

# **A Facile Biginelli Reaction on Grinding Using Nano-Ordered MCM-41-SO<sub>3</sub>H as an Efficient Solid Acid Catalyst**

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## **Abstract**

A facile protocol for the one-pot synthesis of pyrimidinone derivatives through Biginelli reaction in the presence of catalytic amount of the nano-ordered MCM-41-SO<sub>3</sub>H anchored sulfonic acid (MCM-41-SO<sub>3</sub>H) has been described. The reaction proceeds smoothly under solvent-free conditions on grinding of a mixture of different aldehydes, ethyl acetoacetate and urea in a mortar.

**Keywords:** Biginelli Reaction, Nano-Ordered Solid Acid, Multicomponent Reaction (MCR), Grinding, Green Chemistry

## 1. INTRODUCTION

Multi component reactions (MCRs) such as Biginelli reaction are powerful strategies for the facile and one-pot synthesis of organic compounds such as Dihydropyrimidinone derivatives (DHPMs). Biginelli reaction involves the cyclocondensation of an aldehyde, a  $\beta$ -ketoester and urea (or thiourea) [1]. Some Biginelli products have potential pharmaceutical applications such as antiviral, antitumor, antibacterial, anti-inflammatory, antihypertensive and alpha antagonists [2]. On the other hand, heterogeneous catalysts such as MCM-41-SO<sub>3</sub>H have been applied in organic reactions in recent years,. MCM-41-SO<sub>3</sub>H is a bench-top catalyst which is reusable, cheap, readily available, eco-friendly, versatile and efficient for promotion of many acid catalyzed organic reactions [3]. Furthermore, organic reactions without the use of harmful solvents have attracted much attentions. Due to the deterioration of the environment, since 1990's, the use of green protocols in the chemical reactions has become the trend setter. One of the methods belonging to such a protocol is grindstone method. This mechanically activated solvent-free reaction helps in reducing the toxic waste produced, and therefore, becomes less harmful to the environment [4]. In this study, we report our results for the DHPMs using MCM-41-SO<sub>3</sub>H under solvent free conditions by grinding.

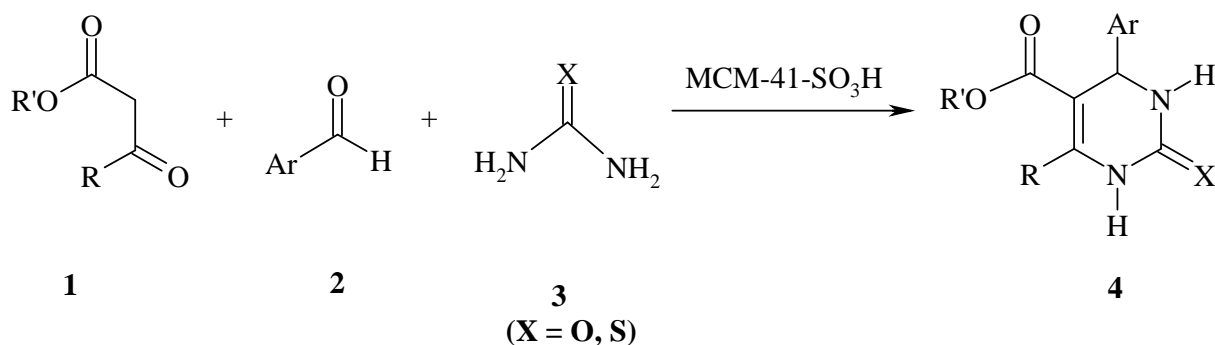
## 2. EXPERIMENTAL

### Typical Procedure for Preparation of 3,4-Dihydropyrimidinones (4a)/ thiones (4b) in the Presence of MCM-41-SO<sub>3</sub>H

A model experiment was performed by grinding together equivalent amounts of benzaldehyde **1**, ethyl acetoacetate **2**, urea **3a** (or thiourea **3b**), and a small amount of the solid acid catalyst MCM-41-SO<sub>3</sub>H. Grinding of the mixture at 70 °C in a large porcelain bowl for 10-30 min led to a solid mass that proved to be mostly the desired dihydropyrimidinone. After completion of the reaction (monitored by TLC), the crude product was washed with cold water to remove the color. Final purification was achieved by crystallization from acetone –EtOH.

## 3. RESULTS AND DISCUSSION

In a model reaction, the reaction of equivalent amounts of 4-chlorobenzaldehyde **1b**, ethylacetoacetat **2** and urea **3** in the presence of catalytic amount of the solid acid catalyst MCM-41-SO<sub>3</sub>H was studied (Scheme 1).



**Scheme 1.** Three component Biginelli reaction of different aldehydes **1**, ethylacetoacetat **2** and urea (or thiourea) **3**.

The effect of different factors including solvents, reaction temperature, catalyst loading and reaction time was examined. The results have been summarized in Table 1. It was found that 0.02 g of the catalyst is sufficiently enough to promote the model reaction efficiently under grinding conditions at 70 °C (entry 5).

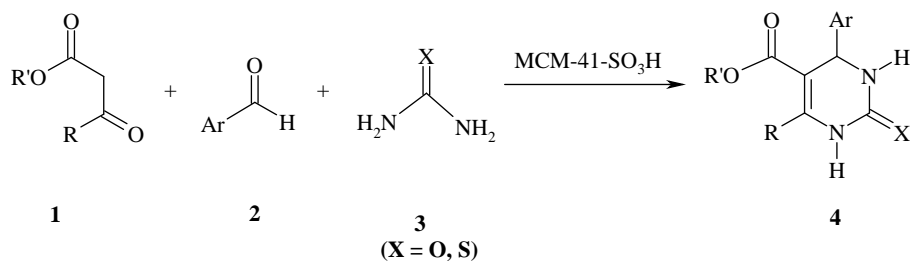
**Table 1.** Optimization of condensation of 4-chlorobenzaldehyde **1b**, ethylacetoacetat **2** and urea **3a** catalyzed by MCM-41-SO<sub>3</sub>H

Entry	Solvent	Amount of Catalyst (g)	Time	Yield <sup>a</sup> (%)
1	EtOH	0.02	18 h	trace
2	Acetone	0.02	12 h	40
3	EtOAc	0.02	15 h	30
4	Solvent-free	0.04	10 min	78
5	Solvent-free	0.02	25 min	87
6	Solvent-free	0.01	30 min	60

<sup>a</sup> Isolated Yields.

Encouraged by these results, different aromatic aldehydes, ethylacetoacetat and urea (or thiourea) were subjected to Biginelli reaction under the optimized reaction conditions. The results have been summarized in Table 2.

**Table 2.** MCM-41-SO<sub>3</sub>H-catalyzed synthesis of dihydropyrimidinones/thiones under the optimized reaction conditions



Entry	Ar	R	X	Time (min)	Yield <sup>a</sup> (%)	Mp (°C) (found)	Mp (°C) (reported) [6]
1	C <sub>6</sub> H <sub>5</sub>	OEt	O	25	87	205	206-207
2	C <sub>6</sub> H <sub>5</sub>	OEt	S	20	85	190	192-194
3	4-Cl-C <sub>6</sub> H <sub>4</sub>	OEt	O	15	90	213	213-214
4	4-Cl-C <sub>6</sub> H <sub>4</sub>	OEt	S	12	92	175	176-177
5	3-Nitro-C <sub>6</sub> H <sub>4</sub>	OEt	O	15	93	231	230-233

<sup>a</sup> Isolated Yields.

In all cases, the Biginelli reaction proceeded smoothly to give the corresponding dihydropyrimidinones/thiones (entries 1-5). The reaction with aromatic aldehydes carrying electron-withdrawing substituents such as *p*-chloro or *p*-nitro (entries 3 and 5) gave the corresponding products in good yields and in high purity. The reaction time required for MCM-41-SO<sub>3</sub>H, as catalyst, are shorter compared to another catalysts used for this transformation [4-6].

## 4. CONCLUSION

In conclusion, we have developed a catalytic method for Biginelli reaction using MCM-41-SO<sub>3</sub>H under grinding conditions. This procedure is much simpler and faster than the protocols published to date. It is also consistent with a green chemistry approach since no solvent is needed, except for recrystallization of the products. Another useful aspect of this procedure is its energy efficiency.

## 5. REFERENCES

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