

Kaolin: an efficient, reusable and inexpensive catalyst for the one-pot synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones

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Abstract: An efficient catalytic method for synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones using kaolin as an inexpensive and reusable catalyst is reported.

Keywords: Biginelli reaction; Kaolin; Dihydropyrimidin-2(1H)-ones; Multi-component reaction

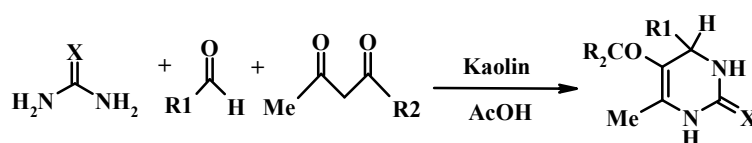
Introduction

The multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry [1,2]. The diversity, efficiency and rapid access to small and highly functionalized organic molecules makes this approach of central current interest in the construction of combinatorial libraries and optimization in drug discovery process [3-5]. The dihydropyrimidinone core and its derivatives form an important class of compounds, as it is present in along family of natural products with broad biological activities. They generally possess intriguing therapeutic and pharmacologic properties [6-8]. Several of their functionalized derivatives are used as calcium channel modulators and antihypertensive α_{1a} -antagonist [9-12].

The original one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-one was firstly reported by Pietro Biginelli in 1893 performing the three component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Brønsted acid catalysis [13]. A serious limitation of this protocol is that it

produced low yields of the desired heterocycle when substituted aromatic and aliphatic aldehydes were used. This has led to the recent disclosure of several improved reaction protocols for the synthesis of dihydropyrimidinones (DHPMs), either by modification of the classical one pot Biginelli approach itself [14-17], or by the development of novel, but more complex multistep strategies [18,19], or by using clays or montmorillonit and long reaction times [20,21].

In this paper, we describe a new methodology for synthesis of Biginelli type compounds using kaolin as catalyst. Kaolin is a soft, white clay mineral with aluminosilicate structure and acidic nature. Kaolin has been employed in organic synthesis [22-24]. Herein, we wish to disclose that it can be used as a catalyst in Biginelli type reaction. In fact, treatment of β -dicarbonyl compound, aryl aldehyde and urea or thiourea in the presence of a catalytic amount of kaolin in acetic acid affords (dihydropyrimidinones) DHPMs in good yields. (Scheme1)



Scheme 1

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Table 1: Biginelli type reaction using kaolin as catalyst

Entry	R ₁	R ₂	X	Time (h)	Yield (%) ^a	m.p.	
						Found	Reported ^{Lit.}
1	Ph-	OEt	O	2.5	82	205	205-206 ¹⁴
2	2-MeO Ph	OEt	O	3.0	80	259	257-259 ²⁵
3	4-MeO Ph	OEt	O	3.0	75	203	201-203 ¹⁴
4	4-Cl Ph	OEt	O	2.7	75	216	214-215 ¹⁴
5	2-NO ₂ Ph	OEt	O	2.7	82	220	218-220 ¹⁵
6	3-NO ₂ Ph	OEt	O	2.5	80	230	227-229 ²⁶
7	4-NO ₂ Ph	OEt	O	2.6	80	211	209-211 ¹⁴
8	2-furyl	OEt	O	2.7	60	205	203-205 ²⁷
9	Tiophene	OEt	O	2.6	75	211	209-210 ²⁸
10	Ph	OMe	O	2.2	75	210	207-210 ¹⁴
11	4-chloro Ph	OMe	O	2	73	208	204-207 ¹⁷
12	Ph	OEt	S	1.7	55	207	205-206 ²⁹
13	4-MeO Ph	OEt	S	2	60	152	152-153 ³⁰
14	Ph	Me	O	3	35	237	234-235 ³¹

^aYields refer to the isolated pure products

Result and Discussion

In recent years considerable emphasis has been placed on improvement in environmental impact of industrial chemical processes. It is well recognized that solids can play a significant role in the development of cleaner technologies through their abilities to act as catalysts, support reagents, avoid aqueous work-up and influence product selectivity [32,33]. Aluminosilicate clays are well characterized by their surface acidities, which render them efficient, versatile supports or catalysts [34,35]. While montmorillonit (bentonites) have achieved very wide use, kaolin-based reagents or kaolin assisted reactions appear to be extremely limited [36]. Kaolin due to its acidic nature can be suitable replacement for various homogenous acid catalysts. It has been used in protection reaction of carbonyl compounds [22], alkylation of benzene [23] and bromination and chlorination of aromatic compounds [24]. Along with these waves of interest we investigated further use of kaolin as solid catalyst in organic reactions. We used kaolin as an efficient catalyst for Biginelli reaction. Our approaches not only preserved the simplicity of Biginelli's one-pot reaction, but also consistently provide good yields of dihydropyrimidinones. 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 (entry1 in table1) in the presence of montmorillonit KSF, sulfuric acid, zeolit, Haulendite, Silica sulfuric acid, BF₃.OEt₂/CuCl and kaolin with respect to the reaction times and yields of products (Table2). The results show that kaolin promotes the reaction more effectively than sulfuric acid. Reaction in the presence of montmorillonit KSF, Silica sulfuric acid, Haulendite, BF₃.OEt₂/CuCl and zeolit required longer reaction times. We have found that kaolin is a reusable catalyst and even after 5 runs for the Biginelli reaction, the catalytic activity of kaolin was almost the same as that of the freshly used catalyst. Catalyst could be separated by a simple filtration and washed with diethylether and reused in the same reaction. Results of the first experiment and subsequent were the same in the course of the reaction of benzaldehyde ethylacetoacetate and urea. The efficiency of acetic acid without catalyst was studied for this reaction, but reaction did not go to complete when benzaldehyde was reacted with urea and ethylacetoacetate.

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

Entry	Catalyst	Time(h)	Yield(%)	Ref.
1	Montmorillonit KSF	48	82	36
2	Sulfuric acid	18	71	13
3	Zeolit	12	80	37
4	Silica sulfuric acid	6	91	38
5	Haulendite	4-5	75	21
6	BF ₃ .OEt ₂ /CuCl	18	71	14
7	Kaolin	2.5	82	This work

Conclusion

In conclusion we have developed an eco-friendly method using inexpensive, reusable and available catalyst for the direct synthesis of dihydropyrimidinones with good yields. We believed that this methodology can find usefulness in industry.

Experimental

All products are known compounds and were characterized by their physical and spectra data [14,15], [25-31].

Synthesis of 4-aryl-3, 4-dihydropyrimidin-2(1H)-ones: General procedure:

A mixture of aldehyde (10 mmol), β -dicarbonyl compound (10mmol), urea or thiourea (15mmol) and kaolin (0.5 g) was refluxed in glacial acetic acid (20 mL) for 1.7-3 h. after completion of reaction (monitored by TLC) the catalyst was separated by a simple filtration and the mixture was cooled to room temperature. The filtrate poured on to ice-water (60 mL). The resulting solid product was filtered and recrystallized from ethanol to give the pure products (Table1). The products are identified via comparison with authentic samples. The filtered catalyst was washed with diethyl ether and reused.

Acknowledgments

We like to express our sincerest appreciation for partial financial support from Azzahra University research council.

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