

Improvement of the catalytic activity of an Algerian clay by acid treatment under solvent and solvent-free conditions for 3,4-dihydropyrimidin-2(1H)-one synthesis

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ABSTRACT

This work aims to study the effects of acid treatment on the structural and catalytic properties of Algerian montmorillonite. Acid activation of montmorillonite is carried out by sulfuric acid (H₂SO₄) at different concentrations under controlled conditions. The structural changes of the montmorillonite are investigated by XRD, FTIR, XRF, and BET techniques. The results of the proposed study indicated that acid activation causes significant changes in the structure of the samples. This leads to an increase in specific surface area and pore volume. The FTIR spectrum of adsorption of pyridine on montmorillonite showed an increase of the acidic sites depending on the concentration of the treatment solution. The activated montmorillonite is then used as a heterogeneous acid catalyst for the synthesis of dihydropyrimidinone molecule (DHPM) by Biginelli reaction using different solvents, and under solvent-free conditions. It was found that the reaction under solvent-free conditions simplifies the preparation process and gives excellent yields (92%, 8 h), in addition, it is an environmentally friendly process and deals with green chemistry. In this work, the importance of the order of introduction of the reagents is proven, thus allowing us to propose a reaction mechanism.

KEYWORDS

Heterogeneous catalysis, Green chemistry, Montmorillonite, Biginelli reaction

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INTRODUCTION

The Biginelli reaction allows obtaining the dihydropyrimidinones (DHPMs) molecules and their derivatives which have various pharmacological and therapeutic properties.¹ DHPMs molecules exhibit antibacterial, antiviral, anti-inflammatory, antitumor, antiepileptic, antifungal as well as antioxidant activities.²⁻⁴ In addition, DHPMs were also used as modulators of calcium channels in cardiovascular disease.⁵

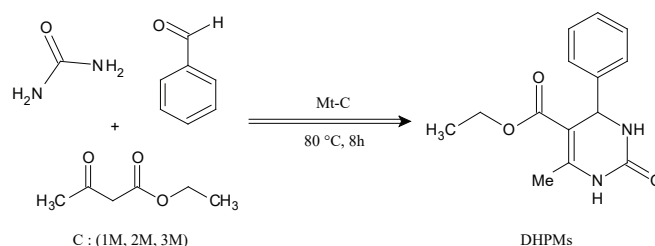
The classical Biginelli procedure developed in 1893 by the Italian chemist Pietro Biginelli, aimed to prepare DHPMs by a single operation of cyclo-condensation reaction with three reagents. This reaction consists of the mixture of aldehyde, ethyl acetoacetate, and urea where ethanol was used as a solvent, under strongly acidic conditions (HCl) while heating at reflux. The main drawbacks of the conventional synthesis are the requirement of prolonged reaction times with low yields and severe reaction conditions.^{6,7} Furthermore, the traditional catalysts used are toxic and difficult to separate from the reaction medium; which, is a significant obstacle to the regeneration step. To overcome the mentioned drawbacks, researchers are developing new strategies for the classical synthesis to produce DHPMs in good yields.^{7,8} Recently, a series of operating protocols have been proposed⁹ such as the use of microwave or ultrasound irradiation,^{9,10} the use of various homogeneous and heterogeneous catalysts like Lewis acids,¹¹ Brønsted acids,⁴ ionic liquids,¹² organo-catalysts,^{13,14} nano-catalysts,¹³ transition metal salts and hetero-poly acids.^{15,16}

Montmorillonite has been successfully used in various fields, and continues to attract the attention of many researchers, especially in heterogeneous catalysis for organic synthesis.¹⁷ This interest is justified

by its numerous advantages such as its low cost, abundance in nature, cation exchange capacity, its high specific surface area,¹⁸⁻²⁰ as well as its non-toxic and non-corrosive characteristics.²¹ Moreover, it is reusable and acts as a Lewis/Brønsted acid.²¹ All the above advantages make the montmorillonite one of the most important clay minerals.

Montmorillonite is a 2:1 phyllosilicate formed by stacking octahedral and tetrahedral layers so that an octahedral layer is interposed between two tetrahedral layers.²²⁻²⁴ Properties of montmorillonite can be improved by several physicochemical treatments,²⁵ such as organic, inorganic and organometallic intercalation,¹⁹ heat treatment, and acid activation.²⁶ The acid activation method allows the replacement of exchangeable interlayer cations by H⁺ at low acid concentrations, and the destruction of octahedral and tetrahedral layers at high acid concentrations. Furthermore, different modifications occurred during the acid attack such as volume of the pores, specific surface area, number and/or the nature of active site were observed notably on the crystal lattice.²⁶⁻²⁸

The proposed work deals with green chemistry by applying heterogeneous catalysis and solvent-free conditions. An Algerian montmorillonite is used as a solid acid catalyst for the preparation of the DHPM (Scheme 1). We investigated the effect of the acid treatment of the Algerian montmorillonite on the yield of the Biginelli



Scheme 1. Biginelli reaction catalyzed by acid-activated montmorillonite.

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reaction. Therefore, we highlighted the effect of other parameters such as the mass of the catalyst, the solvent, the solvent-free conditions, and the introduction order of the reagents, which allows us to propose a mechanism for the reaction. Finally, the development method is a simple, efficient and environmentally friendly catalytic system to synthesize DHPM in high yields.

MATERIALS AND METHODS

Materials and characterization methods

The clay raw material used in this study is an Algerian montmorillonite, obtained from the deposits of Hammam Boughrara in Maghnia in western Algeria, marketed by the national company of useful substances and non-ferrous materials (ENOF).

Sulfuric acid (95%, VWR Chemicals), benzaldehyde (99%, Sigma-Aldrich), ethyl acetoacetate (99%, Sigma-Aldrich), urea (99%, Sigma-Aldrich), methanol (99%, Honeywell Riedel-de-Haën™), ethanol (99%, VWR Chemicals), acetonitrile (99.9%, Merck), cyclohexane (99.8%, Sigma-Aldrich) and acetic acid (99.5%, Honeywell Fluka™) were used in the current research activity without further purification.

To evaluate the structural changes of montmorillonite after acid activation, different characterization techniques were used (XRD, FTIR, FRX, and BET). The recording of the diffractograms of the samples were carried out using a D8 Advance Bruker AXS diffractometer with CuK α radiation equipped with a curved graphite monochromator. The data were collected in the 2θ range of 5–80° with a step interval of 0.03° per second.

The specific surface area of sodium montmorillonite and activated montmorillonite, at different concentrations, was determined by BET method using the Micro metrics 3 Flex Adsorption Analyzer (Version 4.03). The samples were analyzed under a nitrogen atmosphere (adsorption-desorption isotherm at 77 K). Before the measurement, the samples were heated at 200 °C for 2h. The total pore volume was deduced from the amount of nitrogen gas adsorbed at $P/P_0 = 0.95$. FTIR spectra were obtained by a Shimadzu Fourier Transform Infrared Spectrophotometer (FTR-8400S) over a range of 500 cm^{-1} to 4000 cm^{-1} . The elemental composition of the studied samples was determined by X-ray fluorescence (XRF) using a ZSX Primus spectrometer. All reactions were controlled by analytical thin-layer chromatography (TLC). The melting point of DHPMs was determined with a BÜCHI-B540 melting meter and the ^1H NMR spectra were recorded with an Advance Bruker spectrometer (300 MHz) using CDCl_3 as solvent. Chemical shifts are conducted in parts per million (δ , ppm).

Catalyst preparation

The clay was activated by a sulfuric acid solution at different concentrations (1 mol/L, 2 mol/L, and 3 mol/L) at 60 °C and under stirring for 24 h, clay proportions were 20 g for 250 mL of solution. The clay/acid mixture was then separated by filtration; this process was repeated 4 times. The solid precipitate is washed with distilled water to eliminate the excess sulfuric acid. The precipitate was dried at 100 °C for 24 h in oven, crushed and then stored in a dry place. The activated montmorillonite, at different concentrations, was designated Mt-1M, Mt-2M and Mt-3M, and the sodium montmorillonite was designated by Mt-Na.

Biginelli reaction for the synthesis of the DHPM

The Biginelli reaction occurred in a 50 mL sample trial, where benzaldehyde (5 mmol), urea (6.25 mmol), ethyl acetoacetate (12 mmol), and montmorillonite (20% of benzaldehyde amount) were mixed in two ways. For the first one with 5 mL of solvent, while the second without solvent. The mixture is heated to 80 °C at reflux with stirring for 8 h.

At the end of the reaction, the mixture is washed with hot methanol, the filtrate is collected, and the methanol is removed at 65 °C. To obtain an analytically pure product, the product was recrystallized in ethanol. Compounds obtained, using this procedure, have been identified by: melting points, FTIR and ^1H -NMR.

RESULTS AND DISCUSSION

Characterization of catalyst

X-ray diffraction (XRD)

Figure 1 depicts the XRD spectra, for sodium montmorillonite and activated montmorillonite, at different concentrations of sulfuric acid.

The characteristic peaks for Mt-Na are located at $2\theta = 6.21^\circ$, 20° , 35° and 62° ; they are attributed to reflections (001), (020), (200,130) and (060,330), respectively.²⁹ We can also note the existence of certain impurities such as quartz at $2\theta = 21^\circ$, 26° , 50° , and 68° .^{30,31} The main peak of sodium montmorillonite is at $2\theta = 6.21^\circ$ and gives the interfoliar space distance $d_{001} = 14 \text{ \AA}$.

The XRD spectra reveal very significant structural changes due to the acid attack. For all concentrations, the characteristic peak of montmorillonite (001) completely disappeared. As the protons penetrate the montmorillonite sheets, they replace the exchangeable cations in the interfoliar space and attack the OH groups of the tetrahedral and octahedral sheets. This leads to the dissolution of the central atoms and the destruction of the chemical bonds as well as the disappearance of the basal spacing. The disappearance of the peaks at $2\theta = 20^\circ$, 35° , and 62° for the three catalysts clearly confirms that the two-dimensional montmorillonite lattice is completely lost by attack with sulfuric acid. Also, it is important to mention that the peaks at $2\theta = 26^\circ$ and 50° characterizing quartz, are present in the three catalysts but with different intensities, which shows the formation of silica due to the acid activation process.

Nitrogen adsorption (BET)

Figure 2 shows the nitrogen adsorption-desorption isotherms for sodium montmorillonite and treated montmorillonite at different acid concentrations. Table 1 summarizes the results of BET surface area and total pore volumes. According to the IUPAC classification, the adsorption-desorption isotherm of various catalysts is of type II. It has been described in the case of macro-porous solids^{32,33} and non-porous solids.³³ The adsorption isotherm of sodium montmorillonite represents an H4-type hysteresis loop characteristic of sheet-shaped particles with slit pores.³⁴ While, after acid activation, isotherms show a significant increase in the volume of adsorbed nitrogen.

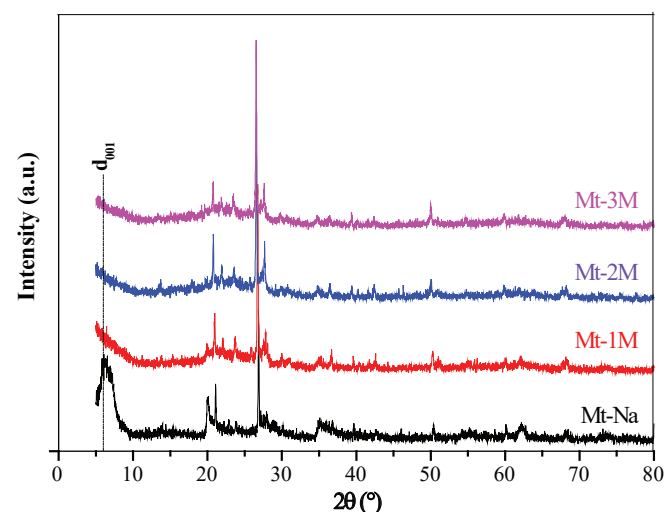


Figure 1. XRD diffraction patterns of Mt-Na, Mt-1M, Mt-2M and Mt-3M.

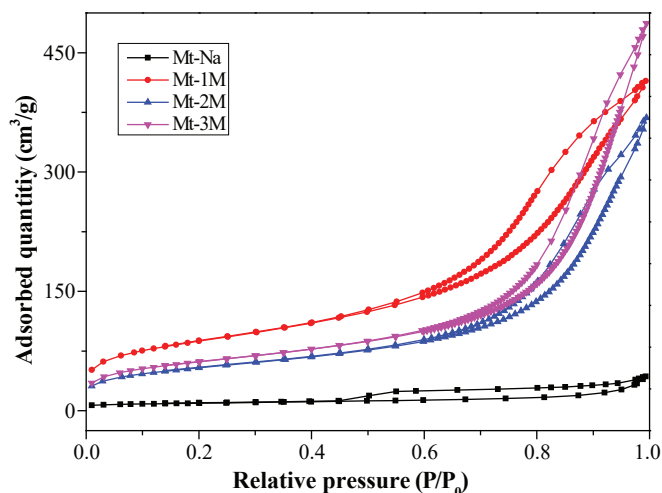


Figure 2. N₂ Adsorption-desorption isotherms of Mt-Na, Mt-1M, Mt-2M and Mt-3M.

Table 1. Structural parameters of Mt-Na, Mt-1M, Mt-2M and Mt-3M.

	S_{BET} (cm ² g ⁻¹)	V_t (cm ³ g ⁻¹)
Mt-Na	32.67	0.041
Mt-1M	310.0	0.57
Mt-2M	191.8	0.46
Mt-3M	219.2	0.59

This could be attributed to the formation of new pores due to acid treatment.¹⁹ The below isotherms show an H3 type hysteresis loop which generally defines mesoporous materials with microstructure mainly composed from capillary pores.^{35–37} Sodium montmorillonite presents a low specific surface area of 33 cm² g⁻¹, which reaches a maximum of 310 cm² g⁻¹ for the Mt-1M and then decreases to 192 cm² g⁻¹ and 219 cm² g⁻¹ for the Mt-2M and Mt-3M, respectively (Table 1). We observed an increase in surface area of Mt-1M; and this could be attributed to the exfoliation and/or destruction of adjacent layers of the multi-segmented clay due to acid attack, as well as the dissolution of structural cations from octahedral layer which leads to formation of new pores.^{19,20} Surface area of Mt-2M and Mt-3M clays were decreased; and this could be attributed to pore clogging associated with the formation of mineralized phases which resist acid attack.^{19,38} The specific surface area of the Mt-3M is greater than that of the Mt-2M which means that the mineralized phases formed at the 2 M concentration are also attacked, thus causing the creation of new cavities in the structure of Mt-3M.

Infrared Spectroscopy (FTIR)

FTIR spectra of the studied samples are shown in Figure 3. The data in Table 2 summarize the vibrational modes of characteristic bands of montmorillonite.

From Figure 3, the absorption bands at 3620 cm⁻¹, 979 cm⁻¹, 915 cm⁻¹, and 839 cm⁻¹ are attributed to the vibrations of hydroxyl groups bound with the cations Al³⁺ and Mg²⁺. After acid activation, all the above absorption bands were completely disappeared. This disappearance can be explained by the phenomenon of leaching of cations Al³⁺ and Mg²⁺ structuring the octahedral layer. An increase in the intensity of the bands at 1089 cm⁻¹ and 788 cm⁻¹ is also noticed after the acid treatment, especially for the Mt-1M. This increase indicates the formation of three-dimensional structures of Si-O-Si units.⁴²

The infrared results are in good agreement with those of: XRD (the increase of the intensity of characteristic peaks of quartz), XRF (increase in the percentage of silica and decrease in the percentage of cations structuring the octahedral layer) and BET (increase of surface area due to the dissolution of the octahedral layer).

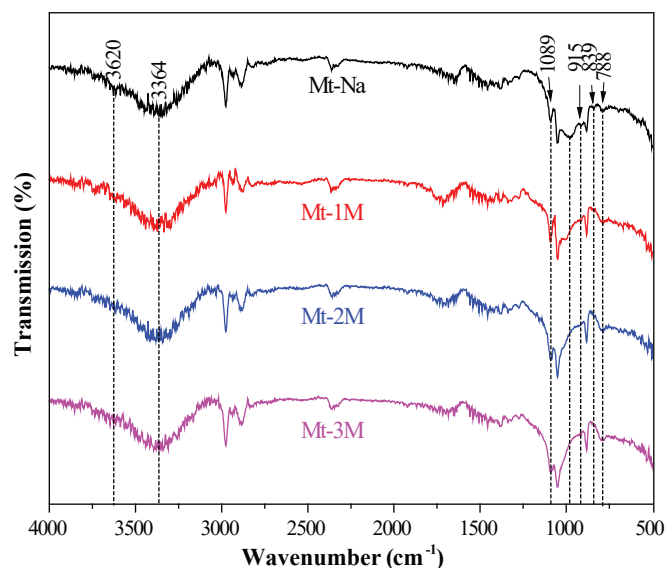


Figure 3. FTIR spectra of Mt-Na, Mt-1M, Mt-2M and Mt-3M.

Table 2. Vibrational modes of the Mt-Na bands.

Wavenumber (cm ⁻¹)	Vibration mode
3620	Stretching vibration Al ₂ OH with Al-Mg-OH. ³⁹
3364	Stretching vibration H-O-H.
1089	Stretching vibration Si-O.
915 and 839	Stretching vibration Al ₂ OH and Al-Mg-OH. ⁴⁰
788	Bending vibration Si ₂ OH. ⁴¹

Catalysts acidity analysis

Acidic properties of raw and treated montmorillonite were investigated using FTIR spectra of pyridine adsorbed on the material (Figure 4). The results are shown in the region of 1600–1400 cm⁻¹, as this region gives more information about the type of acidity in the material. Also three bands can be seen in Figure 4; the peak around 1540 cm⁻¹ corresponds to pyridine adsorbed on the Brønsted acid sites, the peak around 1450 cm⁻¹ is attributed to pyridine adsorbed on the Lewis acid sites and the band around 1490 cm⁻¹ is due to the vibrations of the H-linked pyridine which involves the two types of acid sites, this band is then characteristic of the total acidity of the material.⁴³ The spectra clearly shows that the intensities of characteristic peaks of different types of acids, increase with the

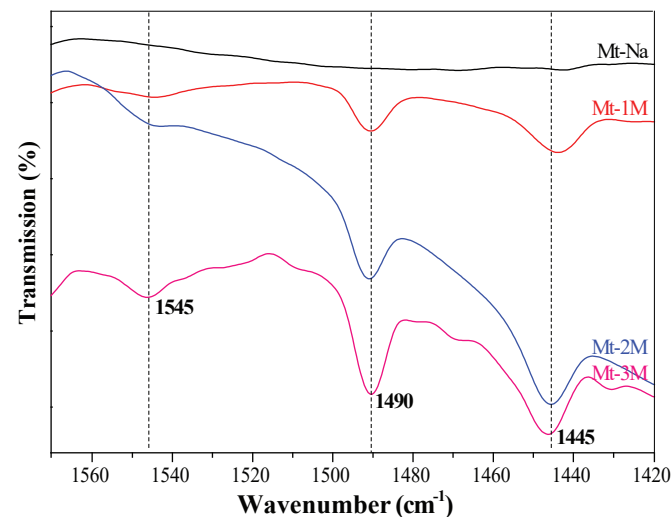


Figure 4. FTIR spectra of pyridine adsorbed on Mt-Na, Mt-1M, Mt-2M and Mt-3M.

concentration of the acid treatment solution, thus we can affirm that Mt-3M has a greater number of acid sites responsible for the catalytic properties. This improves its reactivity as it is well known that in heterogeneous catalysis, the catalyst efficiency depends strongly on the number of active surface sites.

X-Ray Fluorescence (XRF)

XRF is a non-destructive analytical technique used for qualitative and quantitative determination of the chemical composition of materials. The results of elemental chemical analysis given in Table 3, provides the percentage of oxide weight of Mt-Na, Mt-1M, Mt-2M and Mt-3M. They reveal that silicon and aluminum are the main constituents of natural montmorillonite. After acid activation, data in Table 3 clearly indicate considerable changes in the contents of oxides constituting the montmorillonite. The percentages of oxides decreased significantly in the case of Mt-1M, while the percentages of silicon, potassium and titanium increased. The decrease in the fractions of aluminum, iron and magnesium can be attributed to leaching of Al^{+3} , Fe^{+2} and Mg^{+2} cations structuring the octahedral layer, which leads to the dissolution of this layer.⁴⁴ A considerable reduction was also observed in the contents of interfoliar cations (Na^+ and Ca^{2+}) translating the phenomenon of cationic exchange of these two cations by the H^+ protons of the acid solution.¹⁹ For the Mt-2M, a slight variation has been noticed in the composition of the clay and this is due to the passivation phenomenon of montmorillonite.²⁸ Indeed at this concentration, montmorillonite becomes more resistant to acid attack because of the formation of insoluble mineralogical phases containing silicon, potassium and titanium precipitated on the fragments of the non-destroyed silicates and which are protected against any new acid attack.^{19,28} In reference of Mt-3M, the structure of montmorillonite is destroyed and this can be explained by the sharp decrease in the percentages of interfoliar cations and cations structuring octahedral layer. The XRF results are in good agreement with the results obtained by BET analysis; the specific surface area increases for Mt-1M due to the leaching of the octahedral cations. While it decreases for Mt-2M due to the formation of insoluble mineralogical phases containing silicon, potassium and titanium, leading to the blockage of the clay pores then it increases for Mt-3M, due to complete destruction of montmorillonite structure.

Table 3. Chemical composition of Mt-Na, Mt-1M, Mt-2M and Mt-3M.

Metal oxide	Chemical composition (% weight)			
	Mt-Na	Mt-1M	Mt-2M	Mt-3M
SiO ₂	62.1	81.4	82.3	87.4
Al ₂ O ₃	15.6	6.64	5.33	3.96
Na ₂ O	5.37	0.981	1.21	0.735
CaO	1.33	0.359	0.664	0.332
Fe ₂ O ₃	5.76	2.10	1.44	0.679
MgO	4.68	0.548	0.560	0.162
K ₂ O	4.82	7.25	7.78	6.23
Ti ₂ O ₃	0.34	0.672	0.706	0.532

Table 4. Reaction yields in the presence of the three catalysts in different solvents and solvent-free conditions.

	Yield (%)				
	Ethanol	Acetonitrile	Cyclohexane	Acetic acid	Solvent-free
Mt-1M	33	22	33	79	60
Mt-2M	34	42	65	87	65
Mt-3M	46	74	92	89	73
Without catalyst	-	16, (12h30mn)	26, (9h30mn)	40, (9h30mn)	-

Characterizations of 3, 4-dihydropyrimidin-2(1H)-one (DHPM)

The characteristics of the final product are as follows: $T_f = 206\text{ }^\circ\text{C}$.^{45,46} IR (KBr) ν : 3233, 3101, 2940, 1718, 1697, 1595, 1218 cm^{-1} . ¹H NMR (300 MHz, CDCl₃) δ : 1.22 (t, 3H), 2.36 (s, 3H), 4.07 (q, 2H), 5.29 (s, 1H), 5.91 (s, 1H), 7.09-7.21 (m, 5H), 8.28 (s, 1H).

Catalytic activity

Firstly, the reaction was conducted without catalyst and then various catalysts were used to test their effects on the reaction yield and time.

Effect of solvent on catalytic reaction

The reaction progress in the presence of the three catalysts Mt-1M, Mt-2M and Mt-3M with an amount of 20 wt% of benzaldehyde for 8 h was investigated (Table 4). As can be seen in Table 4, the reaction yield was higher in the presence of catalyst and tended to increase with the montmorillonite treatment concentration of sulfuric acid. This confirms that the reaction yield is influenced by the acidity of the clay and not by the specific surface area. Also, the nature of the solvent plays an important role in the synthesis of DHPMs. The reaction using cyclohexane provided a yield of 92%, whereas the acetic acid and acetonitrile gave lower yields of 89% and 74%, respectively (Mt-3M). This difference in yield can be explained by the phenomenon of specific interaction between the solvent and the catalyst.

Parametric studies

From an economic and ecological point of view, the process of solvent-free reactions remains a goal to be achieved. In this perspective, we have examined the reaction under solvent-free conditions and only for the Mt-3M, which presented better yields (Table 4).

Effect of catalyst dose

The considered doses of catalyst are 20%, 40%, and 60% (Table 5). The results show that, increasing the catalyst load from 20% to 40% effectively improves the reaction yield, this can be explained by the increase in the number of catalytic sites and consequently the catalyst can bind more reagent molecules, therefore it will be more efficient. Note that the best yield is obtained with a catalyst percentage of 40%. This value was estimated as the optimal load. While, when the dose of 60% is used, the mixture becomes pasty, with high density, difficult to stir, this minimize the catalyst–reagent contacts, and consequently the yield decreases.

Effect of the introduction order of the reagents

In heterogeneous catalysis, the adsorption step is decisive in the catalytic act because it can modify the nature of the reagents and this can decrease or increase their reactivity. Therefore, the order of introduction of the reagents becomes paramount. To see the effect

Table 5. Yield of solvent free reactions with different amount catalyst.

Catalyst amount (% weight)	20	40	60
Yield (%)	73	92	38
Time (h)	8	8	8

of this step in our case study, we carried out three different orders distributed on six processes according to Table 6.

- Order 1: Put the three reagents with the Mt-3M clay at the same time under stirring.
- Order 2: Put two reagents with the Mt-3M clay under stirring and after 2 h, add the 3rd reagent.
- Order 3: Put one of the three reagents with the Mt-3M clay under stirring and after 2 h, add the two remaining reagents. Note that, as urea is solid, it cannot be stirred with solid montmorillonite. Therefore, this order contains just two processes of starting with benzaldehyde and ethyl acetoacetate, respectively.

Table 6 reveals that the introduction order of the reagents is highly important. The best reaction yields are obtained with process 0 and process 4. These results are directly related to the adsorption step of the reagents and/or the intermediates which may result from their interactions. Note that when the reagents are introduced according to process 1, process 3 and process 5, the yields are low.

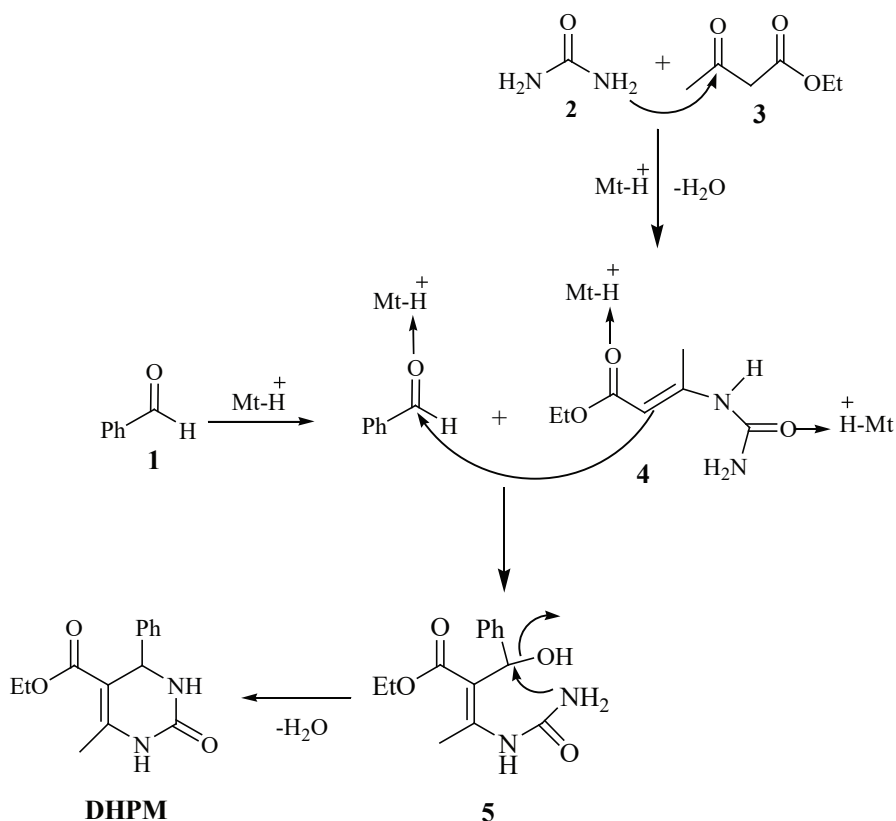
From the literature, three main mechanisms have been proposed for the Biginelli reaction (Iminium, Enamine and Knoevenagel mechanisms).⁴⁷ As process 0 and process 4 have the best yields (Table 6), we propose, in Scheme 2, a mechanism based on the enamine pathway for the Biginelli reaction catalyzed by montmorillonite (Mt-3M). The first step corresponds to the adsorption of benzaldehyde **1** on montmorillonite, the addition of urea **2** and ethyl acetoacetate **3** leads to their condensation thus giving the intermediate enamine **4** catalyzed and stabilized by montmorillonite, this intermediate reacts with the adsorbed benzaldehyde to give intermediate **5**, after intramolecular cyclisation and dehydration, dihydropyrimidinone (DHPM) is obtained.

Catalyst recyclability

The efficiency of a heterogeneous catalyst is highly dependent on its regeneration and repetitive use. Generally, catalysts can be regenerated by several ways, such as high temperature calcination and chemical

Table 6. Effect of the introduction order of the reagents on the reaction yield.

		Step 1		Step 2		
		Reagents	Operating conditions	Reagents	Operating conditions	Yield (%)
Order1	Process 0	Benzaldehyde + Urea + Ethyl acetoacetate + Mt-3M	→		Reflux, 8h	92
Order 2	Process 1	Benzaldehyde + Urea + Mt-3M	Stirring, 2 h	Ethyl acetoacetate	Reflux, 8 h	49
	Process 2	Ethyl acetoacetate+ Urea + Mt-3M	Stirring, 2 h	Benzaldehyde	Reflux, 8 h	76
	Process 3	Benzaldehyde+ Ethyl acetoacetate + Mt-3M	Stirring, 2 h	Urea	Reflux, 8 h	14
Order 3	Process 4	Benzaldehyde + Mt-3M	Stirring, 2 h	Ethyl acetoacetate + Urea	Reflux, 8 h	91
	Process 5	Ethyl acetoacetate + Mt-3M	Stirring, 2 h	Benzaldehyde + Urea	Reflux, 8 h	48



Scheme 2 Proposed mechanism.

cleaning. Microwaves and ultrasound can also significantly intensify the regeneration process.^{48,49} In this respect, the Mt-3M clay used under optimized reaction conditions is regenerated by simple filtration, and washed several times with hot ethanol, and then dried at 90 °C for 24 h. The final product was reused for three further catalytic cycles (Figure 5). After the third recovery of the catalyst, the reaction yield was reduced to 76%. This could be attributed to the accumulation of reagents or organic compounds resulting from the reaction on the montmorillonite surface.

Comparison of the catalytic performance

To appreciate the results obtained in the proposed work, we performed some comparisons with other recently published works from literature, as shown in Table 7. The comparison covers temperature, solvent, reaction time and yield. It confirms that the present protocol using Algerian montmorillonite activated with sulfuric acid is one of the most effective protocols for the synthesis of DHPMs.

A comparison of our process with published works mentioned in Table 7 shows the following:

- In the first work referenced,⁵⁰ a synthetic catalyst with solvent is used, while our catalyst is natural and abundant, moreover the process we propose is solvent-free, which makes it less expensive and more ecological.
- The second work referenced⁵ used a synthetic catalyst while ours is natural and gives comparable performance, which makes our product more competitive because it is less expensive, abundant and more ecological.
- The third work referenced⁸ used a toxic acid as a homogeneous catalyst with hard separation from the reaction medium in addition to its toxicity, which makes our product much more efficient.
- Finally, compared to the fourth work referenced,⁵¹ our process is much more efficient whether in terms of temperature, reaction time or yield.

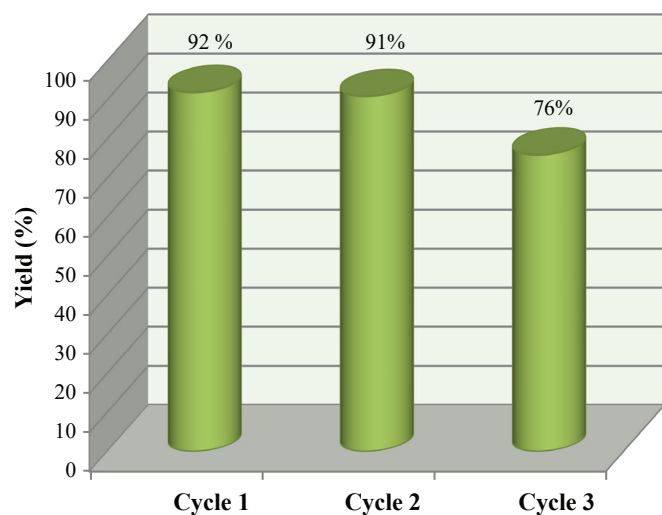


Figure 5. Yields of reaction in recycling tests of Mt-3M catalyst under solvent-free conditions.

CONCLUSION

To carry out the Biginelli reaction efficiently, a series of experiments were performed using Algerian montmorillonite as a solid acid catalyst under different conditions. The catalyst was easily prepared by a simple ion exchange with a sulfuric acid solution. This exchange process leads to the leaching of Al^{3+} , Mg^{+2} and Fe^{+3} cations structuring the octahedral layer; this is accompanied by an increase in the specific surface area and surface acidity of the activated montmorillonite. The reaction carried out in absence of any catalyst gave low yields for relatively long reaction times, which justifies the importance of the catalyst. The results obtained in the presence of activated clay, clearly show that the acidity of the clay is the parameter which influences the yield.

The nature of the solvent plays an important role in the Biginelli reaction while the reaction without solvent gives good yields. It makes the DHPMs preparation process safer and eco-friendly. The effect of the catalyst dose is also to be considered as well as the introduction order of the reagents. Furthermore, we have shown that the studied clay is reusable and keeps its catalytic reactivity after three regeneration tests.

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Table 7. Comparison between Mt-3M and the different catalysts used in recent literature.

Catalyst	Conditions	Solvent	Time (h)	Yield (%)	Ref
$\text{Fe}_3\text{@SiO}_2\text{-ZnCl}_2$	80 °C	EtOH	2	95	⁵⁰
Ag-Fe-MOF	90 °C	Solvent free	5	94.5	⁵
Phosphorofluoric acid	60 °C	Solvent free	4	90	⁸
PPh ₃	100 °C	Solvent free	12	74	⁵¹
Mt-3M	80 °C	Solvent free	8	93	Present work

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