Research Article

A Green and Efficient Method for the Preparation of 3,4-Dihydropyrimidin-2(1*H*)-ones Using Quaternary Ammonium-Treated Clay in Water

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

1. 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 intrasurface 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, ionic liquid, 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 an MCR [5–7] attracts a high attention because of its ability for the preparation of compounds with potential biological and pharmaceutical properties. 3,4-Dihydropyrimidin-2(1*H*)-ones 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, only few examples were developed with the aim of replacing conventional toxic and polluting Brønsted and Lewis acid catalysts with reusable solid acid heterogeneous catalysts, for the development of ecofriendly processes with reduced environmental impact [10–12].

Herein as part of our continued efforts to develop green and new catalysis systems with a reduced 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.

2. 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 (Figure 1), NCH₃ (C–H) stretching vibration is observed at 3042 cm^{–1}. Furthermore, the 2940 and 2850 cm^{–1}

TABLE 1: Optimization of experimental conditions for synthesis of DHPMs.

Entry	Catalyst	Temperature	Time (h)	Result
1	CTAB-modified clay (0.02 g)	Reflux	0.5	Not completed, 44% yield
2	CTAB-modified clay (0.04 g)	Reflux	0.5	Not completed, 77% yield
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% yield
5	Clay	Reflux	0.5	No reaction

Reaction conditions: benzaldehyde (1 mmol), acetylacetone (1 mmol), and urea (1.5 mmol).

FIGURE 1: The FT-IR spectra of (a) clay, (b) treated clay.

FIGURE 2: TGA curve of CTAB-modified clay.

peaks correspond to asymmetric and symmetric vibration of methylene group. This confirms the successful exchange of CTAB with sodium ions in the clay structure.

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

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

Entry	R	R ₁	Time (h)	Yield (%) ^{a,b}
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.

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

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 (Figure 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.

According to the obtained results, it is assumed that the reactants are brought together in among CTAB tails as

3. Experimental

3.2. General Procedures for the Preparation of Organoclay. Cetyltrimethylammonium 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, montmorillonite (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 for 1 h. The later process was repeated

3.3. General Procedures for the Preparation of 3,4-Dihydropyrimidin-2(1H)-Ones. A mixture of aromatic aldehyde (1 mmol), acetylacetone or ethyl acetoacetate (1 mmol), urea (1.5 mmol), and 0.5 g organoclay in 5 mL water was stirred 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.

5-Acetyl-6-methyl-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one **4e**. m.p. 248–250°C, ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 2.02 (s, 3H), 2.29 (s, 3H), 3.82 (s, 3H), 5.57 (d, 1H), 6.89 (t, 1H), 7.05–7.00 (m, 2H), 7.36 (br s, 1H), and 9.14 (br s, 1H).

FIGURE 4: Schematic illustration of the reaction.

5-Acetyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one **4f**. m.p. 204–206°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 2.14 (s, 3H), 2.28 (s, 3H), 5.25 (d, 1H), 7.26 (d, 2H), 7.39 (d, 2H), 7.85 (s, 1H), and 9.22 ppm (s, 1H).

5-Acetyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one **4g**. m.p. 228–229°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 2.05 (s, 3H), 2.33 (s, 3H), 5.67 (s, 1H), 7.27–7.45 (m, 4H), 7.72 (s, 1H), and 9.26 (s, 1H).

5-Acetyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one **4h**. m.p. 203–205°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 2.08 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 5.21 (d, 1H), 7.13 (s, 4H), 7.76 (s, 1H), and 9.13 ppm (s, 1H).

5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4i**. 201–203°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 1.09 (t, 3H), 2.25 (s, 3H), 3.98 (q, 2H), 5.15 (d, 1H), 7.23–7.25 (m, 3H), 7.30–7.34 (m, 2H), 7.76 (br s, 1H), and 9.22 (br s, 1H).

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4j**. m.p. 183–185°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 1.05–1.10 (t, 3H), 2.25 (s, 3H), 3.95–4.00 (q, 2H), 5.14 (s, 1H), 7.12–7.28 (m, 4H), 7.76 (s, 1H), and 9.23 (s, 1H).

5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4k**. m.p. 170–173°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 1.04–1.12 (t, 3H), 2.23 (s, 3H), 2.26 (s, 3H), 3.95–4.00 (q, 2H), 5.10 (s, 1H), 7.12 (s, 4H), 7.70 (s, 1H), and 9.17 (s, 1H).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4l**. m.p. 199–200°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 1.10 (t, 3H), 2.24 (s, 3H), 3.72 (s, 3H), 3.98 (q, 2H), 5.09 (d, 1H), 6.88 (d, 2H), 7.15 (d, 2H), 7.69 (br s, 1H), and 9.17 (br s, 1H).

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4m**. m.p. 208–210°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 1.10 (t, 3H), 2.26 (s, 3H), 3.98 (q, 2H), 5.15 (s, 1H), 7.26 (d, 2H), 7.40 (d, 2H), 7.80 (br s, 1H), and 9.27 (s, 1H).

5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4n**. m.p. 222–224°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 0.99 (t, 3H), 2.30 (s, 3H), 3.72 (s, 3H), 3.89 (q, 2H), 5.63 (d, 1H), 7.25–7.32 (m, 3H), 7.41 (d, 1H), 7.73 (br s, 1H), and 9.30 (br s, 1H).

5-Ethoxycarbonyl-4-(4-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **4o**. m.p. 254–256°C, ^1H NMR (DMSO- d_6 , 400 MHz): δ = 1.11 (t, 3H), 2.23 (s, 3H), 2.86 (s, 6H), 3.95 (q, 2H), 5.04 (s, 1H), 6.64 (d, 2H), 7.02 (d, 2H), 7.60 (s, 1H), and 9.10 (s, 1H).

4. 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 workup, recovery, and reusability of heterogeneous catalyst and high yield of the products.

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