

(CTA)₃[SiW₁₂]-Li⁺-MMT: Efficient nanocatalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions

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ABSTRACT

A highly practical and efficient preparation of 3,4-Dihydropyrimidin-2(1H)-one derivatives was developed via an efficient and simple nanocatalyst and promoted multi-component reaction of ethyl acetoacetate, aromatic aldehyde, and urea in the presence of a catalytic amount of (CTA)₃[SiW₁₂]-Li⁺-MMT under solvent-free conditions. In comparison to the conventional methods, the salient features of this method are green reaction conditions, short reaction time, high quantitative yields, high atom economy, low cost, no column chromatographic separation and easy isolation of products. All the products were characterized by melting point, IR, ¹HNMR and ¹³CNMR and were determined by comparison of their spectra with those of valid samples.

Keywords: Aldehydes, Multi-component reaction, (CTA)₃[SiW₁₂]-Li⁺-MMT, 3,4-Dihydropyrimidin-2(1H)-one.

1. Introduction

Montmorillonite (MMT) is one of the abundant silica materials, use of which has received considerable attention as a carrier for functional materials. Owing to its layered structure, high modulus, large specific surface area, chemical and mechanical stability and high exchange capability, it has been widely applied in pharmaceuticals, decolorizing agents and support catalysts [1-4]. The building blocks of this kind of clay contain an aluminum octahedral layer [Al(OH)₆]⁻³ sandwiched by two tetrahedral silicon-oxygen (Si₂O₅)⁻² layers [5]. Due to the ion-exchange properties of montmorillonite, the interlamellar cations such as Mg²⁺ and Fe²⁺ can be easily replaced by other organic cations thus leading to the modification of the MMT features. According to these substitutions, a permanent negative electric charge appears in the MMT layers, and these net negative charges can be balanced by alkali cations or earth alkalines such as Na⁺, K⁺, and Ca⁺ between the clay layers in the gallery spaces [6]. Montmorillonite layers with a thickness of approximately 1 nm and lateral dimensions of 30 nm or a little more are nanoporous with a regular structure [7].

The common phenomenon of the broken bonds on the edge of the layered silicate leads to the formation of hydroxyl groups utilized as the support to synthesize heterogenized catalysts that are more available to the reagents [8-10]. It is necessary to mention that the distribution feature of the MMT in water increases its basic distance and this swell can be related to the cations collection in its interlayers.

Dihydropyrimidinones (DHPMs) are important classes of heterocyclic molecules receiving special attention from many pharmaceutical and organic chemists, essentially due to their numerous applications in biological and pharmaceutical researches such as antibacterial, antioxidant, anti HIV and anticancer activities [11,12]. Of late, various derivatives of these structural motifs have exhibited calcium channel modulators for the treatment of cardiovascular diseases and neuropeptide Y (NPY) antagonist [13]. Biologically active 3,4-Dihydropyrimidin-2(1H)-ones can be prepared by the one-pot condensation of an aldehyde, β-ketoester and urea under strongly acidic conditions [14]. A variety of elegant multicomponent strategies have been utilized to facilitate the Biginelli reaction [15-24]. However, many of these methods are associated with several disadvantages such as harsh reaction conditions, the need for excess amounts of the catalyst, the use of toxic organic solvents, low yield,

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prolonged reaction time and tedious work-up. Therefore, introduction of efficient, simpler, and milder procedures has attracted more attention. Recently, we have reported the preparation and characterization of a novel, efficient and simple nanocatalyst ((CTA)₃[SiW₁₂]-Li⁺-MMT), and its performance in the synthesis of the functionalized 2-amino-4H-chromenes [25]. In continuation of this study and in order to overcome the above-mentioned limitations, this research studied the performance of this nanocatalyst in the promotion of the synthesis of 3,4-Dihydropyrimidin-2(1H)-one derivatives, requiring the acidic catalyst to speed-up.

2. Experimental

2.1. General procedure

All chemicals were purchased from Merck or Fluka. All compounds were identified by comparing their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC) on silica gel PolyGram SILG/UV 254 plates. The IR spectra were recorded using a PerkinElmer PXI instrument with KBr pellets. ¹HNMR and ¹³CNMR spectra were recorded on a Bruker Avance-400 MHz spectrometer.

2.2. Preparation of Li⁺-MMT

To prepare Li⁺-MMT, Na⁺-Cloisite was slowly dispersed into LiCl solution with vigorous stirring. The mixture was stirred at 40°C for 48 hours. Then, Li⁺-MMT was separated by filtration and washed with deionized water and then dried in a vacuum oven at 60°C for 24 hours. The analysis of atomic absorption for this solid metal demonstrated that it had 0.05 mol% concentration of dissolved Li⁺ ions.

2.3. Preparation of CTA-Li⁺-MMT

Li⁺-montmorillonite (4.50 g) was dispersed in 50 mL of distilled water. In addition, hexadecyltrimethyl ammonium bromide (CTAB) (2.90 g, 5 mmol) was dissolved in 20 mL distilled water and two solutions were then mixed together and stirred for 1 day. Then, reaction mixture was collected by centrifugation and 250 mL deionized water was added to the filtrated solution to remove the free CTAB. The resulting material was maintained at 100°C for 2 days to obtain CTA-Li⁺-MMT as a white powder.

2.4. Preparation of (CTA)₃[SiW₁₂]-Li⁺-MMT

1.40 g of H₄SiW₁₂O₄₀ (HPA) was dissolved in methanol (20 mL) and then 50 mL aqueous suspension of CTA-Li⁺-MMT (4.70 g) was added to the resulting mixture. The mixture was stirred at room temperature

for 1 day. After 1 day, the heterogeneous catalyst was separated and washed thoroughly with deionized water, and dried in an oven at 120°C for 7 hours to obtain (CTA)₃[SiW₁₂]-Li⁺-MMT.

2.5. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones in the presence of (CTA)₃[SiW₁₂]-Li⁺-MMT

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol), and (CTA)₃[SiW₁₂]-Li⁺-MMT (10 mg) was stirred at 90°C under solvent-free conditions. The reaction progress was monitored using silica gel coated on aluminum sheets and ethyl acetate-petroleum ether as eluent. Upon completion of the reaction, the reaction mixture was filtered off and the catalyst was washed twice with EtOH (10 mL). The pure product was obtained via recrystallization from ethanol.

3. Results and Discussion

To optimize the reaction conditions, the reaction of ethyl acetoacetate, 4-nitrobenzaldehyde, and urea (molar ratio 1:1:1.2) leading to 3,4-dihydro-5-etoxy carbonyl-4- (4-nitrophenyl)-6- methylpyrimidine-2(1H)-one (4l) was chosen as a trial reaction in different conditions (Table 1). The primary optimization results illustrated that the desired product 4l is not formed in the absence of catalyst even at 90°C under solvent-free conditions (entry 1). To choose the reaction catalyst amount, various amounts of the catalyst such as 5, 10, and 15 mg (entries 2-4) were used and the best results were achieved with 10 mg of the (CTA)₃[SiW₁₂]-Li⁺-MMT (entry 3). Increasing and decreasing the amount of catalysts required for the reaction did not improve the yield of the product to a great extent (entries 2 and 4). Furthermore, the utilization of different solvents such as H₂O, EtOH, CH₂Cl₂, CHCl₃, DMF, DMSO, and toluene in the presence of 10 mg of the catalyst resulted in good-to-moderate yields under reflux conditions (entries 5-11). However, the trial reaction in the presence of EtOH produced the desired product 4l in a slightly higher yield compared to other solvents (entry 6). Moreover, to determine the role of temperature in the trial reaction, the reaction was investigated with and without heating with the same amounts of the catalyst (10 mg) (entries 12-14). As can be observed, the use of heating improved the yield of the desired product. It was also observed that the reaction at 90°C proceeded in the highest yield and shortest time (entry 3).

Table 1. Optimization of the reaction conditions in different solvents.^a

Entry	Solvent	Amount of catalyst (mg)	Temperature (°C)	Reaction time (min)	Yield (%) ^b
1	----	----	90	60	----
2	----	5	90	8	91
3	----	10	90	8	98
4	----	15	90	8	95
5	H ₂ O	10	Reflux	45	52
6	EtOH	10	Reflux	45	75
7	CH ₂ Cl ₂	10	Reflux	45	41
8	CHCl ₃	10	Reflux	45	42
9	DMF	10	Reflux	45	39
10	DMSO	10	Reflux	45	40
11	Toluene	10	Reflux	45	72
12	----	10	----	8	45
13	----	10	70	8	87
14	----	10	80	8	93

^aReaction conditions: A mixture of 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol) and (CTA)₃[SiW₁₂]-Li⁺-MMT (10 mg).

^bIsolated yield.

To establish the optimum conditions, we explored the reaction of ethyl acetoacetate (1) with a range of appropriate aldehydes (2a-t), and urea (3) under similar conditions ((CTA)₃[SiW₁₂]-Li⁺-MMT (10 mg)/ 90 °C/ solvent-free), and furnished the respective 3,4-Dihydropyrimidin-2(1*H*)-one derivatives (4a-t) in high yields (Scheme 1).

Table 2 lists the optimized results. As can be observed, electron-withdrawing groups and halogens (Table 2, entries 2-12) in the ortho, meta, and para positions on the aromatic aldehydes produced higher yield of products than their electron-donating counterparts (Table 2, entries 13-20). Additionally, the results revealed that the reaction of aromatic aldehydes having electron-withdrawing groups was rapid compared to the reaction of aldehydes having electron-donating groups.

To illustrate the efficiency of the presented method, the obtained results in the synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one derivatives by

(CTA)₃[SiW₁₂]-Li⁺-MMT were compared to those by other earlier homogeneous and heterogeneous catalysts reported in the literature (Table 3). It is obvious that a proper methodology in terms of reaction time, green conditions and product yield compared to several others was expanded.

In the next phase of the study, a series of the catalytic cycles were run to study the stability of the catalytic activity. In this regard, preparation of 4l was selected as the model reaction. In each cycle, the catalyst was separated and then utilized for the next experiment directly. The data showed that the (CTA)₃[SiW₁₂]-Li⁺-MMT could be reused at least five times with negligible changes in terms of the reaction time and yield. The yield of product was reduced from 98% to 95% after the 5th run.

Furthermore, the fresh and recovered (CTA)₃[SiW₁₂]-Li⁺-MMT was characterized by FT-IR spectra (Fig. 1). The spectra are virtually identical and prove the fine reusability of the catalyst as expanded.

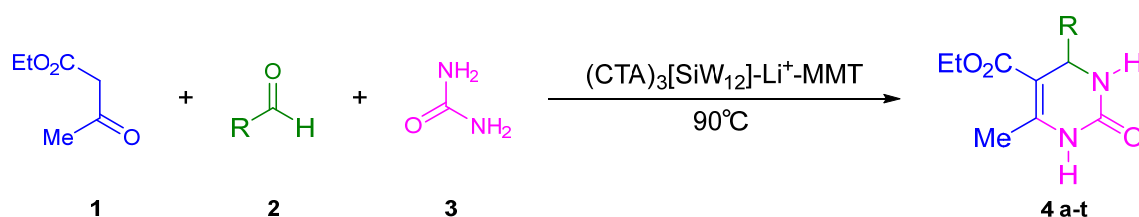
**Scheme 1.** One-pot three-component reaction of ethyl acetoacetate, different aldehydes, and urea.

Table 2. The (CTA)₃[SiW₁₂]-Li⁺-MMT catalyzed three-component Biginelli coupling.^a

Entry	R	Yield (%) ^b	Time (min)	m.p. (°C) ^c		Ref.
				Found	Reported	
4a	C ₆ H ₅ -	93	8	201-203	202-203	[26]
4b	2-(Cl)-C ₆ H ₄ -	96	8	217-219	215-218	[17]
4c	3-(Cl)-C ₆ H ₄ -	95	8	191-193	192-193	[33]
4d	4-(Cl)-C ₆ H ₄ -	96	8	213-215	212-214	[15]
4e	2,4-(Cl) ₂ -C ₆ H ₃ -	96	8	250-252	251-252	[29]
4f	3,4-(Cl) ₂ -C ₆ H ₃ -	95	8	221-222	222-223	[31]
4g	4-(F)-C ₆ H ₄ -	95	8	175-177	175-177	[14]
4h	4-(CF ₃)-C ₆ H ₄ -	95	8	174-176	173-175	[27]
4i	3-(Br)-C ₆ H ₄ -	92	8	185-187	185-186	[30]
4j	2-(NO ₂)-C ₆ H ₄ -	96	8	219-221	220-222	[18]
4k	3-(NO ₂)-C ₆ H ₄	94	8	225-227	226-228	[26]
4l	4-(NO ₂)-C ₆ H ₄ -	98	8	208-210	208-211	[32]
4m	2-(HO)-C ₆ H ₄ -	92	8	198-200	199-201	[28]
4n	4-(HO)-C ₆ H ₄ -	92	8	230-232	231-233	[26]
4o	2-(OCH ₃)-C ₆ H ₄ -	92	8	260-262	259-260	[34]
4p	3-(OCH ₃)-C ₆ H ₄ -	91	8	208-210	207-208	[35]
4q	4-(OCH ₃)-C ₆ H ₄ -	92	8	201-203	203-204	[26]
4r	3,4-(OCH ₃) ₂ -C ₆ H ₃ -	91	8	172-174	174-176	[31]
4s	3-(CH ₃ O)-4-(HO)-	91	8	178-181	173-175	[26]
4t	4-(CH ₃)-C ₆ H ₄ -	91	8	216-218	216-217	[27]

^aReaction conditions: Aldehyde (1mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol) and (CTA)₃[SiW₁₂]-Li⁺-MMT (10 mg), 90 °C.^bIsolated yield.^cMelting points are uncorrected.

Scheme 2 presents a reasonable pathway for the synthesis of 3,4-Dihydropyrimidin-2(1H)-ones in the presence of (CTA)₃[SiW₁₂]-Li⁺-MMT as a promoter. The acylimine intermediate (5) was formed initially by the nucleophilic addition of urea (3) to the aldehyde (2) in the presence of (CTA)₃[SiW₁₂]-Li⁺-

MMT. Then, the resulting adduct (5) underwent dehydration to give the compound (6). Michael addition of the ethyl acetoacetate (1) on the compound (5), pursued by intramolecular cyclization and final tautomerization of intermediates acquired the desired product (4).

Table 3. Comparison of the present method with other reported strategies to synthesize of 3,4-dihydro-5-etoxy carbonyl-4-(4-phenyl)-6-methylpyrimidine-2(1H)-one.

Entry	Catalyst and Conditions	Reaction time (h)	Yield(%) ^b	Ref.
1	Silica sulfuric acid/EtOH/heat	6	91	[34]
2	Sulfated tungstate/Solvent-free/80°C	1	92	[21]
3	CD-SO ₃ H/Solvent-free/80°C	2	89	[36]
4	IRMOF-3/Solvent-free/reflux	5	89	[23]
5	SnCl ₂ -nano SiO ₂ /EtOH/reflux	40min	92	[37]
6	(CTA) ₃ [SiW ₁₂]-Li ⁺ -MMT /90°C	8 min	93	This work

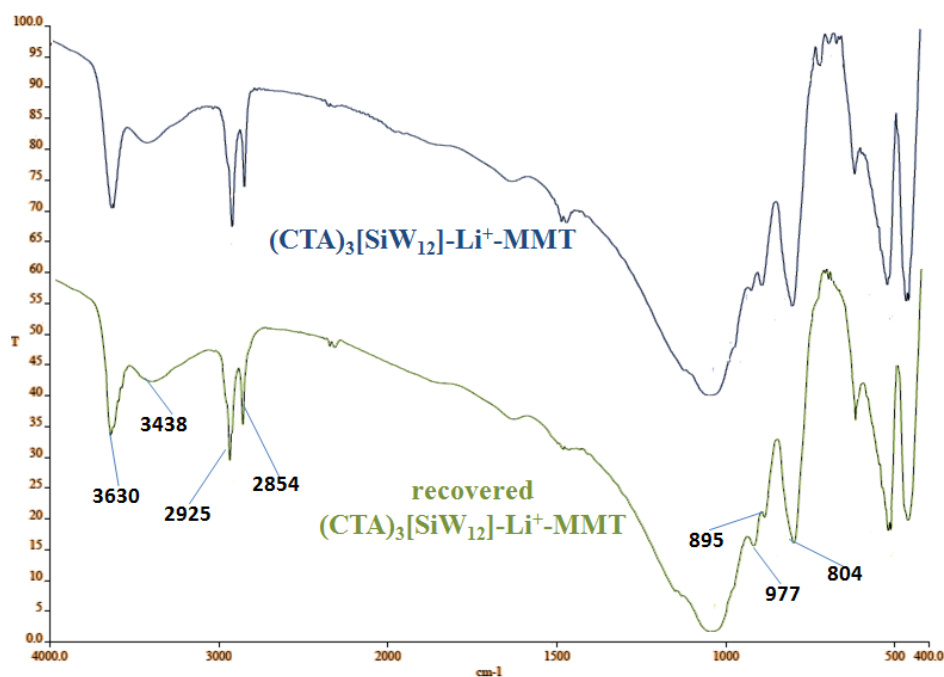
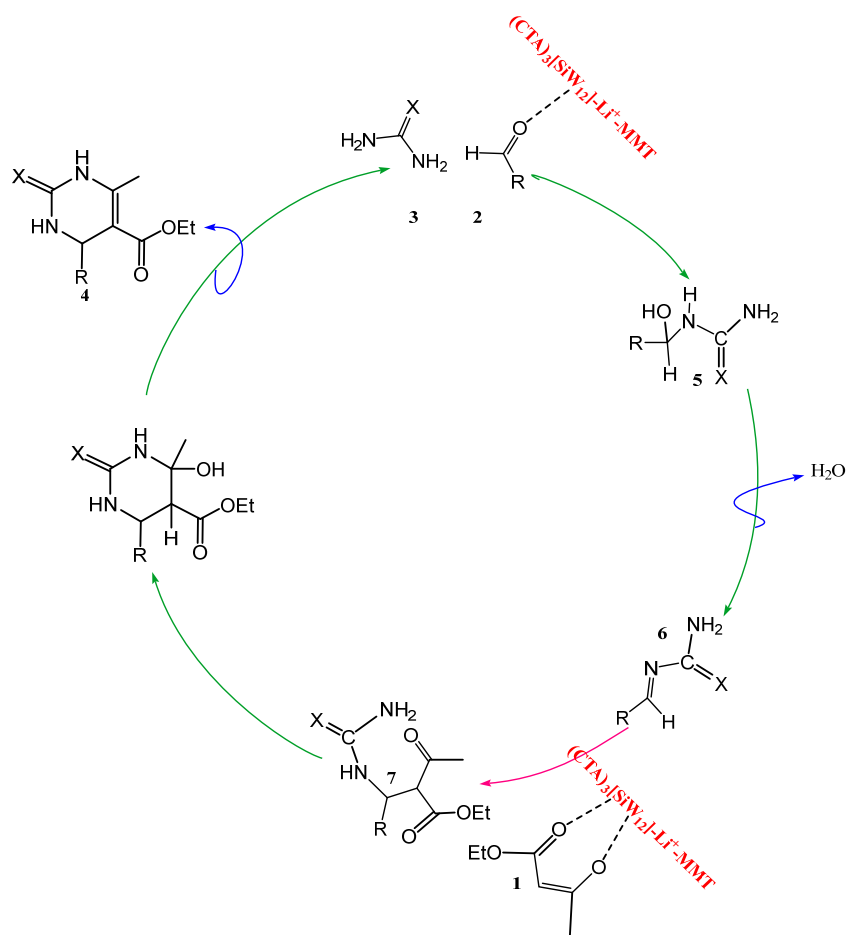


Fig. 1. FT-IR spectra of fresh and recovered $(\text{CTA})_3[\text{SiW}_{12}]\text{-Li}^+\text{-MMT}$.



Scheme 2. The proposed mechanism for the synthesis dihydropyrimidin-2(1H)-ones in the presence of $(\text{CTA})_3[\text{SiW}_{12}]\text{-Li}^+\text{-MMT}$.

4. Conclusion

In conclusion, a simple, facile, green and conveniently practical one-pot methodology was introduced to synthesize a wide range of biologically and pharmacologically interesting functionalized 3,4-Dihydropyrimidin-2(1*H*)-ones in the presence of (CTA)₃[SiW₁₂]-Li⁺-MMT as an eco-friendly and reusable nanocatalyst via a one-pot condensation of ethyl acetoacetate, aldehyde and urea under solvent-free conditions. The use of a cost-effective and eco-friendly catalyst, the absence of solvents, good-to-excellent yields, and avoidance of tedious separation procedures as well as the reusability of the reaction media are the most important advantages of the present method.

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