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Heterogeneous Polyoxometalates: Efficient, Facile and Reusable Catalysts for One-Pot Synthesis of Dihydropyrimidinones

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Polyoxometalates (POMs) used as efficient catalysts for the three-component condensation reaction of an aldehyde, with β-ketoester and urea in acetonitrile to afford the dihydropyrimidinones. Compared to the classical Biginelli reaction conditions, the present method consistently has the advantage of excellent yields and short reaction times. Furthermore, the catalyst could be easily recovered after completion of the reaction and reused without a considerable change in its activity.

Key Words: Biginelli reaction, Polyoxometalates, Heteropoly acid, Heterogeneous, Montmorillonite k10 clay, Poly(4-acetyrilmethyl) pyridinium chloride.

INTRODUCTION

Many functionalized dihydropyrimidinones have emerged as the integral backbones of several calcium channel blockers, antihypertensive, α_{1a}-adrenergic antagonists and neuropeptide Y antagonists[1]. The synthesis of dihydropyrimidinones is currently important because of their wide range of pharmaceutical and biological properties. Particularly, aryl 3,4-dihydropyrimidinones are found to exhibit a wide spectrum of biological activities such as antiviral, antitumor, antibacterial and antiinflammatory behaviour[2]. The most simple and straightforward procedure reported by Biginelli in 1893 involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea to obtain a heterocyclic system of dihydropyrimidinone (DHPM) (**Scheme-I**) under strong acidic conditions[3].

Reactions in which three or more reactants come together in a single reaction vessel to form a new product that contains portions of all the components are called multicomponent reactions. The multicomponent reactions are one of the important protocols in organic synthesis and medicinal chemistry[4].

Although the most straightforward method for synthesis of dihydropyrimidinone is the one-pot acid-catalyzed Biginelli condensation reaction in ethanol in the presence of catalytic amounts, it provides only low to moderate yields of the desired target molecules of type dihydropyrimidinone, particularly when substituted aromatic aldehydes or thioureas are employed[5-8].

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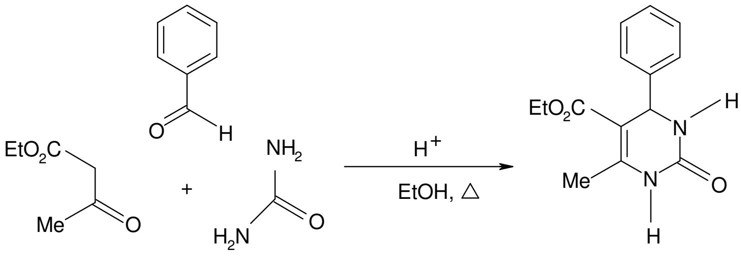


Scheme-I

Synthetic strategies for the dihydropyrimidinone nucleus involve both one-pot and multi-step approaches. Until now, several improved procedures have been reported using catalysts such as Lewis acids, triflates, soluble polymer-supported liquid phase synthesis, silica-sulfuric acid and silver salt of heteropoly acid[9-39].

The development of efficient and versatile catalytic systems for Biginelli reaction is an active ongoing research area and thus, there is scope for further improvement toward milder reaction conditions, variations of substituents in all three components and better yields. In this regard, polyoxometalates are in the center of focus to inorganic chemists. In view of this, the polyoxometalates as efficient Lewis acid catalysts for the Biginelli three-component one-pot synthesis have been utilized.

Polyoxometalaes belong to a large class of nanosized metal-oxygen cluster anions[40,41]. The chemistry of polyoxometalates [heteropoly acids (HPAs) and heteropoly salts], started by Berzelius back in 1826, has now reached maturity. But it is still a rapidly developing field interconnected with many disciplines[42].

The applications of polyoxometalates (especially polyoxotungstates) for environmental protection and remediation have attracted much attention in recent years. The majority of polyoxometalates have structures composed of molybdenum and tungsten polyhedrons. Other elements occur in small amounts in these structures. Polyoxotungstates and polyoxomolybdates decompose in alkaline media to form simple tungstate and molybdate ions and therefore, they can be determined in these forms[43-54].

The relative activity of keggin heteropoly acids primarily depends on their acid strength. Other properties, such as the oxidation potential as well as the thermal and hydrolytic stability are also important properties for the most common heteroply acids are summarized below:

Acid strength	PW > SiW = PMo > SiMo
Oxidation potential	PMo > SiMo = PW > SiW
Termal stability	PW > SiW > PMo > SiMo
Hydrolytic stability	SiW > PW > SiMo > PMo

Usually, tungsten heteropolyacids are the catalysts of choice because of their stronger acidity, higher thermal stability and lower oxidation potential compared to molybdenum acids. Generally, if the reaction rate is controlled by the catalyst acid strength, $H_3[PW_{12}O_{40}]$ shows the highest catalytic activity in the Keggin series. The acids $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ are readily available and most frequently used as catalysts. These acids have fairly high thermal stabilites, decomposing at 465 and 375 ºC, respectively[42].

Hydrogen forms (or free acids) of heteropoly acids usually have low surface areas. Supported heteropoly acid catalysts have much greater surface areas. Many attempts have been made to disperse and fix heteropoly acid catalysts on various supports. Supporting materials such as silica, carbon and organic resins have been applied with varying levels of success, with new supporting materials and methods being actively pursued. Although the structure and composition of supported heteropoly acids are sometimes uncertain, high catalytic activities are often observed and separation made easier[42].

The concept of heterogenization of homogeneous catalysts is still an important goal for chemists interested in catalysts designed to take advantage of the many possibilities of molecular design and optimization of reaction selectivity inherent to the use of homogeneous catalysts together with the practical advantages of simple post-reaction work-up indigenous to heterogeneous catalysis. Over the years, many ideas and methods have been considered for heterogenization of homogeneous catalysts and these are still the scope of further studies.[55,56].

We believe that one promising reaction system for achieving these goals, is the use of heterogeneous catalysis. By using heterogeneous catalysis, the procedure can be simplified, providing an easier work up and isolation of products and quantitative recovery of the catalyst[57,58].

Herein, we wish to report a facile, efficient and practical method for the use of montmorillonite K10, as inorganic support and poly (4-acetyril methyl) pyridinium chloride (PMP)[58,59], as an organic support with Keggin-type polyoxometalates ($H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$) for preparation of heterogeneous catalysts.

The use of clays as catalysts and catalyst supports has received considerable attention recently. Expandable layer lattice clays such as montmorillonites have magnetic field acidity (H_0) values between 1.5 and -3 and their acidities may be tuned further by metal ion exchange with the introduction of a large number of Lewis acidic sites[60,61].

EXPERIMENTAL

Tungstophosphoric acid (HTP) and molybdatophosphoric acid (HMP), which are cheap, reusable, heterogeneous and easily available catalysts, were purchased from Merck and were purified by extraction with Et_2O from aqueous solution of the acid. After evacuation at 150-300 ºC for 1-2 h under reduced pressure, pure HTP and HMP were obtained[48]. All solvents were reagent grade. All reaction mixtures were stirred magnetically and were monitored by TLC using on 0.25 mm E-Merck silica gel 60 F_{254} precoated glass plates, which were visualized with UV light and then developed by using silicagel 60-120 mesh. Melting points were recorded on a Bamstead Elentrothermal 9200 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT/IR-Impact 400 D spectrophotometer with KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker A W 500 MHZ spectrometer in DMSO-d_6 using TMS as an internal standard.

General procedure for the synthesis of the supported polyoxometalates: The supported $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ catalysts were prepared by method of incipient wetness. In a typical process a 400 mg portion of $H_3PW_{12}O_{40}$ or $H_3PMo_{12}O_{40}$ were dissolved in methanol and impregnated dropwise in to 1600 mg poly (4-acetylmethyl)pyridinium chloride (PMP) or montmorillonite K10 clay, with constant agitation. The resulting pastes were dried for 4 h at 110 ºC (for PMP-POM and montmorillonite k10-POM) and then calcined for 4 h at 250 ºC (only for montmorillonite k10-POM)[62-64].

The infrared spectrum of PMP-$H_3PW_{12}O_{40}$ exhibited strong vibrations at 1080 (P=O), 973 (W=O), 900 and 819 cm^{-1}, while that of $H_3PW_{12}O_{40}$ exhibited them at 1080, 982, 893 and 808 cm^{-1}. The result suggests the structure of the phosphotungstic acid of unit PMP-POM was similar to that of $H_3PW_{12}O_{40}$.

General procedure for the synthesis of dihydropyrimidinones: In the presence of supported-POM (0.4 g), the reaction of ethyl acetoacetate **1** (1 mmol), aldehyde **2** (1 mmol) and urea or thiourea **3** (1.5 mmol) were carried out in a one-pot condensation employing refluxing CH_3CN (15 mL) as the solvent (**Scheme-2**) for the appropriate times (Tables 2 and 3). After the reaction was completed, as indicated by TLC analysis, the solvent was evaporated, the residue was dried and washed with water and the resulting solid was treated with hot ethanol and filtered again. The filtrate was concentrated to afford the recrystallized product. The products were characterized by IR, ^{1}H NMR spectral data and by comparison with melting points of the reported compounds.

Spectroscopic data of some 3,4-dihydropyrimidin-2(1*H*)-ones

Ethyl-6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a): m.p. 211 ºC; IR (KBr, ν_{max}, cm^{-1}): 3326, 3152, 1691, 1562, 1232, 1051, 783; ^{1}H NMR (DMSO-d_6) δ (ppm): 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 (br, s, 1H, NH), 9.19 (brs 1H, NH).

Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b): m.p. 208 ºC; IR (KBr, ν_{max}, cm^{-1}): 3230, 3120, 1730, 1710, 1650; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.11 (t, *J* = 7.5 Hz, 3H), 2.29 (s, 3H), 4.00 (q, *J* = 7.5 Hz, 2H), 5.29 (d, *J* = 3.0 Hz, 1H), 7.51 (d, *J* = 10 Hz, 2H), 7.91 (br, s, 1H), 8.23 (d, *J* = 8.76 Hz, 2H, arom CH), 9.37 (s, 1H, NH).

Ethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c): m.p. 217 ºC; IR (KBr, ν_{max}, cm^{-1}): 3300, 3120, 1710, 1690, 1630; ^{1}H NMR (DMSO-d_6) δ (ppm): 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 (br, s, 1H), 8.09-8.20 (m, 2H), 9.34 (br s, 1H).

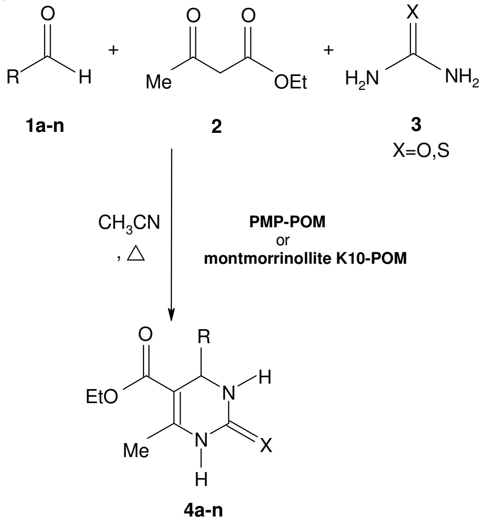
Ethyl-6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d): m.p. 220 ºC ; IR (KBr, ν_{max}, cm^{-1}): 3240, 3100, 1710, 1650; ^{1}H NMR (DMSO-d_6) δ (ppm): 0.94 (t, *J* = 7.5 Hz, 3H), 2.30 (s, 1H), 3.88 (q, *J* = 7.5 Hz, 2H), 5.81 (d, *J* = 3.0 Hz, 1H), 7.49-7.98 (m, 5H), 9.39 (br, s,1H).

Ethyl-6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e): m.p. 216 ºC ; IR (KBr, ν_{max}, cm^{-1}): 3220, 3100, 1720, 1700; ^{1}H NMR (DMSO-d_6) δ (ppm): 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).

Ethyl-6-methyl-4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f): m.p. 215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3360, 3220, 1690, 1640; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.08 (t, *J* = 7.5 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3) 3.91 (q, *J* = 7.5 Hz, 2H, OCH_2) 5.67 (d, *J* = 2.5 Hz, 1H) 7.22-7.46 (m, 4H, arom H)7.72 (br s, 1H, NH) 9.30 (br s, 1H, NH).

RESULTS AND DISCUSSION

The reaction of aldehyde **1**, ethyl acetoacetate **2** and urea or thiourea **3** in the presence of catalytic amounts of supported-POM in refluxing acetonitrile resulted in formation of dihydropyrimidinones **4** (**Scheme-II**).



Scheme-II

Effect of solvent: We have studied a series of sequential condensations of ethyl acetoacetate and urea with 4-nitro benzaldehyde as a model substrate and PMP-HTP as a model catalyst. In a typical reaction, it seems that acetonitrile is much better solvent in terms of yields (92 %) than all other tested solvents such as dichloromethane (67 %), methanol (54 %), tetrahydrofuran (43 %), chloroform (35 %) and water (15 %). The results are shown in Table-1.

TABLE-1
EFFECT OF SOLVENT IN BIGNELLI REACTION WITH SUPPORTED-POM SYSTEM[a]

Solvent	Yield (%) after 1 h	Yield (%) after 4.5 h
Acetonitrile	80	92
Dichloromethane	50	67
Methanol	40	54
Tetrahydrofuran	20	43
Chloroform	10	35
Water	10	15

[a]Reaction conditions: 4-nitrobenzaldehyde (1 mmol), PMP- $H_3PW_{12}O_{40}$ (0.4 g), ethyl acetoacetate (1 mmol) and urea (1.5 mmol).

Several aromatic and aliphtic aldehydes were examined under the optimized conditions to give the corresponding dihydropyrimidinones in moderate to excellent yields (Tables 2 and 3). Under these conditions, the yields were significantly increased to 70-98 % for the classical Biginelli reaction, but the reaction time was shortened from 18 to 4-9 h (by PMP-POM) and to 5-12 h (by montmorillonite k10 -POM). Many pharmacologically relevant substitution patterns could be introduced on the aromatic ring with high efficiency. Most importantly, aromatic aldehydes carrying either electron-donating (Tables 2 and 3; **4b-4h**) or electron-withdrawing (Tables 2 and 3; **4i,4j**) substituents all reacted very well, giving moderate to excellent yields.

Effect of catalyst: The Biginelli reaction was performed in the presence of organic (PMP) and inorganic (montmorillonite k10 clay) supported-POMs (HTP and HMP) under reflux conditions.

There was no appreciable reaction when 4-nitrobenzaldehyde was allowed to react with ethyl acetoacetate and urea in the absence of catalyst in ethanol as solvent, but in the presence of supported -POMs (HTP and HMP), this conversion proceeded efficiently in short times under similar reaction conditions (Tables 2 and 3). Furthermore, the use of 0.4 g of supported-POM (*ca.* 0.0003 mol POM, analyzed by neutron activation) in acetonitrile is sufficient to promote the reaction and no other additives are required for this conversion. No improvements were observed in the reaction yields by increasing the amount of supported-POM from 0.4-0.6 g. The reusability of the catalysts was also examined through a series of sequential condensations of ethyl acetoacetate and urea with 4-nitro benzaldehyde as a model substrate. In a typical reaction, the catalysts were simply filtered from the reaction mixture and reused for five (montmorillonite k10 -HTP) and six (PMP- HTP) cycles (Fig. 1). The reaction proceeded smoothly with a yield of 70-92 %, indicating that the catalyst dose not lose its activity and can be reused. The generality and scope of the reaction are summarized in Table-4.

It is suggested that both of the (organic and inorganic) supported-POMs, were effective catalysts for the Biginelli reaction.

TABLE-2
SYNTHESIS OF DIHYDROPYRIMIDINONES (DHPMs) USING PMP-POMs ($H_3PW_{12}O_{40}$ AND $H_3PMo_{12}O_{40}$) AS CATALYSTS

DHPMs	Substrate (R)	X	Type of metal in POM	Time, h	Yield (%)[a,b,c]	m.p. (^{0}C)	
						Found	Reported
4a	4-(Me)-C_6H_4	O	W	4.0	90	211	214-216[20]
			Mo	5.0	79		
4b	4-(NO_2)-C_6H_4	O	W	4.5	92	208	209-212[18]
			Mo	5.5	94		
4c	3-(NO_2)-C_6H_4	O	W	6.0	94	217	227-228[32]
			Mo	7.0	83		
4d	2-(NO_2)-C_6H_4	O	W	4.5	70	220	220[23]
			Mo	7.0	87		
4e	4-(Cl)-C_6H_4	O	W	7.0	89	216	209-211[18]
			Mo	9.0	95		
4f	2-(Cl)-C_6H_4	O	W	5.0	90	215	215-216[32]
			Mo	6.5	78		
4g	4-(OH)-C_6H_4	O	W	6.5	78	227	228-230[18]
			Mo	9.0	93		
4g'	4-(OH)-C_6H_4	S	W	7.0	83	191	193-194[18]
			Mo	6.5	91		
4h	2-(OH)-C_6H_4	O	W	6.0	93	200	199-201[19]
			Mo	6.0	98		
4i	4-(OMe)-C_6H_4	O	W	7.0	73	203	199-202[18]
			Mo	6.5	96		
4i'	4-(OMe)-C_6H_4	S	W	4.5	96	155	153-155[18]
			Mo	4.0	92		
4j	3-(OMe)-C_6H_4	O	W	5.0	93	201	207-208[16]
			Mo	5.0	79		
4k	Ph-CH=CH	O	W	6.0	82	229	227-230[20]
			Mo	8.5	85		
4l	Ph-CH-CH_3	O	W	4.0	86	156	–
			Mo	4.5	88		
4m	2-furyl	O	W	6.0	80	205	203-205[18]
			Mo	8.5	76		
4p	C_6H_5	S	W	6.0	87	192	190-192[27]
			Mo	9.0	80		

[a]POM, $H_3PW_{12}O_{40}$ or $H_3PMo_{12}O_{40}$, (0.2 mmol), ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and urea (1.5 mmol) were carried out in a one-pot condensation employing refluxing CH_3CN (15 mL) as the solvent; [b]Isolated yield; [c]Identification of the products was ascertained by NMR and IR analysis.

Conclusion

Polyoxoanions can be used directly (bulk material) or deposited on different supports (supported material). Unfortunatly, the useful HPAs are found to be thermally unstable, decomposing at temperatures higher than 723 K and easily soluble in both water and alcohol, which makes the separation of HPAs, reactants and product

TABLE-3
SYNTHESIS OF DIHYDROPYRIMIDINES (DHPMs) USING
MONTMORILLONITE K10-POMs($H_3PW_{12}O_{40}$ AND $H_3PMo_{12}O_{40}$) AS CATALYSTS

DHPMs	Substrate (R)	X	Type of metal in POM	Time, h	Yield (%)[a,b,c]
4a	4-(Me)-C_6H_4	O	W	5.5	95
			Mo	5.0	89
4b	4-(NO_2)-C_6H_4	O	W	5.5	90
			Mo	7.0	89
4c	3-(NO_2)-C_6H_4	O	W	6.0	94
			Mo	7.5	70
4d	2-(NO_2)-C_6H_4	O	W	5.5	79
			Mo	8.0	87
4e	4-(Cl)-C_6H_4	O	W	6.0	87
			Mo	6.0	85
4f	2-(Cl)-C_6H_4	O	W	7.5	80
			Mo	11	89
4g	4-(OH)-C_6H_4	O	W	6.5	92
			Mo	6.5	90
4g'	4-(OH)-C_6H_4	S	W	7.0	83
			Mo	6.5	89
4h	2-(OH)-C_6H_4	O	W	8.0	93
			Mo	9.0	83
4i	4-(OMe)-C_6H_4	O	W	8.5	79
			Mo	7.0	90
4i'	4-(OMe)-C_6H_4	S	W	6.5	96
			Mo	6.5	90
4j	3-(OMe)-C_6H_4	O	W	5.5	90
			Mo	9.0	79
4k	Ph-CH=CH	O	W	8.0	89
			Mo	12	80
4l	Ph-CH-CH_3	O	W	4.5	80
			Mo	5.5	83
4m	2-furyl	O	W	6.0	88
			Mo	8.0	92
4p	C_6H_5	S	W	7.5	92
			Mo	10	92

[a]POM, $H_3PW_{12}O_{40}$ or $H_3PMo_{12}O_{40}$, (0.2 mmol), ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and urea (1.5 mmol) were carried out in a one-pot condensation employing refluxing CH_3CN (15 mL) as the solvent; [b]Isolated yield; [c]Identification of the products was ascertained by NMR and IR analysis.

difficult. These drawbacks may subsequently limit the practical application of HPAs. Hydrogen forms (or free acids) of HPAs usually have low surface areas. The drawback of the HTP and HMP is their low surface area (1-5 $m^2 g^{-1}$) and low porosity (< 0.1 $cm^3 g^{-1}$). Supported heteropoly acid catalysts have much greater surface areas. Many attempts have been made to disperse and fix HPA catalysts on various supports. Support materials such as silica, carbon, clay and organic resins have been applied with varying levels of success, with new supporting materials and methods being actively pursued. Although the structure and composition of supported HPAs are

TABLE-4
INVESTIGATION OF ORDER OF USE OF SUPPORTED-POM ($H_3PW_{12}O_{40}$) IN BIGINELLI REACTION

Order of use of catalyst	Yield (%)	
	PMP-$H_3PW_{12}O_{40}$	Montmorillonite k10-$H_3PW_{12}O_{40}$
1	92	87
2	90	85
3	90	83
4	90	76
5	81	70
6	79	13
7	37	–

[a]Reaction conditions: 4-Nitrobenzaldehyde (1 mmol), supported-$H_3PW_{12}O_{40}$ (0.4 g), ethyl acetoacetate (1 mmol) and urea (1.5 mmol).

(a) (b)

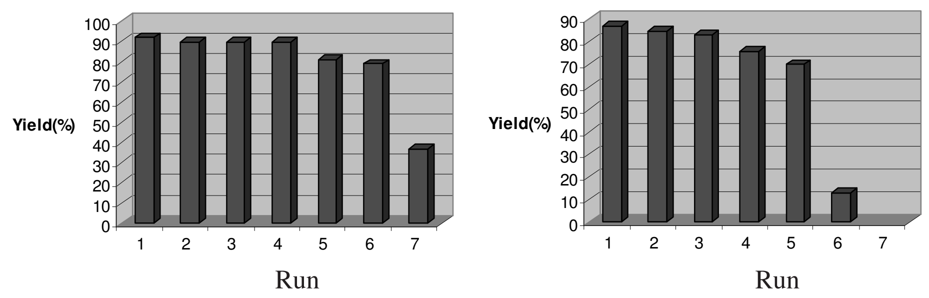


Fig. 1. Representation of order of use of supported-POM based on data in Table-4. (a) PMP-$H_3PW_{12}O_{40}$, (b) montmorillonite k10-$H_3PW_{12}O_{40}$

sometimes uncertain, high catalytic activities are often observed and separation made easier. For various reasons, such as efficiency, better accessibility to the active sites, cost, *etc*. depositing on a support is currently favoured.

In conclusion, a simple modification of the Biginelli dihydropyrimidinone synthesis has been described by using organic (PMP) and inorganic (montmorillonite k10 clay) supported-POMs (HTP and HMP) as the catalysts in refluxing acetonitrile. High yields of the products, short reaction times, mild reaction conditions and simple experimental procedure and product isolation make this protocol complementary to the existing methods. Further, the catalysts can be reused for 5 or 6 times but they will be less active.

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