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Ammonium Dihydrogen Phosphate Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

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Abstract: A one-pot three component Biginelli condensation of different substituted aromatic and aliphatic aldehydes with ethyl acetoacetate and urea to the respective 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent-free conditions that is simple, effective, and environmentally friendly was shown. Ammonium dihydrogen phosphate ($NH_4H_2PO_4$) was used as a non-toxic, inexpensive, and easily available catalyst. The facile reaction condition and simple isolation and purification procedures of this method make it a good option for the synthesis of dihydropyrimidinones.

Key words: 3,4-dihydropyrimidin-2-(1*H*)-one; ammonium dihydrogen phosphate; solvent free; condensation

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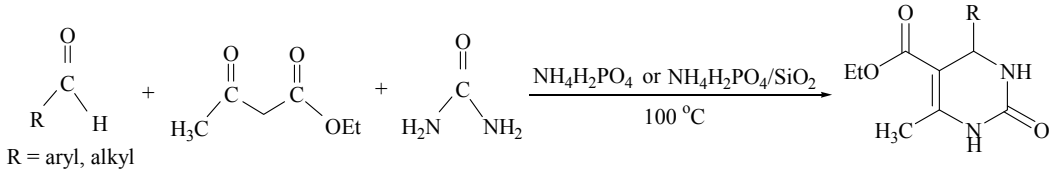
3,4-Dihydropyrimidin-2(1*H*)-ones have a wide range of therapeutic and pharmacological properties [1], such as antiviral [2], antibiotic [3], anticarcinogenic [4], antihypertensive [5], and anti-inflammatory properties. Moreover, several natural marine alkaloids, most notably batzelladine, have interesting biological activities that are mainly attributed to the presence of a dihydropyrimidinone moiety [6]. The simplest and the most straightforward approach for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, which was first reported by Biginelli [7], involves the one-pot reaction of β-ketoester or β-diketone, aryl-aldehyde, and urea. However, this reaction needs harsh conditions and long time, and gives low yields [8]. Multi-component condensation constitutes an attractive synthetic strategy because the products are formed in a single step. Several complex multi-step procedures have been reported to give high yields of 3,4-dihydropyrimidin-2(1*H*)-ones. However, many of these methods lack the simplicity of the original one-pot Biginelli protocol.

Biginelli's reaction has received renewed interest and several improved reaction protocols have recently been reported [9,10]. Different acid catalysts including chiral phosphoric acids [11], inorganic solid acids such as zeolite [12], mesoporous silica [13], and Lewis acids as well as protic acids such as concentrated HCl [14], BF_3 [15], polyphosphonate ester [16], montmorillonite [17], $InCl_3$ [18], ceric ammonium nitrate [19], $Mn(OAc)_3$ [20], and many ionic salts were established as effective catalysts [21]. However, most of these protocols involve expensive reagents, strongly acidic conditions, long reaction time, high temperatures, and stoichiometric amounts of catalysts, and give unsatisfactory yields. Therefore, the discovery of a new and inexpensive catalyst for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones under mild conditions is important.

From our research on the development of useful synthetic methodologies [22–30] and interest in $NH_4H_2PO_4$ catalyzed reactions, we have found a convenient and practical one-pot three component procedure for the preparation of 3,4-dihydropyrimidin-2(1*H*)-one derivatives under solvent-free condition with the use of ammonium dihydrogen phosphate as a non-toxic, inexpensive, and easily available catalyst (Scheme 1). The heterogenization of $NH_4H_2PO_4$ on mesoporous silica as support was further investigated to



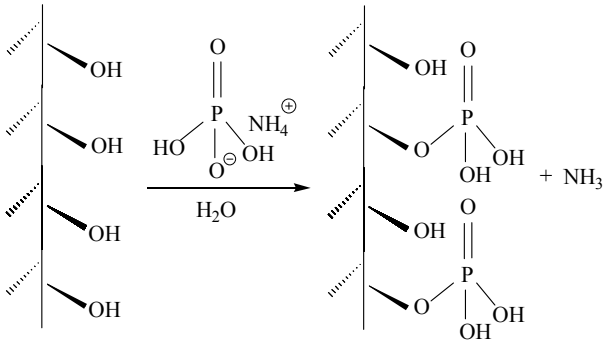
Scheme 1. Three component condensation of urea, aldehyde, and ethyl acetoacetate.

improve the catalytic reaction conditions, recoverability, and reusability of the catalyst.

1 Experimental

1.1 Preparation of $NH_4H_2PO_4/SiO_2$

The catalyst was prepared by mixing silica gel (1.5 g, Merck grade 60, 230–400 mesh) with a solution of $NH_4H_2PO_4$ (0.6 g, 5 mmol) in distilled water (10 ml). The resulting mixture was stirred for 30 min to adsorb the ammonium dihydrogen phosphate on the surface of silica gel (Scheme 2). After the slow removal of water, the solid powder was dried at 120 °C for 4 to 5 h. The drying temperature was maintained below the decomposition temperature of the ammonium salt [31]. The heteropolyacid catalysts were prepared and characterized according to the literature procedure [30].



Scheme 2. Immobilization of $NH_4H_2PO_4$ on mesoporous silica.

1.2 Preparation of 3,4-dihdropyrimidin-2(1*H*)-ones

A solution of ethyl acetoacetate (0.26 g, 2 mmol), aldehyde (2 mmol), and urea (2.5 mmol) was heated to 100 °C under solvent-free condition in the presence of $NH_4H_2PO_4$ (0.01 g, 5 mol %). The reaction was monitored by thin layer chromatography (TLC). At the end of the reaction, the resulting mixture was poured into cold water and the solid product was separated by filtration. Impure product was re-crystallized from *n*-hexane/ethyl acetate (3:1) when necessary. Infrared spectra were recorded on a 8700 Shimadzu Fourier Transform spectrophotometer. Silica gel 60 (230–400 mesh) was used for the column chromatography. The spectral data of some selected compounds [32] are listed as follows.

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate. IR (KBr, cm^{-1}): ν 3238, 3113, 2980, 1724, 1649, 1465, 1290. ^{1}H NMR (DMSO-d_6): δ 1.09 (t, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.99 (q, 2H, CH_2), 5.13 (d, 1H, H-4), 7.21–7.34 (m, 5H, H_{arom}), 7.73 (s, 1H, NH), 9.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.5, 18.2, 54.5, 59.7, 99.8, 126.7, 127.7, 128.8, 145.3, 148.8, 152.8, 165.8.

Ethyl-6-methyl-4-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. IR (KBr, cm^{-1}): ν 3267, 3109, 2958, 1726, 1703, 1639, 1487, 1286. ^{1}H NMR (DMSO-d_6): δ 1.04 (t, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.789 (s, 3H, CH_3), 3.93 (q, 2H, CH_2), 5.50 (d, 1H, H-4), 6.87–7.28 (m, 4H, H_{arom}, 1H, NH), 9.1 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.5, 18.2, 49.3, 55.8, 59.4, 98.0, 111.6, 120.6, 127.5, 129.1, 132.1, 149.3, 152.7, 157.0, 165.8.

Ethyl-6-methyl-4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. IR (KBr, cm^{-1}): ν 3354, 3236, 3111, 2978, 1693, 1641, 1226, 1095. ^{1}H NMR (DMSO-d_6): δ 0.99 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.90 (q, 2H, CH_2), 5.63 (d, 1H, H-4), 7.25–7.41 (m, 4H, H_{arom}), 7.71 (s, 1H, NH), 9.27 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.4, 18.1, 51.9, 59.5, 98.3, 128.2, 129.2, 129.5, 129.8, 132.1, 142.2, 149.8, 151.8, 165.4.

Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. IR (KBr, cm^{-1}): ν 3215, 1731, 1707, 1641. ^{1}H NMR (DMSO-d_6): δ 1.07 (t, 3H, 3J 6.8 Hz, CH_3), 2.26 (s, 3H, CH_3), 3.97 (q, 2H, 3J 5.4 Hz, OCH_2), 5.27 (s, 1H, CH), 7.50 (d, 2H, 3J 7.3 Hz, $H_{arom.}$), 7.87 (s, 1H, NH), 8.20 (d, 2H, 3J 7.2 Hz, $H_{arom.}$), 9.33 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.5, 18.3, 54.2, 59.8, 98.7, 124.2, 128.1, 147.2, 149.8, 152.2, 152.5, 165.5.

Ethyl-6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. IR (KBr, cm^{-1}): ν 3326, 3152, 1691, 1562, 1232, 1051, 783. ^{1}H NMR (DMSO-d_6): δ 1.12 (t, J = 7.5 Hz, 3H), 2.28, 2.30 (s, 3H), 4.00 (q, J = 7.5 Hz, 2H), 5.11 (d, J = 3.0 Hz, 1H), 7.25 (m, 4H), 7.70 (brs, 1H, NH), 9.19 (brs, 1H, NH).

Ethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. IR (KBr, cm^{-1}): ν 3300, 3120, 1710, 1690, 1630. ^{1}H NMR (DMSO-d_6): δ 1.11 (t, J = 7.5 Hz, 3H), 2.29 (s, 3H), 4.02 (q, J = 7.5 Hz, 2H), 5.31 (d, J = 3.0 Hz, 1H), 7.65–7.75 (m, 2H), 7.95 (brs, 1H), 8.09–8.20 (m, 2H), 9.34 (brs, 1H).

Ethyl-6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. IR (KBr, cm^{-1}): ν 3220, 3100, 1720, 1700. ^{1}H NMR (DMSO-d_6): δ 1.10 (t, J = 7.2, 3H), 22 (s, 3H), 3.96 (q, J = 7.2, 2H), 5.02 (s, J = 3.2, 1H), 6.64 (d, J = 8.4, 2H), 7.02 (d, J = 8.4, 2H), 7.57 (s, 1H), 9.07 (s, 1H).

2 Results and discussion

The optimization of the three-component Biginelli condensation of ethyl acetoacetate, benzaldehyde, and urea in the presence of 5 mol% $NH_4H_2PO_4$ under solvent-free condition resulted in 80% yield of 3,4-dihydropyrimidin-2(1*H*)-one after 2 h. The condition was that the condensation reaction was performed with a low catalyst concentration at

ambient condition, and it was selective and led to a high yield of the 3,4-dihydropyrimidin-2(1*H*)-one.

The catalytic efficiency of ammonium dihydrogen phosphate for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones was studied with various amount of $NH_4H_2PO_4$ (Table 1). To determine the role of the catalyst, a blank reaction of 4-nitrobenzaldehyde, ethyl acetoacetate, and urea was carried out in the absence of catalyst. The reaction did not give the desired product efficiently in the absence of catalyst, and it gave many impurity byproducts after an extended time of 8 h (entry 1). The presence of the catalyst, only 0.5 mol% of $NH_4H_2PO_4$, gave 47% conversion after 3 h (entry 2), which showed that the catalyst has high catalytic activity. Table 1 shows that increasing catalyst amount initially led to high yield at short reaction time. However, 5 mol% of the catalyst was enough for the reaction. With more catalyst (10 mol%), the yield progressed very smoothly to 93% without decreasing the reaction time (entry 5). Even more catalyst (>10 mol%) not only failed to improve the yield, but also decreased the efficiency of the catalytic system (Fig. 1). This behavior was explained by the changes in polarity, pH, and components of the reaction mixture in the solvent-free system. Thus, 5 mol% of $NH_4H_2PO_4$ was selected for all the reactions.

The effect of urea concentration on the efficiency of the three component condensation of 4-nitrobenzaldehyde, ethyl acetoacetate, and urea was studied. The production of the corresponding dihydropyrimidinone was increased with a larger urea from 2 to 2.5 mol%. The desired product was obtained in 90% yield in the presence of 2.5 mmol of urea after 2 h, while only 67% yield was achieved by 2 mmol of urea after 5 h. A further increase in urea concentration only reduced the time (1.2 h) needed to reach the maximum conversion of 73%–84% (Fig. 2).

Table 1 Effect of $NH_4H_2PO_4$ amount on the condensation of 4-nitrobenzaldehyde with ethyl acetoacetate and urea

Entry	$NH_4H_2PO_4$ amount (mol%)	Time (h)	Yield (%)
1	0	8.0	< 10 (very impure)
2	0.5	3.0	47
3	2	2.5	87
4	5	2.0	90
5	10	2.5	93
6	30	4.0	78
7	40	4.0	68

Reaction conditions: 4-nitrobenzaldehyde 0.30 g (2 mmol), ethyl acetoacetate 0.26 g (2 mmol), urea 0.15 g (2.5 mmol), 100 °C.

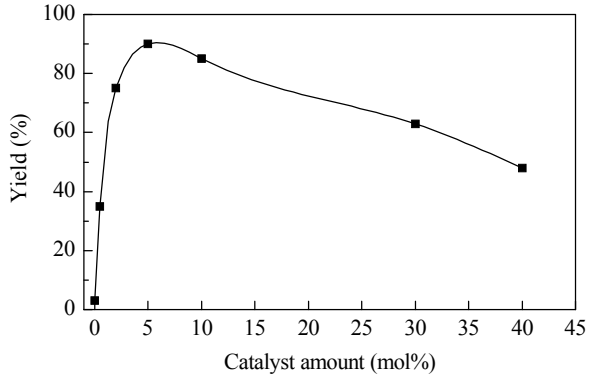


Fig. 1. Effect of catalyst amount on the condensation of 4-nitrobenzaldehyde with ethyl acetoacetate and urea after 2 h.

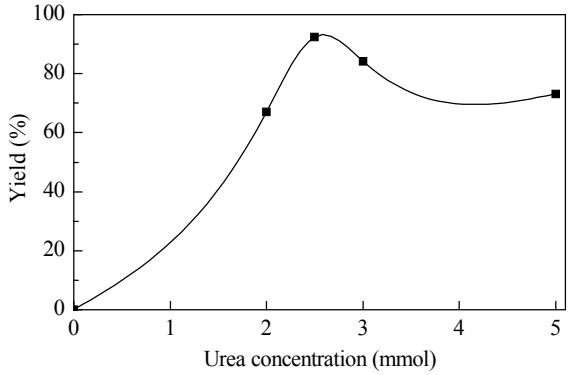


Fig. 2. Effect of urea concentration on the condensation of 4-nitrobenzaldehyde with ethyl acetoacetate and urea after 3 h.

The effect of ethyl acetoacetate concentration on the efficiency of the catalytic system (Table 2) was also investigated. Increasing ethyl acetoacetate concentration decreased the efficacy of the reaction. On increasing the concentration of this reagent from 2 to 5 mmol, the reaction time was prolonged more than five times in order to get ~82% conversion.

Table 2 Effect of ethyl acetoacetate concentration on the condensation with benzaldehyde and urea in the presence of $NH_4H_2PO_4$

Ethyl acetoacetate (mmol)	Time (h)	Yield (%)
2	2	90
3	9	81
5	10	82

Reaction conditions: 4-nitrobenzaldehyde 2 mmol, urea 2.5 mmol, $NH_4H_2PO_4$ 5 mol%, 100 °C.

The effect of the reaction temperature on the three component condensation of urea with 4-nitrobenzaldehyde and ethyl acetoacetate to synthesize the corresponding 3,4-dihydropyrimidin-2(1*H*)-one in the presence of 5 mol% $NH_4H_2PO_4$ was studied. The yield and reaction time were markedly influenced by temperature. Increasing the reaction temperature from 50 to 80 °C enhanced the conversion ~2.2 times and reduced the required time about 1.4 times (Fig. 3). More increase in reaction temperature slightly affected the yield. Increasing the reaction temperature from 100 to 140 °C led to the reduction of reaction time to reach 90% of conversion from 2 to 1.2 h. From technical considerations, a reaction temperature of 100 °C was selected for all the reac-

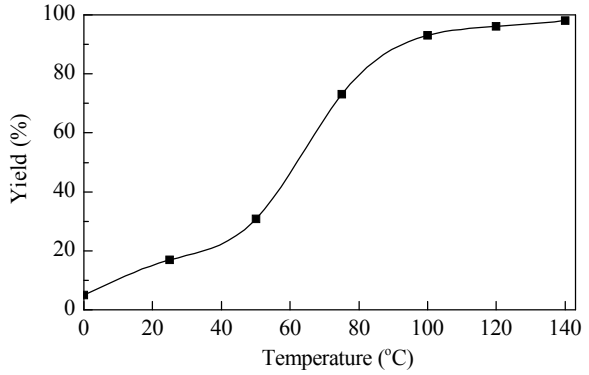


Fig. 3. Effect of reaction temperature on the three component condensation of urea with 4-nitrobenzaldehyde and ethyl acetoacetate after 3 h. Reaction conditions: 4-nitrobenzaldehyde 2 mmol, urea 2.5 mmol, ethyl acetoacetate 2 mmol, $NH_4H_2PO_4$ 5 mol%.

tions.

Table 3 compares the efficiency of the present catalyst, $NH_4H_2PO_4$, with different simple metal oxides and complex metal-oxo compounds, and heteropolyacids. It can be seen that 5 mol% of ammonium dihydrogen phosphate was sufficient for good conversion at 2 h (entry 1). Zinc, zirconium, and titanium oxide were less effective and needed longer time and higher amount of catalyst. Among the simple transition metal oxides examined, $ZrOCl_2$ gave the highest yield (94%) but with 10 mol% of catalyst and a long time of 4.5 h (entry 10). Among the catalysts, $NH_4H_2PO_4$ was the best since it is commercially cheap and easily available.

The catalytic activities of various phosphates (5 mol%) with different cations were investigated and the results are given in Table 3. $NH_4H_2PO_4$ gave the best result. KH_2PO_4 and NaH_2PO_4 were less efficient. The order of the catalytic activities of these three phosphates was $NH_4H_2PO_4$ > NaH_2PO_4 > KH_2PO_4. The sodium and potassium salts of $H_2PO_4^-$ were clearly more effective than the HPO_4^{2-} counterparts. Another distinct feature of Table 3 was the catalytic activity of $NH_4H_2PO_4$ supported on silica gel. Only 2.5 mmol of ammonium dihydrogen phosphate in supported form was enough to be efficient. 88% of conversion was obtained with 21 mg of $NH_4H_2PO_4/SiO_2$ after 4 h (entry 7), but a lower conversion (79%) was attained with the higher amount of 42 mg in the same time. The study of the catalytic efficiency of supported $NH_4H_2PO_4$ on different solid materials is under investigation.

Table 3 Three component condensation of urea, ethyl acetoacetate, and 4-nitrobenzaldehyde to the corresponding 3,4-dihydropyrimidin-2(1H)-one catalyzed by different catalysts

Entry	Catalyst	Catalyst amount (mol%)	Time (h)	Yield (%)
1	$NH_4H_2PO_4$	5	2.0	90
2	KH_2PO_4	5	6.3	74
3	NaH_2PO_4	5	5.3	65
4	Na_2HPO_4	5	5.0	62
5	K_2HPO_4	5	5.0	very impure
6	$NH_4H_2PO_4/SiO_2$	42 mg	4.0	79
7	$NH_4H_2PO_4/SiO_2$	21 mg	4.0	88
8	ZnO	5	5.0	53
9	ZrO_2	10	8.5	74
10	$ZrOCl_2$	10	4.5	94
11	TiO_2	10	8.5	84
12	nano-ZnO	0.7	5.0	58
13	nano-CuO	0.7	8.5	61
14	$H_6P_2W_{18}O_{62}$	2	0.7	98
15	$H_3PW_{12}O_{40}$	2	2.3	97
16	$H_5SiW_9Mo_2VO_{40}$	2	4.0	98

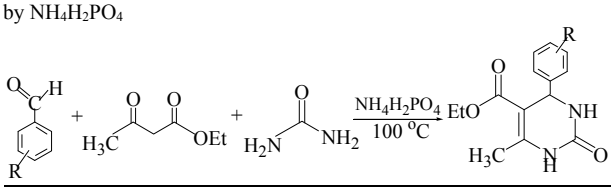
Reaction conditions: 4-nitrobenzaldehyde 2 mmol, ethyl acetoacetate 2 mmol, urea 2.5 mmol, 100 °C.

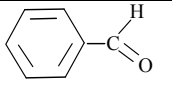
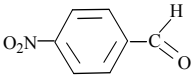
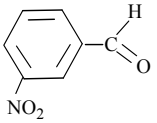
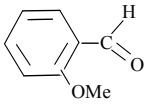
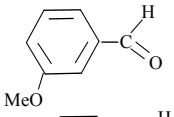
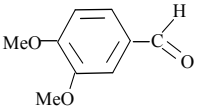
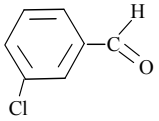
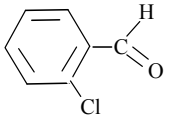
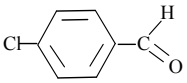
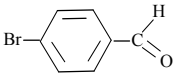
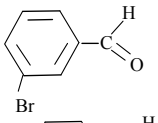
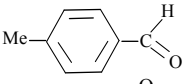
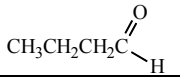
The catalytic activity of the complex metal-oxo structured heteropolyacids is the highlight in Table 3 (entries 14–16). They showed very good catalytic activity and only 2 mol% led to complete conversion. Among the heteropolyacids, $H_6P_2W_{18}O_{62}$ (2 mol%) with a Wells-Dawson structure showed the best catalytic activity, giving 98% ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydrop yrimidine-5-carboxylate after 40 min. The most familiar Keggin type heteropolyacid, $H_3PW_{12}O_{40}$, gave 97% of the desired product after 2.3 h. The mixed metal vanadium substituted heteropolyacid, $H_5SiW_9Mo_2VO_{40}$, showed less catalytic activity and gave about the same conversion in the longer time of 4 h.

After optimizing the reaction conditions, the generality of the protocol was evaluated by the reaction of several substituted aliphatic and aromatic aldehydes with different electron withdrawing and electron releasing substituents on the phenyl ring in the presence of 5 mol% of $NH_4H_2PO_4$ catalyst (Table 4). Aromatic aldehydes with either electron donating or withdrawing substituents gave high yields of products in high purity. Aliphatic aldehydes, which normally show extremely poor yields in the acid catalyzed Biginelli reaction due to decomposition or polymerization under acidic conditions [33], were also converted to their corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones, but with lower yields after longer reaction time than the aromatic aldehydes. The procedure not only preserved the simplicity of the Biginelli reaction, but also gave good yields of 3,4-dihydropyrimidin-2(1*H*)-ones.

The superiority of the present method over other reported protocols can be seen by comparing the present results with those reported previously (Table 5). The three component condensation of urea, acetoacetate, and 4-nitrobenzaldehyde to ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate was selected as a model reaction and the comparison was made in terms of the catalyst, reaction time, and percentage yield. Although some of the

Table 4 Three component condensation of urea, ethyl acetoacetate, and different aldehydes to 3,4-dihydropyrimidin-2(1*H*)-ones catalyzed by $NH_4H_2PO_4$

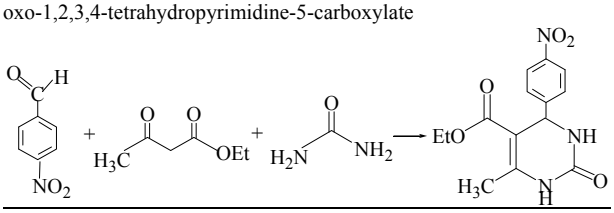


Entry	Aldehyde	Time (h)	Yield (%)	Melting point (°C) Found	Reported
1		2.0	85	201–203	200–201 [34]
2		2.0	90	203–206	205–207 [35]
3		5.0	74	225–227	227–228 [36]
4		3.0	91	254–257	258–259 [37]
5		3.5	75	206–208	207–208 [18]
6		6.0	70	202–204	—
7		4.5	78	191–193	193–195 [38]
8		4.5	73	215–218	215–216 [36]
9		5.5	69	208–210	209–211 [35]
10		5.0	94	209–211	—
11		5.0	80	198–201	—
12		5.0	82	211–214	212–214 [39]
13		6.5	56	176–178	153–155 [39]

Reaction conditions: aldehyde 2 mmol, ethyl acetoacetate 2 mmol, urea 2.5 mmol, $NH_4H_2PO_4$ 5 mol%, 100 °C.

other catalysts gave marginally higher conversions, however, they required long reaction time and a higher amount of catalyst. The present method used a small amount (5 mol%) of a cheap and environmentally friendly catalyst

Table 5 Comparison of the activity of $NH_4H_2PO_4$ with some other catalysts used for the synthesis of ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate



Catalyst	Catalyst amount (mol%)	Time (h)	Yield (%)	Ref.
$NH_4H_2PO_4$	5	2	90	this work
$LaCl_3·7H_2O$	50	5	80	[39]
NH_4Cl	40	3	83	[21]
NBS	20	10	85	[40]
$InCl_3$	10	4	78	[38]
$ZrCl_4$	10	6	88	[41]

under solvent-free condition and required a relatively short reaction time.

The stability of the catalyst was evaluated by reusing the recycled catalyst in the three component condensation of urea, acetoacetate, and 4-nitrobenzaldehyde. For this purpose, the catalyst was separated from the reaction mixture and washed with chloroform. Then, it was dried under vacuum and reused for a fresh catalytic run. When the reaction was repeated with recovered $NH_4H_2PO_4$, the conversion was similar to the first run. The catalyst was found to be reusable for at least seven cycles without loss of activity. The catalytic activity of the used catalyst was as good as the freash catalyst, demonstrating the stability of the catalyst (Fig. 4). The FT-IR spectrum of the recovered $NH_4H_2PO_4$ after the fifth run did not reveal any significant change in the structure of ammonium dihydrogen phosphate, that is, the identity of the catalyst was retained (Fig. 5).

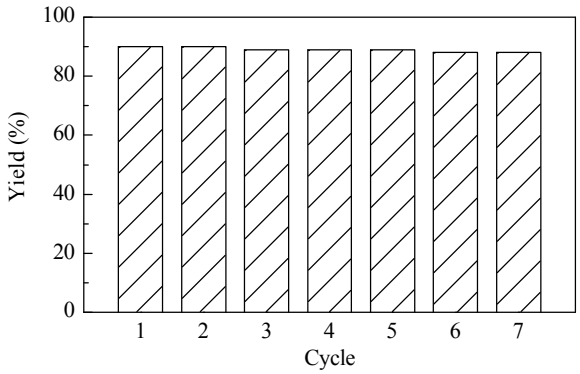


Fig. 4. Reusability of $NH_4H_2PO_4$ in the three component condensation of urea, ethyl aetoacetate, and 4-nitrobenzaldehyde.

The Biginelli reaction mechanism has been studied extensively by several research groups [41]. A pathway for the three component condensation of urea, ethyl acetoacetate, and aldehyde to 3,4-dihydropyrimidin-2(1*H*)-one in the

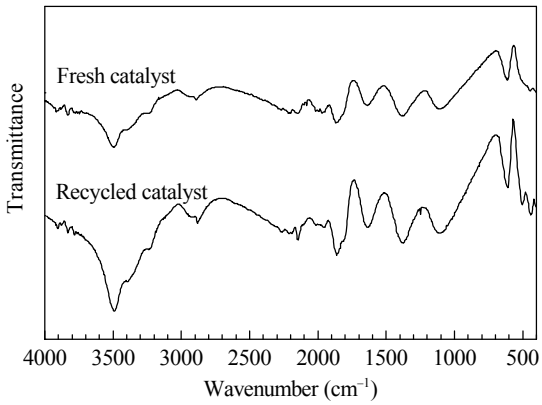
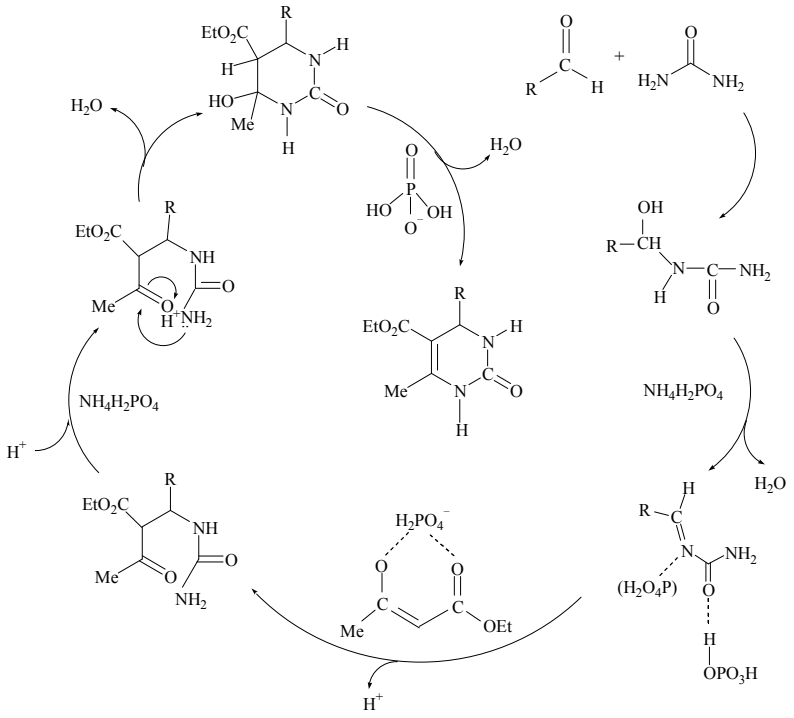


Fig. 5. FT-IR spectra of fresh and recycled $NH_4H_2PO_4$ catalyst after the seventh run.

presence of $NH_4H_2PO_4$ is given in Scheme 3. The first step is the formation of an acylimine intermediate formed by the reaction of the aldehyde with urea in the presence of the catalyst. Then, the iminium ion intermediate interacts with ethyl acetoacetate to produce an open chain ureide that subsequently cyclizes to the dihydropyrimidinone by removing a water molecule from it. The empty 3*d* orbitals of the phosphorous atom in $NH_4H_2PO_4$ stabilize the iminium ion intermediate by the formation of coordinative bonds.

3 Conclusions

An economic and environmentally benign procedure was developed for the one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones in a short reaction time. The method offers several advantages including high yield of product and easy workup. In many cases, the products were crystallized directly from the reaction mixture in high purity. Since a non toxic and commercially available catalyst was used, the procedure should find important applications in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.



Scheme 3. Proposed mechanism for the three component condensation of urea, ethyl acetoacetate, and aldehyde to 3,4-dihydropyrimidin-2(1*H*)-one in the presence of $NH_4H_2PO_4$.

References

1 Weber L. *Drug Discov Today*, 2002, **7**: 143
2 Kappe C O. *Eur J Med Chem*, 2000, **35**: 1043
3 Kamal A, Shaheer Malik M, Bajee S, Azeeza S, Faazil S, Ramakrishna S, Naidu V G M, Vishnuwardhan M V P S. *Eur J Med Chem*, 2011, **46**: 3274
4 Akhaja T N, Raval J P. *Eur J Med Chem*, 2011, **46**: 5573
5 Russowsky D, Canto R F S, Sanches S A A, D'Oca M G M, de Fátima A, Pilli R A, Kohn L K, Antônio M A, de Carvalho J E. *Bioorg Chem*, 2006, **34**: 173
6 Fattorusso E, Taglialatela-Scafati O eds. Modern Alkaloids: Structure, Isolation, Synthesis and Biology. Weinheim: Wiley-VCH, 2008
7 Biginelli P. *Gazz Chim Ital*, 1893, **23**: 360
8 Wipf P, Cunningham A. *Tetrahedron Lett*, 1995, **36**: 7819
9 Hajipour A R, Seddighi M. *Syn Commun*, 2012, **42**: 227
10 Yu J, Shi F, Gong L-Z. *Acc Chem Res*, 2011, **44**: 1156
11 Li N, Chen X-H, Song J, Luo S-W, Fan W, Gong L-Z. *J Am Chem Soc*, 2011, **132**: 10953

12 Radha Rani V, Srinivas N, Radha Kishan M, Kulkarni S J, Raghavan K V. *Green Chem*, 2001, **3**: 305
13 Choudhary V R, Tillu V H, Narkhede V S, Borate H B, Wakharkar R D. *Catal Commun*, 2003, **4**: 449
14 Saloutin V I, Burgart Y V, Kuzueva O G, Kappe C O, Chupakhin O N. *J Fluor Chem*, 2000, **103**: 17
15 Hu E H, Sidler D R, Dolling U H. *J Org Chem*, 1998, **63**: 3454
16 Kappe C O, Falsone S F. *Synlett*, 1998: 718
17 Bigi F, Carloni S, Frullanti B, Maggi R, Sartori G. *Tetrahedron Lett*, 1999, **40**: 3465
18 Ranu B C, Hajra A, Jana U. *J Org Chem*, 2000, **65**: 6270
19 Yadav J S, Reddy B V S, Bhaskar Reddy K, Sarita Raj K, Prasad A R. *J Chem Soc*, *Perkin Trans 1*, 2001: 1939
20 Kumar K A, Kasthuraiah M, Reddy C S, Reddy C D. *Tetrahedron Lett*, 2001, **42**: 7873
21 Shaabani A, Bazgir A, Teimouri F. *Tetrahedron Lett*, 2003, **44**: 857
22 Alizadeh M H, Tayebee R. *J Braz Chem Soc*, 2005, **16**: 108
23 Tayebee R. *J Kor Chem Soc*, 2008, **52**: 23
24 Tayebee R, Alizadeh M H. *Monatsh Fur Chem*, 2007, **138**: 763
25 Tayebee R. *Chin J Chem*, 2008, **26**: 2273
26 Tayebee R, Alizadeh M H. *Monatsh Fur Chem*, 2006, **137**: 1063
27 Tayebee R, Alizadeh M H, Kamini J, Kulkarni M, Raghavaswamy V, Roy P S, Mishra P K. *Curr Sci*, 2007, **93**: 133
28 Tayebee R, Mahdavi B. *Asian J Chem*, 2009, **21**: 1565
29 Tayebee R. *Chin J Chem*, 2007, **25**: 1031
30 Rezaei-Seresht E, Zonoz F M, Estiri M, Tayebee R. *Ind Eng Chem Res*, 2011, **50**: 1837
31 Mahdavinia G H, Rostamizadeh S, Amani A M, Emdadi Z. *Ultrasonics Sonochem*, 2009, 167
32 Zendehdel M, Mobinikhaledi A, Asgari A. *J Inclusion Phenom Macrocycl Chem*, 2008, **60**: 353
33 Adharvana Chari M, Syamasundar K. *J Mol Catal A*, 2004, **221**: 137
34 Shaabani A, Bazgir A. *Tetrahedron Lett*, 2004, **45**: 2575
35 Gangadasu B, Palaniappan S, Rao V J. *Synlett*, 2004: 1285
36 Mitra A K, Banerjee K. *Synlett*, 2003: 1509
37 Fu N-Y, Yuan Y-F, Cao Z, Wang S-W, Wang J-T, Peppe C. *Tetrahedron*, 2002, **58**: 4801
Yadav J S, Reddy B V S, Srinivas R, Venugopal C, Ramalingam T. *Synthesis*, 2001, 1341
38 Lu J, Bai Y J, Wang Z J, Yang B Q, Ma H R. *Tetrahedron Lett*, 2000, **41**: 9075
39 Hazarkhan H, Karimi B. *Synthesis*, 2004: 1239
40 Venkateshwar Reddy Ch, Mahesh M, Raju P V K, Ramesh Babu T, Narayana Reddy V V. Tetrahedron *Lett*, 2002, **43**: 2657