.4 Hz, Ar—H), 7.02 (d, 2H, J = 8.3 Hz, Ar—H), 8.32 (s, 1H, —OH), 8.45 (brs, 1H, —NH—). ESI-MS: m/z 356 [M^+].

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