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Highly efficient multicomponent Biginelli's synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by Al-MCM-41 under solvent-free conditions

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ABSTRACT

In this study, an efficient and green process for the synthesis of dihydropyrimidin-2(1H)-ones (DHPMs) via a clean multi-component Biginelli reaction has been developed. The synthesis was performed by condensation aromatic benzaldehydes, ethyl acetoacetate and urea using mesoporous aluminosilicate Al-MCM-41 as a heterogeneous catalyst and microreactor under solvent-free conditions and at 80 ℃. The advantages of this method are easy work-up procedure, clean and neutral reaction conditions. The separation and reuse of the solid acid nanocatalyst Al-MCM-41 were simple and could be reused without a significant loss of catalytic activity. Moreover, the products were achieved in good to excellent yields (78-94%).

***Keywords**: Biginelli reaction; Al-MCM-41; Dihydropyrimidinones; Heterogeneous catalyst.*

1. Introduction

Since the first successful synthesis of highly ordered and porous silica phases M41S by Mobil's researchers in 1992 [1,2], MCM-41 molecular sieves have received much attention and become the most popular member of the mesoporous silicates [3]. MCM-41 consists of hexagonal channels and possesses some advantageous properties, such as extremely high surface area (~1000 m^2/g), narrow pore size distribution, controllable pore size ranging from 2 to 100 nm, high thermal stability [4-6], leading to many potential applications, such as catalysis and adsorption, sensors, nanoelectronics, enzyme encapsulation, and drug delivery [7].

Moreover, it is well known that catalytic activity of MCM-41 increases by introducing aluminum inside the pore walls [8-10]. Aluminum incorporated MCM-41, Al-MCM-41, shows remarkable acidic properties and has been found to catalyze several organic transformations under vapor phase or high-temperature reaction conditions. Furthermore, Al-MCM-41 could catalyze liquid-phase reactions under mild reaction conditions [11-15].

Over a century ago, the italian chemist pietro biginelli reported the acid-catalyzed one-pot condensation reaction of ethyl acetoacetate, benzaldehyde, and urea for the synthesis of dihydropyrimidine derivatives [16]. Due to the important role in organic and medicinal chemistry, recently, newer catalytic systems have been developed to improved reaction conditions [17-19]. However, many of these methods are associated with expensive and highly acidic catalysts, long reaction times, unsatisfactory yields, difficult product isolation and incompatibility with wide range of functional groups [20-22]. Hence, it is still desirable to develop novel strategies for this important transformation.

In continuation of our effort to introduce new catalytic processes with a lower environmental impact [23-26], herein we report a general synthetic method for the synthesis of dihydropyrimidinones (DHPMs) via Biginelli three-component condensation, using Al-MCM-41[27] as a highly efficient heterogeneous catalyst.

2. Experimental

2.1. General

All chemical materials were purchased from Aldrich and Merck Chemical companies and used without further purification. Products were characterized by comparison of their physical data, IR, ^1H & ^{13}CNMR spectra with known samples. NMR spectra were recorded in $CDCl_3$ or on a Bruker Advance DPX 400

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MHz instrument spectrometer using TMS as internal standard. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrometer. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

2.2. General procedure for the synthesis of dihydropyrimidinones

A neat mixture of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (3 mmol) and 100 mg Al-MCM-41 was stirred with heating in oil bath at 80 ºC (table 2). After completion of the reaction that was monitored by TLC (*n*-hexane: ethyl acetate; ratio=5:1), the reaction mixture was cooled and washed with water. The obtained crude product was dissolved in hot ethanol and filtered to remove the catalyst. The combined filtrates were evaporated under reduced pressure to give the desired product. The solid crude products were recrystallized from ethanol.

Selected spectral data

*Compound (**4f**):*

^{1}HNMR (400 MHz, DMSO): δ= 1.04-1.12 (3H, t, C$\underline{H}_3$-C$\underline{H}_2$), 2.23 (3H, s, C$\underline{H}_3$), 2.26 (3H, s, p-C$\underline{H}_3$), 3.95-4.00 (2H, q, C$\underline{H}_2$), 5.10 (1H, s, C$\underline{H}$), 7.12 (4H, s, Ar), 7.70 (1H, s, NH), 9.17 (1H, s, NH) ppm.

*Compound (**4g**):*

^{1}HNMR (400 MHz, DMSO): δ= 1.05-1.10 (3H, t, C$\underline{H}_3$-C$\underline{H}_2$), 2.25 (3H, s, C$\underline{H}_3$), 3.95-4.00 (2H, q, C$\underline{H}_2$), 5.14 (1H, s, C$\underline{H}$), 7.12-7.28 (4H, m, Ar), 7.76 (1H, s, NH), 9.23 (1H, s, NH) ppm.

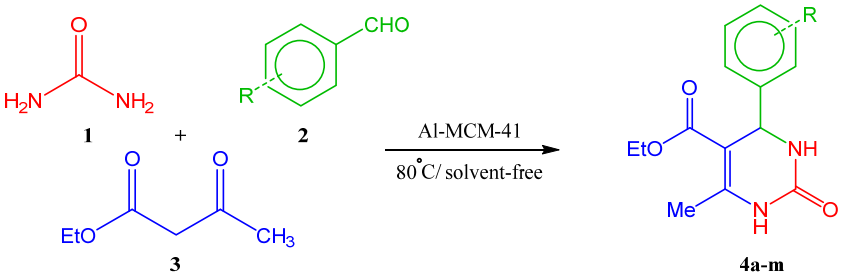
*Compound (**4h**):*

^{1}HNMR (400 MHz, DMSO): δ= 1.11(3H, t, C$\underline{H}_3$-C$\underline{H}_2$), 2.23 (3H, s, C$\underline{H}_3$), 2.86 (6H, s, NC$\underline{H}_3$), 3.95 (2H, q, C$\underline{H}_2$), 5.04 (1H, s, C$\underline{H}$), 6.64 (2H, d, Ar), 7.02 (2H, d, Ar), 7.60 (1H, s, NH), 9.10 (1H, s, NH) ppm.

3. Results and Discussion

The synthetic utility of this modified mesoporous was studied by the preparation of dihydropyrimidine derivatives via Biginelli three-component condensation (Scheme 1).

Short reaction times with high to excellent yields express the effect of the catalyst on accelerating the reactions. The effects of the solvent and molar ratio of the catalyst to substrate were investigated. The reaction was carried out in different solvents such as ethanol, dichloromethane, acetonitrile, water and under solvent-free conditions. The results in table 1 were clearly shown that although ethanol was the best solvent among those tested, the best result was obtained under solvent-free conditions. Also, our results showed that it was necessary to control the molar ratio of the reactant. The product was obtained in higher yield when the molar ratio of ethyl acetoacetate: benzaldehyde: urea was 1:1:1.5 using 50 mg of catalyst.



Scheme 1. Synthesis of dihydropyrimidinones

Table 1. Optimization of reaction condition for the synthesis of 4a.

Entry	Amount of catalyst (mg)	Condition	Solvent	Time (min)	Result
1	50	reflux	ethanol	60	85%
2	50	reflux	dichloromethane	60	36%
3	50	reflux	acetonitrile	60	47%
4	50	reflux	water	60	Nil
5	50	120 ˚C	neat	30	65%
6	50	80 ˚C	neat	30	94%
7	50	60 ˚C	neat	30	65%
8	25	80 ˚C	neat	30	40%
9	-	80 ˚C	-	60	35%

Then, the generality of this method was examined by the reaction of several substituted aldehydes, ethyl acetoacetate, and urea using Al-MCM-41 as a heterogeneous catalyst under solvent-free conditions (Table 2).

It is noteworthy that the nature and position of the electron-withdrawing or electron-donating substituent had no significant effect on the reaction rate and yield. All of the aldehydes with different substituents on aryl ring (-NO_2, -Cl, -Br, -OCH_3) were well tolerated and produced the desired products.

As seen in table 1 (entry 9), in the absence of any catalyst the reaction proceeded slowly and the corresponding product was obtained in low yield. It is believed that, Al-MCM-41 can catalyze the formation of dihydropyrimidine in two ways. Firstly, this catalyst can provide the necessary microenvironment for the substrates to be in the vicinity of each other for carrying out the reactions. Secondly, the hydroxyl functionalities on the Al-MCM-41 can interact through H-bonding with the oxygen of the ethyl acetoacetate and benzaldehyde to facilitate the interception of the *N*-acyliminium ion by ethyl acetoacetate and consequently the ring was closed by the nucleophilic attack by the amine on the carbonyl group (Scheme 2).

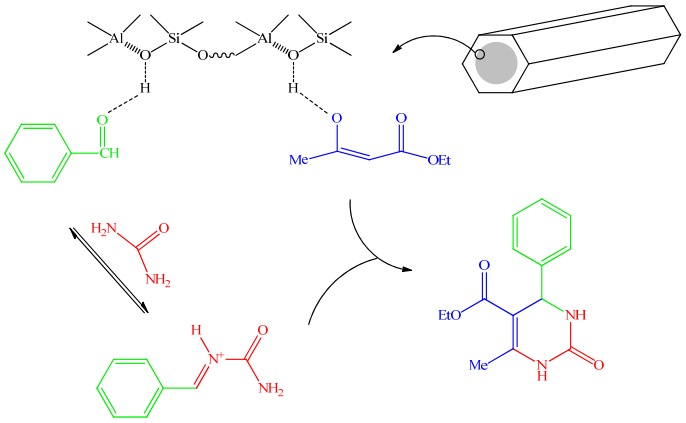
After completion of the reactions the spent catalyst was filtered and washed with hot ethanol, washed and dried. The Al-MCM-41 could be used as catalyst for three times without considerable loss in its efficiency (Yield was 94, 90 and 89 for three times).

To show the efficiency and superiority of using Al-MCM-41 as catalyst for the synthesis of DHPMs, this procedure has been compared with that of the previously reported methods in Table 3. The results of this comparison study revealed that the current catalyst accelerated the rate of the reaction considerably at the same time as providing a high yield of the desired product.

Table 2. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by Al-MCM-41 under solvent-free conditions[a].

Entry	R	Time (h)	Yield (%)[b]	m.p. (˚C)		Ref.
				Found	Reported	
a	H	0.5	94	201-203	200-202	[22]
b	4-NO_2	0.25	84	205-207	205-207	[22]
c	4-MeO	0.25	88	199-200	199-201	[20]
d	4-Cl	0.25	83	208-2010	209-211	[28]
e	2-Cl	0.15	90	222-224	223-224	[20]
f	4-CH_3	0.25	82	170-173	170-172	[24]
g	4-F	0.15	85	183-185	182-184	[28]
h	4-$(CH_3)_2N$	1.5	92	254-256	256-258	[28]
i	2,4,6-$(CH_3O)_3$	0.5	83	181-183	180-182	[24]
j	2-OH	2.25	78	202-204	201-202	[28]
k	4-Br	0.25	88	207-209	205-208	[24]
l	5-Br,2-OH	0.75	92	230-232	231-233	[28]
m	4-CN	0.15	82	163-165	160-164	[24]

[a]Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol) and 50 mg Al-MCM-41 at 80 ˚C.
[b]Isolated yields.



Scheme 2. Postulated roles of Al-MCM-41 in Biginelli reaction.

Table 3. Comparison of various catalytic protocols with Al-MCM-41 for the reaction of benzaldehyde, ethyl acetoacetate and urea.

Entry	Catalyst, condition	Time	Yield (%)	Ref.
1	$Cu(OTf)_2$, 100 °C, Microwave	60 min	Quantitative	[20]
2	$Y(OAc)_3.xH_2O$, AcOH, reflux	4 h.	92	[22]
3	quinine-derived amine, HCl, THF, 0 °C	6 d.	81	[29]
4	Zeolite, EtOH, reflux	24 h.	62.5	[30]
5	PPA-SiO_2, reflux	30 min	85	[31]
6	Al-MCM-41, 80 °C, Solvent-Free	30 min	94	This work

4. Conclusions

In summary, we described a novel and efficient method for the synthesis of dihydropyrimidines in the presence of Al-MCM-41 as a heterogeneous catalyst. This method offers several advantages including mild reaction conditions, high conversions, short reaction times, clean reaction profiles, reusability of the catalyst, which makes it a useful and attractive process for the synthesis of dihydropyrimidines.

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