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A Cheap and Efficient Methodology for the Solvent-Free, One-pot and Multi-component Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Catalyzed by Mesoporous $NH_4H_2PO_4$/MCM-48 and Comparison of Its Catalytic Efficacy with $NH_4H_2PO_4$/MCM-41

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The catalytic efficiency of ammonium dihydrogenphosphate was evaluated in the two heterogeneous forms of $NH_4H_2PO_4$/MCM-48 and $NH_4H_2PO_4$/MCM-41, as mesoporous catalysts, in the solvent free synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones through one-pot three-component condensation of ethyl acetoacetate, an aryl aldehyde and urea. Different reaction parameters including catalytic efficacy, solvent effect, and urea concentration are considered.

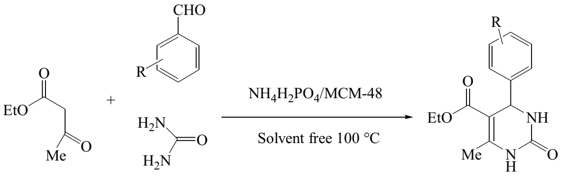
Keywords: 3,4-Dihydropyrimidin-2(1*H*)-ones; $NH_4H_2PO_4$; MCM-48; MCM-41.

INTRODUCTION

Dihydropyrimidinones are important biologically active synthons which have numerous applications in mammalian cells,[1] and have been considered as a lead for the development of new anticancer drugs.[2] They also exhibit various types of pharmacological properties such as antibacterial and antifungal,[3] antiviral,[4] antioxidative,[5] α-adrenergic and neuropeptide Y antagonists,[6] as well as anti-inflammatory.[7] Additionally, it has been proved that several structurally related marine natural products, such as batzelladine, are effective in the inhibition of binding of HIV gp-120 to CD4 cells, so offering new insights towards the development of AIDS therapy.[8] Therefore, development of new and efficient protocols for the preparation of these compounds are of prime importance and still remains a challenge for organic chemists.

Recently, we used $NH_4H_2PO_4$ as a non-toxic, inexpensive, and easily available catalyst in synthesis of 3,4-dihydropyrimidin-2(1*H*)-one.[9] Moreover, heterogenization of $NH_4H_2PO_4$ on the mesoporous MCM-41 is also investigated.[10] From our research on the development of useful synthetic methodologies and interest in $NH_4H_2PO_4$ catalyzed reactions, we have found a 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 $NH_4H_2PO_4$ grafted on MCM-48 (Scheme I).

Scheme I Three component condensation of urea, aldehyde and ethylacetoacetate



EXPERIMENTAL

General remarks. The chemicals, solvents and starting materials were obtained from Aldrich, Merck or Fluka. All products were characterized by comparison of their spectral and physical data with those reported in the literature.[11] Progress of the reactions was monitored by TLC. Infrared spectra were recorded (KBr pellets) on 8400 Shimadzu Fourier Transform spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE instrument using TMS as an internal reference. Melting points were determined in open capillary tubes in a Stuart BI Branstead Electrothermal Cat No: IA9200 apparatus and uncorrected. Data for ^1H NMR are reported as chemical shift (δ) and multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, qt: quintuple, dq: doublet of quartets, br: broad). **Synthesis of MCM-48.** *n*-Hexadecyltrimethylammonium bromide ($C_{16}H_{33}(CH_3)_3NBr$, template) was dissolved in deionized water, and sodium hydroxide and tetraethoxysilane (TEOS) were added. The molar composition of the gel was 1 M TEOS/0.25 M Na_2O/0.65 M $C_{16}H_{33}(CH_3)_3NBr$/62 M H_2O. The solution was stirred for about 1 h, charged into a polypropylene bottle and then heated at 383 K for 3 days. The product was filtered, washed with water and calcined at 823 K for 6 h.[12] MCM-41 was prepared according to the procedure described before.[10] **Preparation of $NH_4H_2PO_4$/MCM-48.** In order to prepare the heterogeneous catalyst, MCM-48 (1.5 g) was mixed with a solution of $NH_4H_2PO_4$ (0.6 g) in dis-

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tilled water (10 mL). The resulting mixture was stirred for 12 h to absorb $NH_4H_2PO_4$ on the surface of MCM-48. The mixture was dried at 120 °C for 12 h to remove the water. The drying temperature was maintained below the decomposition temperature of the ammonium salt.[13] Infrared spectra of MCM-48 and the supported catalyst was compared. Appearance of absorption related to P=O stretching vibrations of OPO_3H_2 groups in the region 1400 cm^{-1} in the supported catalysts spectra proved that $NH_4H_2PO_4$ has been successfully supported. $NH_4H_2PO_4$/MCM-41 was prepared similarly.[10] (Infrared spectra of MCM-48 and $NH_4H_2PO_4$/MCM-48 are shown in Fig. 1). **General procedure for the preparation of 3,4-dihdropyrimidin-2(1H)-ones.** A mixture of ethyl acetoacetate (2 mmol), aldehyde (2 mmol) and urea (2.5 mmol) was heated to 100 °C under solvent-free condition in the presence of $NH_4H_2PO_4$/MCM-48 (0.04 g). Progress of the reaction was monitored by TLC. At the end of the reaction, the resulting mixture was filtered and the heterogeneous catalyst was separated. Then, the filtrate was poured into cold water and the solid product was separated by filtration. The impure product, if necessary, was re-crystallized from n-hexane/ethyl acetate (3:1).

RESULTS AND DISCUSSION

Comparison of the structural features of MCM-48 with MCM-41

Several drawbacks such as difficulties in separation of products, reusing and recycling of catalyst, production of acidic wastes, and low product selectivity limited the practical applications of homogeneous catalytic systems. Therefore, immobilization of homogeneous catalysts on solid supports would be an effective solution to the above problems.

The investigation for new molecular sieves in the late 1980s led Mobil researchers to the finding of a family of nano-structured mesoporous materials known as M41S (Fig. 2).[14] MCM-41 is undoubtedly the best known and most widely studied of this family of materials, synthesized via a self-assembled liquid crystal mechanism involving sol–gel precursors which form a hexagonally packed rod-shaped micelle structure.[15] The cubic MCM-48 is another member of the M41S family. Silica is widely carried out as the main building block of mesoporous materials since it is inexpensive, chemically inert, thermally stable, harmless[16] and abundantly available in the Earth's crust. These mesoporous materials are highly ordered with large specific surface area and uniform mesoporous channel. Especially for MCM-41 and MCM-48, the pore size could be controlled and widely used as adsorbent, catalyst, and support.[17]

The main objective of this report is focused on the comparison of MCM-48 with MCM-41 as supporting materials for $NH_4H_2PO_4$ and studying their catalytic efficacy for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

Studying efficacy of MCM-41 versus MCM-48 as the supporting materials

Efficiency of the synthesis of 3,4-dihdropyrimidin-2(1H)-ones was mainly affected by the amount of catalyst. Our previous findings revealed that the target reaction is obviously dependent to the presence of catalyst and simple heating of a neat mixture of aldehyde, acetoacetate and urea at 100 °C under solvent free condition obtained a highly impure product after 9 h.[9] 0.02 g of $NH_4H_2PO_4$/MCM-48 catalyst (containing 2.5 mol% of $NH_4H_2PO_4$) provided 28% of product after 4.4 h; While 74% yield was afforded in the presence of 0.04 g $NH_4H_2PO_4$/MCM-48 after 4.4 h. It should be mentioned that $NH_4H_2PO_4$/MCM-41 has been shown the best catalytic activity and 85% of conversion was obtained after 2.5 h under the same reaction conditions.[10] Enhancing amount of the heterogeneous catalyst directly affected conversion. 0.08 g of catalyst supported on MCM-48 (involving 10 mol % $NH_4H_2PO_4$) produced 87% yield after 4.4 h; Whereas, the same amount of $NH_4H_2PO_4$/MCM-41 led to 88% yield after 2.4 h. Thus, MCM-41 acted better than MCM-48 as supporting material considering time and conversion% (Fig. 3).

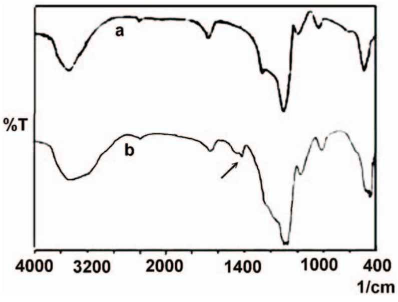


Fig. 1. Infrared spectra of (a) MCM-48 and (b) $NH_4H_2PO_4$/MCM-48.

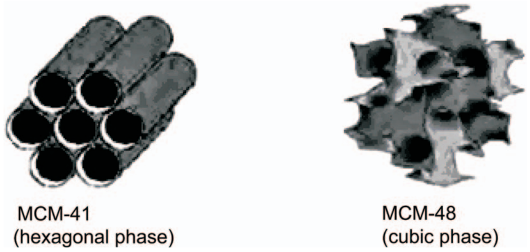


Fig. 2. The M41S family of materials including MCM-41 and MCM-48.[9]

As we reported before,[9,10,11] one of the most important points in synthesis of 3,4-dihdropyrimidin-2(1H)-ones is that aldehydes with electron donating and electron withdrawing groups took part in the Biginelli reaction uniformly. Some sensitive functional groups such as $-NO_2$, $-Cl$, $-Br$ attached to the ring were compatible with this reaction protocol. The aliphatic aldehydes participated in the reaction very smoothly. Table 1 compares efficiency of the two heterogeneous catalysts ($NH_4H_2PO_4$/MCM-48 versus $NH_4H_2PO_4$/MCM-41) on the preparation of some 3,4-dihydropyrimidin-2(1*H*)-ones using different aromatic aldehydes bearing electron withdrawing and electron releasing substituents on the phenyl ring. $NH_4H_2PO_4$/MCM-48 made lower yields than MCM-41 and need more time to complete the reaction.

To study role of solvents on the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in the presence of $NH_4H_2PO_4$ supported on MCM-48 and MCM-41 (0.04 g), the control reaction was performed with different solvents at 60 °C. As presented in Table 2, chloroform and acetonitrile behaved as the most preferred solvents (entry 3 and 4). However, the catalytic system resulted in the best yield in the absence of solvent (entry 5).

$NH_4H_2PO_4$ was immobilized on different supporting materials to compare their catalytic efficacy. Findings revealed that MCM-41 is the most favored bed considering reaction time and yield% (Fig. 4). MCM-41 led to 85% conversion after 2.5 h. Whereas, commercial silica-gel (mesh 70-230) produced 76% (after 5.6 h). SBA-15 and ZrO_2 showed moderate efficiency and produced 77-80% conversion after 3.3-3.5 h. The effect of supporting material structure on the catalytic reactivity of this catalyst was approved by these experiments.

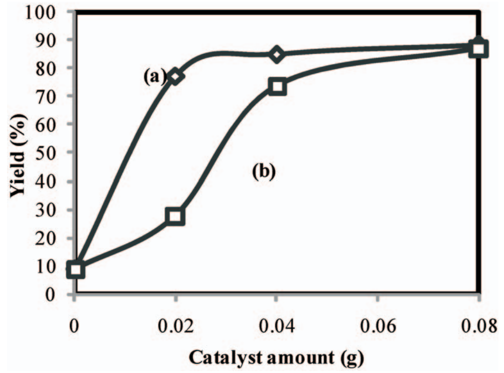
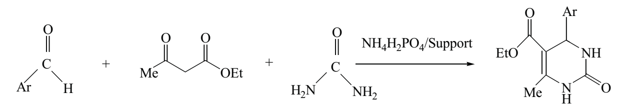
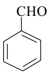
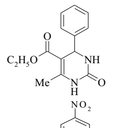
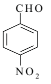
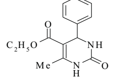
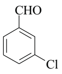
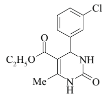
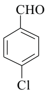
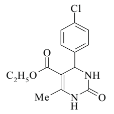
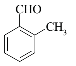
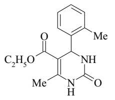


Fig. 3. Effect of (a) $NH_4H_2PO_4$/MCM-41 and (b) $NH_4H_2PO_4$/MCM-48 amount on the Biginelli reaction under solvent free condition.

Table 1. Comparison of $NH_4H_2PO_4$/MCM-48 and $NH_4H_2PO_4$/MCM-41 on the solvent-free condensation of ethyl acetoacetate, urea and different aldehydes



ArCHO	Time (h) MCM-41 /MCM-48	Yield (%) MCM-41 /MCM-48	Product	TOF[a] (h^{-1}) MCM-41 /MCM-48
	6/6	72/45		2.4/1.5
	2.5/4.4	85/74		6.8/3.3
	5/5	58/25		2.3/1.0
	3.7/3.7	72/74		3.9/4.0
	5/5	47/53		1.9/2.1

Reaction condition: 4-nitrobenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2.5 mmol) and 0.04 g catalyst. 0.04 g of $NH_4H_2PO_4$/MCM's involves 5 mol% $NH_4H_2PO_4$ (0.1 mmol).
[a]: Turn over frequency is defined as moles of substrate converted per mole of catalyst per hour.

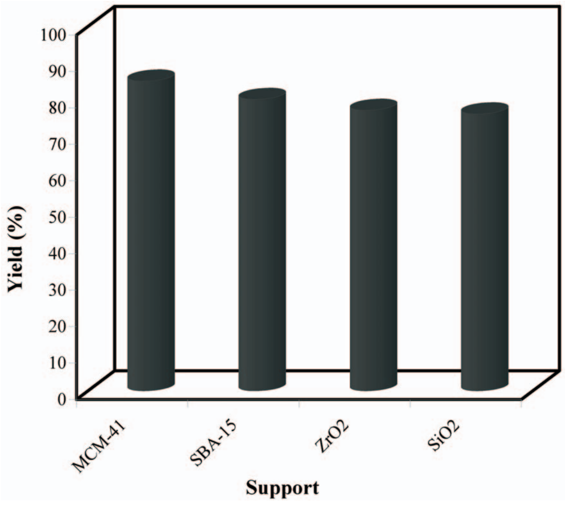


Fig. 4. Condensation of 4-nitrobenzaldehyde, ethyl acetoacetate and urea in the presence of $NH_4H_2PO_4$ supported on different solid materials.

Table 2. Effect of solvent on the synthesis of Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate catalyzed by $NH_4H_2PO_4$/MCM-48 and $NH_4H_2PO_4$/MCM-41

Entry	Solvent	Time (h)	Yield(%)	
			$NH_4H_2PO_4$/ MCM-48	$NH_4H_2PO_4$/ MCM-41
1	MeOH	5	33	50
2	EtOH	5	55	58
3	$CHCl_3$	5	82	79
4	MeCN	5	71	73
5	free	2.5	48	85

Reaction condition is described below Table 1.

Effect of urea concentration was also investigated on the Biginelli reaction of 4-nitrobenzaldehyde (2 mmol) and ethyl acetoacetate (2 mmol) in the presence of $NH_4H_2PO_4$/MCM-48 (0.04 g) at 100 °C under solvent free condition after 4.4 h (Fig. 5). Clearly, yield% was enhanced with increasing urea concentration from 1.5 to 4.5 mmol.

As described in Scheme II, three mechanistic routes could be suggested for the preparation of 3,4-dihydropyrimidinones.[18] According to our previous findings, we think the second route using iminium intermediate would be the most plausible route for the synthesis of 3,4-dihydropyrimidinone in presence of catalyst. Further investigations are underway to clarify the exact route. Obviously, yield% of the desired product was higher in the presence of catalyst and reaction goes in forward direction effectively. Although, in our previous report,[10] we emphasized on the iminium ion route, however, our new data showed more ambiguity and obviously more distinct and precise mechanistic studies should be carried out.

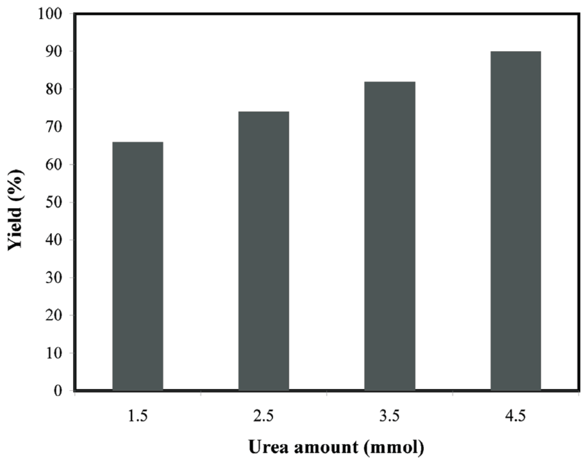
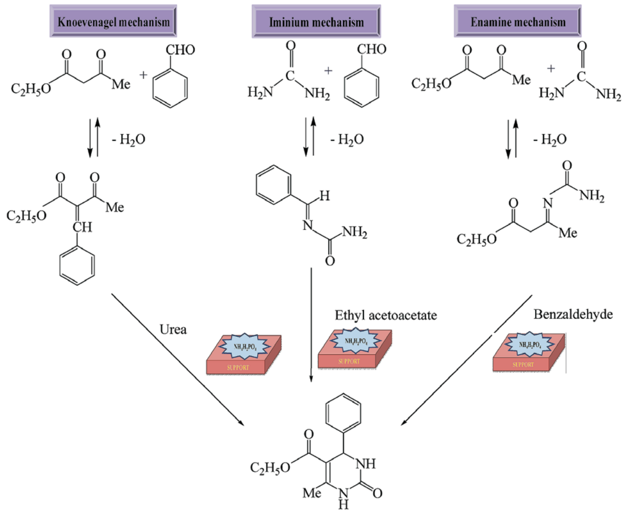


Fig. 5. Effect of urea concentration on the condensation of 4-nitrobenzaldehyde with ethyl acetoacetate and urea in the presence of $NH_4H_2PO_4$/MCM-48 after 4.4 h.

Scheme II The proposed reaction mechanisms for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones



Studying reusability of $NH_4H_2PO_4$/MCM-48

Recycling of $NH_4H_2PO_4$/MCM-48 was studied in the same manner as described for $NH_4H_2PO_4$/MCM-41.[10] For this purpose, condensation of 4-nitrobenzaldehyde, ethyl acetoacetate and urea was carried out in the presence of 0.04 g $NH_4H_2PO_4$/MCM-48 as model reaction. After completion of the reaction, the reaction mixture was diluted with hot methanol and the catalyst separated and reused in subsequent reactions. No significant reduction was observed in yield even after five runs. In conclusion, $NH_4H_2PO_4$/MCM-48 is also a recyclable catalyst as $NH_4H_2PO_4$/MCM-41.

CONCLUSIONS

A simple methodology is described for the synthesis of some biologically important 3,4-dihydropyrimidin-2(1*H*)-ones through one-pot three-component reaction of ethyl acetoacetate, aryl aldehyde and urea under solvent free condition using the heterogeneous $NH_4H_2PO_4$/MCM-48 catalyst. Effect of supporting material MCM-48 versus MCM-41 was fully studied in this report. Both catalysts could be reused after a simple work-up and reused several times without noticeable reduction in the catalytic activity. Different reaction parameters including catalytic efficacy, solvent effect and urea concentration were considered in the comparison of MCM-48 with MCM-41. Clearly, MCM-

41 showed better efficacy than MCM-48 as supporting material considering time and conv%.

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