

A green and efficient method for the preparation of 3, 4-dihydropyrimidin-2(1H)-ones using quaternary ammonium-treated clay in water

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Abstract: In this study, a variety of 3, 4-dihydropyrimidin-2(1H)-ones derivatives were synthesized via three-component Biginelli reaction. The quaternary ammonium- treated clay -catalyzed process proved to be simple, efficient, and environmentally friendly.

Keywords: Organoclay, 3, 4-dihydropyrimidin-2(1H)-ones, Multicomponent Reactions, Biginelli reaction

Introduction

Clays, nanoparticles with layered structures and hydrophilic nature are used as Brønsted and/or Lewis acids, or as bases to catalyze various types of organic reactions [1]. Otherwise, hydrophobic modification of the clay intra-surface allows many organic guest molecules to be easily intercalated [2]. In the modification of clay by ion exchange, the interlayer accessible compensating cations can be exchanged with a wide variety of hydrated inorganic cations or organic cations including those of amines, quaternary ammonium salts or ionic liquid, and also oxonium, sulfonium, phosphonium and more complex cationic species such as methylene blue and cationic dyestuffs [3].

Multicomponent Reactions (MCRs) are broadly defined, as “one-pot” processes that combine three or more substrates either simultaneously or through a sequential-addition procedure that does not involve any change of solvent. By minimizing the number of synthetic operations while maximizing the buildup of structural and functional complexity, these highly step economical reactions are particularly appealing in the context of target-oriented synthesis [4].

A literature survey showed that the Biginelli dihydropyrimidine synthesis as a MCR [5-7], attract a high attention because of its ability for the preparation of compounds with potential biological and

pharmaceutical properties. 3,4-Dihydropyrimidin-2(1*H*)-one derivatives (DHPMs) are one of these compounds which can be synthesized by cyclocondensation reaction of aldehyde, urea and an easily enolizable carbonyl compound [8,9].

Although various methods are reported for the synthesis of DHPMs, but only few examples were developed with the aim of replacing conventional toxic and polluting Bronsted and Lewis acid catalysts with reusable solid acid heterogeneous catalysts, for the development of eco-friendly processes with reduced environmental impact [10-12].

Herein; as part of our continues effort to develop green and new catalyst systems with reduce environmental impact [13-16]; we decided to investigate the application of organophilic clay as a catalyst for synthesis of various 3, 4-dihydropyrimidin-2(1*H*)-ones in water.

Results and discussion

Modification of clay by ion exchange makes hydrophilicity decrease and enhances the organophilicity in the interlayers of clay [17]. Therefore, treated clay may play an efficient role in the synthesis of DHPMs.

The catalyst was prepared by the cation exchange of Na⁺ with cetyltrimethylammonium (CTAB) and characterized with FT-IR spectroscopy. In the spectrum of CTAB treated clay (Fig. 1), NCH₃ (C-H) stretching vibration observed at 3042 cm⁻¹. Furthermore, the 2940 and 2850 cm⁻¹ peaks correspond to asymmetric and symmetric vibration of methylene group. This confirms the successful exchange of CTAB with sodium ions in the clay structure.

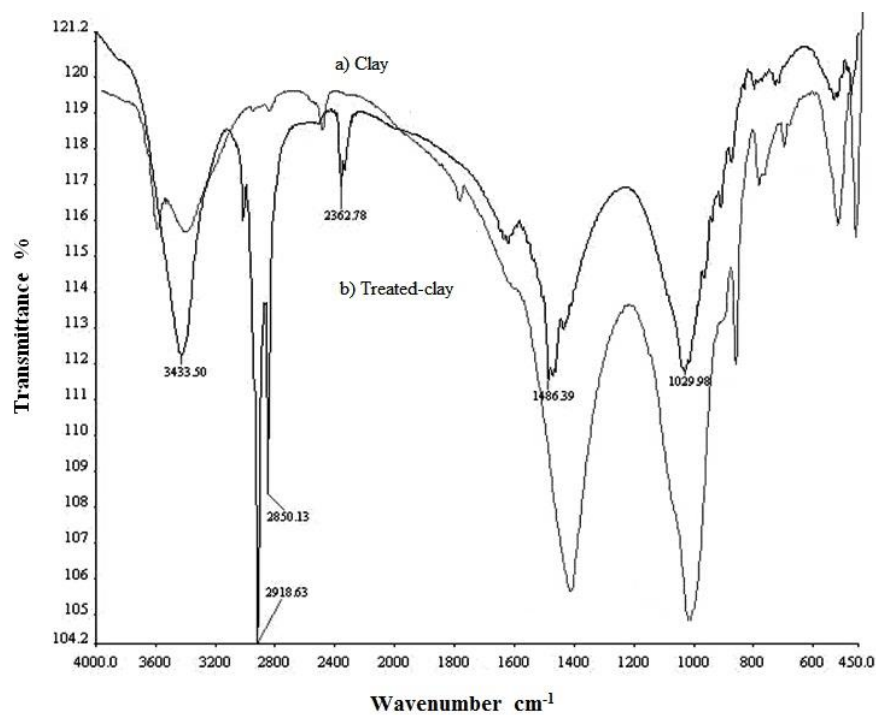


Figure 1 The FT-IR spectra of a) Clay, b) Treated-clay

Also, the thermogravimetric analysis (TGA) of the organocatalyst was performed with a TGA/DSC simultaneous thermal analyzer apparatus, using a nitrogen atmosphere (Fig. 2). TGA thermogram exhibits a 40 % weight loss in the range of 220-240 °C which is due to breakdown of organic cations in the organocatalyst.

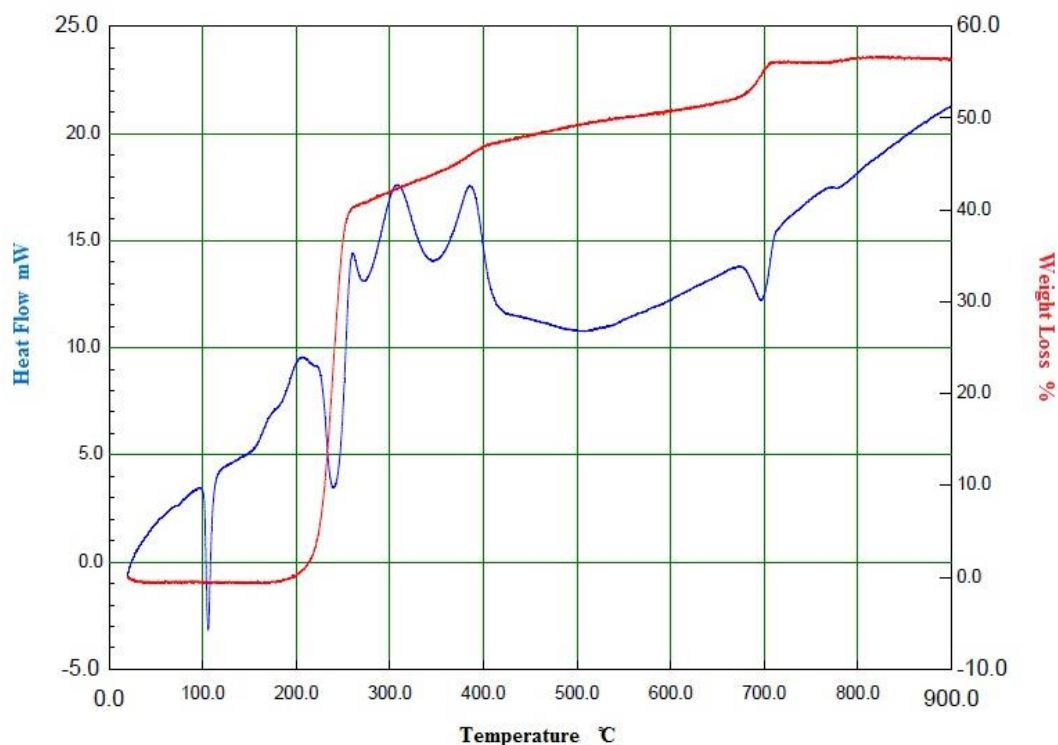


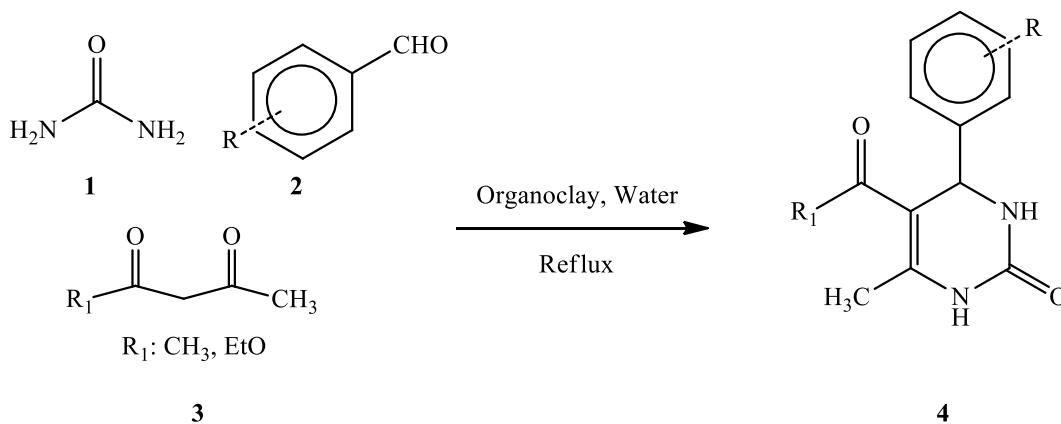
Figure 2 TGA curve of CTAB-modified clay

Optimization of the reaction condition was carried out employing benzaldehyde as the substrate and the best result obtained by refluxing mixture of 1 mmol aldehyde, 1 mmol acetylacetone, 1.5 mmol urea and 0.5 g catalyst in water (Table 1). To examine the scope and versatility of this method, the reaction was reinvestigated with various types of arylaldehyde bearing different electron-withdrawing and electron-donating substituted under the same reaction conditions (Scheme 1). In all case, the desired 3, 4-dihydropyrimidin-2(1H)-one has produced in appropriate time and high yield (Table 2).

Table 1 Optimization of experimental conditions for synthesis of DHPMs

Entry	Catalyst	Temperature	Time	Result
1	CTAB-modified clay (0.02 g)	reflux	0.5	Not completed, 44%
2	CTAB-modified clay (0.04 g)	reflux	0.5	Not completed, 77%
3	CTAB-modified clay (0.05 g)	reflux	0.5	Completed, 89% Yield
4	CTAB-modified clay (0.05 g)	r.t	0.5	Not completed, 35%
5	Clay	reflux	0.5	No reaction

Reaction Conditions: Benzaldehyde (1 mmol), acetylacetone (1mmol), urea (1.5 mmol)



Scheme 1 Synthesis of DHPMs

Table 2 Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones catalyzed by CTAB-modified clay

Entry	R	R ₁	Time (h)	Yield
4a	H	CH ₃	0.5	89
4b	4-NO ₂	CH ₃	0.75	91
4c	3-NO ₂	CH ₃	1.0	92
4d	4-OH	CH ₃	0.75	87
4e	2-MeO	CH ₃	1.0	88
4f	4-Cl	CH ₃	0.5	85

4g	2-Cl	CH ₃	1.0	88
4h	4-CH ₃	CH ₃	0.5	89
4i	H	EtO	0.75	89
4j	4-F	EtO	0.75	85
4k	4-CH ₃	EtO	0.5	90
4l	4-MeO	EtO	0.75	87
4m	4-Cl	EtO	0.5	90
4n	2-Cl	EtO	0.75	86
4o	4-NMe ₂	EtO	0.75	84

^a Products are known and were identified by comparison of their physical and spectral data with those of authentic samples [18-22].

^b Isolated yields.

With the increasing interest in human health and environmental protection, more attention is being paid to green chemistry. With this view we used benzaldehyde as a model and studied the recyclability and reusability of the catalyst. After completion of the reaction the separated catalyst was washed with hot ethanol and dried (Fig. 3). The catalyst was used for several subsequent cycles. To our surprise negligible depression in the performance of the catalyst was observed in the following cycles.

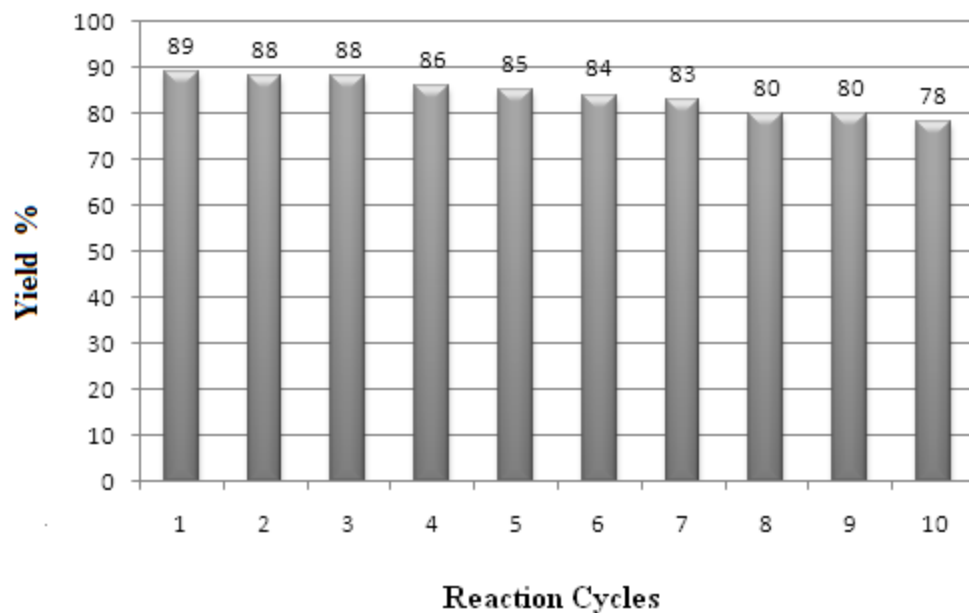


Figure 3 Reusability of catalyst

According to the obtained results, it is assumed that the reactants are brought together in between CTAB tails as organophilic regions and make a micro-vessel which accelerates the reaction (Fig 4).

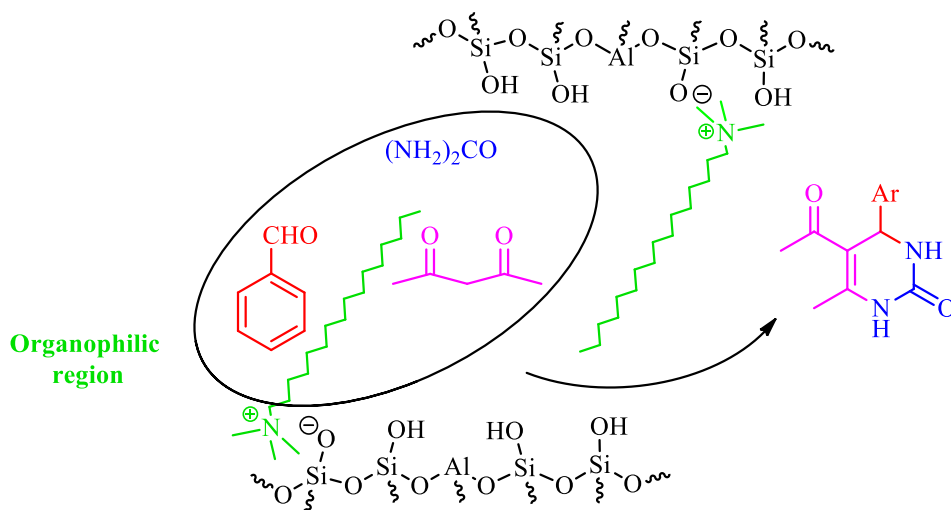


Fig 4 Schematic illustration of the reaction

Experimental

General information

Natural Na⁺-montmorolite clay was provided from Khorasan Mines, Iran (XRF analysis: SiO₂=51.2%, Al₂O₃=10.7%, CaO=12.8) and was ground, sieved (200-mesh), washed with water and dried in 80°C for 2h before using. All chemicals were purchased from Merck Chemical Company. The purity determination of the products and reaction monitoring was accomplished by TLC on polygram SILG/UV 254 plates. IR spectra were recorded on BomemMB-Series 1998 FT-IR spectrometer. ¹H NMR and ¹³C NMR spectra were taken on a 400 MHz Bruker spectrometer. GLC analyses were performed on a Shimadzu GC-12 a chromatograph equipped with a 3-m Thermon-1000 column.

General Procedure for the preparation of organoclay

Cetyltrimethyl ammonium bromide (1.5 mmol, 0.546 g) was dissolved in 100 ml of 0.01 M HCl solution and stirred at 80 °C until a clear solution was obtained. Then, montmorolite (1.0 g) was added to salt solution and vigorous stirring was continued for another 6.0 h. The precipitate formed was recovered by filtration and dispersed in hot water by mechanical stirring during 1 h. The later process was repeated twice to get chloride free organoclay. The final precipitate was thoroughly dried in an oven at 60°C for 24 h to obtain the CTAB modified organoclay.

General Procedure for the preparation of 3, 4-dihydropyrimidin-2(1H)-ones

A mixture of aromatic aldehyde (1mmol), acetylacetone or ethylacetoacetate (1 mmol), urea (1.5 mmol) and 0.5 g organoclay in 5 mL water was stirring under reflux condition for appropriate time (Table 1). After completion of the reaction that was monitored by TLC, the reaction mixture was cooled. The obtained was washed with water (3×10), dissolved in hot ethanol and filtered to remove the catalyst. The combined filtrates were evaporated under reduced pressure to dryness to give desired product. The solid crude products were recrystallized from ethanol.

Conclusion

In conclusion, we have reported here the use of CTAB-modified clay as an efficient catalyst in the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones in water. This environmentally benign protocol offers

several advantages such as a green and cost-effective procedure, short reaction time, easy work-up, recovery, and reusability of heterogeneous catalyst and high yield of the products.

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