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Research Article

Enamino ester synthesis using a proton exchanged Algerian montmorillonite clay as acid eco-friendly catalyst

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Abstract:

An efficient and straightforward methodology has been developed for the synthesis of β-enamino ester derivatives (3a-h). This transformation involves the direct condensation of alkyl or aromatic amines (2a-d) with β-ketoesters (1a-b), facilitated by protonated Algerian montmorillonite clay (MMT-H+) as a heterogeneous, eco-friendly catalyst. The protocol yields the target products in good to excellent yields.The key advantage of this method lies in the utilization of the MMT-H+ catalyst, which is notable for its natural abundance, low cost, and non-toxic nature. As a solid acid, it simplifies the work-up procedure and can be recovered and reused over several cycles without a significant decrease in its catalytic performance. This approach, characterized by its operational simplicity, cost-effectiveness, and environmental friendliness, represents a sustainable alternative for the preparation of these valuable synthetic intermediates.

1. Introduction

Enamino esters and enaminones are important synthetic intermediates. 1-6 They have been used in the synthesis of numerous natural products and pharmaceutically active compounds such as pyrazoles, oxazoles, quinolines, dibenzodiazepines, pyridinones, tetrahydrobenzoxazines, tetronic acids, and tetrahydrophenanthridines. 7-13 They have been used in the preparation of various important antibacterial, 14 anticonvulsant, 15 anti-inflammatory, 16 and antitumor agents. 17They are also important precursors for the synthesis of 3-aminosugar derivatives, 18 β-aminoketones, 19 azo compounds, 20 hexahydroazulenes, 21 and indolizidine alkaloids. 22

The synthesis of enaminones, or enamines of β-dicarbonyl compounds, is generally carried out by the condensation of β-dicarbonyl compounds with amines. 23,24 Most of these syntheses rely on conventional thermal methods in the presence of organic solvents and various catalysts such as acetic

acid, 25 Zn(ClO4)2.6H2O, 26 bismuth (III) trifluoroacetate Bi(TFA)3, 27 cerium chloride hepta hydrate CeCl3.7H2O,28 lanthanum trichloride hepta hydrate LaCl3.7H2O,29 ceric ammonium nitrate,30 Pd(0), 31 ferric (III) ammonium nitrate, 32 NaAuCl4, 33 cobalt(II)chloride 34or Sc(OTf)3.35 Therefore, it is necessary to develop a simple and environmentally friendly catalyst, usable under moderate conditions, for the preparation of enaminoesters and enaminones.

In this work, we describe a simple, efficient, and environmentally friendly method for the synthesis of enaminoester derivatives by reacting β-ketoesters with amines in the presence of Maghnite-H+.

The catalyst used in this study is a green, non-toxic, inexpensive, recyclable, and non-polluting montmorillonite clay called Maghnite-H+.36 It has recently been used in the synthesis of Schiff bis-bases 37 and in the synthesis of macromonomers and polymers by cationic polymerization. 38-41 Maghnite-H+ offers a potential new route for the synthesis of enaminoesters with good to excellent yields.

2. Experimental Materials

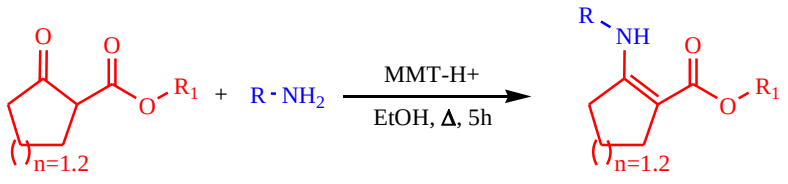
All chemicals were obtained from sigma Aldrich and Biochem and were used withoutfurther purification. Raw-Maghnite, Algerian montmorillonite clay was procured from "BENTAL" (Algerian Society of Bentonite). Thin layer chromatography (TLC) was done on silica gel TLC aluminium plates (E. Merck Kieselgel 60 F-254) and were visualized by exposure to UV-light at 254 nm or iodine vapor for few seconds. 1H and 13C NMR spectra were acquired on a Bruker AQS-AVANCE spectrometer (400 MHz) at 25°C using CDCl3 as solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS, δ = 0.00 ppm).

General procedure for the preparation of Maghnite-H+ catalyst (MMT-H+)

The reaction was catalyzed by Maghnite-H+. It was prepared according to the following method 42, 43: An amount of 20g of raw-Maghnite in powder form was dried for two hours at a temperature of 105°C to remove any traces of water. After drying, the Maghnite was put in an Erlenmeyer containing 500ml distilled water, then 0.23M sulfuric acid solution was added at once to the mixture Maghnite / water and agitated by a mechanical stirrer for about two days at room temperature. After that, the mineral part of the whole mixture was washed by distilled water until it become a free from sulfate and finally dried at 105°C for about 2hours.

General method for synthesis of β-enamino ester derivatives (3a-h)

Alkyl or aromatic amines 2a-d (1mmol) is added to β-cetoesters 1a-b (1mmol) in 10ml ethanol with catalytic amount of montmorillonite-H+ (10%). The reaction mixture is refluxed for 5h. The progress of reaction is monitored by TLC. The crude product is dissolved with hot ethanol and then filtered to remove the solid catalyst. The filtrate is cooled to give the solid product. The resulting product is filtered, washed with ethanol and dried at 60-70°C to afford compound 3a-h (Scheme 1). All the products were fully characterized on the basis of their spectral data (1H NMR and 13C NMR).

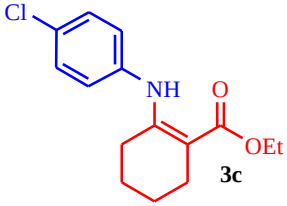


1a-b **2a-d** **3a-h**

R = aryl or alkyl

Figure 1. *Synthesis of β-enamino esters derivatives 3a-h catalyzed by MMT-H+*

Table 1. *Catalytic effect on synthesis of β-enamino esters derivatives 3a-h catalyst by Maghnite-H⁺.*

Entry	Cat (%)	Time(h)	T(°C)	Yield(%)
 **3c**	**10**	5	Reflux	**92.8**
	20			84.5
	30			78.61

Cat: Maghnite-H⁺

Ethyl 2-(2,2-dimethoxyethylamino) cyclohex-1-enecarboxylate (3a) : yield: 91%; 1H NMR (CDCl3) δ in ppm : 1.20 (t, J=7 Hz, 3H, CH3), 1.43-1.64 (m, 4H, -CH2-), 2.14-2.29 (m, J=5.29 Hz, 4H, -CH2-), 3.24 (dd, J=5 Hz, 2H, -CH2-), 3.34 (s, 6H, CH3), 4.08 (q, J=7 Hz, 2H, -CH2-), 4.35 (t, J=5 Hz, 1H), 8.90 (s,1H, NH) ; 13C NMR (CDCl3) δ in ppm : 14.60, 22.28, 22.63, 23.85, 26.58, 44.03, 54.13, 58.65, 90.66, 103.53, 158.66, 170.73 C=O.

Ethyl 2-(phenylamino) cyclohex-1-enecarboxylate (3b) : yield: 90%; 1H NMR (CDCl3) δ in ppm : 1.25 (t, J=7 Hz, 3H, CH3), 1.69 (d, J=6.61, 4H, -CH2-), 2.27-2.44 (dt, J=5.86 Hz, 22.66 Hz, 4H, -CH2-), 4.14 (q, J= 7 Hz, 2H, -CH2-), 7.10-7.20 (m, 3H, Harom), 7.30-7.40 (m, 2H, Harom), 10.81 (s,1H, NH); 13C NMR (CDCl3) δ in ppm : 14.62, 21.93, 22.24, 23.75, 27.65, 58.90, 92.43, 124.20, 127.40, 129.22, 139.37, 156.51, 170.00 C=O.

Ethyl 2-(4-chlorophenylamino) cyclohex-1-enecarboxylate (3c) : yield: 93%; 1H NMR (CDCl3) δ in ppm : 1.25 (t, J=7 Hz, 3H, CH3), 1.46-1.64 (m, 4H, -CH2-), 2.17-2.34 (m, 4H, -CH2-), 4.20 (q, J= 7 Hz, 2H, -CH2-), 6.75 (d, J=2.2, 2H, Harom), 8.10 (d, J=2.2, 2H, Harom), 9.10 (s,1H, NH); 13C NMR (CDCl3) δ in ppm : 14.65, 22.25, 22.69, 23.82, 26.01, 58.64, 90.14, 122.45, 127.37, 135.49, 140.99, 152.50, 170.88 C=O.

Ethyl 2-(3-chlorophenylamino) cyclohex-1-enecarboxylate (3d) : yield: 92%; 1H NMR (CDCl3) δ in ppm : 1.24 (t, J=7 Hz, 3H, CH3), 1.40-1.70 (m, 4H, -CH2-), 2.05-2.40 (m, 4H, -CH2-), 4.10 (q, J= 7 Hz, 2H, -CH2-), 6.25 (d, J=2.2, 1H, Harom), 6.80- 7.15 (m, 3H, Harom), 8.95 (s,1H, NH); 13C NMR (CDCl3) δ in ppm : 14.30, 21.61, 21.92, 23.43, 27.33, 58.64, 92.11, 118.88, 123.88, 128.90, 133.05, 136.25, 139.05, 156.50, 169.68 C=O.

Méthyle 2-(2,2-dimethoxyethylamino)cyclopent-1-enecarboxylate (3e) : yield: 90%; 1H NMR (CDCl3) δ in ppm : 1.47-1.87 (m, 2H, -CH2-), 2.43-2.60 (m, 4H, -CH2-), 3.27 (dd, J=5.5 Hz, 2H, -CH2-), 3.38 (s, 6H, CH3), 3.65 (s, 3H, CH3), 4.34 (t, J=5.5 Hz , 1H), 7.42 (s,1H, NH); 13C NMR (CDCl3) δ in ppm : 20.85, 29.13, 32.20, 46.75, 50.14, 54.49, 94.15, 103.76, 155.33, 168.60 C=O.

Méthyle 2-(phenylamino)cyclopent-1-enecarboxylate (3f) : yield: 89%; 1H NMR (CDCl3) δ in ppm : 1.76-1.91 (m, 2H, -CH2-), 2.44-2.66 (dt, 4H, -CH2-), 3.76 (s, 3H, CH3), 6.68-6.81 (m, 3H, Harom), 6.97-6.10 (m, 2H, Harom), 8.71 (s,1H, NH); 13C NMR (CDCl3) δ in ppm : 20.93, 27.24, 32.65, 50.90, 91.48, 124.10, 124.30, 129.82, 138.42, 155.53, 169.80 C=O.

Méthyle 2-(4-chlorophenylamino)cyclopent-1-enecarboxylate (3g) : yield: 92%; 1H NMR (CDCl3) δ in ppm : 1.76-1.91 (m, 2H, -CH2-), 2.44-2.66 (dt, 4H, -CH2-), 3.76 (s, 3H, CH3), 6.85 (d, J=2.2, 2H, Harom), 7.92 (d, J=2.2, 2H, Harom), 8.72 (s, 1H, NH); 13C NMR (CDCl3) δ in ppm : 20.87, 27.65, 32.62, 50.81, 90.88, 123.90, 124.32, 130.12, 138.47, 154.62, 169.72C=O.

Méthyle 2-(3-chlorophenylamino)cyclopent-1-enecarboxylate (3h) : yield: 91%; 1H NMR (CDCl3) δ in ppm : 1.68-1.89 (m, 2H, -CH2-), 2.42-2.68 (dt, 4H, -CH2-), 3.67 (s, 3H, CH3), 6.28 (d, J=2.2, 1H, Harom), 6.92- 7.18 (m, 3H, Harom), 8.92 (s,1H, NH); 13C NMR (CDCl3) δ in ppm : 21.61, 26.92, 31.88, 50.64, 92.11, 121.88, 123.76, 129.87, 135.22, 136.37, 138.92, 156.15, 169.73 C=O.

3. Results and Discussions

In this work, a green, non-toxic and recyclable catalyst (proton-exchanged Algerian montmorillonite MMT-H+) was used for the synthesis of β-enamino esters derivatives (Scheme 1).

To investigate the catalytic effect on the reaction yield, tests are carried out with different amounts of catalyst for the compound (3c). The results shown (Table 1) show that the use of 10% of catalyst at 79°C. Is the most effective and the yield obtained was 93% for 5 hours in ethanol (scheme 1).

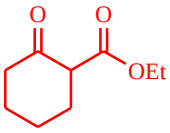
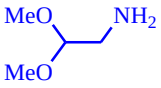
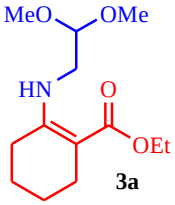
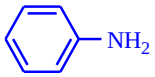
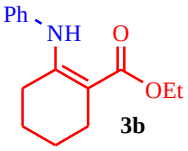
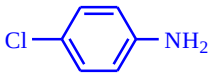
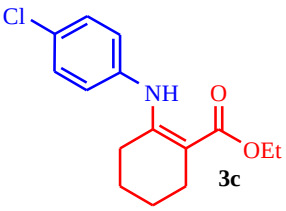
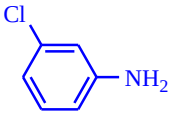
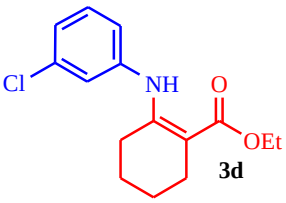
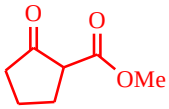
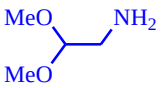
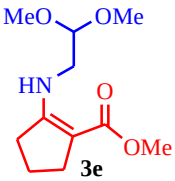
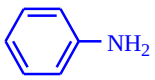
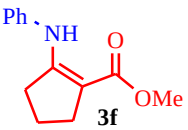
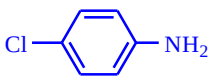
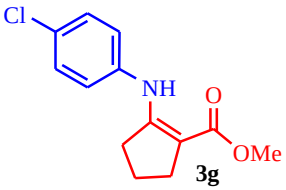
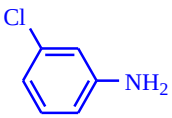
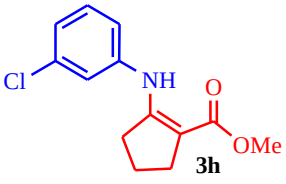
In general, β-enamino esters derivatives 3a-h were obtained in good to excellent yields when mixtures of Alkyl or aromatic amines (2a-d) with β-ketoesters (1a-b) and 10% Maghnite-H+ were refluxed in ethanol for 5 hours (Table 2). The desired products precipitate upon cooling of the reaction mixture and filtration yields analytically pure material. The experimental results (Table 2) obtained by this reaction show good to excellent yields compared to those in the literature.

A mechanism, shown in (Scheme 2), is proposed to explain the role of the proton exchange montmorillonite catalyst (MMT-H+) in the synthesis of β-enamino esters 3a-h. The structures of the 3a-h compounds were confirmed by their spectral data (1H and 13C spectroscopy), compared to values from the literature.

4. Conclusions

The montmorillonite-H+ (MMT-H+) was found to be an efficient green heterogeneous acidic catalyst for the synthesis of β-enamino esters derivatives 3a-h. This catalyst was easy to prepare, environmentally friendly, highly stable and can be recycled without

Table 2. *Physical data of the synthesized compounds (3a-h) using Maghnite-H*$^{+}$

Entrée	β-étoesters	Amine	Produits obtenus	Yield* (%) Exp **	(Lit.)
1			 **3a**	91	- -
2			 **3b**	90	85 [25]
3			 **3c**	93	88 [25]
4			 **3d**	92	86 [25]
5			 **3e**	90	- -
6			 **3f**	89	- -
7			 **3g**	92	- -
8			 **3h**	91	- -

(*) Isolated yield of product using montmorillonite-H^{+}. The structure of products are determined by NMR and all spectral data are in good agreement with those of literature.

(**) Exp.: Experimental value (Lit.: literature value).

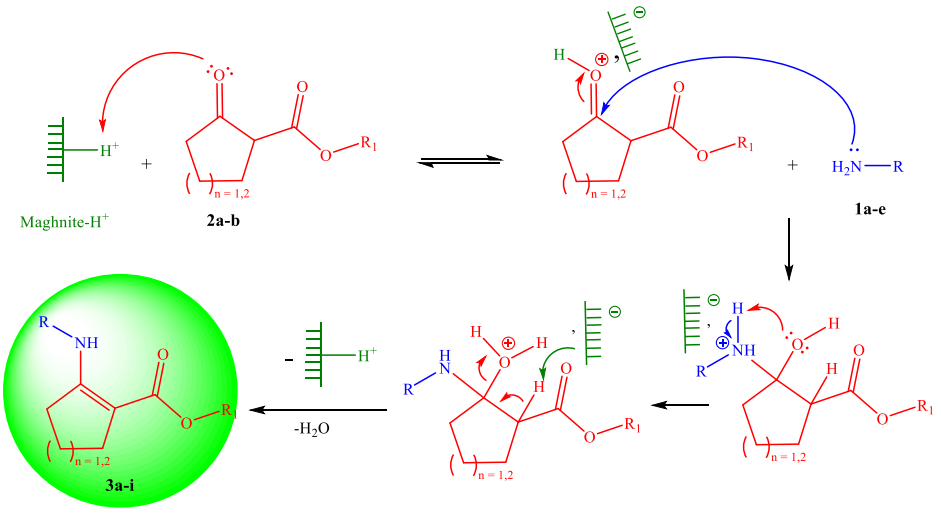


Figure 2. *Proposed mechanism of the synthesis of β-enamino esters derivatives 3a-h using Maghnite-H+*

significant loss of activity. The distinguished advantageous of present synthetic method are use of inexpensive catalyst, simple reaction workup, good to excellent yields and reusability of catalyst. Other applications of this catalyst in synthetic processes are under study.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
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- **Author contributions:** The authors declare that they have equal right on this paper.
- **Funding information:** The authors declare that there is no funding to be acknowledged.
- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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