Research Article

Ceric Ion Loaded MCM-41 Catalyzed Synthesis of Substituted Mono- and Bis-dihydropyrimidin-2(1*H*)-ones

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An effective one-pot three-component reaction of aromatic aldehydes with 1,3-diketone and urea or thiourea under solvent-free condition leads to the formation of mono- and bis-dihydropyrimidin-2(1*H*)-ones using Ce-MCM-41 as a recyclable solid acid catalyst. This method has several advantages like simple and easy work-up with shorter reaction time, reusability of catalyst, and high yields of Biginelli products.

1. Introduction

Multicomponent reactions (MCRs) have been received significantly as a valuable synthetic tool in the field of modern organic synthesis and drug discovery research due to their ability to synthesize target compounds with greater efficiency in single step operations of three or more different mono-functionalized reactants. Moreover, MCRs offer some distinct advantages including atom economy, structural variations, complexity of molecules, and simplicity over conventional step by step synthetic procedures [1–8].

Biginelli reaction is a well-known, simple, and straightforward method for the synthesis of 3,4-dihydropyrimidinones (DHPMs) which involves the three-component condensation of an aliphatic or aromatic aldehyde, β -ketoester, and urea or thiourea. The original reaction was first reported by Biginelli in 1893 catalyzed by mineral acids [9]. Different functionalized 3,4-DHPMs synthesized have exhibited a variety of pharmacological activities such as calcium channel modulation [10], mitotic kinesin Eg5 inhibition (monastrol) [3], antiviral [11], antibacterial, antifungal [12], and anticancer [13]. DHPMs are also used as starting materials for the synthesis of so called “superstatin” rosuvastatin, a selective and competitive inhibitor of HMG-CoA reductase [14], the enzyme responsible for the biosynthesis of cholesterol. Moreover, the 3,4-DHPM motif is present in many products isolated from natural material like several species of sponges.

Due to the wide range applications, several methods have been reported for the synthesis of dihydropyrimidinones that include the utilization of $\text{BF}_3 \cdot \text{OEt}_2 / \text{CuCl}$ [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 Bronsted acids, such as *p*-toluenesulfonic acid [24], silica sulfuric acid [25], KHSO_4 [26], and also solid acids like montmorillonite KSF [27], natural HEU-type zeolite [28], and HY-zeolite [29]. However, many of these reported methods suffer from drawbacks such as low yield of products, harsh reaction conditions and long experimental procedures, and toxic and costly catalysts. Therefore, there is a need to develop new catalysts which are easily available or prepared, cost-effective, recoverable, and environment friendly and almost all these requirements may be easily met by the supported reagents. In this paper, we wish to report for the first time a simple, facile, and highly efficient method for the synthesis of 3,4-dihydropyrimidin-2-ones in excellent yields by the three-component reaction of aldehydes, urea, and β -ketoester using Ce-MCM-41 as a solid heterogeneous catalyst.

2. Experimental

2.1. Materials. All aldehydes, β -ketoesters, urea, and thiourea were purchased from commercial sources and used without

FIGURE 1: EDX and SEM image of MCM-41 material.

purification. All reactions were performed in a reaction vessel open to the atmosphere and monitored by thin layer chromatography (TLC). ^1H and ^{13}C NMR spectra were recorded on 400-MHz Bruker spectrometer. Fourier transform infrared (FT-IR) spectra were obtained using KBr technique.

2.2. Catalyst Preparation

2.2.1. Synthesis of MCM-41. About 1.988 g of cetyl trimethyl ammonium bromide (CTAB, 98%) was dissolved in 120 mL of water at room temperature. After complete dissolution, 8 mL of aqueous ammonia (32% in water) was added and then 10 mL of tetraethyl orthosilicate (TEOS, 99%) was added with vigorous stirring (300 rpm). The hydrolysis of TEOS happened during the first 2 min at room temperature (the solution becomes milky and slurry forms) and the condensation of the mesostructured hybrid material was achieved after 2 h of reaction. The material was then filtered and allowed to dry under static air at 80°C for 12 h. The mesoporous material was finally obtained by calcining the hybrid structure at 550°C for 5 h.

2.2.2. Preparation of Ce(IV) Loaded MCM-41. 0.1 g of activated MCM-41 was added into the acetone solution of 0.11 g of ceric ammonium nitrate (CAN). The yellow colored mixture was slowly evaporated to dryness with stirring. The yellow solid has been warmed slightly to make it completely dry. Then the solid was calcined for about 1 h to remove the nitrate ions (liberated as yellow fumes). After calcinations, the yellow colored powder was kept for activation in muffle furnace for 4 h yielding the catalyst with 20 mol% of ceric ions. Various concentrations of ceric ion such as 10%, 20%, 30%, and 40% were loaded on MCM-41 employing the above method.

2.2.3. Characterization

2.2.4. SEM and EDX Analysis. Figures 1, 2, 3, and 4 show the surface morphology and EDX analysis of MCM-41, 10,

20, and 30 mol% of ceric ion loaded MCM-41. The particle size of the Ce containing MCM-41 material was ranging from 200 to 350 nm. Here, the size of the nanoparticles decreased compared to the particle size of normal MCM-41. This may be attributed to the addition of ceric ion onto MCM-41 which prevents the agglomeration of the particles. The EDX analysis result shows the presence of cerium, oxygen, and silicon at 21.59 wt%, 41.87 wt%, and 36.54 wt%, respectively, which proves the formation of ceric ion functionalized MCM-41. SEM micrographs for the calcined blank MCM-41 along with the 10 mol% Ce-MCM-41, 20 mol% Ce-MCM-41, and 30 mol% Ce-MCM-41 composites are shown in Figures 1, 2, 3, and 4, respectively. Spherical particles formation was observed for the MCM-41 material, and this spherical morphology was preserved for the composite materials.

2.3. General Synthetic Procedure for the Preparation of DHPM Derivatives (4a–v). A mixture of aldehyde (1 mmol), β -ketoester (1 mmol), urea or thiourea (1.5 mmol), and Ce-MCM-41 (100 mg) was finely ground and heated at 80°C for specified time. After the reaction, the crude product from the reaction mixture was dissolved in hot ethanol and the catalyst was separated by filtration. The filtrate was suspended in water to precipitate the resulting product. The solid product was then crystallized from hot ethanol.

2.4. General Synthetic Procedure for the Preparation of Bis-DHPM Derivatives (5a–d). A mixture of bis-aldehyde (1 mmol), β -ketoester (2 mmol), urea or thiourea (3 mmol), and Ce-MCM-41 (100 mg) was finely ground and heated at 80°C for specified time. After the reaction, the pure product can be discovered by the above procedure.

2.5. Product Characterization. All the mono- and bis-dihydropyridimin-2-one or pyrimidine-2-thione derivatives are known and were characterized by their m.p., IR, ^1H , and ^{13}C -NMR spectral data.

FIGURE 2: EDX and SEM image of 10 mol% Ce loaded MCM-41 material.

FIGURE 3: EDX and SEM image of 20 mol% Ce loaded MCM-41 material.

2.6. Reusability. After completion of the reaction, the catalyst recovered by simple filtration from the reaction mixture was repeatedly washed with ethanol and the catalyst was reused after activation for successive experiments under similar reaction conditions.

3. Results and Discussion

Biginelli reaction deals with the condensation of aldehydes and 1,3-dicarbonyl compounds with urea leading to the formation of dihydropyrimidinone (DHPM) derivatives (Scheme 1).

Initially, we have tried to carry out the condensation of benzaldehyde, ethyl acetoacetate, and urea in various organic

solvents under reflux conditions using 100 mg of 20 mol% of ceric ion loaded MCM-41 as a catalyst. Due to the environmental concerns, we have tried this reaction under solvent-free conditions also. Among the different organic solvents studied, no major difference was observed in the yields of the products, but the solvent-free conditions remained to be the best in terms of reaction time and yield. This may be due to the close proximity of substrates in the solid state reactions rather than in solvent medium (Table 1). Biginelli reaction of benzaldehyde, ethyl acetoacetate, and urea under the described reaction conditions did not proceed in the absence of catalyst, whereas in the presence of 10 mol% ceric ion loaded MCM-41 as catalyst under classical heating resulted in 39% of yield even after longer reaction time, indicating that

FIGURE 4: EDX and SEM image of 30 mol% Ce loaded MCM-41 material.

SCHEME 1: Ce-MCM-41 catalyzed synthesis of DHPMs.

ceric ion is the main promoter for this reaction. Maximum amount of conversion has been achieved by using 20 mol% of ceric ion loaded MCM-41 as a catalyst.

Impressed by the high conversion, we have carried out the above reaction using terephthalaldehyde instead of other monoaromatic aldehydes, with ethyl or methyl acetoacetate and urea or thiourea under same reaction conditions where the yield of about 78–85% has been achieved (Scheme 2).

The mechanism for Biginelli condensation is well reported in the literature [9]. With supported reagent, the proposed mechanism for the Biginelli reaction may involve the solid acid catalyzed formation of an intermediate of the type **I** from aldehyde and urea components. Interception of the iminium ion by ethyl acetoacetate produces an open chain ureide **II** which subsequently cyclizes to the dihydropyrimidinones **III** (Figure 5).

3.1. Effect of Reaction Temperature. To evaluate the effect of reaction temperature, Biginelli condensation of benzaldehyde,

urea, and ethyl acetoacetate in the presence of Ce-MCM-41 was carried out at different temperatures. At room temperature the reaction rate was found to be very slow and was increased with increase in temperature. At 80°C, the maximum reaction rate was observed and further increase in temperature did not show any significant raise on the yields (Tables 2 and 3).

3.2. Characterization of Products

3.2.1. 5-Ethoxycarbonyl-6-phenyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-one (4a). Colorless needles; Mp 157–159°C; (Yield 94%); IR: ν_{max} (KBr) 3384, 3309, 3224, 3116, 3058, 3031, 3006, 2988, 2979, 2960, 2934, 2902, 1703, 1667, 1637, 1600, 1494, 1473, 1456, 1445, 1413, 1396, 1372, 1350, 1335, 1291, 1281, 1267, 1247, 1187, 1159, 1130, 1099, 1030, 1014 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (400 MHz, DMSO- d_6) 1.10 (3H, t, CH_2CH_3), 3.71 (2H, q, CH_2CH_3), 5.24 (1H, d, CH), 7.27–7.31 (3H, m), 7.36–7.43 (7H, m), 7.85 (1H, d, NH), 9.28 (1H, s, NH).

3.2.2. 5-(Ethoxycarbonyl)-4-(p-anisyl)-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one (4b). White solid; Mp 203–204°C;

SCHEME 2: Ce-MCM-41 catalyzed synthesis of 1,4-phenylene-bis-pyrimidones.

TABLE 1: Synthesis of DHPMs using different catalysts under different reaction conditions^a.

S. no.	Catalyst	Solvent	Time (h)	Yield ^b (%)
1	MCM-41	EtOH	6.0	44
2	SO ₄ -MCM-41	EtOH	4.5	48
3	Ce-MCM-41	MeOH	4.0	61
4	Ce-MCM-41	EtOH	3.5	64
5	Ce-MCM-41	CHCl ₃	4.0	53
6	Ce-MCM-41	CH ₃ CN	4.0	58
7	Ce-MCM-41	Solvent free	1.0	94

^aCondensation of benzaldehyde, EAA, and urea with 20 mol% of Ce-MCM-41 (100 mg).^bIsolated yield.TABLE 2: Ce-MCM-41 catalyzed synthesis of 3,4-dihydropyrimidinones^a.

S. no.	R ¹	R ²	X	Product	Time (h)	Yield (%) ^b
1	H	Et	O	4a	1.0	94
2	4-OMe	Et	O	4b	1.5	90
3	4-Cl	Et	O	4c	1.0	93
4	4-NO ₂	Et	O	4d	1.5	89
5	4-OH	Et	O	4e	1.5	88
6	2-OH	Et	O	4f	2.0	87
7	2-Cl	Et	O	4g	1.5	84
8	3-NO ₂	Et	O	4h	2.0	86
9	2-NO ₂	Et	O	4i	1.0	81
10	H	Me	O	4j	1.0	93
11	4-Cl	Me	O	4k	1.0	90
12	4-NO ₂	Me	O	4l	1.5	87
13	3-NO ₂	Me	O	4m	2.0	85
14	2-OH	Me	O	4n	1.5	83
15	4-OCH ₃	Me	O	4o	2.0	89
16	H	Et	S	4p	1.0	89
17	4-Cl	Et	S	4q	1.5	91
18	4-NO ₂	Et	S	4r	1.5	86
19	3-NO ₂	Et	S	4s	1.5	84
20	H	Me	S	4t	1.0	90
21	4-Cl	Me	S	4u	1.0	91
22	4-NO ₂	Me	S	4v	1.5	87

^aCe-MCM-41 catalyzed Biginelli reaction under solvent-free conditions.^bIsolated yields.

TABLE 3: Ce-MCM-41 catalyzed synthesis of 1,4-phenylene-bis-dihydropyrimidinones^a.

S. no.	R ¹	X	Product	Time (h)	Yield (%) ^b
1	Et	O	5a	1.0	84
2	Et	S	5b	1.25	80
3	Me	O	5c	1.0	82
4	Me	S	5d	1.25	79

^aCe-MCM-41 catalyzed Biginelli reaction under solvent-free conditions.^bIsolated yields.

FIGURE 5: Plausible mechanism for the Ce-MCM-41 catalyzed Biginelli reaction.

(Yield 90%); IR (KBr) ν : 3246, 3111, 1709, 1649, 1462, 1285, 1089, 787 cm^{-1} ; $^1\text{H-NMR}$ $\delta(\text{ppm})$ (400 MHz, DMSO-d_6): 2.01 (3H, t, CH_3), 2.92 (3H, s, CH_3), 3.91 (2H, q, CH_2), 5.14 (1H, d, CH), 6.85 (3H, m), 7.23 (1H, d), 7.74 (1H, br s, NH), 9.15 (1H, s, NH). ^{13}C (DMSO-d_6) $\delta(\text{ppm})$: 165.8, 158.9, 152.6, 148.4, 137.5, 127.8, 127.7, 114.1, 114.0, 100.0, 59.9, 55.5, 53.8, 18.2, 14.5.

3.2.3. 5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4c). White needles; Mp 230–232°C; (Yield 93%); IR: ν_{max} (KBr) 3243, 3118, 2981, 1702, 1648, 1575, 1490, 1461, 1422, 1367, 1323, 1292, 1220, 1182, 1170, 1088, 1026, 1011 cm^{-1} ; $^1\text{H-NMR}$ $\delta(\text{ppm})$ (400 MHz, DMSO-d_6) 1.09 (3H, t, CH_2CH_3), 2.24 (3H, s, CH_3), 3.95 (2H, q, CH_2CH_3), 5.13 (1H, d, CH), 7.23 (2H, d), 7.37 (2H, d), 7.77 (1H, br s, NH), 9.24 (1H, br s, NH).

3.2.4. 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4d). White needles; Mp 216–217°C (Yield 89%); IR: ν_{max} (KBr) 3353, 3228, 3113, 2979, 1697, 1639, 1572, 1454, 1369, 1321, 1299, 1255, 1227, 1145, 1096, 1027 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) $\delta(\text{ppm})$ 1.01 (3H, t, CH_2CH_3), 2.31 (3H, s, CH_3), 4.11 (2H, q, CH_2CH_3), 5.34 (1H, d, CH), 7.08–7.33 (3H, m, arom.), 7.40 (1H, d, arom.), 7.71 (1H, br s, NH), 9.28 (1H, s, NH). ^{13}C NMR: $\delta(\text{ppm})$ 193.96, 151.93, 151.55, 149.09, 148.97, 146.69, 127.69, 123.83, 109.46, 53.13, 53.04, 40.33, 40.05, 39.76, 39.50, 39.22, 38.94, 38.67, 30.65, 19.12, 19.05.

3.2.5. Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4g). Bright yellow needles

(Yield 84%); Mp 212–214°C; IR: ν_{max} (KBr) 3479, 3325, 3252, 3125, 2962, 1718, 1703, 1652, 1606, 1583, 1557, 1463, 1377, 1349, 1319, 1287, 1223, 1173, 1142, 1089, 1014 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (400 MHz, DMSO-d_6) 0.74 (3H, t, CH_2CH_3), 2.31 (3H, s, CH_3), 3.69–3.80 (2H, m, CH_2CH_3), 5.29 (1H, d, CH), 7.52 (1H, d), 7.58–7.61 (1H, m), 7.90 (1H, br s, NH), 8.21–8.24 (2H, m), 9.38 (1H, s, NH).

3.2.6. 5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4h). Yellow solid; Mp 222–224°C; (Yield 86%); $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) $\delta(\text{ppm})$ 1.09 (3H, t, CH_2CH_3), 2.27 (3H, s, CH_3), 4.00 (2H, q, CH_2CH_3), 5.30 (1H, d, CH), 7.71 (2H, m), 7.91 (1H, s), 8.15 (1H, s), 8.15 (1H, br s, NH), 9.28 (1H, s, NH).

3.2.7. Methyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4j). White crystal (Yield 93%), Mp 208–210°C; IR: ν_{max} (KBr) 3246, 1732, 1664 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) $\delta(\text{ppm})$ 2.2 (s, 3H, $-\text{CH}_3$), 2.6 (s, 3H, $-\text{COOCH}_3$), 5.32 (d, 1H, $-\text{CH}$), 7.35 (m, 5H), 7.94 (s, 1H, H), 9.30 (s, 1H, NH). ^{13}C NMR $\delta(\text{ppm})$ 194.29, 152.15, 152.11, 152.09, 148.14, 148.02, 144.23, 128.54, 127.36, 126.44, 109.59, 53.80, 53.70, 40.33, 40.05, 39.78, 39.50, 39.22, 38.94, 38.67, 30.33, 18.92, 18.85.

3.2.8. Ethyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (4p). Colorless needles; Mp 149–150°C; (Yield 89%); $^1\text{H-NMR}$ δ_{H} (400 MHz, DMSO-d_6) 1.10 (3H, t, CH_2CH_3), 3.71 (2H, q, CH_2CH_3), 5.24 (1H, d, CH),

7.27–7.31 (3H, m), 7.36–7.43 (7H, m), 7.85 (1H, d, NH), 9.28 (1H, s, NH).

3.2.9. Diethyl-4,4'-(1,4-phenylene)-bis-(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) (5a). Mp 318–320°C; (Yield 84%); IR: ν_{max} (KBr) 3329, 3110, 2972, 1692, 1246 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ (ppm) 9.12 (sbr, 2H, NH), 7.72 (s, 2H, NH), 7.06 (s, 4H, Ar), 5.31 (d, 2H, CH), 3.77 (q, 4H, CH_2CH_3), 2.21 (s, 6H, Me), 1.05 (t, 6H, CH_2CH_3); ^{13}C NMR δ (ppm) 172.2, 153.9, 149.2, 146.7, 132.2, 100.1, 60.1, 49.5, 18.6, 13.9.

3.2.10. Dimethyl-4,4'-(1,4-phenylene)-bis-(6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) (5c). Mp 314–316°C; (Yield 82%); IR: ν_{max} (KBr) IR (KBr): 3228, 3119, 1694 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ (ppm) 2.25 (s, 6H), 3.48 (s, 6H), 5.17 (d, 2H), 7.09 (s, 4H), 7.68 (s, 2H), 9.21 (s, 2H). ^{13}C NMR δ (ppm) 8.64, 51.23, 53.19, 125.17, 130.79, 144.63, 147.35, 151.11.

4. Conclusion

Synthesis of mono- and bis-dihydropyrimidin-2(1H)-ones (DPHMs) has been achieved using 20 mol% of ceric ion loaded MCM-41 as a catalyst under solvent-free conditions. The present method has some distinct advantages in terms of simple manipulation with the use of ordinary laboratory reagents, their inexpensiveness and nontoxic nature, and excellent yields. The above things make the current procedure an attractive addition to existing methodologies.

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