

MONTMORILLONITE MODIFIED AS AN EFFICIENT AND ENVIRONMENT FRIENDLY CATALYST FOR ONE- POT SYNTHESIS OF 3, 4-DIHYDROPYRIMIDINE-2(1H) ONES

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Abstract: Montmorillonite modified was used as an efficient environmental friendly catalyst for synthesis of 3,4-dihydropyrimidine-2(1H) ones under one-pot-three-component reaction. The preparation was performed with an aldehyde, 1,3-dicarbonyl compounds, urea or thiourea under solvent-free conditions. In comparison with the other methods of biginelli reaction, this new method has short reaction time, inexpensive catalyst and in addition excellent yields were obtained.

Keywords: Montmorillonite, Pillaring treatment, Acid activation, Dihydropyrimidine

1. INTRODUCTION

Clay minerals have a different and interesting set of properties. They are very effective catalysts for a wide variety of organic reactions because of their environmental compatibility, low cost and high selectivity [1]. In order to improve activity of natural occurring clay minerals to catalyze organic reactions, most frequent modification techniques used such as acid activation and pillaring treatment [2, 3].

Montmorillonite has used further than other mineral clays due to its peculiar physiochemical properties. Unitary layer of montmorillonite (TOT, 2:1) has two silica tetrahedral (T) sheets bonded to a central alumina octahedral (O) sheet. Montmorillonite powders are formed by the

agglomeration of TOT layers whose thicknesses vary between 0.96 and 1.5 nanometer and whose widths vary between tens to hundreds of nanometers. Montmorillonite crystals carry a charge arising from isomorphous substitutions of certain atoms in their structure for other atoms of a different valence. When this is the case, a charge deficiency occurs and a negative potential at the surface of the crystal is created. These negative charges neutralized by cations are held at the interlayer spaces. The cations are hydrated cations of Na, Ca and occasionally K [4]. The cations in the interlaminar region of natural montmorillonite can be exchanged with other

ions when the clay mineral is brought in to contact with its salt solutions. The most frequent used metal cations in the preparation of cation-exchanged clay of catalytic interest are Al^{3+} , Fe^{3+} , Cr^{3+} , Zn^{2+} , Mg^{2+} , Ni^{2+} , Cu^{2+} and Co^{2+} . They are known to be good catalysts because of the dissociation of water molecules by generating Bronsted acidity [5]. However, these catalysts dehydrate and undergo layer collapse at high temperatures.

A way of overcoming this disadvantage is to incorporate large polyoxocation species into the interlayer region of expandable clay minerals followed by calcination; this process is known as pillaring. In addition to the high thermal stability, high surface area and structural integrity, the pillars themselves may be catalytically active. A variety of inorganic metal oxides such as Al_2O_3 , ZrO_2 , TiO_2 , Cr_2O_3 and Ga_2O_3 , mixed metal oxides: $Al_2O_3-Ga_2O_3$ and $Al_2O_3-SiO_2$ have been successfully pillared in montmorillonite [5, 6].

Dihydropyrimidinone (DHPMS) derivatives have been accepted in an increasing attention. These compounds are in great demand because of their unique nature for biological activity and high performance in material science. For example they can serve as the integral backbones of several calcium channel blockers anti-viral, anti-bacterial, anti-inflammatory and anti-hypertensive agents [7-11]. The dihydropyrimidinone core is also found in many

natural products that explained the important efforts devoted to synthesis of this heterocycles [12, 13]. The classical Biginelli reaction of an aldehyde, 1, 3-dicarbonyl and urea or thiourea was first reported in 1893 which strongly requires acidic condition with relatively low yields [13, 14]. In the recent years the Biginelli reaction has received renewed interest and several improved method have been reported [16-19].

In this procedure there is a variety of suitable reaction conditions traditionally with strong Bronsted acid to improve the efficiency of Biginelli reaction such as LaCl_3 -graphite [20], LiBr [21], $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ [22], $\text{Cu}(\text{OTf})_2$ [23], $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ [24], BiCl_3 [25]. Other works have been devoted to the use of ionic liquids, microwaves irradiation [11-15], solid face reagents and polymer-supported catalysts. Some of them are really captivating from the synthetic Chemist's points of view. However, some disadvantages still remain. For example, some catalysts are expensive, complex or unavailable and organic solvents are always used which is harmful to the environment.

2. EXPERIMENTAL SECTION

2. 1. General

All of the reagents and solvents were obtained from Merck Chemical. Co. and were used without further purification. The montmorillonite used in this study were supplied from north of Kerman province (Iran). Sample was collected and grounded to 74 microns with Cross Beater Mill (Retch SK100), X-ray Diffraction patterns of sample were obtained using a D8Advanced Bruker diffractometer with $\text{CuK}\alpha$ radiation ($\lambda = 0.1542 \text{ nm}$) operated at 40kV and 30mA at a scanning rate 2θ of 2° min^{-1} . Chemical analysis obtained by X-ray Fluorescence Spectrometer (XRF ARL Advant,x). Morphology of the catalyst was analyzed using scanning electron microscopy (Cam Scan MV2300). IR spectra were obtained using KBr pellets on a Matson-1000 FT-IR spectrometer. The proton and carbon-13 NMR spectra were recorded with a Bruker DRX-500 Advance spectrometer at 500 and 125.7 MHz respectively with Me_4Si as an

internal standard in CDCl_3 as a solvent. Mass spectrometer operating at an ionization potential of 70 eV.

2. 2. The procedure of preparing catalyst

2. 2. 1. Acid activated montmorillonite:

The ground montmorillonite (5g) was refluxed with a 5.0 M H_2SO_4 solution (100 mL) at 80°C for 12h by stirring. The slurry was cooled, filtered and washed thoroughly with hot distilled water several times, until the filtrate was free from SO_4^{2-} ions. It was dried initially at room temperature followed at 120°C for 6h, and then powdered.

2. 2. 2. TiO_2 -pillared montmorillonite:

The pillaring agent was prepared by adding TiCl_4 into a 6.0 M HCl solutions and diluted with distilled water to obtain solutions with final Ti^{4+} and HCl concentrations of 0.8 and 0.4 M, respectively. The pillaring agent was used without prior ageing. 100 mL TiCl_4 pillaring solution (10 mmol Ti/g clay) was slowly added to 400 mL of distilled water containing 4g of montmorillonite which was vigorously stirred for 4-5 h. pH of suspension was adjusted to 2-3 with ammonia and the suspension was vigorously stirred for 4 h. Then it was centrifuged, washed with ethanol and water for several times, dried at 70°C and Calcined at 500°C for 1 h, and then powdered.

2. 3. Catalytic reaction

In order to investigation of catalytic activity of the catalysts, synthesis of 3,4-dihydropyrimidine-2(1H) ones was used. According to scheme 1, A mixture of ethyl acetoacetate or acetyl acetone 1 (2 mmol), appropriate aldehyde 2 (2 mmol), urea or thiourea 3 (3 mmol) and catalyst (0.54 g) was placed in a test tube and was heated in a bathe oil under free solvent for 50 minutes. After cooling the reaction mixture, ethanol was added to the reaction mixture and catalyst was removed by filtration. The filtrate was poured in to the crushed ice water and the resulting precipitate



Scheme 1

was recrystallized from hot ethanol to afford pure product. All of the compounds were characterized by MP, FT-IR, ¹H-NMR.

3. RESULTS AND DISCUSSION

3. 1. Structural Analysis

3. 1. 1. Acid Activated Montmorillonite

A suggested schematic of acid effect on montmorillonite is shown in Figure 1.

During acid activation of montmorillonite, exchangeable cations (Na^+ , K^+ , Ca^{2+}) replaced by H^+ ions and partial dissolution of octahedral cations (Al^{3+} or Mg^{2+}) occurred. The tetrahedral cations (Si^{4+}) not changed by acid treatment. In

fact acid activation leaves large number of highly active silanol groups (Si-OH) on the adsorbent sites and enhances Bronsted and Lewis acidity of montmorillonite. The chemical compositions of natural and acid activated montmorillonite (Table 1) confirm this suggested schematic.

The XRD patterns of natural montmorillonite presented in Fig. 2a. It exhibits a strong peak at a 2θ of $\sim 7^\circ$, which is commonly assigned to the basal d(001) reflection of the characteristic layer structure in montmorillonite. In XRD patterns of acid activated montmorillonite (Fig. 2c) the characteristic 001-order reflections were decreased. The main unchanged peaks of acidic sample related to cristobalite which shows that the crystal structure of this mineral is not damaged by acid treatment.

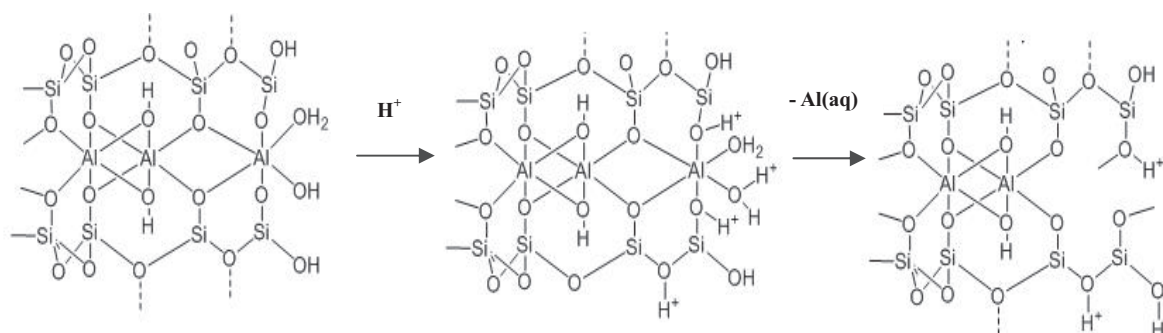


Fig. 1. Schematic of acid activation of montmorillonite

Table 1. chemical composition of natural and acid activated montmorillonite

Composition	SiO_2	Al_2O_3	Fe_2O_3	MgO	CaO	Na_2O	K_2O	L.O.I	CEC
Natural Mont	67.32	14.92	4	2.8	1.68	2.33	0.44	5.82	80
Acidic Mont	76.27	11.76	2.68	1.66	0.77	1.05	0.28	4.62	35.4

3. 1. 2. TiO_2 - Pillared Montmorillonite

XRD patterns of TiO_2 - pillared montmorillonite (Fig.2b) are characterized by a peak centered at 25.14° is related to anatase, indicating that TiO_2 has been loaded on the montmorillonite. The d001 reflection of the clay are weakened and shifted toward the lower 2θ angle.

Figure 3 shows SEM images of TiO_2 -montmorillonite. These images indicate the micro structure of the catalyst. In fact TiO_2 particles in a square shape located on the layer surface of montmorillonite while the particle size

distribution was from $1.5\ \mu\text{m}$ to $7\ \mu\text{m}$.

These results indicate during mixing of Ti agent and montmorillonite the species of titanium hydroxycations that formed by partial hydrolysis of TiCl_4 are intercalated on the internal and external clay surfaces. When the sample is heated, water molecules are simultaneously released, and condensation takes place between the OH groups of the Ti hydroxycations and lattice hydroxyls of the silicate layer. The resultant Ti oxide is linked via oxygen to the silica tetrahedral sheet of montmorillonite.

IR spectra of the natural and the TiO_2 -pillared montmorillonite are shown in Figure 4.



Fig. 2. XRD patterns of samples, a: natural montmorillonite, b: pillared montmorillonite, c: acid activated montmorillonite

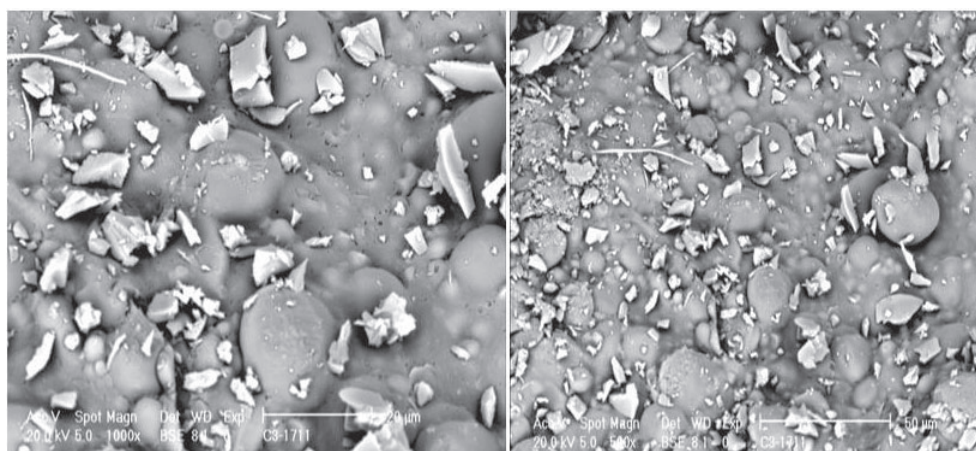


Fig. 3. SEM images of TiO_2 -pillared montmorillonite



Fig. 4. FTIR spectra of samples, a: natural montmorillonite, b: pillared monmorillonite

In IR spectra of the natural montmorillonite (Fig. 3a) a band around 3624.75 cm^{-1} was attributed to the Al_2OH group of the octahedral layer. A broad band around 3448.36 cm^{-1} was ascribed to the $-\text{OH}$ stretching vibrations of water molecules on the external layer. Bending vibrations of water molecules caused a peak around 1639.88 cm^{-1} . The band around 1039.47 cm^{-1} was attributed to asymmetric stretching vibrations of SiO_2 tetrahedral in the montmorillonite. Several bands around 917.18 , 862.31 and 794.87 cm^{-1} were attributed to

stretching vibration of Al-IV tetrahedral. From the IR spectra of the TiO_2 - montmorillonite (Fig. 3b) the bands around 3442.87 and 1636.51 cm^{-1} corresponded to the stretching vibration of OH groups that were linked with titanium atoms (Ti-OH) and to the bending vibrations of H-O-H .

3. 2. Optimization of Reaction

To choose optimum conditions for reaction (scheme1) , first, the effect of temperature on the

rate of the reaction were studied for the preparation of 5-acetyl-6-methyl-4-phenyl-3, 4-dihydro-1H-pyrimidin-2-one from the three-component condensation reaction of aromatic aldehyde, ethyl acetoacetate and urea under solvent-free conditions (Table 2). In comparison with other method for synthesis of organic compounds, that ordinary carry out in solvent under reflux condition, this method was performed only by simple test tube in oil bath without any laboratory equipment. Therefore simplicity of this method is clear. At 90 °C, the reaction proceeded smoothly and almost complete conversion of product was observed. Further increase in temperature to, 110 and 120 °C increased the rate of reaction. Therefore, we kept the reaction temperature as 110 to 120 °C. Next, the study set out to determine optimal amount of montmorillonite modified, the reaction was carried out by varying amount of the catalyst (Table 2).

Maximum yield was obtained with 0.54 g of catalyst. Further increase in mount of catalyst in the mention reaction not only did not have any significant on the product yield but also decreased the isolated product. According to

Table 2. Different amount of catalyst and reaction temperature for synthesis of 5-acetyl-6-methyl-4-phenyl-3, 4-dihydro-1H-pyrimidin-2-ones

Entry	Catalyst	T (°C)	Time (min)	Yield
1	0.65 g	110	30	67
2	0.54 g	110	30	73
3	0.42 g	110	45	64
4	0.28 g	110	50	62
5	0.14 g	110	84	60
6	0.54 g	110	50	89
7	0.54 g	120	50	95
8	0.54 g	90	50	84

Table 2, the reaction has been completed almost below 50 min, indicates short reaction time of defined procedure. The optimized condition utilizes a 2: 2.1: 3 ratio of ethyl acetoacetate 3, aldehyde 1 and urea 2 in the presence modified montmorillonite catalyst (acid activated or pillared, 0.54 g) under heating in oil bath and solvent free conditions (Scheme 1 and Table 2). Table 3 shows the reaction yields and products with use of different aldehyde in optimized condition (Scheme 1).

Table 3. Synthesis of dihydropyrimidin-2(1H)-ones with use of modified montmorillonite

Entry	Product	R ²	R ¹	X	Yields (%)		MP (°C)	
					Pillared	Acid activated	Observed	Reported
1	4a	OEt	C ₆ H ₆	O	96	94	204-206	206-207
2	4b	OEt	4-Cl-C ₆ H ₅	O	90	88	214-216	213-215
3	4c	OEt	3-Cl-C ₆ H ₅	O	91	89	192-194	195-197
4	4d	OEt	2-Cl-C ₆ H ₅	O	89	85	215-217	216-219
5	4e	OEt	4-NO ₂ -C ₆ H ₅	O	67	63	209-213	212-213
6	4f	OEt	3- NO ₂ -C ₆ H ₅	O	69	65	232-233	230-231
7	4g	OEt	4-CH ₃ -C ₆ H ₅	O	94	92	213-215	215-216
8	4h	OEt	2-CH ₃ O-C ₆ H ₅	O	93	92	257-259	255-258
9	4i	OEt	CH ₃ CH ₂ CH ₂	O	89	87	183-185	180-182
10	4j	OEt	C ₆ H ₅	S	90	90	202-204	205-207
11	4k	OEt	4-CH ₃ -C ₆ H ₅	S	87	85	210-213	212-214
12	4l	OEt	4-Cl-C ₆ H ₅	S	85	84	186-187	184-185
13	4m	OEt	4-NO ₂ -C ₆ H ₅	S	65	62	110-112	109-111
14	4n	Me	C ₆ H ₆	S	70	69	217-219	219-222
15	4o	OEt	4-CH ₃ O-C ₆ H ₅	O	93	90	205-207	203-204

According to Table 3, in all of the cases, aromatic aldehydes in presence of modified montmorillonite (acid activated and TiO_2 -pillared) as a catalyst reacted smoothly with 1,3-dicarbonyl compounds and urea or thiourea under free-solvent conditions to afford the desired 3,4-dihydropyrimidines derivatives in high yields. In fact modified montmorillonite has suitable acidity sites therefore this characteristic make modified montmorillonite to efficient catalyst. Thus an aromatic aldehyde carrying either electron-donating or electron-withdrawing substituent afforded high yield of product. In addition, montmorillonite clay is a cheap mineral material that has been found plenty in the world. Rather than this clay is not toxic component and agreeable with environment and after being catalytic activity is recycled by simple solvent.

3. 3. Spectral Data for Selected Compound:

Selected data for compound 4a: IR (KBr): 3235, 3136, 2985, 1700, 1652 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 8.29 (s, 1H, NH), 7.16 (s, 1H, NH), 7.23-7.62 (m, 5H, ArH), 5.42 (d, 1H, $J = 2.5$, CH), 4.13 (q, 2H, $J = 7.11$, O- CH_2), 2.37 (s, 3H, - CH_3), 1.21 (t, 3H, $J = 7.11$, - CH_3). ^{13}C NMR (500 MHz, CDCl_3): δ 168.03, 166.07, 153.84, 146.77, 144.15, 129.13, 128.36, 127.02, 126.50, 101.77, 60.43, 56.15, 19.06, 14.66.

3. 4. Mechanistic Aspects

The suggested mechanism of the montmorillonite modified (acid activated and pillared) transformations are shown in Fig. 5 and Fig. 6.

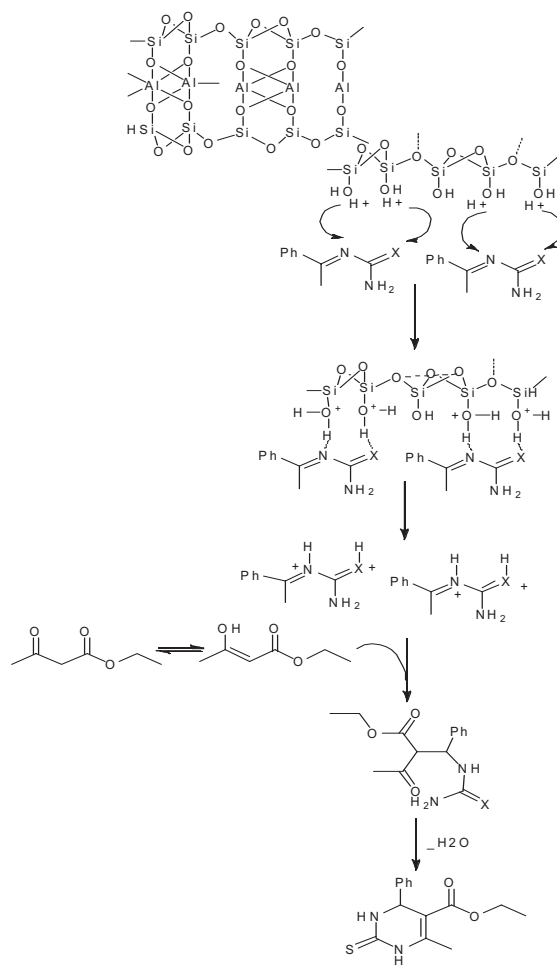


Fig. 5. Suggested mechanism of the acid activated catalyzed transformations



Fig. 6. Suggested mechanism of the TiO_2 -montmorillonite catalyzed transformations

Acid activated montmorillonite act as an enrich source of the protons (H^+) which can be release proton to catalyze of the reaction in the mild condition. In fact these acidic sites can serve as an effective binding site permitting the attachment of aldehyde, ethyl acetoacetate and imino-structure intermediate (Fig. 5). The TiO_2 -pillared montmorillonite has two active site for catalyze of reaction because it operates both as a Bronsted acid and Lewis acid. In this reaction may proceed via acyl imine intermediate, formed by the reaction of the aldehyde and urea which was catalyzed and stabilized by Si-O-Ti- . Subsequent addition of β -ketoester enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding dihydropyrimidine (Fig. 6).

4. CONCLUSION

Montmorillonite modified was prepared by acid activation and pillaring treatment has shown to be excellent catalysts, for one pot three-component synthesis of dihydropyrimidine derivatives under solvent free conditions. Therefore we have developed a simple, efficient and new methodology with several advantages such as high yields of the products, short reaction

times, inexpensive catalyst and environmental friendly procedure

5. ACKNOWLEDGMENT

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