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A Simple and Efficient One-Pot Synthesis of 1,4-Dihydropyridine and Polyhydroquinoline Derivatives Using Phosphosulfonic Acid as a Heterogeneous Catalyst under Solvent-Free Conditions

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Phosphosulfonic acid (PSA) was found to be an efficient catalyst for the one-pot three-component Hantzsch condensation reaction of arylaldehydes, ethylacetoacetate and ammonium acetate to afford the corresponding 1,4-dihydropyridine and polyhydroquinoline derivatives in high yields. PSA was also applied for the one-pot preparation of polyhydroquinolines *via* four-component reaction of arylaldehydes, ethylacetoacetates, dimedone and ammonium acetate. The main advantages of the present approach are short reaction times, clean reaction profiles, catalyst recyclability, and facile experimental and workup procedures.

Keywords: 1,4-Dihydropyridines, Polyhydroquinolines, Phosphosulfonic acid, Recyclable heterogeneous catalyst, Solvent-free conditions

INTRODUCTION

The increasing use of catalyst-based production methods in the emerging industries has been favored by the continuous innovation observed over the last decade for the different catalytic processes. Efficient catalysts are key materials in chemical technologies which supply useful substances to society and assist maintaining the environment as healthy as possible: in short, catalysts represent a key technology for a sustainable society [1].

Five- and six-member heterocyclic compounds are important constituents, often existing in biologically active natural products and synthetic compounds of medicinal interest. Among them, 1,4- dihydropyridines (1,4-DHPs) heterocyclic rings are a common feature of various bioactive compounds such as vasodilator, bronchodilator, anti-atherosclerotic, anti-cancer and anti-diabetic agents [2-4]. They serve as key intermediates in biogenesis of indole alkaloids [5]. Additionally, 1,4-dihydropyridines (1,4-DHPs) have several other medicinal applications which include neuroprotecting [6] and cerebral anti-ischemic properties for the treatment of Alzheimer's disease [7].

Classical method for the synthesis of these compounds is one-pot condensation of aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol [8]. Due to the wide range of their applications, other improved procedures have been subsequently reported include the condensation of aldehyde with β-dicarbonyl compounds and amines in the presence of different catalysts and solvents. Recently, a number of modified methods have been developed [9]. Other procedures comprise the use of Microwave [10], Ionic Liquids [11], TMSCl-NaI [12], $SiO_2/NaHSO_4$ [13], $SiO_2/HClO_4$ [14], CAN [15] Organocatalysts [16,17], TFE [18], Silica Supported 12-Tungstophosphoric Acid [19], Molybdenum(VI) Complex [20], Cellulose Sulfuric Acid [21] and Ytterbium [22]. Unfortunately many of these processes suffer major or minor limitations such as drastic reaction conditions, low yields, tedious work-up procedures or use of volatile organic solvents. Moreover, in some cases, no recycling of the catalyst renders these methods environmentally unsound. So, there has been considerable interest to perform solvent-free Hantzsch reaction with a reusable catalyst which can be particularly attractive from an economic and

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environmental point of view.

In continuation of our previous works on the applications of reusable acid catalysts in organic synthesis [23-26], we have recently reported PSA as a heterogeneous catalyst under solvent-free conditions [27]. The catalytic activity of PSA has been further explored by our research group and also other scientists [24,27-30]. Now, we aim to present an efficient and convenient procedure for the one-pot synthesis of 1,4-dihydropyridine (Scheme 1) and polyhydroquinoline derivatives (Scheme 2).

EXPERIMENTAL

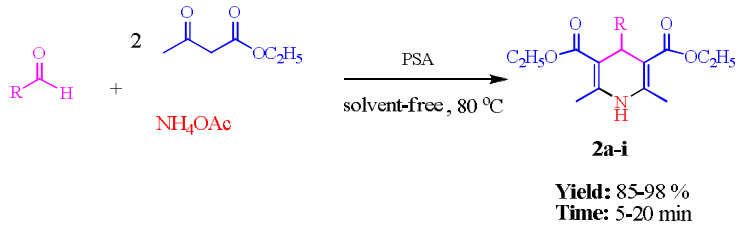
General

Chemicals were either prepared in our laboratories or purchased from Merck and Fluka 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 a BOMEM MB-Series 1998 FT-IR spectrophotometer as KBr disks. Melting points were recorded on an electrothermal Thermo apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a DPX 400 MHz spectrometer in $CDCl_3$ as the solvent relative to TMS.

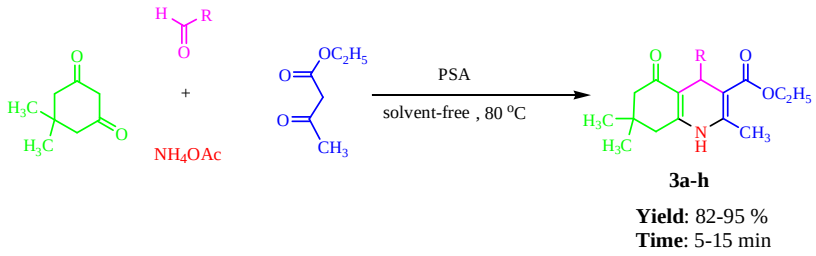
Preparation of phospho sulfonic acid (PSA). Suspension was prepared by mixing diammonium hydrogen phosphate (2 g, 15 mmol) and 5 ml dried CH_2Cl_2. Afterwards, 3 ml (5.24 g, 45 mmol) chlorosulfonic acid in 25 ml CH_2Cl_2 was added dropwise to the suspension by means of the dropping funnel over a period of 30 min at room temperatur. Durig the whole process of addition, the reaction was under the N_2 atmosphere. After completion of the addition, the mixture was stirred for additional 2 h, while the residual HCl gas was eliminated by suction. Then, the mixture was washed with excess dried CH_2Cl_2. Finally, a white solid powder (4.2 g) was obtained [27].

General procedure for the synthesis of 1,4-dihydropyridine derivatives using PSA as catalyst. A mixture of aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1.5 mmol) and PSA (20 mg, 4.5 mol%) was heated at 80 °C in a test tube with stirring for 5-20 min. After the completion of the reaction as indicated by TLC, the reaction mixture was washed with ice cold water and extracted with EtOAc, followed by water and brine solution and dried with anhydrous Na_2SO_4. The solid residue recrystallized from aqueous ethanol to give compounds **2a-i** in high yields.

General procedure for the synthesis of polyhydroquinoline derivatives using PSA as catalyst. A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), dimedone (1 mmol), ammonium acetate (1.5 mmol) and PSA (20 mg, 4.5 mol%) was heated at 80 °C in a test tube



Scheme 1. Synthesis of 1,4- dihydropyridine



Scheme 2. Synthesis of polyhydroquinolines

with stirring for 5-15 min. After the completion of reaction as indicated by TLC, the reaction mixture was washed with ice cold water and extracted with EtOAc, followed by water and brine solution and dried with anhydrous Na_2SO_4. The solid residue recrystallized from aqueous ethanol to give compounds **3a-h** in high yields.

Spectral Data for Respective Compounds

Dimethyl-1,4-dihydro-2,6-dimethyl-4-(4-chloro-phenyl) pyridine-3,5-dicarboxylate (2b). IR (KBr) ν_{max} (cm^{-1}): 3350, 1691, 1645, 1212, 1126, 779; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.22 (t, 6H, J = 6 Hz), δ 2.33 (s, 6H), δ 4.09 (m, 4H, J = 4 Hz), δ 4.96 (s, 1H), δ 5.70 (s, 1H), δ 7.17-7.25 (Aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2, 19.3, 39.3, 59.8, 103.4, 127, 129.0, 131.8, 143.5, 146.9, 167.4.

Dimethyl-1,4-dihydro-2,6-dimethyl-4-(4-cyano-phenyl) pyridine-3,5-dicarboxylate (2d). IR (KBr) ν_{max} (cm^{-1}): 3345, 2229, 1701, 1680, 1207, 1109, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.22 (t, 6H, J = 6 Hz), δ 2.35 (s, 6H), δ 4.10 (m, 4H, J = 4 Hz), δ 5.05 (s, 1H), δ 5.69 (s, 1H), δ 7.26-7.52 (Aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2, 19.4, 40.3, 59.9, 103.2, 109.7, 119.3, 128.8, 131.8, 144.6, 153.0, 167.1.

2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (3b). IR (KBr) ν_{max} (cm^{-1}): 3273, 3201, 3076, 1706, 1648, 1279, 1214; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (s, 3H), 1.07 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H), 2.12-2.35 (m, 4H), 2.37 (m, 3H), 4.06 (q, J = 7.2 Hz, 2H), 5.02 (s, 1H), 6.13 (s, 1H), 7.15 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H).

RESULTS AND DISCUSSION

In order to carry out the synthesis of 1,4-dihydropyridine under environmentally benign conditions, initially, the synthesis of 2,6-dimethyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylate was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1.5-2 mmol) in the presence of various amounts of PSA at different temperatures under solvent free conditions. As can be seen from Table 1, the shortest time and best yield are achieved in the presence of 0.02 g (4.5 mol%) of catalyst at 80 °C (Table 1, Entry 4).

The reactions of various aldehydes possessing either electrondonating or electron withdrawing substituents with ethyl acetoacetate and ammonium acetate in the presence of a catalytic amount (0.02 g, 4.5 mol%) of PSA afforded high yields of the corresponding 1,4-DHPs (87-95%) in short times. The results are presented in Table 2. In all cases, crude products were obtained by extracting the reaction mixtures with ethyl acetate and were then purified by crystallization from ethanol.

With regard to the substituents, both aldehydes with electron withdrawing and electron donating groups participated in the reaction, but the former were better. The products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

After successfully synthesizing a series of Hantzsch esters in excellent yields, we turned our attention towards the synthesis of polyhydroquinoline derivatives *via* unsymmetrical Hantzsch reaction under similar conditions. We carried out the four-component coupling reaction of cyclic 1,3-diketone, aldehyde, acetoacetate ester and ammonium acetate in solvent-free conditions (Scheme 2). Aromatic aldehydes afforded the desired products in high yields under the same reaction conditions, as shown in Table 3. It is noteworthy to mention that the structural variation of the aldehyde and substituents on the aromatic ring did not show any obvious effect on this conversion, because the desired products were obtained in high yields in relatively short reaction times.

Due to the toxicity of chemicals and the increasing need for protecting human health and environmental protection, more attention is being paid to the green chemistry. With this viewpoint in mind, we studied the recyclability and reusability of the catalyst. After the completion of reaction, the reaction mixture was cooled to room temperature and washed with brine. The catalyst was separated by filtration, washed with ethyl acetate, dried and reused for the similar reaction. As shown in Fig. 1, the catalyst could be used at least five times with only slight reduction in catalytic activity.

With the same method, the reusability of the catalyst in the reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate at 80 °C under solvent-free

Table 1. Optimum Conditions for the Condensation Reaction of Benzaldehyde, Ethyl Acetoacetate and Ammonium Acetate under Solvent-Free Conditions

Entry	NH_4OAc (mmol)	Catalyst (g)	Temp. (°C)	Yield (%)	Time (min)/(h)
1	1.5	0.20	90	-	(12)
2	1.5	0.10	90	42	(3)
3	1.5	0.05	90	90	5
4	1.5	0.02	80	98	5
5	1.5	0.01	90	82	30
6	1.5	0.02	25	-	(12)
7	1.5	0.02	60	45	35
8	1.5	0.02	70	74	25
9	1.5	0.02	90	95	5
10	1.5	0.02	100	93	5
11	1.0	0.02	80	70	45
12	2.0	0.02	80	96	5

Table 2. Synthesis of 1,4-Dihydropyridines by Condensation of Aldehydes, Ethyl Acetoacetate and Ammonium Acetate Using PSA (0.02 g, 4.5 mol%) as Catalyst under Solvent-Free Conditions

Entry	R	Product	Time (min)	Yeild (%)
1	C_6H_5	**2a**	15	98
2	4-Cl C_6H_4	**2b**	15	85
3	4-OH C_6H_4	**2c**	15	90
4	4-CN C_6H_4	**2d**	10	90
5	4-$N(CH_3)_2$ C_6H_4	**2e**	15	88
6	4-NO_2 C_6H_4	**2f**	5	92
7	2-NO_2 C_6H_4	**2g**	8	93
8	2-Cl C_6H_4	**2h**	8	87
9	2-OH C_6H_4	**2i**	20	88

Table 3. Synthesis of Polyhydroquinoline by Condensation of Aldehydes, Dimedone, Ethyl Acetoacetate and Ammonium Acetate Using PSA (0.02 g, 4.5 mol%) as Catalyst under Solvent-Free Conditions

Entry	R	Product	Time (min)	Yeild (%)	M.P. (°C)	M.P. (°C)
					Found	Lit [31]
1	C_6H_5	**3a**	5	90	198-201	202-203
2	4-Cl C_6H_4	**3b**	8	84	244-246	245-246
3	4-OH C_6H_4	**3c**	15	89	228-231	232-234
4	4-$CH_3C_6H_4$	**3d**	10	80	259-262	261-263
5	4-$N(CH_3)_2$ C_6H_4	**3e**	15	94	224-227	229-230
6	2-NO_2 C_6H_4	**3f**	8	82	208-210	210-212
7	2-Cl C_6H_4	**3g**	10	95	208-211	208-210
8	4-NO_2 C_6H_4	**3h**	5	86	240-243	241-242

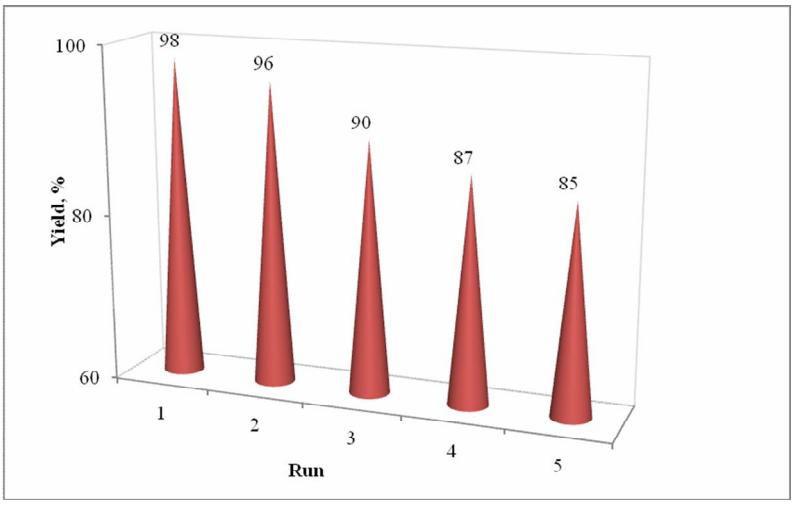


Fig. 1. Reusability of the catalyst in the reaction of benzaldehyde, ethyl acetoacetate and ammonium acetate at 80 °C under solvent-free conditions.

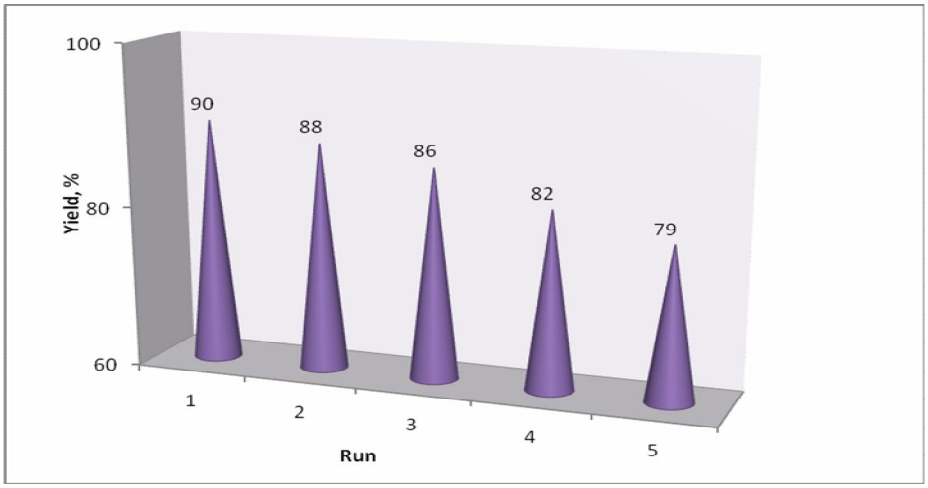


Fig. 2. Reusability of the catalyst in the reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate at 80 °C under solvent-free conditions.

Table 4. Comparison of PSA with Reported Catalysts in the Reaction of Benzaldehyde, Ethyl Acetoacetate and/or Dimedone and Ammonium Acetate

Entry	Catalyst/Condition	Catalyst loading	Time	Yield (%)	Ref.
1	Silica gel/$NaHSO_4$	5 mol%	6 h	85	[13]
2	$HClO_4$-SiO_2/80°C	0.05 g	20 min	95	[14]
3	CAN	5 mol%	1 h	92	[15]
4	L-Proline	10 mol%	0.5 h	95	[16]
5	PSA	4.5 mol%	15 min	98	This work

conditions was evaluated. As shown in Fig. 2, the catalyst could be reused at least five times with only slight reduction in catalytic activity.

To demonstrate the superiority of PSA over the reported catalysts, the reaction of benzaldehyde, ethyl acetoacetate and/or dimedone and ammonium acetate was considered as a representative example (Table 4). While in most of these cases (except Entry 1) comparative yields of the desired product were obtained following the PSA-catalyzed procedure, the reported procedures required long reaction time (Entries 1, 3, 4), or high catalyst loading (Entry 4). These results clearly demonstrate that PSA is an equally or more efficient catalyst for this reaction.

CONCLUSIONS

In conclusion, we have reported a new simple catalytic method for the synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives by one-pot condensation reaction of ethylacetoacetate, arylaldehydes, and ammonium acetate using PSA 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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