Preparation of Mg/Al-layered double hydroxide and its application in the synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones

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Abstract

An efficient green protocol for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones (DHPM) using Mg/Al-LDH (3:1) as heterogeneous base catalyst has been developed. The Mg/Al-layered double hydroxide was prepared by co-precipitation method, with ratio $Mg^{2+}/Al^{3+} = 3$, at pH 10. And the physicochemical characterization has been done by XRD, TG-DTA, IR and BET. In this paper, we have reported the synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones (DHPM) by treating substituted aromatic aldehydes with urea and ethyl acetoacetate in (1:1:1) mole ratio in the presence of Mg/Al−LDH (3:1) as a catalyst. The attractive features of this protocol are: mild reaction conditions, good yields and easiness of the catalyst separation from the reaction mixture.

Keywords: Heterogeneous catalyst , Mg/Al-Layered Double Hydroxide , 3, 4-Dihydropyrimidin-2(1H)-one (DHPM), Multicomponent synthesis,

INTRODUCTION

Layered double hydroxides (LDHs) are a large class of anionic layered materials with highly tunable composition and controllable morphology. They can be expressed as $[M^{2+}_{1-x} M^{3+}_{x}(OH)_2](A^{n-})_{x/n}.mH_2O$, where M^{2+} and M^{3+} are divalent and trivalent metal cations respectively, and A^{n-} is the interlayer anion compensating for the positive charge. Their thermal decomposition occurs trough dehydration, dehydroxylation and decarbonization. Thus, it leads to the formation of active Mg-AL-mixed oxides with high surface area and basic character, which is attributed to structural hydroxyl groups, O^{-2}-M^{+n} acid-base pairs and O^{2-} anions. So, they are potentially useful as heterogeneous base catalysts and catalytic supports [1, 2].

Indeed, heterogeneous catalysis has been known for many years and it has become strategically vital for the efficient and ecofriendly organic synthesis during the past few decades [3,4]. In this field, a large variety of heterogeneous catalysts, such as LDHs (hydrotalcites), zeolites, mixed metal oxides, solid-supported catalysts, resins…etc., has been used [5].

The 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) and their derivatives constitute an important class of synthetic products. The interest in their synthesis comes from their much attention in organic and medicinal chemistry. Currently, they were known to show important biological activities like antiviral, antitumor, antibacterial and anti-inflammatory properties [6-7].

The most simple and straightforward procedure for the synthesis of dihydropyrimidinones, first reported by Biginelli in 1893, involves the one-pot condensation of an aldehyde, β-ketoester and urea under strongly acidic [8]. In order to solve this problem and ameliorate the efficiency synthesis of 3,4-dihydropyrimidin-2(1H)-ones, several homogeneous and heterogeneous catalysts have been utilized like $LaCl_3.7H_2O$ [9], zirconium (IV) chloride [10], p-TsOH.H_2O [11]. [Al $(H_2O)_6$](BF_4)$_3$ [12], L-(+)-tartaric acid-dimethylurea [13], $HClO_4$-SiO_2 [14], PPh_3 [15], Iron (III) tosylate [16], H_3BO_3 [17], MnO_2-MWCNT nanocomposites [18], L-proline nitrate [19], CAN/HCl [20]. In addition, many methods have been developed to prepare the DHPMs including: microwave irradiation [21], ultrasound irradiation [22].However, it often suffers from low yields of the products especially in the cases of some substituted aromatic or aliphatic aldehydes and requires harsh conditions and long reaction time. In continuation of our interest in the Biginelli reaction, we report here an efficient use of Mg/Al−LDH (3:1) as a heterogeneous base catalyst to synthesize 3,4-dihydropyrimidine-2-(1*H*)-ones under solvent-free conditions (Scheme.1).
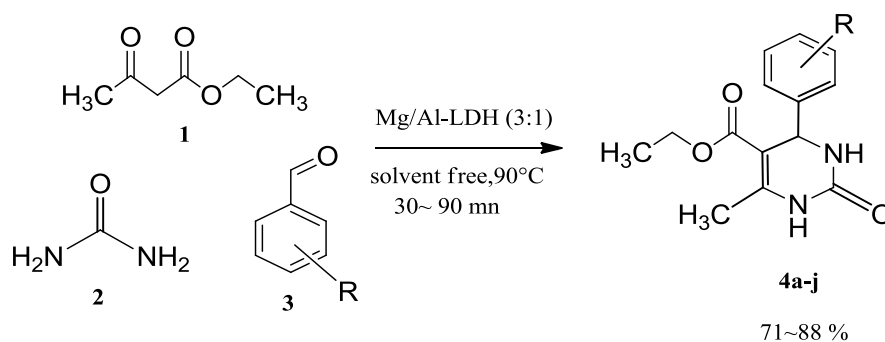
Scheme 1. Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones using Mg/Al-LDH (3:1)

MATERIALS AND METHODS

Catalyst Preparation

Layered double hydroxides precursors (LDHs) were prepared by a coprecipitation method, which was previously described by Didier TICHIT et al. [23]. While stirring vigorously, an aqueous solution containing $MgCl_2.6H_2O$ and $AlCl_3.9H_2O$ with $Mg/Al = 3$ was slowly dropped into a basic carbonate solution (1.0 M and pH = 10), which was prepared by dissolving appropriated amounts of Na_2CO_3 and NaOH in distilled water. Then the resulting gel was heated to 60-70°C and maintained *at* this temperature for 17h. After filtration, the collected solid was washed with distilled water (90°C) until reaching pH = 7. This material named Mg/Al-LDH (3:1).

Catalyst Characterization

Thermal Analysis (TGA–DTA) of Mg/Al-LDH (3:1)

TGA results of Mg/Al-LDH (3:1) are shown in Figure 1 and only two different weight losses were observed. The first mass loss below 234°C corresponds to the dehydratarion of interlayer water and to the beginning of dehydroxylation (usually below 150°C and above 150°C respectively). The second mass loss at T > 273°C is due to two possesses, the complete dihydroxylation, which is indicated by the endothermic peak at 424°C, and the decomposition of the interlayer carbonates anions into carbon dioxide and oxide ion.
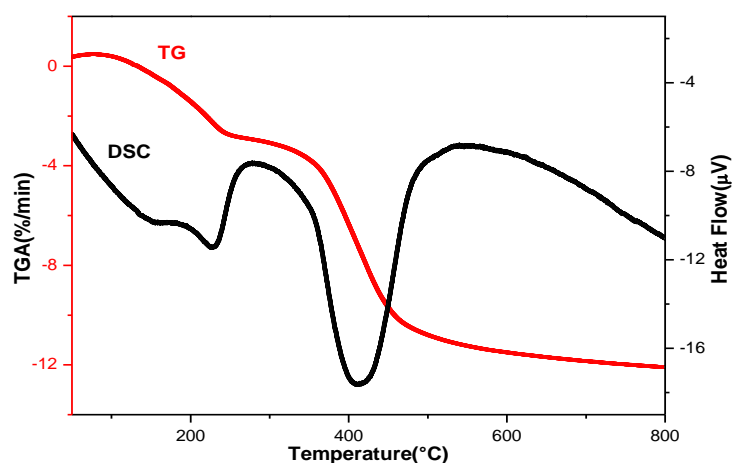
Figure 1. TGA–DTA thermograms of Mg/Al- LDH (3:1)

X-Ray Analysis

The X-ray diffraction (XRD) pattern of the prepared Mg/Al-LDH (3:1) is shown in Figure 2 and the X- ray source was Cu Kα radiation (λ = 1.5406 Å). The peaks 00l are generally observed in X-ray diffraction spectra of lamellar compounds belonging to the Layered Double Hydroxide family, and the entire diffraction peaks are in agreement with standard JCPDS data (card No.14-0191). This identification allowed attributing (hkl) Miller indices to Bragg peaks, in conformity with the parameters of hexagonal cell: a = b = 3.04 Å, c = 23.34 Å, α = β = 90°, γ = 120°, which was characterized with R3m space group.
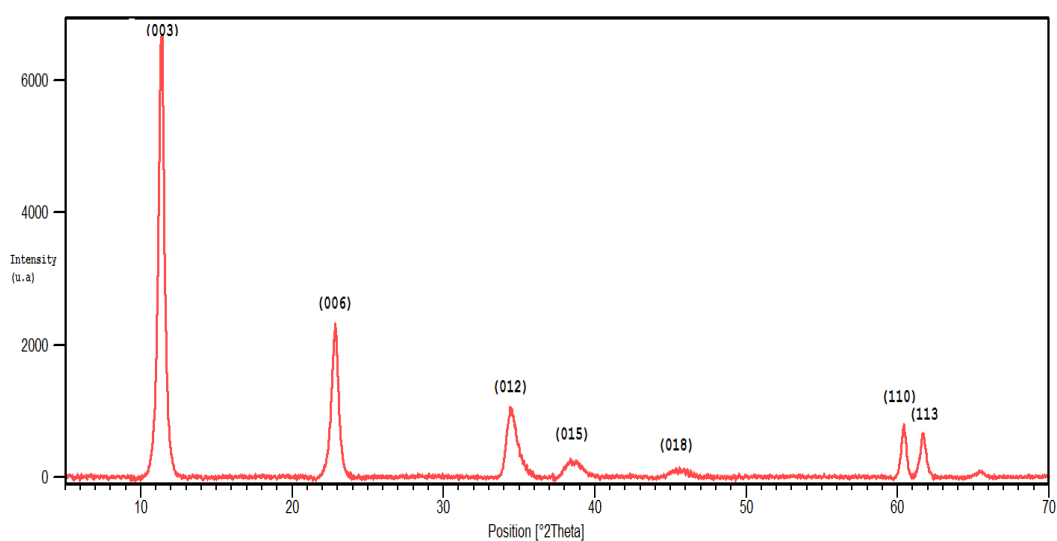

Figure 2. X-Ray Powder Diffractogram of Mg/Al- LDH (3:1)

The diffraction peaks shown in Figure.2 are indexed in Table.1.

The interlayer distances d_{00l} are calculated from 2θ values by using Bragg's equation:

$$n\lambda = 2d_{hkl}\sin\theta$$

Where λ is the wavelength of the X-ray, n is the order of diffraction, d_{hkl} is the interlayer spacing for hkl peak, and θ the Bragg's angle, which is determined by diffraction peak.

Table 1: Indexation of the experimental XRD pattern of Mg/Al-LDH (3:1)

2θ (°)	d_{hkl} (Å)	hkl
11 .26	7.84	003
23.00	3.86	006
34.75	2.58	012
38.83	2.32	015
46.19	1.96	018
60.72	1.52	110
62.01	1.49	113

Infrared Spectroscopy

The infrared spectra were recorded from 400 to 4000 cm^{-1} on a Bruker Tensor 27 FT-IR spectrometer, with a spectral resolution of 2 cm^{-1} was used.
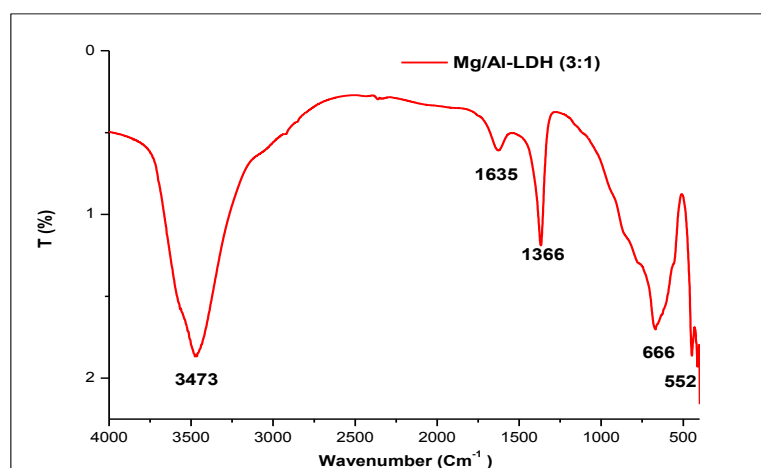
Figure 3: IR spectra of Mg/Al- LDH (3:1)

The FTIR spectrum of Mg/Al- LDH (3:1) (Figure 3) shows that in the low-frequency region (500-1000 cm^{-1}), the absorption peaks are ascribed to metal-oxygen vibrations. The peak centered at 1366 cm^{-1} can be attributed to the valence vibration of carbonate anion that is converted from CO_2 captured from air during washing. The weak band that appeared at 1635 cm^{-1} is assigned to the deformation mode of water molecules.

In LDHs studies, the IR spectra revealed the presence of coordinated water molecules, which is indicated by absorption band in high frequency region. In fact, the band at around 3473 cm^{-1} is attributed to stretching vibrations of the OH groups of water molecules.

BET Specific Surface Area and Porosity of Mg /Al-LDH (3:1)

Surface characterization of Mg/Al-LDH 3:1 was carried out using a nitrogen gas adsorption-desorption technique (Brunauer Emett and Teller theory) at 77.35 K, with a Micromeritics ASAP 2010. The experimental adsorption isotherms are depicted in Figure .4 and the parameters calculated from nitrogen adsorption data are included in Table 2.

Table 2: Physical parameters deduced from nitrogen adsorption at on Mg/Al -LDH (3:1)

Surface area	76.3362 m² g^{-1}
Pore volume	0.19213 cm^{3}g^{-1}
Pore size	14.4243 nm
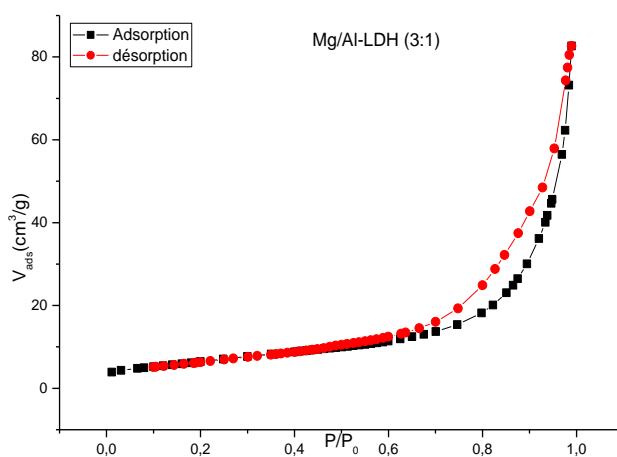
Figure 5 : Nitrogen adsorption-desorption isotherm of Mg /Al-LDH (3:1)

General Procedure for the synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one Derivatives

A mixture of ethyl acetoacetate (10 mmol), urea (10 mmol), aromatic aldehyde (10 mmol), and 0.03 gram of Mg/Al-LDH (3:1) was heated at 90 °C and allowed to stir for a short time (from 0.5h to 1.5h). After completion of the reaction as indicated by TLC, acetone/n-hexane (8:2).

The resulting crude mixture was dissolved in 300 ml of dichloromethane and the catalyst was recovered by filtration. Evaporation of the organic layer gave the crude product, which was further purified by recrystallization in ethanol to afford the pure product 3,4-dihydropyrimidin-2(1*H*)-one derivative.

RESULTS AND DISCUSSION

For this reaction model (Scheme.1), a catalytic amount of the Mg/Al-LDH (3:1) and stoichiometric amounts of benzaldehyde, ethyl acetoacetate and urea have been used. A series of DHPMs were synthesized and the results are listed in Table 3.

To investigate the substituent effect of benzaldehyde on the reaction yield, some electron donating groups have been chosen (see entries 2-6). In all cases, the desired product 4a-e has been obtained in good yields ranging from 71% to 83%. Thus, the results revealed no significant effect of substituent on the product yields. However, the furfural gave lower yield than benzaldehyde.

Table 3 : The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using Mg/Al-LDH (3:1) under solvent-free conditions at 90°C.

Entry	Aldehyde	Product 4	Time (min)	Yield[a] (%)	M.p. (°C) Found/(Reported)
1	C_6H_5-CHO	4a	40	88	202–203/(200-202)[24]
2	4-Cl-C_6H_4-CHO	4b	50	83	113-115/(112-114)[25]
3	4-CH_3O- C_6H_4-CHO	4c	35	82	203-205/(203-204)[26]
4	4-CH_3- C_6H_4-CHO	4d	65	78	211-214/(209-212)[27]
5	4-$(CH_3)_2$N-C_6H_4-CHO	4e	55	71	251-252/(249-250)[28]
6	3-CH_3- C_6H_4-CHO	4f	90	77	229-230/(228-230)[29]
7	Furfural (FF)	4g	40	82	207-208/(206-208)[25]

Reaction conditions: benzaldehyde (10 mmol), ethyl acetoacetate (10mmol), urea (10 mmol) and catalyst under solvent-free conditions; [a] Isolated yield.

Effect of thermal decomposition of Mg/Al-LDH (3:1)

The decomposition of Mg/Al-LDH (3:1) has been carried out at 600° C and the resulting mixed metal oxides has been used as catalyst in the condensation reaction of benzaldehyde, ethyl acetoacetate and urea (see table.4).

As mentioned previously, thermal decomposition of Mg/Al-LDH (3:1) is a means of preparing mixed metal oxides, which have strong basicity and therefore the catalytic activity can be improved. In fact, a slight increase in yield was observed.

Table 4 : Synthesis of dihydropyrimidin-2(1*H*)-one (4a) catalyzed by Mg/AL-LDH (3:1) calcined at 600°C

Benzaldehyde	Product 4	Time (min)	Yield (%)	M. p. (°C) Found/(Reported)
C_6H_5-CHO	4a	35	92	202-204/(200-202)[25]

Reaction conditions: benzaldehyde (10 mmol), ethyl acetoacetate (10mmol), urea (10 mmol) and amount catalyst (0.03g Of Mg/AL-LDH (3:1) calcined at 600°C for 1h, solvent-free, 90°C.

Catalyst reusability

To evaluate the reusability of the catalyst Mg/Al-LDH (3:1), we have studied the reaction,between benzaldehyde, ethyl acetoacetate and urea. The catalyst was recovered by filtration from the reaction mixture after dilution with CH_2Cl_2 and wash with Ethanol. And then, it was dried and weighed. The recycling experiments revealed that the prepared catalyst could be utilized successfully for three successive cycles without any significant loss of activity (Table 5).

Table 5: Reusability of the catalyst Mg/Al-LDH (3:1) for the reaction between benzaldehyde, ethyl acetoacetate and urea.

Run	Time ((min	Yield (%)
1	40	88
2	44	80
3	50	78

The spectroscopic characterization data of the synthesized compounds is given below.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a): ^{1}H NMR (300 MHz, DMSO): δ (ppm): 1.07 (t, 3H, CH_3); 2.27 (s, 3H, CH_3), 3.98 (m, 2H, CH_2), 5.51(s, 1H, CH), 7.18 -7.33 (m, 5H, Ar), 9.64(s, 1H, NH), 10.31(s, 1H, NH)

^{13}C NMR (75 MHz, DMSO): δ (ppm): 14.4, 17.61, 54.5, 60.1, 101.2, 126.8 , 128.2, 137.4, 129 , 143.9, 145.4, 165.6 , 174.5 , 182.5

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b): ^{1}H NMR (**300 MHz**, DMSO): δ (ppm): 1.16 (t, 3H, CH_3); 2.33 (s, 3H, CH_3), 4.08(m, 2H, CH_2), 5.37(s, 1H, CH); 6.03(s, 1H, CH), 7.25 -7.65(m, 4H, Ar), 8.10(s, 1H, NH), 9.98(s, 1H, NH).

^{13}C NMR (**75 MHz** ,DMSO): δ (ppm): 14.1, 18.6 , 55.0 , 60.3 , 101.6, 125.6 , 128.1 , 129.5 , 130.1 , 141.7 , 142.1 , 145.9 ,145,9, 165.2

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c): ^{1}H NMR (300 MHz, DMSO): δ (ppm): 1.08 (t, 3H, CH_3); 2.21 (s, 3H, CH_3), 3.69(s,3H,CH3), 3.95(m,2H,CH2); 5.06(s,1H,CH), 6.83 -7.12(m,4H, Ar), 7.64(s,1H,NH), 9.12(m, 2H, CH_2)

^{13}C NMR (**75 MHz**, DMSO): δ (ppm): 14.51, 18.21, 53.77 , 55.52 , 59.63 , 100.03, 114.16 , 127.86 , 137.4 , 148.4 , 148.4 , 152.6 , 158.8 , 165.8

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g) : ^{1}H NMR (**300 MHz**, DMSO): δ (ppm): 1.10 (t, 3H, CH_3); 2.20 (s, 3H, CH_3), 3.99(m, 2H, CH_2), 5.19(s, 1H, CH), 6.06 -7.52 (m, 3H, Ar), 7.79(s, 1H, NH), 9.31(s, 1H, NH)

^{13}C NMR (**75 MHz**, DMSO) : δ (ppm): 14.6, 18.2, 48.4 , 59.7 , 97.3, 105.8 , 110.8 , 142.7 , 149.8 , 153.0 , 156.3 , 160.3 , 165.5

CONCLUSION

 In conclusion, we have developed a novel and efficient catalyst, Mg/Al-LDH (3:1), for the synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one derivatives under solvent-free conditions. The present method offers several advantages such as inexpensive and reusable catalyst, being environment-friendly, short reaction times and affording very good yields. All these advantages make this method attractive to the classical Biginelli condensation.

ACKNOWLEDGMENTS

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