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Synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs) using mesoporous aluminosilicate (AlKIT-5) catalyst with cage type pore structure

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ABSTRACT

Here we demonstrate on the synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs) and their derivatives through a three-component condensation reactions of aldehyde, β-ketoester and urea or thiourea using mesoporous aluminosilicate (AlKIT-5) nanocage as catalyst and acetonitrile as solvent under reflux conditions. The catalyst was found to be highly active and selective, affording a high yield of DHPMs. Compared to the classical Biginelli reaction conditions, this new approach consistently has the advantage of excellent yields (80–96%) and short reaction times, 3.0–4.0 h. The effect of the acidity and the concentration of the catalyst on the above process was investigated. We also demonstrate the synthesis of various multifunctional Biginelli compounds using the highly active AlKIT-5 catalysts.

1. Introduction

Aryl substituted 3,4-dihydropyrimidin-2-ones (DHPMs) and their derivatives have been receiving much attention in the recent years owing to their enormous application in the field of drugs and pharmaceuticals.[1] They also exhibit a wide range of biological activities[2] and are extensively used in the pharmaceutical industry as calcium channel blockers, antihypertensive, α-antagonist, antibacterial, antiviral, antitumour, antiinflammatory and HIV agents.[3,4] DHPMs are generally synthesized by the Biginelli reaction pathway, which involves the one-pot condensation of an aldehyde, β-ketoester and urea or thiourea[5] using acidic catalysts. Several reports are available on the synthesis of DHPMs. In most of the cases, homogenous catalysts such as concentrated HCl, $BF_3 \cdot OEt_2$, clays, $InCl_3$, $LaCl_3$, lanthanide triflate, H_2SO_4, ceric ammonium nitrate, $Mn(OAc)_3$, ion-exchange resin, 1-*n*-butyl-3-methyl imidazolium tetra fluoroborate, $BiCl_3$, $LiClO_4$, $InBr_3$, $FeCl_3$, $ZrCl_4$, $Cu(OTf)_2$, $Bi(OTf)_3$, LiBr, ytterbium triflates, NH_4Cl, $MgBr_2$ and other reagents have been used for this transformation.[6–25] Homogenous catalyst supported on the solid matrix has also been used for the synthesis of DPHMs.[21] Unfortunately, many of these catalysts suffer from one or more limitations, such as long reaction times, low yields, occurrence of several side reactions, drastic reaction conditions and tedious workup procedure. In addition, the solid oxide catalyst used previously had poor textural parameters such as low surface area and pore volume, which do not support a better performance in the synthesis of DHPMs. These factors stimulate us to search for a better catalyst, which has to offer a high activity for the synthesis of DHPMs under mild reaction conditions.

Recently, the use of heterogeneous catalysts[26–31] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup and recoverability of catalysts. Especially, mesoporous heterogeneous catalysts have been receiving much attention in the field of organic syntheses and catalysis owing to their excellent textural characteristics and well-ordered mesostructure with uniform pores.[29,32–37] Among the mesoporous solid acid catalysts, materials with three-dimensional (3D) mesopore structures are found to be more advantageous than the catalysts with one-dimensional (1D) mesoporous structure as the former can offer more resistant to pore locking and allow faster diffusion of reactants, which are highly necessary to obtain a stable and a high catalytic activity.[36,38–40] Dubey et al. reported the synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones in the liquid phase using SBA-15 impregnated with Al as catalyst, which was prepared by post-synthetic grafting method.[41] As the catalyst was prepared by post-synthesis grafting method, there is a possibility that the Al species

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may be leached out during the reaction. Recently, Vinu et al. reported the direct synthesis of aluminium incorporated mesoporous KIT-5 material (AlKIT-5), which possesses 3D mesostructure with *Fm*3*m* symmetry and a high acidity and a large pore diameter.[39,40] Although these materials possess interesting textural and catalytic properties, unfortunately, with the best of our knowledge, there has been no report available on the synthesis of DHPMs using such materials as catalysts in the open literature so far. Here, we demonstrate a simple, convenient and efficient method for the synthesis of DHPMs under acetonitrile solvent using AlKIT-5 catalyst through one-pot condensation reaction of aldehyde, β-ketoester and urea or thiourea.

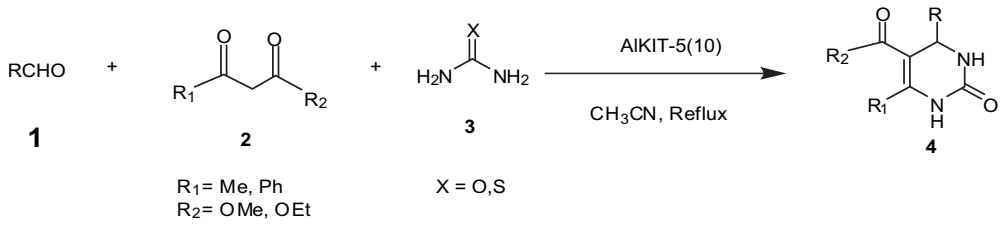
2. Results and discussion

Initially we performed the Bignelli's one-pot condensation reaction of benzaldehyde (106 mg, 1.0 mmol) with ethyl acetoacetate (156 mg, 1.2 mmol) and urea (72 mg, 1.2 mmol) using AlKIT-5(10)[42,43] catalyst (150 mg) under reflux and acetonitrile solvent conditions for 3 h (Scheme 1).

Table 2
Effect of the weight of AlKIT-5(10) on the synthesis of DHPMs

Weight of AlKIT-5(10) (mg)	Reaction time (h)	Yield (%)
50	3.0	40
100	3.0	72
150	3.0	96
200	3.0	96

Reaction conditions: substrate=aldehydes, ethyl acetoacetate, urea or thiourea, reaction temperature=reflux, solvent=acetonitrile.



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2-ones.

The catalyst was found to be highly active, affording 96% isolated yield of **4a** in 3 h. It must be noted that no product was obtained when the reaction was carried out without any catalyst. In order to understand the role of acidity of AlKIT-5 on the yield of the final product, we carried out the synthesis of DPHMs using AlKIT-5 with different acidity. The acidity of the materials was controlled by simple adjustment of the amount of Al content in the silica framework of KIT-5. As can be seen in Table 1, the acidity of the materials increases with increasing the Al content in the silica matrix. Table 1 also shows the textural parameters including specific surface area, pore volume and pore diameter of the AlKIT-5 samples with different Al contents. The specific surface area, pore volume, pore diameter, cage diameter and the acidity of the AlKIT-5(10) are found to be 989 m^2/g, 0.68 cm^3/g, 6 nm, 12 nm, and 0.51 mmol of NH_3/g, respectively. The detailed characterization results of the materials and their discussion can be found in our earlier reports.[39,40] As expected, the activity of the catalyst increases with increasing the amount of Al content in AlKIT-5, confirming the role of acidity of the catalyst in this transformation. Among the AlKIT-5 catalysts studied, AlKIT-5(10) was found to be highly active, which exhibits better textural parameters and higher acidity than those of other materials used in the study and has been used for the remaining catalytic studies under the optimized reaction conditions. It has been also found that the activity of our catalyst is much better than the reported catalysts such as AlSBA-15, Amberlyst-70 and MCM-41-R-SO_3H.[30,31,41]

The effect of the catalyst concentration on the synthesis of DHPMs was also investigated over different amounts of AlKIT-5(10) at reflux temperature for 3.0 h and the results are presented in Table 2. It has been found that the concentration of the catalyst significantly alters the outcome of the final product. The yield of the final product increases from 40 to 96% with increasing the weight of the catalyst from 50 to 200 mg, respectively. This could be mainly due to the availability of huge number of surface acidic sites in the reactant mixture as the weight of the catalyst is increased.

The synthesis[43,44] of various DHPMs using several aromatic and aliphatic aldehydes under the optimized conditions was also carried out using AlKIT-5(10) catalyst (150 mg) and results are summarized in Table 3. The reaction proceeded very smoothly in refluxing conditions with the AlKIT-5(10) catalyst and all the reactions were almost completed within 3–4 h of reaction time. The catalyst showed an excellent activity in all the cases, showing 80–96% isolated yield of the corresponding derivatives of DHPMs. Another important feature of this procedure is the stability of a variety of functional groups such as ether, hydroxy, halides, nitro, etc., under these reaction conditions. This procedure not only preserves the simplicity of Biginelli reaction but also produces DHPMs in excellent yields. Thus this procedure offers an easy access to substituted DHPMs with a variety of substitution patterns.

The effect of solvents on the synthesis of DPHMs was also investigated. Among various solvents like acetonitrile, methanol, methylene chloride and THF studied, methanol and acetonitrile were found to be the excellent solvent for this transformation. Thiourea has also been used to obtain the corresponding thio derivatives of dihydropyrimidinones, which were reported to have good biological activities.[3] Thiophene, furfural, cinnamal aldehydes

Table 1
Textural parameters, acidity and the catalytic activity of the AlKIT-5 catalysts with different Al contents

Catalyst	a_0 (nm)	n_{Si}/n_{Al}		S_{BET} (m^2/g)	V_p (cm^3/g)	Dp_{ads}, BJH (nm)	Cage diameter (nm)	Acidity (mmol/g)	Yield (%)
		Gel	Product						
AlKIT-5(10)	18.44	7	10	989	0.68	6.0	12.0	0.50	96
AlKIT-5(28)	17.76	10	28	815	0.56	5.6	11.2	0.32	81
AlKIT-5(44)	16.97	12	44	713	0.45	5.2	10.3	0.14	60

a_o unit cell constant; S_{BET} specific surface area; V_p specific pore volume; Dp pore diameter; reaction conditions: substrate=benzaldehyde, ethyl acetoacetate and urea, weight of the catalyst=150 mg, reaction temperature=reflux, solvent=acetonitrile.

Table 3
Mesoporous aluminosilicate-AlKIT-5(10) catalyzed synthesis of dihydropyrimidinones and thio derivatives

Entry	Aldehyde	X	R_1	R_2	Product	Time (h)	Yield (%)
1	C_6H_5CHO	O	Me	OEt	**4a**	3.0	96
2	*o*-$NO_2C_6H_4CHO$	O	Me	OEt	**4b**	3.0	96
3	*p*-$NO_2C_6H_4CHO$	O	Me	OEt	**4c**	3.0	93
4	*m*-$NO_2C_6H_4CHO$	O	Me	OEt	**4d**	3.0	86
5	*p*-ClC_6H_4CHO	O	Me	OEt	**4e**	3.0	88
6	*p*-$CH_3OC_6H_4CHO$	O	Me	OEt	**4f**	3.0	89
7	*m*-$(C_6H_5O)C_6H_4CHO$	O	Me	OEt	**4g**	3.0	84
8	2-OHC_6H_4CHO	O	Me	OEt	**4h**	3.0	88
9	3-OHC_6H_4CHO	O	Me	OEt	**4i**	3.0	83
10	5-Cl-2-OHC_6H_4CHO	O	Me	OEt	**4j**	3.0	82
11	$C_6H_4CH{=}CHCHO$	O	Me	OEt	**4k**	3.0	88
12	2-Thiophene carboxaldehyde	O	Me	OEt	**4l**	3.0	92
13	Furfuraldehyde	O	Me	OEt	**4m**	3.0	92
14	C_6H_5CHO	O	Me	OMe	**4n**	4.0	86
15	C_6H_5CHO	O	Ph	OEt	**4o**	4.0	90
16	C_6H_5CHO	S	Me	OEt	**4p**	4.0	91
17	*o*-$NO_2C_6H_4CHO$	S	Me	OEt	**4q**	4.0	91
18	*p*-$NO_2C_6H_4CHO$	S	Me	OEt	**4r**	4.0	88
19	*m*-$NO_2C_6H_4CHO$	S	Me	OEt	**4s**	4.0	80
20	*p*-ClC_6H_4CHO	S	Me	OEt	**4t**	4.0	88
21	*p*-$CH_3OC_6H_4CHO$	S	Me	OEt	**4u**	4.0	82
22	*m*-$(C_6H_5O)C_6H_4CHO$	S	Me	OEt	**4v**	4.0	84
23	2-OHC_6H_4CHO	S	Me	OEt	**4w**	4.0	84
24	3-OHC_6H_4CHO	S	Me	OEt	**4x**	4.0	82
25	5-Cl-2-OHC_6H_4CHO	S	Me	OEt	**4y**	4.0	82
26	$C_6H_4CH{=}CHCHO$	S	Me	OEt	**4z**	4.0	86
27	2-Thiophene carboxaldehyde	S	Me	OEt	**4**	4.0	90
28	Furfuraldehyde	S	Me	OEt	**4**	4.0	90
29	C_6H_5CHO	S	Me	OMe	**4**	4.0	82
30	C_6H_5CHO	S	Ph	OEt	**4**	4.0	88

and *meta*-phenoxy benzaldehyde also worked well to synthesize multifunctionalised DHPMs using AlKIT-5(10).

It is also important to note that the workup of the reaction mixture is very simple. The catalyst can be filtered out easily and the solvent was evaporated. Recycling experiments were conducted to find out the stability of the catalyst after the reaction. The catalyst was easily separated by centrifugation and reused after activation at 500 °C for 3–4 h. The efficiency of the recovered catalyst was verified with the Biginelli reaction (entry 1). Using the fresh catalyst, the yield of product (**4a**) was 96%, while the recovered catalyst in the three subsequent recycling experiments gave the yields of 95, 92 and 90%, respectively. These results reveal that the catalyst can be recycled several times without losing much activity.

In summary, we have developed a simple, convenient and effective method for the synthesis of DPHMs and their derivatives using substituted aldehydes, β-ketoester, urea or thiourea at reflux temperature using 3D mesoporous aluminosilicate catalyst with cage type pore. This method is applicable to a wide range of substrates including aromatic, aliphatic, α,β-unsaturated and heterocyclic aldehydes. The catalyst gave a high isolated yield of the DHPMs in a shorter reaction time at reflux temperature and can be recycled several times. The mesoporous AlKIT-5 catalysts are promising heterogeneous catalysts in all circumstances where the aluminosilicate matrix is highly stable and we strongly hope that this catalyst could also be used for other acid catalyzed organic transformation and help to replace the existing toxic, corrosive and expensive homogenous catalysts.

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42. *Experimental section*: all chemicals and solvents were obtained from Aldrich and used without further purification. Column chromatographic separations were carried out on silica gel 100–200 mesh size. The ^1H NMR spectra of samples were recorded on a JEOL 300 MHz NMR spectrometer using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on a MALDI-MS. FT-IR spectra of all the final products were recorded on a Perkin Elmer 100 instrument by averaging 50 scans with a resolution of 2 cm^{-1} measuring in absorbance mode by using the KBr self-supported pellet technique.

43. *Preparation of the catalyst*: the AlKIT-5 materials with different n_{Si}/n_{Al} ratios were synthesized using polymeric Pluronic F127 as a template, and tetraethyl orthosilicate (TEOS) and aluminium isopropoxide as the sources of silicon and aluminium, respectively. In a typical synthesis, pluronic F127 (5 g) was dissolved in concd HCl (3 g, 35 wt %) and distilled water (240 g). To this mixture, TEOS (24 g) and the required amount of the aluminium source were added, and the resulting mixture was stirred for 24 h at 45 °C. Subsequently, the reaction mixture was heated for 24 h at 100 °C under static condition for hydrothermal treatment. After hydrothermal treatment, the final solid product was filtered off and then dried at 100 °C without washing. The white coloured product was calcined at 540 °C for 10 h. The samples are denoted as AlKIT-5(x) where x denotes the n_{Si}/n_{Al} ratio in the final product. The molar gel composition of the reaction mixture was 1.0:0.041–0.071:0.0035:0.25:116.6 SiO_2–Al_2O_3–F127–HCl–H_2O.[39,40]
44. *General procedure for the synthesis of DHPMs*: a solution of aldehyde (1.0 mmol), ethyl acetoacetate (156 mg, 1.2 mmol), and urea (72 mg, 1.2 mmol) in acetonitrile (6 ml) was heated under reflux conditions in the presence of AlKIT-5(10) catalyst (150 mg) for 3.0–4.0 h. Completion of the reaction was monitored by TLC. The reaction mixture was then poured onto crushed ice and the solid product separated was filtered and recrystallized from methanol. All products were characterized by spectral (NMR and IR) data and by comparison with those of authentic samples and also by the melting points of the samples mixed with the authentic ones[18]. The spectral data of some of the compounds are given below. Compound (**4g**): solid, mp 193–194 °C. ^{1}H NMR (DMSO-d_6): δ 1.15 (t, 3H, J=6.8 Hz), 2.37 (s, 3H), 4.10 (q, 2H, J=6.8 Hz),5.35 (s, 1H), 5.82 (br s, NH), 6.84 (m, 1H), 7.05–7.10 (m, 5H),7.45 (m, 3H), 8.40 (br s, NH). EIMS: m/z 352 (M^+), 323, 279,183, 155, 137, 91, 69. IR (KBr): ν 3242, 3112, 2981, 1712,1654, 1582, 1487, 1245, 1097, 786. Anal. Calcd for $C_{20}H_{22}N_2O_4$ (354.16): C, 67.78; H, 6.26; N, 7.90; O, 18.06. Found: C, 67.79; H, 6.26; N, 7.94; O, 18.10. Compound (**4k**): solid, mp 229–231 °C (lit. 232–235 °C). ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3H, J=7.0 Hz), 2.50 (s, 3H), 3.95(q, 2H, J=7.0 Hz), 4.24 (d, 1H, J=6.0 Hz), 6.0 (d, 1H, J=16.4 Hz), 6.2 (d, 1H, J=16.4 Hz), 7.20–7.25 (m, 5H), 7.45 (d, NH, J=1.7 Hz), 8.95 (br s, NH). EIMS: m/z 286 (M^+), 252, 224,196, 149, 84. IR (KBr): ν 3335, 3242, 3098, 2978, 1689, 1642,1492, 1373, 1218, 1121, 785. Anal. Calcd for $C_{16}H_{20}N_2O_3$ (288.15): C, 66.65; H, 6.99; N, 9.72; O, 16.65. Found: C, 66.68; H, 6.99; N, 9.75; O, 16.67.