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Short communication

Sonochemical synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones by amine-modified montmorillonite nanoclay

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ABSTRACT

Ultrasound irradiation was applied for the rapid and clean synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones through condensation of hydroxylamine hydrochloride, ethyl acetoacetate and benzaldehyde derivatives. This methodology was effectively catalyzed by amine functionalized montmorillonite K10 nanoclay (NH_2-MMT). Compared with conventional methods, this protocol has promising features for the reaction response such as shorter reaction times, easier work-up, ease of separation of pure product with high yields and simplicity in the experimental procedure.

1. Introduction

Isoxazoles are important heterocycles and possess various pharmacological activities. These heterocyclic compounds can act as immunosuppressive, antibacterial, antifungal [1], anticancer [2], anticancer [3], analgesic [4], antitumor [5] and show hypoglycemic activity [6]. Recently, organic chemists are interested in the synthesis of isoxazole scaffolds due to wide importance in medicinal, industrial and the field of synthetic organic chemistry [7]. The conventional synthesis of the title compound consists of two consecutive steps. In the first step, the formation of oxime is occurred by the reaction of ethyl acetoacetate and hydroxylamine hydrochloride followed by ring closure affords 3-methyl-isoxazole-5(4H)-one. Then, in second step, the Knoevenagel condensation reaction between 3-methyl-isoxazole-5(4H)-ones and aromatic aldehydes, which finally gives 3-methyl-4-arylmethylene-isoxazole-5(4H)-ones [8].

More recently, different catalyst such as sodium citrate [9], sodium sulfide [10], DABCO [11], sodium saccharin [12], sodium silicate [13], sodium tetraborate [14], DABCO and pyridine [15] and some new methods such as solid state grinding, solid state heating [16], stirring in water [17] and visible light induced reaction [8] have appeared to be effective techniques. In general, these methods have its own merits as well as demerits such as expansive catalyst and solvent, harsh reaction condition, longer reaction time, poor yields and difficulties in work-up procedure [18]. Therefore, the introduction of a simple and efficient procedure based on green methodology is still in demand. The development of solid basic catalytic systems utilizing inexpensive, clean, environmentally benign, and commercially available catalysts has been a challenge in the synthesis of isoxazoles.

On the other hand, the use of clays particularly montmorillonite K10 (MMT-K10) as a catalyst and catalyst support has received considerable attention in chemical synthesis [19]. The nanolayered structure of MMT-K10 by encapsulating organic substrates can be act as a nanoreactor for the chemical reactions and a drug nanocarrier for pharmaceutical purposes. Organo-modified MMT has received a great deal of attention in catalytic processes because of their nano-size, large surface area, high surface reactivity, cheap and nonhazardous, high stability and relatively simple processing [20]. MMT-K10 has been modified by introducing 3-aminopropyltriethoxysilane and used in organic transformation. The amine-modified MMT is used as nanocatalyst in a variety of chemical reactions and as a good support for heterogeneous catalytic processes, such as Ullmann coupling reaction [21], the synthesis of heterocyclic compounds [22], Henry reaction [23], C—S coupling reactions [24], Knoevenagel reaction [25], and other process.

In this communication, we disclosed an eco-friendly methodology for the synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones using NH_2-MMT nanoclay as a solid acid–base catalyst under sonication conditions (Scheme 1).

2. Experimental

2.1. Chemicals and apparatus

All chemicals were purchased from the Merck, Aldrich and Sigma Chemical Companies. NanoClay (Cloisite 30B) is a commercial

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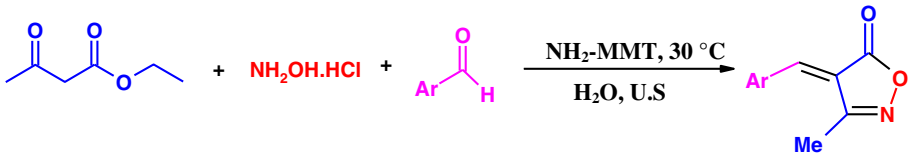


Scheme 1. Sonochemical synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones by NH_2-MMT.

organically modified montmorillonite with specific surface area of 250 m^2/g, pH = 3–4, with a grain diameter of 10–30 nm, prepared by Southern Clay Products, Inc. and was used as received. Melting points were determined on an Electrothermal MK3 apparatus using an open-glass capillary and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. FT-IR spectra were obtained with KBr pellets in the range 400–4000 cm^{-1} with a Perkin-Elmer 550 spectrometer. Nanostructures were characterized using a Holland Philips Xpert X-ray diffraction (XRD) diffractometer (CuK, radiation, λ = 0.154056 nm), at a scanning speed of 2°/min from 10° to 100° (2θ). A Bandelin Sonorex Super 10P Ultrasonic Bath (water) (with a frequency of 35 kHz and a nominal power 100 W) was used.

2.2. Synthesis of NH_2-MMT nanoclay

NH_2-MMT was prepared according to reported procedure in the literature. MMT (0.50 g) was further was diluted with n-hexane (15 mL) containing 3-aminopropyl-triethoxysilane (APTES) (1.2 mmol) and stirred at room temperature under mechanical stirring for 2 h. Then, the solvent was removed by filtration and the functionalized MMT was washed with ethanol and n-hexane. The NH_2-MMT was dried at 50 °C under vacuum [24].

2.3. General procedure for the synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol) and NH_2-MMT (0.01 g) in distilled water (5 mL) as a solvent in a 50 mL round-bottomed flask and irradiated under sonication at 30 °C. After completion of the reaction (monitored on TLC), the nanocatalyst was separated by filtration, and reused as such for the next experiment and the solvent was evaporated. The filtrate was concentrated to dryness, and the crude solid product was crystallized from EtOH to afford the pure product in high yield.

3. Results and discussion

The objectives of the present investigation are: (i) to prepare 3-methyl-4-arylmethylene isoxazole-5(4H)-ones, (ii) heterogenization of homogeneous organocatalyst based on MMT nanoclay as recyclable catalytic system, (iii) to develop an efficient ultrasound-assisted synthetic process for the facile one-pot reaction under optimal conditions.

For the surface modification, the MMT was functionalized with APTES via silanization reaction to obtain NH_2-MMT (scheme S1) [24]. The results of elemental analysis of the NH_2-MMT (Anal. found. (%): C 7.46, H 1.98, N 2.38, C/N 3.13) suggest that N was grafted onto the nanoclay at 1.57 mmol g^{-1}.

Fig. S1 shows the FT-IR spectra of MMT and NH_2-MMT. In Fig. S1(a) for pure MMT, the absorbance bands at 3590 and 1045 cm^{-1} are related to Al—O—H and O—Si stretching vibration, respectively. The other bands related to H—O—H stretching and bending vibrations could be found at 3432 and 1632 cm^{-1} respectively. In the case of NH_2-MMT in Fig. S1(b), the two weak peaks at 2927 and 2870 cm^{-1} correspond to the —CH stretching mode and a broad band peak at 3417 cm^{-1} is attributed to the NH_2 groups on the nanoclay surface. In addition, the peak at 525 and 467 cm^{-1} is the stretching vibration due to the interactions of Al—O and Mg—O bonds respectively. NH_2-MMT showed an absorption peak at 1560 cm^{-1} corresponding to the NH_2 bending vibration. Since both the NH_2 and CH_2 groups are attached to the APTMS skeleton, the above observations suggest the presence of organosilane on the surface of MMT [22,24,26].

The SEM micrographs of samples are shown in Fig. 1(a) and (b). It shows that naked MMT nanoclay has a layered morphology consisting of broken plates. The morphology of the NH_2-MMT was quite similar to that of the parent nanoclay, as can be seen from the inset of Fig. 1(b). The micrographs of NH_2-MMT clearly show highly porous morphology [25].

The broad angle XRD spectra of MMT and NH_2-MMT are shown in Fig. 2(a). The hkl and two dimensional hk reflections for MMT can be seen in two the samples. However, some peaks are also present due to many impurities such as cristobalite, quartz and feldspar. The similarities in the spectra of the two samples suggest no structural changes

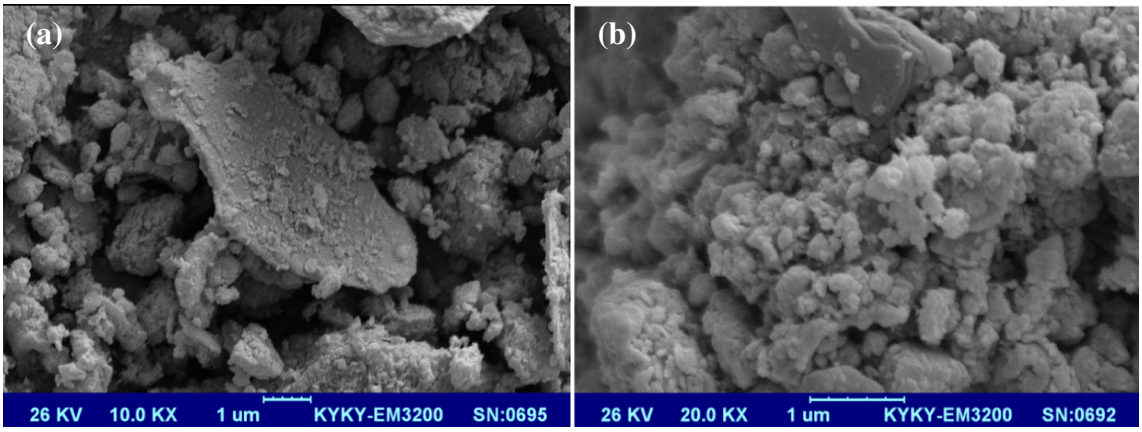


Fig. 1. SEM micrographs of (a) MMT and (b) NH_2-MMT.

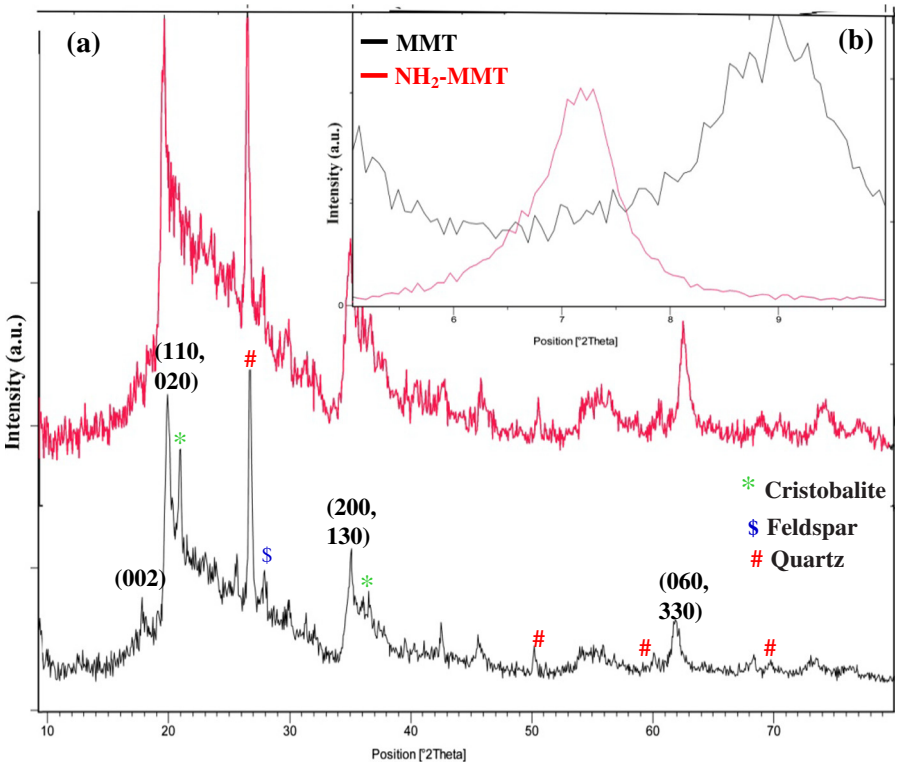


Fig. 2. (a) XRD patterns of MMT and NH_2-MMT; (b) Low angle XRD spectra of MMT and NH_2-MMT.

have occurred in the clay matrix after functionalization with the organic groups [21,24]. The low angle XRD spectra of neat and aminosilane modified MMT are shown in Fig. 2(b). The shifting of the (001) peak towards a lower 2θ value suggests the intercalation of NH_2 groups into the nanoclay interlayer.

The TGA curves of nanoclays are shown in Fig. S2, For the NH_2-MMT, there are two steps of mass losses at temperatures of 50–200 and 200–750 °C. The weight loss below 200 °C could be attributed to the physical adsorption of water or solvent in the clays. The weight loss of NH_2-MMT is about 12% at 200–750 °C, corresponding to the thermal decomposition of organic components in nanoclay.

Fig. 3 shows the temperature programmed desorption of carbon dioxide (CO_2-TPD) patterns of MMT before and after the amine modification in the temperature range 10–200 °C. It can be observed that the NH_2-MMT shows one desorption peak at 62 °C that corresponds to the decomposition of the product of alkylamine groups with CO_2. Amine groups in NH_2-MMT react with CO_2 molecules to form carbamate through zwitterionic intermediates. For this purpose, a pair of electrons in the amine groups, attacks the CO_2 carbon atom to produce the zwitterion species. Then, free base deprotonates the zwitterion to produce carbamate [26].

The synthesized NH_2-MMT was assessed for its activity for the synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones. We carried out a reaction of 4-methoxy benzaldehyde, ethyl acetoacetate, and hydroxylamine hydrochloride as the model reaction in the presence of NH_2-MMT catalyst using H_2O as solvent under ultrasound irradiation.

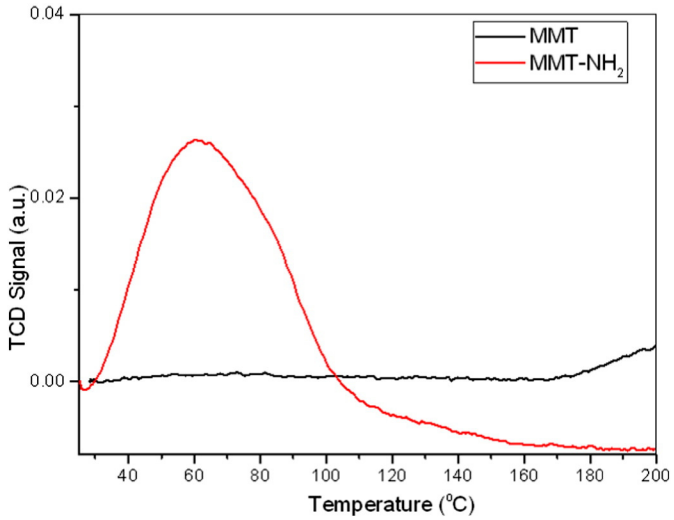


Fig. 3. CO_2-TPD patterns of MMT before and after modification.

Table 1
Optimization of reaction conditions of the model reaction under ultrasound irradiation at 30 °C.[a]

Entry	Solvent	Catalyst (g)	Power intensity (W)	Time (min)	Yield (%)[b]
1	H_2O	0.008	100	90	40[c]
2	H_2O	0.008	100	25	93
3	Ethanol	0.008	100	25	Trace
4	Methanol	0.008	100	25	Trace
5	DCM	0.008	100	25	Trace
6	Solvent free	0.008	100	25	10
7	H_2O	0.006	100	25	80
8	H_2O	0.01	100	25	96
9	H_2O	0.02	100	25	96
10	H_2O	0.03	100	25	93
11	H_2O	0.01	30	25	32
12	H_2O	0.01	70	25	74
13	H_2O	0.01	90	25	92
14	H_2O	None	100	25	30
15	H_2O	MMT	100	25	70
16	H_2O	APTES (0.004 mL)	100	25	55

[a] Ethyl acetoacetate (1 mmol), 4-methoxy benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), and NH_2-MMT in solvent (5 mL) at 30 °C under ultrasound irradiation.
[b] Isolated yield of the pure compound.
[c] Without sonication.

Table 2
Preparation of different isoxazole-5(4H)-ones catalyzed by NH_2-MMT in ultrasonic conditions.[a]

Entry	Ar	Product	Time (min)/yield(%)[b]	Mp (Lit.mp) [Ref]
1	4-OMe-C_6H_4	**4a**	25/96	174–175 (173–174) [12]
2	2-OMe-C_6H_4	**4b**	17/94	137–139
3	3,4-$(OMe)_2$-C_6H_3	**4c**	25/93	134–135 (135) [8]
4	4-OH-C_6H_4	**4d**	15/90	214–215 (213–215) [12]
5	3-OH-C_6H_4	**4e**	30/89	202–203 (202 − 203) [12]
6	2-OH-C_6H_4	**4f**	50/80	197–199 (198–199) [12]
7	4-Me-C_6H_5	**4g**	50/80	130–133 (130 − 132) [12]
8	3-OH-4-OMe-C_6H_3	**4h**	13/94	187–189
9	4-$N(CH_3)_2$-C_6H_4	**4i**	10/97	224–226 (226–228) [12]
10	C_6H_5	**4j**	55/86	141–143 (141–142) [12]
11	3-Indole-carboxaldehyde	**4k**	14/93	243–244 (240) [8]
12	2-Tiophen	**4l**	22/91	144–145 (144–146) [12]

[a] Ethyl acetoacetate (1 mmol), aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), and 0.01 g NH_2-MMT in H_2O (5 mL) at 30 °C under ultrasound irradiation (100 W).
[b] Isolated yield of the pure compound.

The effect of different solvents was examined on the model reaction under ultrasound irradiation (Table 1). In the absence of ultrasound, the reaction must be performed for 90 min to produce only 40% yield (Table 1, entry 1), while under ultrasound irradiation, the yield was 93% after 25 min (Table 1, entry 2). Liquids irradiated with ultrasound can produce cavitational collapse, which generates localized microscopic "hot spots" with transient high temperatures and pressures to induce favorable conditions for organic reactions [27].

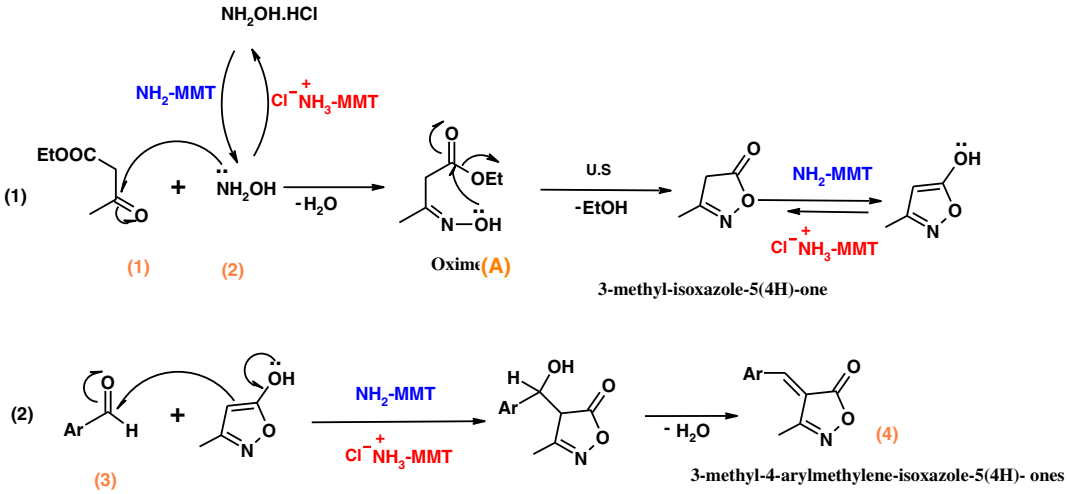
Then, the reaction was evaluated by varying the concentrations of nanocatalyst (0.006–0.03 g). It was observed that the reaction in the presence of 0.01 g NH_2-MMT and ultrasound irradiation gave the best result as the obtained product with 96% isolated yield during 25 min (Table 1, entry 8). The model reaction was evaluated by pure MMT, NH_2-MMT and APTES as catalyst. All catalysts have demonstrated their ability to act as promoters in this process (Table 1, entry 15 and 16). MMT is known as an acid catalyst in chemical transformation [25]. APTES as basic homogeneous catalyst has appeared to be mild catalyst. But, catalyst separation is not easy. Therefore, we used from amine-modified nanocatalyst as a solid acid–base catalyst towards the desired reaction.

After optimization of the reaction conditions, this methodology was evaluated for the synthesis of different isoxazoles from various structurally diverse aldehydes. The results are summarized in Table 2. These results were shown that a wide range of aromatic aldehyde derivatives containing electron withdrawing as well as electron donating groups produced corresponding isoxazoles in excellent isolated yields with high purity.

A plausible reaction mechanism is proposed based on these results and provided mechanism in literature (Scheme 2). As the initiation step (1), the NH_2-MMT helps to generate the hydroxylamine from hydroxylamine hydrochloride (**2**), and the nucleophilic attack of the amino group of NH_2OH on the carbonyl carbon of the ethyl acetoacetate resulted in intermediate oxime (**A**). Then cyclization of intermediate (**A**) was done for the synthesis of 3-methyl-isoxazole-5(4H)-one under ultrasound irradiation. In the next step, the Knoevenagel condensation was occurred between 3-methyl-isoxazole-5(4H)-one and aromatic aldehyde (**3**) in the presence of catalyst, which finally gives 3-methyl-4-arylmethylene-isoxazole-5(4H)-one (**4**) [11,12].

In continuation of this research, the recovery, and reusability of NH_2-MMT were studied for 6 cycles for the model reaction (run 1 and 2: 96%; run 3 and 4: 95%; run 5 and 6: 94%). The recovered nanocatalyst was characterized with FT-IR spectroscopy (Fig. S1(c). There are the two peaks at 3626 and 3431 cm^{-1} correspond to the NH_2 groups, and a weak band peak at 2933 cm^{-1} is attributed to the C—H stretching mode. In addition, the peak at 1563 cm^{-1} is the bending vibration due to the interactions of NH_2.

In conclusion, we have successfully developed an efficient, atom-economical, environment friendly and simple protocol for the synthesis of isoxazole-5(4H)-ones. The use of catalytic amount of NH_2-MMT,



Scheme 2. The plausible mechanism for the formation of 4-arylmethylene isoxazole-5(4H)-ones.

simple manipulation, short reaction time and mild reaction conditions contribute to the significant features of this methodology.

Acknowledgments

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MOL Files. MOL Files ZIP file containing the MOL files of the most important compounds in this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.catcom.2016.08.018. These data include MOL files and InChiKeys of the most important compounds described in this article.

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