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ORIGINAL ARTICLE

Catalytic Synthesis of 3,4-dihydropyrimidin-2(1H)-ones under Green Conditions and by Keggin type Heteropolyacid catalyst $H_7[PMo_8V_4O_{40}]$

Ali GHARIB[1,2,♠], Manouchehr JAHANGIR[1], Mina ROSHANI[1],
J. (Hans) W. SCHEEREN[3], Sara MOGHADASZADEH[2], Armin REZAEE[2]

[1]*Department of Chemistry, Islamic Azad University, Mashhad, IRAN*
[2]*Agricultural Researches and Services Center, Mashhad, IRAN*
[3]*Cluster for Molecular Chemistry, Department of Organic Chemistry, Radboud University Nijmegen, The NETHERLANDS*

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ABSTRACT

This paper describes an improved procedure and simple and green method for the efficient and facile synthesis of 3,4-dihydropyrimidinones with excellent yields using inexpensive heteropolyacid catalyst in the presence of green solvent.

Key Words: *Biginelli reaction; Dihydropyrimidinones; Heteropolyacid; Solvent; Green; Catalyst.*

1. INTRODUCTION

In the past two decades, the broad utility of HPAs as acid and oxidation catalysts in solution as well as in the solid state for various industrial processes has been demonstrated for a wide variety of synthetically transformation of organic substrates.[1] Heteropolyacids are more reactive catalysts than conventional inorganic and organic acids for reactions in solution.[2] Heteropolyacids (HPAs) have been used as catalyst for many of organic transformations, such as synthesis of acylals,[3] tetrahydropyranilation of phenols,[4] thioacetalization and transacetalization reactions.[5] They are also used as industrial catalysts for several Liquid-phase reactions,[6] including alcohol dehydration,[7] alkylation[8] and esterification.[9] Heteropolyacids (HPAs) as catalyst for fine organic synthetic processes have been developed for industrial related to fine chemicals, such as the flavors, pharmaceuticals and food industries.[10] The Biginelli reaction is one of the most important multi-component reactions for the synthesis of dihydropyrimidinones. Dihydropyrimidinone are known

♠Corresponding author, e-mail: aligharib5@yahoo.com

to exhibit a wide range of biological activities such as antiviral, antitumour, antibacterial, and anti-inflammatory properties.[11] In addition, these compounds have emerged[12] as potential calcium channel blockers, antihypertensive, α_{1a}–adrenergic antagonists and neuropeptide antagonists. The Biginelli's reaction consists in the condensation of an aldehyde, a *β*-ketoester and urea in the presence of an acid catalyst.[13] 3,4-Dihydropyrimidin-2(1*H*)-ones are interesting compounds and play an important role in synthetic, therapeutic and bioorganic chemistry. [14] In recent years, new methods for preparation of dihydropyrimidinones have been the subject of research for organic chemists. Consequently, the development of newer Lewis acid catalysts for this purpose has continued with the availability of a wide range of such reagents namely, $BF_3.OEt_2$/CuCl,[15] lanthanide triflate,[16] indium trichloride,[17] vanadium (III) chloride, [18] cupric chloride,[19] LiBr,[20] zirconium (IV) chloride,[21] lithium perchlorate,[22] and polymer-supported ytterbium (II) reagent [23] as well as Brønsted acids, such as *p*-toluene sulfonic acid, [24] silica sulfuric acid[25] and $KHSO_4$.[26] Also, montmorilonite KSF,[27] natural HEU-type zeolite [28] and HY-zeolite[29] have been employed as heterogeneous catalyst for the synthesis of dihydropyrimidinones. However, these reactions suffer from the harsh conditions, long reaction times and frequently low yields. Dihydropyrimidinones are an important class of organic compounds, which show prominent biological activity and are normally prepared using Biginelli reaction.[11] Also, Biginelli's reaction for the synthesis of dihydropyrimidinone has received renewed interest and several improved procedures have recently been reported, involving reagents and catalysts such as such as Fe_3O_4 nanoparticles,[30] N, imidazol-1-yl-acetic acid,[31] N,N'-Dichlorobis(2,4,6-trichlorophenyl)urea,[32] *p*-sulfonic acid calixarenes,[33] and $Yb(PFO)_3$.[34] A large number of reports are available in the literature for this protocol,[35] including a few examples of Biginelli reaction in water.[36] Very recently, Zumpe et al. used propane phosphonic acid anhydride as a catalyst.[37] Although yield is good, the main concern for this protocol is the separation of the catalyst from product that requires column chromatography.

2. EXPERIMENTAL

2.1. Materials

All the chemicals were obtained from Merck Company and used as received.

2.2. Instrument

^{1}H NMR spectra were recorded on a FT NMR Bruker 400 MHz spectrometer and ^{1}H NMR and ^{13}C NMR spectra were recorded at 298 K. Melting points were recorded on an Electrothermal type 9100 melting point apparatus andwere uncorrected. Chemical shifts were reported in ppm (*δ*-scale) relative to internal standard TMS (0.00 ppm); the solvent was used as a reference. LCMS analysis (EI, 70V) were performed on a Hewlett-Packard HP 5971 instrument. IR spectra were obtained with a Buck 500 scientific spectrometer (KBr pellets). The products were identified by comparison of their Mp., IR and NMR spectra with those of authentic samples.

2.3. Catalyst Preparation

Keggin type heteropolyacid, $H_7[PMo_8V_4O_{40}]$ was prepared in accordance with the literature.[38-46]

2.4. General Procedure for the Synthesis of Dihydropyrimidinones:

A mixture of aldehyde (10 mmol), 1,3-dicarbonyl compound (15 mmol), urea or thiourea (15 mmol) and Keggin type heteropolyacid $H_7[PMo_8V_4O_{40}]$, (0.03 mmol) as catalyst was refluxed in glacial acetic acid (30 mL) and water (20 mL) as green solvent for 6 h. The mixture was cooled to room temperature and the catalyst was then removed by filtration and the solution poured on to ice-water (60 mL). After completion of reaction, products were isolated with simple filtration (few ml of water was added to facilitate easy filtration) and the resulting solid product was filtered and recrystalized from ethanol to give the pure products (3,4-dihydropyrimidin-2(1*H*)-ones). After removing the reaction product by filtration and washing the solid catalyst with diethyl ether, it could be reused and subjected to a second, third, fourth and fifth runs of the Biginelli reaction. The results of the first experiment and subsequent experiments were almost consistent in yields.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**): White solid, Yield: 92%, mp 206–208 ^{o}C; IR (KBr) ν_{max}/cm^{-1}: 3240, 1723, 1639; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.24 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.1 Hz, OCH_2), 5.06 (d, 1H, J = 2.15 -CH), 7.27 (m, 5H, Ar-H), 7.76 (s, 1H, NH), 9.21 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.12, 17.95, 54.90, 60.04, 100.96, 112.84, 113.04, 125.16, 125.80, 129.05, 131.20, 150.17, 155.46, 163.80; ESI-MS 261 (M+H); HRMS calcd.

for $C_{14}H_{16}N_2O_3$ 260.1161 found 260.1166.

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4b**):

White solid, Yield: 80%, mp 201–202 ^{o}C; IR (KBr) ν_{max}/cm^{-1}: 3233, 1721, 1639; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H, J = 7.12 Hz, OCH_2CH_3), 2.34 (s, 3H, CH_3), 3.77 (s, 3H, -OCH_3), 4.05 (q, 2H, J = 7.12 Hz, OCH_2CH_3), 5.34 (d, 1H, J = 2.28 -CH), 6.82 (d, 2H, J = 8.60, Ar-H), 7.21 (d, 2H, J = 8.60, Ar-H), 7.75 (s, 1H, NH), 9.25 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.31, 18.80, 55.22, 55.40, 60.18, 101.68, 114.05, 127.96, 136.22, 146.15, 153.58, 159.30, 165.86; ESI-MS 291 (M+H); HRMS calcd. for $C_{15}H_{18}N_2O_4$ 290.1267 found 290.1262.

5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4c**):

Brown solid, Yield: 89%, mp 211– 213 ^{o}C; IR (KBr) ν_{max}/cm^{-1}: 3234, 1740,1630; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.04 Hz, OCH_2CH_3), 2.31 (s, 3H, CH_3), 4.04 (q, 2H, J= 7.12 Hz, OCH_2CH_3), 5.79 (d, 1H, J = 2.28, -CH), 7.50 (d, 2H, J = 9.18, Ar-H), 7.68 (s, 1H, NH), 8.15 (d, 2H, J = 9.16, Ar-H), 9.06 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.23, 18.72, 55.80, 60.15, 101.60, 118.16, 130.38, 138.35, 152.27, 153.41, 159.14, 165.86; ESI-MS 306 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_5$ 305.1012 found 305.1008.

5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**):

White solid, Yield: 96%, mp 215– 216 °C; IR (KBr) ν_{max}/cm^{-1}: 3225, 1720, 1615; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, 3H, J = 7.14 Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.90 (q, 2H, J= 7.16 Hz, OCH_2CH_3), 5.71 (d, 1H, J = 2.28, -CH), 7.22 (d, 2H, J = 9.18, Ar-H), 7.68 (s, 1H, NH), 7.95 (d, 2H, J = 9.18, Ar-H), 9.16 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.19, 18.63, 55.73, 60.20, 101.56, 118.17, 130.33, 142.28, 152.30, 153.39, 159.16, 165.83; ESI-MS 295 (M+H); HRMS calcd. for $C_{14}H_{15}ClN_2O_3$ 294.0771 found 294.0776.

5-(Methoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4e**)

White solid, Yield: 93%, mp 236–238 °C; IR (KBr) ν_{max}/cm^{-1}: 3240, 1713, 1645; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 3.91 (s, 3H, $COOCH_3$), 5.45 (d, 1H, J = 2.15, -CH), 7.14 (d, 2H, J = 9.05, Ar-H), 7.52 (s, 1H, NH), 7.88 (d, 2H, J = 9.06, Ar-H), 9.01 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.65, 52.05, 54.37, 109.58, 113.20, 128.23, 136.26, 148.25, 153.39, 159.18, 167.76; ESI-MS 281 (M+H); HRMS calcd. for $C_{13}H_{13}ClN_2O_3$ 280.0615 found 280.0619.

5-(Methoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4f**):

Brown solid, Yield: 88%, mp 236–238 °C; IR (KBr) ν_{max}/cm^{-1}: 3232, 1725, 1634; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 3.90 (s, 3H, -$COOCH_3$), 5.51 (d, 1H, J = 2.15, -CH), 7.43 (d, 2H, J = 9.11, Ar-H), 7.45 (s, 1H, NH), 8.05 (d, 2H, J = 9.10, Ar-H), 9.05 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.65, 52.40, 55.41, 109.60, 113.22, 128.32, 137.21, 149.66, 155.45, 160.35, 166.21; ESI-MS 292 (M+H); HRMS calcd. for $C_{13}H_{13}N_3O_5$

291.0855 found 291.0851.

5-(Methoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4g**):

White solid, Yield: 84%, mp 192-194 °C; IR (KBr) ν_{max}/cm^{-1}: 3243, 1723, 1635; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 3.91 (s, 3H, -$COOCH_3$), 3.76 (s, 3H, -OCH3), 5.21 (d, 1H, J = 2.21 -CH), 6.75 (d, 2H, J = 8.58, Ar-H), 7.19 (d, 2H, J = 8.58, Ar-H), 7.63 (s, 1H, NH), 9.16 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.62, 53.35, 55.05, 55.88, 108.53, 113.20, 128.47, 137.65, 148.55, 154.17, 160.82, 165.95; ESI-MS 277 (M+H);

HRMS calcd. for $C_{14}H_{16}N_2O_4$ 276.1110 found 276.1106.

5-(Methoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4h**):

White solid, Yield: 82%, mp 209–211 °C; IR (KBr) ν_{max}/cm^{-1}: 3245,1734, 1665; ^{1}H NMR (400 MHz, DMSO-d_6): δ2.18 (s, 3H, CH_3), 3.86 (s, 3H, -$COOCH_3$), 5.03 (d, 1H, J = 2.07 -CH), 7.25 (m, 5H, Ar-H), 7.65 (s, 1H, NH), 9.14 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.65, 52.33, 54.71, 108.46, 113.35, 122.40, 131.18, 130.52, 154.12, 160.20, 164.42; ESI-MS 247 (M+H); HRMS calcd. for $C_{13}H_{14}N_2O_3$ 246.1004 found 246.1007.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (**4i**):

Yellow solid, Yield: 81.5%, mp 208–210 °C; IR (KBr) ν_{max}/cm^{-1}: 3240, 1722, 1643, 1595, 1530; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.21 Hz, OCH_2CH_3), 2.28 (s, 3H, CH_3), 4.12 (q, 2H, J = 7.24 Hz, OCH_2), 5.15 (d, 1H, J = 2.05 -CH), 7.52 (m, 5H, Ar-H), 7.80 (s, 1H, NH), 9.42 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ14.22, 17.92, 54.86, 60.15, 100.90, 112.85, 115.13, 125.16, 126.85, 129.65, 131.45, 150.27, 162.63, 180.25; ESI-MS 277 (M+H); HRMS calcd. for $C_{14}H_{16}N_2O_2S$ 276.0932 found 276.0935.

5-(Ethoxycarbonyl)-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)–thione (**4j**):

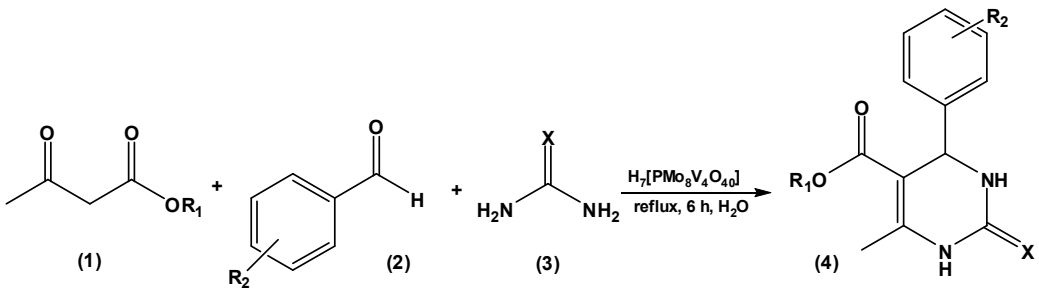
Brown solid, Yield: 87.5%, mp 205–207°C; IR (KBr) ν_{max}/cm^{-1}: 3246, 1723, 1634, 1576, 1545; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, 3H, J = 7.14 Hz, OCH_2CH_3), 2.28 (s, 3H, CH_3), 4.02 (q, 2H, J= 7.11 Hz, OCH_2CH_3), 5.80 (d, 1H, J = 2.06, -CH), 7.24-7.37 (m, 4H, Ar-H), 7.77 (s, 1H, NH), 9.34 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.15, 18.60, 55.65, 60.22, 101.33, 126.26, 128.02, 129.34, 130.74, 135.65, 144.33, 160.40, 165.64, 182.65; ESI-MS 322 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_4S$ 321.0783 found 321.0780.

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (**4k**):

Yellow solid, Yield: 78.5%, mp 153–155 °C; IR (KBr) ν_{max}/cm^{-1}: 3240, 1725, 1635, 1573, 1542; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, 3H, J = 7.11 Hz, OCH_2CH_3), 2.36 (s, 3H, CH_3), 4.13 (s, 3H, -OCH_3), 4.15 (q, 2H, J = 7.10 Hz, OCH_2CH_3), 5.45 (d, 1H, J = 2.15 -CH), 7.12 (d, 2H, J = 8.15, Ar-H), 7.38 (d, 2H, J = 8.11, Ar-H), 7.85 (s, 1H, NH), 9.44 (s, 1H, NH) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.32, 18.05, 55.25, 55.50, 60.46, 101.85, 114.33, 127.74, 137.24, 147.16, 159.45, 165.61, 182.48; ESI-MS 307 (M+H); HRMS calcd. for $C_{15}H_{18}N_2O_3S$ 306.1038 found 306.1042.

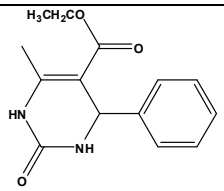
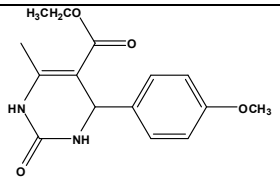
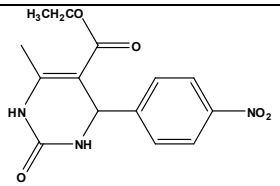
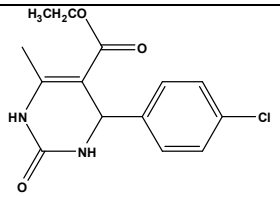
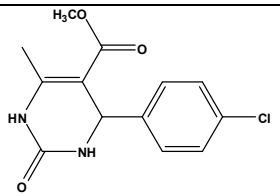
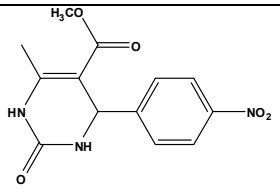
3. RESULTS AND DISCUSSION

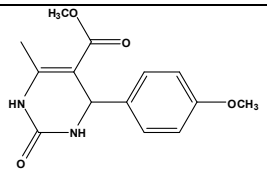
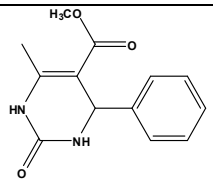
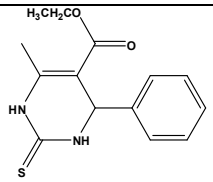
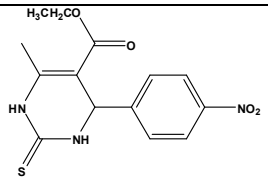
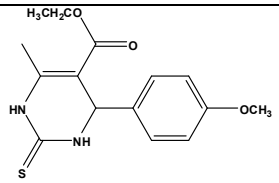
Due to the ever-mounting environmental concern in the field of chemistry, it is advisable to use easily recovered and recycled catalysts, especially expensive or toxic metallic ones for the next use.[38] We wish to report the use of heteropolyacids as a catalyst for the synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme **1**) using Biginelli protocol in water.



Scheme 1. Synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones using heteropolyacid catalyst, $H_7[PMo_8V_4O_{40}]$ in the presence of water as green solvent and under reflux conditions.

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivativess using $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst in the presence of water as green solvent under reflux conditions for 6 h.

Entry	R_1	R_2	X	[b]Dihydropyrimidinones	[a]Yield (%)	[b]References
4a	CH_3CH_2	H	O		92	25-27,32
4b	CH_3CH_2	4-OCH_3	O		80	25-27,32
4c	CH_3CH_2	4-NO_2	O		89	25-27,32
4d	CH_3CH_2	4-Cl	O		96	25-27,32
4e	CH_3	4-Cl	O		93	25-27,32
4f	CH_3	4-NO_2	O		88	25-27,32

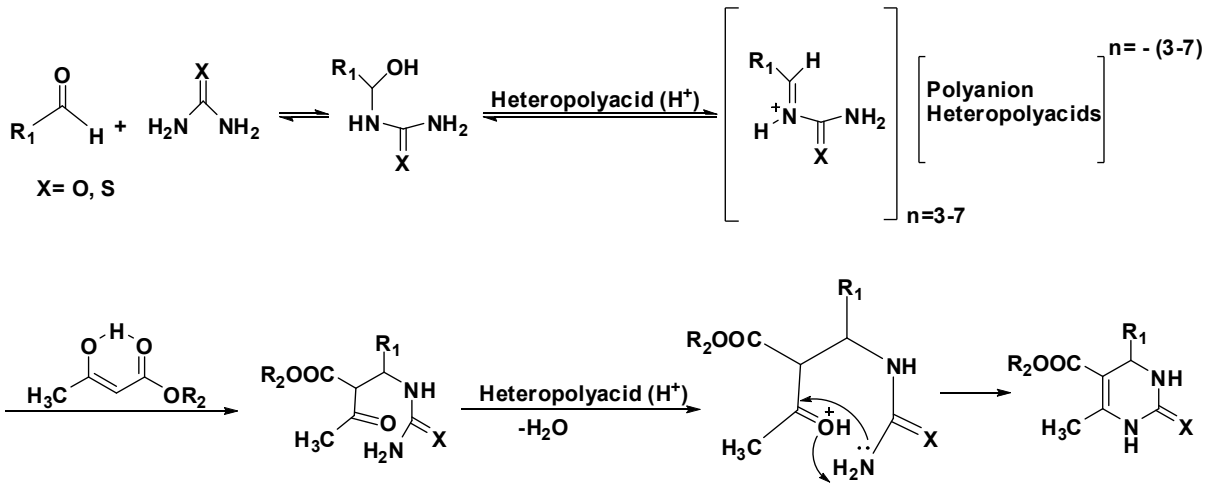
4g	CH_3	4-OCH_3	O		84	25-27,32
4h	CH_3	H	O		82	25-27,32
4i	CH_3CH_2	H	S		81.5	25-27,32
4j	CH_3CH_2	4-NO_2	S		87.5	25-27,32
4k	CH_3CH_2	4-OCH_3	S		78.5	25-27,32

[a]Isolated yields. [a,b]All the compounds are known in the literature and were characterized by ^{1}H NMR.

We studied the condensation of ethyl acetoacetate, 4-chloro benzaldehyde and urea in water under reflux conditions, to establish the feasibility of our strategy to 3,4-dihydropyrimidin-2(1*H*)-ones systems (Table **1, 4a-k**). The best conditions to prepare the dihydropyrimidinones were achieved when both urea (or thiourea), ethylaceto acetate and aldehyde were heated under reflux conditions in the presence of heteropolyacid catalyst and water as green solvent for 6 h, affording the desired products in good yields (Table **1, 4a-4k**). We found that this method is effective with a variety of substituted aromatic aldehydes independently of the nature of the substituents in the aromatic ring, representing an improvement to the classical Biginelli's methodologies.

All the aforementioned reactions, delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both, electron-donating and electron-withdrawing

substituents; substrates with electron-withdrawing groups gave relatively higher yields (Table **1**). The suggested mechanism is illustrated in Scheme **2**.



Scheme 2. Proposed mechanism of the synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones using heteropolyacid catalysts.

3. 1. Selection of the Solvent Type

Due to the increase in environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that avoid the use of harmful organic solvents. One of the most important principles of the green chemistry is the elimination of hazardous solvents in chemical synthesis and avoids using toxic solvent and the generation of waste. The use of water, the most abundant chemical on earth, as a solvent has been neglected for many years by organic chemists since water has been traditionally considered to have destructive effects on many reagents and synthetic reactions, unless water is used as a reagent or in workup procedures. Furthermore, the reaction was carried out in different solvents and under solvent-free conditions. As shown in Table 3, the yields of the reaction in the presence of water as green solvent conditions were greater and the reaction times were generally shorter than the conventional methods. The best result was obtained under reflux conditions for 6 h in the presence of water as green solvent. Increasing the reaction time did not improve the yield (Table **2**).

Table 2. Effect of the reaction time on 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**) synthesis using $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst in the presence of water as green solvent and under reflux conditions.

Entry	Time (h)	[a]Yield (%)
1	6	96
2	8	96
3	10	96
4	12	96.5
5	16	96.5
6	19	96.5
7	22	96.5
8	24	97
9	26	97
10	30	97

[a]Isolated yield.

Also, the effect of various solvents on the rate of the reaction was studied (Table **3**). As can be seen, solvent-free conditions (Table **3**, entries **1** and **5**) and ethanol and water were favorable solvents for this synthesis (Table **3**, entry **11**). But water was chosen, because it is acceptable solvent for green chemistry and environment.

Table 3. Effect of various solvents on 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**) synthesis using $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst in the presence of water as green solvent and under reflux conditions for 6 h.

Entry	Solvent	Time (h)	[b]Yield (%)
1	H_2O	6	96
2	Ethyl acetate	8	81
3	Acetonitrile	9	77
4	Methanol	6	88.5
5	Ethanol	6	94.5
6	DMF	10	64
7	DMSO	9	67
8	$CHCl_3$	9	70
9	CH_2Cl_2	10	69.5
10	CCl_4	12	69
11	Free	7	91.5

[a]Isolated yield.

3.2. Effect of the Catalyst

The hetropolyacids of the series $H_{3+x}PMo_{12-x}V_xO_{40}$ (x = 1-4) showed good to excellent catalytic behaviors in the synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-one derivatives. The results are shown in Table **4**. $H_7[PMo_8V_4O_{40}]$ catalyzes efficiently the formation of substituted 3,4-dihydropyrimidin-2(1*H*)-ones giving a total yield of 96% in water as green solvent. In addition, $H_7[PMo_8V_4O_{40}]$, $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$ and $H_6[P_2W_{18}O_{62}]$ gave a total yield 96%, 93%, 91%, 87.5% and 84.5% in water, respectively (Table **4**, entries **1-9**). In another word, the activities of the $H_{3+x}PMo_{12-x}V_xO_{40}$ (x = 1-4) catalysts in the synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones in water were found to decrease in the following order: $H_7[PMo_8V_4O_{40}] > H_6[PMo_9V_3O_{40}] > H_5[P\ Mo_{10}V_2O_{40}] > H_4[PMo_{11}V_1O_{40}] > H_6[P_2W_{18}O_{62}] > H_3[PW_{12}O_{40}] > H_4[SiW_{12}O_{40}] > H_3[PMo_{12}O_{40}] > H_4[SiMo_{12}O_{40}] > H_2SO_4$> Silica sulfuric acid> $BF_3.OEt_2$/CuCl> $KHSO_4$. The results (Table **4**) show that $H_7[PMo_8V_4O_{40}]$ catalyst is better with respect to yield and to reaction. In all cases, $H_7[PMo_8V_4O_{40}]$ Keggin-type heteropolyacid shows higher activity compared with the heteropolyacids types, H_2SO_4, Silica sulfuric acid, $BF_3.OEt_2$/CuCl and $KHSO_4$ (Table **4**, entries **10–13**). When, $H_7[PMo_8V_4O_{40}]$ Keggin-type heteropolyacid was used in the reaction, the yield for 4d was 96%, but the yields were lower and the reaction times were longer when using H_2SO_4, Silica sulfuric acid, $BF_3.OEt_2$/CuCl and $KHSO_4$ (Table **4**, entries **10–13**). The yields of the product 4d was good by using other Heteropolyacids such as $H_6[PMo_9V_3O_{40}]$, $H_5[P\ Mo_{10}V_2O_{40}]$, $H_4[PMo_{11}V_1O_{40}]$, Wells-Dawson, $H_6[P_2W_{18}O_{62}]$ (Table **4**, entries **2-5**). But, HPAs have several advantages as catalysts which make them economically and environmentally feasible. They are stronger acids than homogeneous acid catalysts such as sulfuric acid. The use of HPAs as catalyst is important in the development of clean technologies, since it avoids the drawbacks of environmental pollution and prevents corrosion of the conventional technologies. Many properties of the heteropoly compounds in the solution depend on the concentration, the reaction time, the reaction temperature, the solvent type, the structure of catalyst and other factors. The Keggin anion has an assembly of 12 corner-shared octahedral MoO_6 from tri-metallic groups $[Mo_3O_{13}]$ around a heteroatom tetrahedron PO_4.[34] The introduction of vanadium(V) into the Keggin framework of $[PMo_{12}O_{40}]^{3-}$ is beneficial for catalysis reactions.[35] Usually positional isomers are possible and coexist when two or more vanadium atoms are incorporated into the Keggin structure (for example 5 and 13 isomers for x=2 and 3, respectively).[36] Studies on these isomers in catalytic reactions indicate that different isomers cause to show different reactivities.[37]

Table 4. Synthesis of 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**), using various catalysts at water as green solvent under reflux conditions for appropriate times.

Entry	Catalyst	Time(h)	[a]Yield (%)
1	$H_7[PMo_8V_4O_{40}]$	6	96
2	$H_6[PMo_9V_3O_{40}]$	6	93
3	$H_5[P\ Mo_{10}V_2O_{40}]$	7	91
4	$H_4[PMo_{11}V_1O_{40}]$	7	87.5
5	$H_6[P_2W_{18}O_{62}]$	7	84.5
6	$H_3[PW_{12}O_{40}]$	7.5	82
7	$H_4[SiW_{12}O_{40}]$	7	72
8	$H_3[PMo_{12}O_{40}]$	7	66
9	$H_4[SiMo_{12}O_{40}]$	7	61.5
10	Silica sulfuric acid	9.5	56.5
11	$KHSO_4$	11	50
12	$BF_3.OEt_2$/CuCl	12.5	53
13	H_2SO_4	9	60
14	Free	20	-

[a]Isolated yield.

As can be seen from Table **5**, 0.03 mmol of $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst gave an excellent yield in 6 h. Blank experiments in the absence of the catalyst showed that the reaction did not give corresponding 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (Table **4**, Entry **14**). Thus, the catalyst had a catalytic effect on the mentioned reaction. The efficiency of the reaction is affected mainly by the amount of $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst (Table **5**). No product was obtained in the absence of the catalyst even after 20 h (Table **5**, entry **6**) indicating that the catalyst is necessary for the reaction. The optimal amount of of $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst was 0.03 mmol (Table 5, entry **3**); increasing the amount of the catalyst beyond this value did not increase the yield noticeably (Table **5**, entries **4, 5**).

Table 5. Optimization of the quantity of $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst in the synthesis of 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2*(*1*H*)-one (**4d**), in the presence of water as green solvent under reflux conditions for 6 h.

Entry	Catalyst (mmol)	Time (h)	[a]Yield (%)
1	0.008	6	62
2	0.02	6	85
3	0.03	6	96
4	0.1	6	96.5
5	0.3	9	96.5
6	Free	20	-

[a] Isolated yield.

3. 3. Effect of the Reaction Temperature

The reacion were carried out at two temperature including room temperature (lowest temperature) and reflux temperature (highest temperature). The maximum yield is reached at reflux temperature (100 ^{O}C). This was expected since increasing the temperature is apparently favorable for the acceleration of the forward reaction. In general, at the room temperature (25 ^{O}C) are not carried out any product.

3.4. Effect of the Reaction Time

Typical time courses of the reactions in the formation of 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(*1H*)-one (**4d**) are shown in Fig **1** under reflux conditions. The results show that in the initial stage of the reaction, the reaction proceeded rapidly (Figure **1**). The effect of reaction time on the % yield of 3,4-dihydropyrimidin-2(1*H*)-ones indicates that, yields strongly depend on the reaction time. TLC analysis showed that the formation of product is starting after 1.5 h The best reaction time has been found to be 6 h under reflux temperature conditions. At any reaction time, $H_7[PMo_8V_4O_{40}]$ was found to be most active catalyst, among other various heteropolyacids.

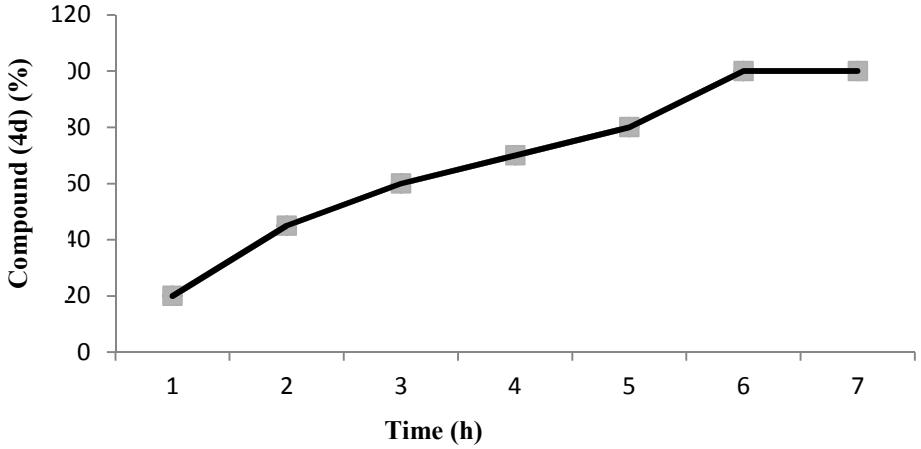


Figure 1. Effect of reaction time in the Synthesis of 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**), using $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst in the presence of water as green solvent and under reflux conditions for 6 h, yields analyzed by GC.

3. 4. Recycling of the Catalyst

It is noteworthy that the catalyst may be reused without significant loss of activity. In order to know whether the catalyst would succumb to poisoning and lose its catalytic activity during the reaction, we investigated the reusability of the catalyst. At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 80 ^{o}C for 1 h, and reused in another

reaction. Even after five runs for the reaction, the catalytic activity of $H_7[PMo_8V_4O_{40}]$ was almost the same as that of the freshly used catalyst. The results were summarized in Table **6**.

Table 6. Reuse of the catalyst for the synthesis of 5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4d**) using $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst at water as green solvent and under reflux conditions for 6 h.

Run	[a]Yield (%)
1	95
2	93
3	92
4	90
5	90

[a] Isolated yield.

4. CONCLUSION

The use of heteropolyacids as catalyst has made this method very cost effective. Another advantage of this method is excellent yield in shorter reaction time with high purity of the products. We here reported a catalytic method for the synthesis of Biginelli-type 3,4-dihydropyrimidin-2(1*H*)-one derivatives using $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst as an efficient, reusable and eco-friendly heterogeneous inorganic catalyst. It is noteworthy to mention that the catalyst is

reusable. Even after five runs for the Biginelli reaction, the catalytic activity of $H_7[PMo_8V_4O_{40}]$ was almost the same as that of the freshly used catalyst. $H_7[PMo_8V_4O_{40}]$ is non-corrosive and environmentally benign and presents fewer disposal problems. High yields, relatively short reaction times, simplicity of operation and easy work-up are some advantages of this protocol.

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