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SHORT COMMUNICATION

MESOPOROUS MOLECULAR SIEVE MCM-41 CATALYZED ONE-POT SYNTHESIS OF 3,4-DIHYDRO-2(1*H*)-PYRIMIDINONES AND –THIONES UNDER SOLVENT-FREE CONDITIONS

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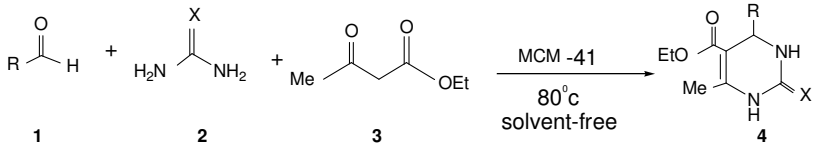
ABSTRACT. An efficient synthesis of 3,4-dihydro-2(1H)-pyrimidinones and -thiones using MCM-41 as the catalyst from an aldehyde, β-keto ester, and urea or thiourea under solvent-free conditions is described.

KEY WORDS: Biginelli reaction, Dihydropyrimidinones, MCM-41, One-pot, Reusable

INTRODUCTION

3,4-Dihydropyrimidin-2(1H)-ones and their sulfur analogs (DHMPs) have been reported to possess diverse pharmacological activities such as antiviral, antibacterial, antitumor, antiflammatory and antihypertensive activity as well as efficacy as calcium channel blockers and α-antagonists [1-4]. Some marine alkaloids recently isolated have been attributed to the presence of a dihyhropyrimidinone moiety and also exhibit interesting biological activities [5]. In addition, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in nature and in potent HIVgp-120-CD_4 inhibitors [6-8]. Thus, the synthesis of dihydropyrimidinones is an ongoing active program in recent years. In the literature, there are many reported methods for the preparation of dihydropyrimidinones employing Lewis acids such as BF_3 [9], $FeCl_3$ [10], $InCl_3$ [11], $ZrCl_4$ [12], $BiCl_3$ [13], $Mn(OAc)_3$ [14], $LiClO_4$ [15], and LiBr [16]. However, many of these methods have some drawbacks such as low yields of the products, long reaction times, high temperature, harsh reaction conditions, difficulties in workup, the use of stoichiometric amounts of catalysts, and the use of metal halides as catalysts. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the workup procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst in terms of operational simplicity, reusability, economic viability, and greater selectivity. The possibility of performing multi-component reactions under solvent-free conditions with solid catalysts could enhance their efficiency from an economic as well as ecological point of view, so solvent free chemical reactions have received much attention. Hence, we report a simple and efficient procedure for the synthesis of dihydropyrimidinones using MCM-41 as a reusable catalyst under solvent-free conditions (Scheme 1).



Scheme 1

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RESULTS AND DISCUSSION

Since the discovery of mesoporous molecular sieves MCM-41 by Mobile [17, 18] in 1992, it has attracted considerable attention for its potential use in catalytic reactions. MCM-41 (Mobil Catalytic Material Number 41) has a hexagonal array of cylindrical pores, cubic ordered pores and lamellar structure, respectively. The main characteristics of this material are large surface areas and very narrow pore size distributions [19-23]. In fact, it has a space enough to accommodate the guest molecules and is used in catalytic reactions [24, 25]. During the course of our studies directed the development of practical, and environmentally friendly procedures for some important transformations [26-29], we developed for the first time the applicability of a novel recyclable heterogeneous MCM-41 for efficient, convenient and facile synthesis of 3,4-dihydro-2(1H)-pyrimidinones and –thiones. Because 3,4-dihydropyrimidin-2(1H)-ones are important biologically active compounds, which have potential medical applications, improvement and the development of a preparation of this type of compound using MCM-41 are worthy of study. The reaction occurred under solvent-free condition and offered several advantages in preparative procedures, such as environmental compatibility, simplifying work-up, formation of cleaner products, reduction of by products. This three component reaction proceeded smoothly and rapidly to give the corresponding dihydropyrimidinones in the presence of catalytic amount of MCM-41 (Scheme 1) in high yields (Table 1). As shown in Table 1, aromatic aldehydes containing both electron donating or withdrawing groups gave the desired products in good yields.

Table 1. MCM-41 catalyzed synthesis of dihydropyrimidinones and thiones.

Entry	R	X	Product	Time (h)	M.p. (ºC)		Yield (%)[a]
					Observed	Reported	
1	Ph	O	**4a**	1	204	202-203 [30]	80
2	4-Me-Ph	O	**4b**	1	214-215	214-216 [31]	78
3	4-MeO-Ph	O	**4c**	1	202-204	199-201 [32]	77
4	4-NO_2-Ph	O	**4d**	1	209-210	206-208 [30]	70
5	4-Cl-Ph	O	**4e**	1	216	216-217 [30]	80
6	3-NO_2-Ph	O	**4f**	1	231	231-235 [31]	68
7	Ph	S	**4g**	1	208-209	208-210 [31]	79
8	4-Cl-Ph	S	**4h**	1	208-210	209-210 [32]	78

[a]Isolated yields.

Table 2. Comparison the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4a**) using different catalysts.

Entry	Catalyst	Time (h)	Yield (%)	References
1	Sulfuric acid	18	71	[33]
2	Zeolite	12	80	[34]
3	$BF_3.OEt_2$/CuCl	18	71	[13]
4	Montmorillonite KSF	48	82	[35]
5	$InBr_3$	7	83	[36]
6	12-Tungstophosphoric cid	6-7	80	[37]
7	HEU	4-5	75	[38]
8	$LaCl_3$	5	95	[39]
9	TiO_2	3	88	[40]
10	MCM-41	2	87	This work

[a] Isolated yields.

In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4a**, entry1 in Table 1) in the presence of several catalysts with respect to the reaction times (Table 2). The yield of product in the presence of MCM-41 is comparable with these catalysts. However, reaction in the presence of these catalysts required longer reaction times than MCM-41.

Reusability of MCM-41

Next, we investigated the reusability and recycling of MCM-41. At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with methanol and subjected to a second run of the reaction process. To assure that catalysts were not dissolved in methanol, the catalysts were weighted after filtration and before using and reusing for the next reaction. The results show that these catalysts are not soluble in methanol. In Table 3, the comparison of efficiency of MCM-41 in synthesis of **4a** after five times is reported. As it is shown in Table 3 the first reaction using recovered MCM-41 afforded similar yield to those obtained in the first run. In the second, third, fourth and fifth runs, the yield were gradually decreased.

Table 3. Reuse of the MCM-41 for synthesis of **4a**.

Entry	Time (h)	Yield (%)[a]
1	1	80
2	1	80
3	1.20	76
4	1.30	74
5	2	70

(a) Isolated yields.

CONCLUSIONS

In conclusion, MCM-41 can serve as an efficient catalyst for the synthesis of dihydropyrimidinones and thiones. This procedure offers several advantages including mild reaction conditions, cleaner reaction, high yields of products and will have wide scope in organic synthesis. This simple procedure combined with easy of recovery and reuse of the catalyst makes this method economic, benign, and a waste-free chemical process for the synthesis of these compounds. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of dihydropyrimidinones and thiones.

EXPERIMENTAL

Preparation of MCM-41

MCM-41 was prepared according to the procedure described previously [41]. A typical procedure was as follow: 1.8 g of fumed silica was added to a solution prepared from dissolving 0.6 g of NaOH in 25 mL of water. The resultant mixture was stirred for 2 h, and then 1.9 g of cetyltrimethyl ammonium bromide (CTABr) in 20 mL of water was added to this solution and stirred for one more hour. The resulting reaction mixture which has the molar composition of 1 SiO_2, 7.5 Na_2O, 5.2 CTABr, 2500 H_2O was kept over night and poured into the teflon lined stainless steel autoclave to make crystallization under static condition at 100 °C. The product was filtered, washed with distilled water, dried at 70 °C and calcined in air at 540 °C for 4 h.

General procedure for the synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-one or thione

A mixture of aldehyde (2 mmol), 1,3-dicarbonyl compound (2 mmol), urea or thiourea (3 mmol) and MCM-41 (2 mol%) was heated with stirring at 80 ºC for 1 h. The mixture was cooled to room temperature and CH_2Cl_2 poured on to the mixture. After filtration (removed the catalyst and catalyst was washed with methanol), the solution poured on to ice-water (10 mL). The resulting solid product was filtered and recrystalized from ethanol to give the pure products.

Synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4a**) [30]. Mp 200-202 ºC; IR (KBr) (ν_{max}, cm^{-1}): 3244, 1724, 1639; δ_H (ppm) (300 MHz, $CDCl_3$) 1.1 (3H, t, *J* 7.1 Hz, CH_3* CH_2O), 2.24 (3H, s, CH_3), 4.01 (2H, q, *J* 7.1 Hz, OCH_2), 5.16 (1H, s, CH), 7.21-7.30 (m, 5H, aromatic CH), 7.76 (s, 1H, NH), 9.24 (s, 1H, NH); *m/z* 260 (M^+).

Synthesis of 5-ethoxycarbonyl-4(4-nitro-pheny)l-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4d**) [30]. Mp 209-210 ºC; IR (KBr) (ν_{max}, cm^{-1}): 3250, 1720, 1636 cm^{-1}; δ_H (ppm) (300 MHz, $CDCl_3$) 1.1 (3H, t, *J* 7.9 Hz, CH_3* CH_2O), 2.27 (s, 3H, CH_3), 3.98 (2H, q, *J* 7.9 Hz, OCH_2), 5.20 (s, 1H, CH), 7.51 (d, 2H, aromatic CH), 7.89 (s, 1H, NH), 8.01 (d, 2H, aromatic CH), 9.33 (s, 1H, NH); *m/z* 304 (M^+), (lit. [30]).

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