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Green procedure for synthesis of 3, 4 dihydropyrimidinones using 12-molybdophosphoric acid, as a catalyst and solvent free condition under microwave irradiation

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Abstract: Simple and improved conditions have been found to carry out the Biginelli reaction for the synthesis of 3, 4-dihydropyrimidin-2(1H) - one derivatives. This synthesis was performed in the presence of 12-molybdophosphoric acid ($H_3PMo_{12}O_{40}$) as catalyst. These reactions were performed under solvent free conditions with microwave irradiation as the energy source. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields (76–96%). The advantages of this novel protocol include the excellent yield, operational simplicity, short time, and the avoidance of the use of organic solvents and friendly preparation. Products were identified using physical and spectroscopic data.

Keywords: *Biginelli reaction; Solvent-free; Microwave-irradiation; One-pot synthesis; Dihydropyrimidinones; 12-molybdophosphoric acid.*

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Introduction

Evolution of organic synthesis involving environmentally clean protocols under solvent free conditions has emerged as an area of great interest from both environmental and economical points of view [1-3]. 3,4-Dihydropyrimidin- 2(1H)-ones are highly important heterocyclic units in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties including antiviral, antitumor, antibacterial and anti-inflammatory activities [4-6]. Other biological activities of these compounds include the α_{1a}-adrenergic receptor antagonists as drug candidates for the treatment of benign prostatic hyperplasia [7]. Owing to their widespread biological applications, the synthesis of 3, 4-dihydropyrimidin-2(1H) - ones has become an area of tremendous importance in current years. Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of an

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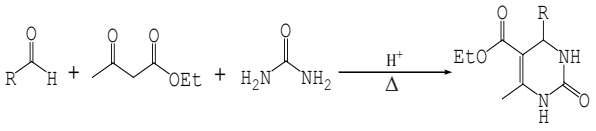
aldehyde, a β-ketoester and urea or thiourea, a procedure known as the Biginelli reaction, is receiving increased attention [8], (Scheme 1).



Scheme 1 Biginelli Reaction

Many new techniques, such as microwave-assisted synthesis technique [9], ionic liquids [10], ultra sound irradiation[11], solvent-free techniques [12], and many new catalysts, such as $InBr_3$[13], $ZrCl_4$[14], $CdCl_2$ [15], $BiCl_3$ [16], $MgBr_2$ [17], silica supported heteropoly acid [18], Si-MCM-41 suported $FeCl_3$ [19], heteropoly acid [20], polyoxometallates [21], propane phosphonic acid [22] for accomplishing this transformation. However, in spite of their potential utility, many of the existing methods involve the use of expensive reagents, strong acidic conditions, longer reaction times, tedious work-up, multi-step preparation of catalyst, environmental disposal problems, the use of volatile and toxic organic solvents as reaction media. Very recently, Gupta et al [23] reported an efficient method for the synthesis of 3,4-dihydropyrimidinones using covalently anchored sulfonic acid onto silica as a recoverable interphase catalyst. However, in this method reaction times remained higher, i.e., 8–12 h to provide better yields of the products, making its utility limited from synthetic viewpoints [25].

Microwave reaction under solvent-free conditions and/or in the presence of a catalyst, resulting in shorter reaction time and higher product yields than those obtained by using conventional heating offer low cost together with simplicity in processing and handling [26]. Recently, Wang et al. reported an efficient Biginelli-type reaction for the synthesis of 3,4–Dihydropyrimidinones by using PEG-SO_3H as catalyst under microwave irradiation [27]. As our continuous investigation on the methodology of green synthesis [28], we report herein the synthesis of various DHPM compounds 4 by one-pot condensation of aldehydes, ethyl acetoacetate and urea or thiourea in the presence of 12-molybdophosphoric acid as a catalyst under microwave irradiation and solvent free condition. The synthesized compound has been fully characterized by NMR (^{1}H and ^{13}C), IR, Mass spectrometry, and elemental analysis.

Experimental

Melting points of the samples were determined by a TG/DTA system under static air at a heating rate of 5 ºC.min^{-1} and Rheometric Scientific STA 1500 apparatus. Microwave irradiation was carried out with a microwave oven Antonpaar (3000MHz, 1000w). ^{1}H-NMR and ^{13}C-NMR (Bruker) spectra were recorded on 300 and 75 MHz, for Methanol-d_4 solution with TMS as an internal standard. Mass spectra were acquired using a Mass spectrometer (Trio 1000-Sison instruments). IR spectra were obtained by a Fourier transform-infrared spectroscopy system (FT-IR, Bruker Victor 22) using the KBr pellet technique. All reactants were obtained from commercial sources and freshly distilled prior to use.

General procedure for the $H_3PMo_{12}O_{40}$ catalyzed synthesis of dihydropyrimidinones

In our work, benzaldehyde (1 mmol), methyl acetoacetate (1 mmol), urea or thiourea (1.5 mmol) and only 2 mol% (0.03 g) of $H_3PMo_{12}O_{40}$ as a catalyst were placed in a glass sample vial (HQ-20) without any solvent and irradiated in a microwave (600 W) at 80 °C for 5 min under neat conditions (scheme 2) and monitored by TLC. After completing the reaction, 50 g was added to the system crushed ice (50g) and the mixture stirred for 5-10 min. The separated solid was filtered under suction, washed twice with cold water (30 mL) and then recrystallized using ethanol to afford the pure yellow crystals in a yield of 80%, m.p.

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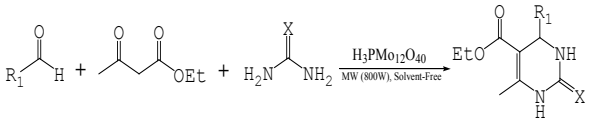
207°C 4a. Moreover, our investigation showed that the best results were observed when the molar ratio of aldehyde, acetoacetate derivative and urea was 1:1:5.



Scheme 2 Optimized Reaction conditions

Entry 1 (4a) 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one

Melting point 207°C. IR (KBr, cm^{-1}): 3233, 3125, 2971, 2965, 1727, 1704, 1655, 1599. ^{1}H-NMR (Methanol-d_4, 300 MHz)δ: 0.98 (t, J = 7.2 Hz, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.98 (q, J = 7.2 Hz, 2H, CH_2), 5.22 (d, J = 2.7 Hz, CH_2), 7.37–7.46 (m, 5H, H-Ar), 7.78 (d, J =2.7 Hz, 1H, H-Ar), 9.25 (s, 1H, NH). 13C NMR (Methanol-d_4, 75 MHz) δ:13.8, 17.5, 56.1, 60.2, 103.1, 127.7, 128.7, 129.6, 144.9, 148.2, 167.2. Mass (70 ev) m/z (%): 263(M^+, 26) ,234(78) ,189(73.4) ,184(100) ,173(38.0) ,156(62.3) ,139(48) ,78(34) ,52(37) ,44(71.2).

It was showed that no desirable product could be detected when a mixture react in the absence of $H_3PMo_{12}O_{40}$, Which indicated that the catalyst should be necessary for Biginelli reactions. Then three-component Biginelli condensation was investigated with different amounts of $H_3PMo_{12}O_{40}$ (0-5 mol%). Yields of the reaction in different conditions were shown in Table 1.

We found that most of the Lewis acids could promote the reaction, but the yields were not so high. In comparison with other catalysts, the use of 2 mol% of $H_3PMo_{12}O_{40}$ could make the yield 79% under the microwave power of 600 W and the irradiation time of 7 min. It could be seen that 2 mol% of $H_3PMo_{12}O_{40}$ gave the best result of this reaction, although other factors could not yet be optimized. Based on the above optimized results, i.e., 2 mol% amount of $H_3PMo_{12}O_{40}$ as a catalyst, we further examined the effects of the microwave power and the irradiation time on the Biginelli reaction, involving benzaldehyde, ethylacetoacetate and urea to afford 4a, as shown in Scheme 2. The results are listed in Table 2. It could be found that with the increase of the microwave power from 250 W to 900 W, the yield of 4a showed a linear increase from 47% to 83% when the irradiation time was 4 min. However, with the micro wave power of 900 W, when we increased the micro wave irradiation time, the yield of 4a increased first, but a slight decrease was observed for more than 7 min. So the optimized microwave power and the irradiation time were 900 W and 7 min, respectively.

In order to study the substrate scope of this Biginelli reaction, various aldehyde with different substituent were used under the above-optimized reaction conditions (Scheme 2). The results are shown in Table 3. From these results, we could see that all reactions proceeded smoothly to afford the corresponding DHPMs in moderate to high yields. We also found that all aromatic aldehydes carrying either electron-donating or electron-withdrawing substituent reacted efficiently to give improved yields compared to the classical Biginelli reaction. Further more, the use of just 2 mol % of $H_3PMo_{12}O_{40}$ is sufficient to promote the reaction.

Table 1 Yields of the reaction in different conditions

Amount of catalyst (% mol)	Reaction time(min) / Temperature (°C)	(%) Yields
0	7.80	32
1	7.80	66
2	7.80	79
3	7.80	76
4	7.80	72
5	7.80	70

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Table 2 Effects of the microwave power and the irradiation time on the formation of 4a

Entry	Time (min)	Power (W)	Yields (%)
1	4	250	47
2	4	300	52
3	4	400	55
4	4	500	58
5	4	600	63
6	4	700	69
7	4	750	71
8	4	800	74
9	4	900	83
10	2	900	36
11	3	900	62
12	5	900	88
13	7	900	97
14	8	900	94
15	9	900	92

Reaction conditions: benzaldehyde 1.0 mmol; ethylacetoacetate 1.0mmol; urea 1.5 mmol; $H_3PMo_{12}O_{40}$ 2 mol%; temperature 80°C

Table 3 The different synthesis conditions of DHPMs catalyzed by $H_3PMo_{12}O_{40}$

Entry	Product	R_1CHO	X	Microwave		Melting Point °C	
				Time (min)	yield (%)[a]	Obs	Lit
1	4a	Benzaldehyde	O	5	80	207	206-207 [9]
2	4b	4-methoxy- benzaldehyde	O	6	95	201	203-204 [9]
3	4c	Furfural	O	5	82	204	206-208 [17]
4	4d	Cinnamaldehyde	O	6	96	240	240-242 [17]
5	4f	4-N,N-dimethylamino Benzaldehyde	O	7	86	256	256-258 [33]
6	4g	salicylaldehyde	O	8	78	204	201-203 [30]
7	4h	4-chloro benzaldehyde	O	7	92	212	213-215 [29]
8	4i	3-Hydroxy benzaldehyde	O	6	94	164	167-170 [31]
9	4j	α-Hexyl benzaldehyde	O	13	87	236	237-238 [30]
10	4k	Benzaldehyde	S	7	78	203	206-208 [27]
11	4l	4-methoxy- benzaldehyde	S	4	91	153	150-152 [27]
12	4m	Furfural	S	9	80	186	185 [28]
13	4n	Cinnamaldehyde	S	7	91	248	244-246 [28]
14	4p	4-N,N-dimethylamino Benzaldehyde	S	7	83	208	209-210 [17]
15	4q	Salicylaldehyde	S	10	76	243	240-241[32]
16	4r	4-chloro benzaldehyde	S	9	93	193	190-192 [27]
17	4s	3-Hydroxy benzaldehyde	S	7	91	181	183-185 [31]

Many of the pharmacologically relevant substitution patterns on the aromatic ring were introduced with high efficiency. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin -2-(1H)-thiones in high yields, which are also of much interest with regard to biological activity. An acid sensitive aldehyde (4c) worked well without formation of any side product. Especially noteworthy is the survival of a variety of functional groups, such as hydroxy, halides, amine, double bond, etc., under the reaction conditions.

Recently, Kappe [29] proposed that the first step of the Biginelli reaction, the acid catalyzed formation of acyl imine intermediate 5 formed by the reaction of aldehyde with urea, is the rate-determining step. Further reaction of the iminium ion by acetoacetate gives an ureido 7 which subsequently cyclizes to Dihydropyrimidinones 8 with expulsion of water. The catalytic effect of $H_3PMo_{12}O_{40}$ probably arises from acidity of $H_3PMo_{12}O_{40}$ catalyzing the slow step as well as the activation of 2, thus facilitating the addition of ethylacetoacetate to the more electrophilic iminium carbon center. The suggested mechanism is illustrated in Scheme 3. In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6- methyl-3, 4-dihydropyrimidin-2(1H)-one (entry1 in Table 3) The yield of the product in the presence of $H_3PMo_{12}O_{40}$ is comparable with these catalysts. However, reaction in the presence of these catalysts required longer reaction times than that of $H_3PMo_{12}O_{40}$.

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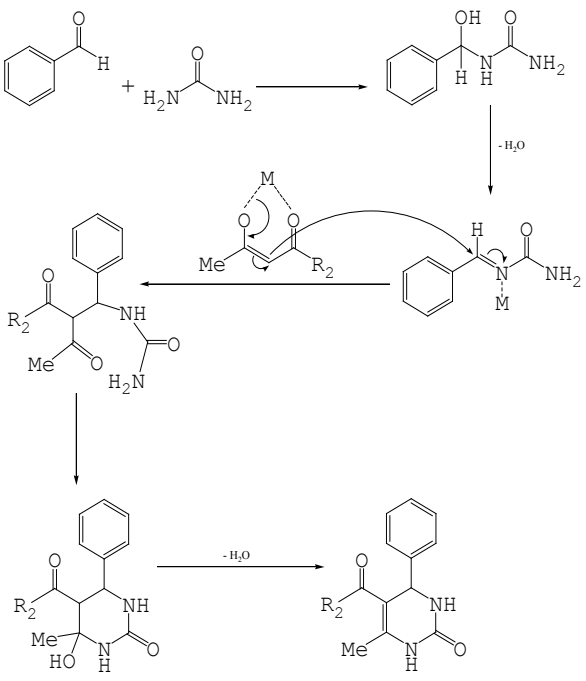

Scheme 3 Proposed mechanism for the synthesis of 4a (M= $H_3PMo_{12}O_{40}$)

Conclusion

We have found that $H_3PMo_{12}O_{40}$ is extremely useful and highly efficient homogeneous acid catalyst for the synthesis of biologically potent aryl 3,4-dihydropyrimidinones by means of MCRs three-component condensations of an aldehyde, 1,3-dicarbonyl compound, and urea or thiourea in a one-pot operation. $H_3PMo_{12}O_{40}$ is non-corrosive and environmentally benign and presents fewer disposal problems.

This method is applicable to a wide range of substrates, including aromatic, aliphatic, a,b-unsaturated, and heterocyclic aldehyde, and provides a variety of biologically relevant dihydropyrimidinones in high-to-quantitative yields in short reaction times under microwave irradiation.

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