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Application of basic clays in microwave activated Michael additions: Preparation of *N*-substituted imidazoles

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Abstract

Imidazole ($C_3H_4N_2$) was condensed with ethyl acrylate ($C_5H_8O_2$) using two basic clays (Li^+ and Cs^+ montmorillonites) as catalysts in a microwave oven. The catalysts were characterized by chemical analyses, nitrogen adsorption isotherms and X-ray diffraction. Under these experimental conditions *N*-substituted heterocycles can be obtained with a high activity and selectivity. The role of alkali promoters (Li^+ and Cs^+) in the montmorillonite for the Michael addition was studied. It was evidenced that the greater the basicity and the irradiation time and power of irradiation were, the higher were the conversion. The yield of the *N*-substituted imidazole presents a maximum for 0.1 g of Cs-montmorillonite at 850 W in only 5 min of irradiation. © 1997 Elsevier Science B.V.

Keywords: Michael addition; Alkaline montmorillonites; Microwave irradiation; Imidazole

1. Introduction

N-susbituted imidazoles and their derivatives obtained through alkylation reactions [1] or Michael additions for instance, are of interest in the pharmaceutical chemistry due to their pharmacodynamic properties [2]. These reactions take place at room temperature and at 50°C catalyzed by K_2CO_3/DMF, processes in which environmentally hazardous residues are generated. For this reason, new methods must be developed for these type of reactions in order to avoid the generation of such residues.

Basic solid catalysts have recently received a great deal of attention to perform efficiently, and in absence of solvent, a series of fine chemistry reactions [3–7]. Usually, more drastic reaction conditions are required when using heterogeneous catalysts instead of the traditional homogeneous catalysts. This is not very convenient when the main target is selectivity, which is fundamental in the production of some specific pharmaceutical products.

Considering all the experimental procedures induced by heterogeneous media [8,9], solid–

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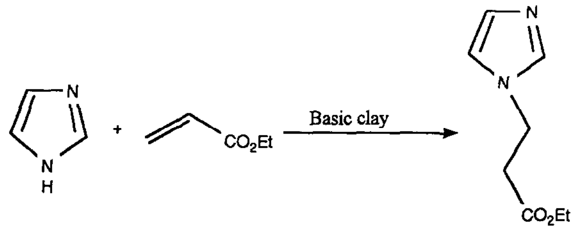

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Scheme 1. Michael addition between imidazole and ethyl acrylate.

liquid phase transfer systems [10], solid inorganic supports [11], among others, the microwave irradiation exhibits, under mild conditions, an interesting reactivity and it has been recently employed to activate some organic reactions catalyzed by inorganic solids [12–14].

In view of this, the aim of the present work is to study the effect of the microwave irradiation on the reaction rate. Consequently, we report here information on the effect of the operating conditions, such as irradiation time, irradiation power, and catalyst. Conventional heating experiments in batch reactor have been carried out in order to compare both reaction system.

The selected reaction is the Michael addition between imidazole and ethyl acrylate (Scheme 1). This reaction has been reported for the preparation of important acyclic nucleoside analogues, e.g., the guanine based anti-viral compounds, penciclovir, acyclovir and famciclovir (Scheme 2) by addition between adenine and different Michael acceptors [15–17].

2. Experimental

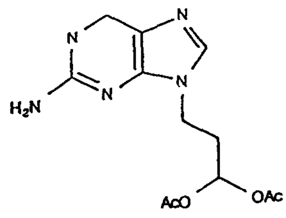
2.1. Catalyst preparation and characterization

Montmorillonite from Gador (Almería, SE of Spain), supplied by Minas de Gador, S.A., was used as raw material. The structural formula of this fraction, on the basis of 12 oxygen atoms, was found to be: $[Si_{3.71}Al_{0.29}][Al_{1.43}Mg_{0.34}Fe_{0.12}Ti_{0.01}Mn_{0.01}]O_{10}(OH)_2$ $(Mg_{0.15}Ca_{0.08}Na_{0.08}K_{0.06})$. The cation exchange capacity (CEC) of this clay, obtained by the Kjeldahl method after NH_4^+-exchanged samples, was 117 meq/100 g of dry montmorillonite (110°C), and the BET surface area is 101 m^2/g.

Li^+- and Cs^+-exchanged samples were prepared from Na^+-montmorillonite by treatment with solutions of the corresponding chlorides. Previously, Na-montmorillonite has been prepared from natural < 2 μm montmorillonite by washing three times with NaCl solutions. 1.4 g of LiCl or 2.6 g of CsCl were added to suspensions of 10 g of Na-montmorillonite in 500 ml of water, stirred for 24 h and then washed with water until no chloride anions could be detected, and dried at 50°C. After drying the samples were pelletized, crushed and sieved to a particle size within 0.074 and 0.140 mm. In both cases, Li^+- and Cs^+-cations were in a large excess with respect to the CEC of montmorillonite. The samples thus prepared are designated as Li^+-M and Cs^+-M, respectively.

The specific surface areas of the catalysts were measured by the BET method with a Micromeritics ASAP 2010 apparatus, from the nitrogen adsorption isotherms at 77 K. The crystal structures of the samples were analyzed by X-ray diffraction (XRD) with a Siemens D500 diffractometer, using filtered Cu K_α radiation. The composition of the catalysts was determined by atomic absorption (AA) on a Perkin Elmer 4100 ZL spectrometer.

The basic strength of the Li^+-M and Cs^+-M was evidenced following the method described by Corma et al. [18] which has been succesfully applied to a wide range of microporous solid materials [5–7,18,19]. According to this method,



Scheme 2. Structure of famciclovir.

the basicity of the montmorillonites increases with the radius of the alkali cation (Li^+-M < Cs^+-M). Most of the basic sites in the samples have $pK_a \leq 10.7$ and only few sites with $13.3 \leq pK_a \leq 16.5$ are present in the more basic Cs^+-M.

Table 1
BET surface areas and chemical analyses of montmorillonite catalysts (mmol per 100 g of catalyst)

Montmorillonite	BET (m^2/g)	Li	Na	Cs	Total
Li-M	105	2.5	19.6	0.0	22.1
Cs-M	130	0.0	41.3	86.1	127.4

3. Reaction procedure

3.1. Microwave activated reaction

Imidazole (2.5 mmol) and different amounts of the corresponding montmorillonite were blended in a flask and ethyl acrylate (2.5 mmol) was added. The mixture, placed in a Teflon 60 ml closed flask, was irradiated in a microwave oven (Sanyo EM 881) at 2450 MHz at different powers. The temperature was measured at the end of each experiment. After cooling, the reaction products were extracted with acetone (20 ml) and filtered. The reaction was followed by GC using a Konik KNK-3000-HRGC gas chromatograph with a BP1 capillary column of 60 m length. The mass spectra of the products were obtained on a Hewlett-Packard HP5971A spectrometer. The conversion is expressed in terms of the amount of **A** obtained in wt%.

3.2. Conventional heating reaction

An equimolar mixture of the two reactants (2.5 mmol) without any solvent, was kept in a batch reactor under stirring, while being heated to the reaction temperature (35°C–75°C). Then, 0.1 g catalyst was added and the reaction started. Samples were taken periodically, and the evolution of the reaction between 1 and 30 min was followed by GC.

4. Results and discussion

4.1. Catalyst characterization

The BET surface areas of the catalysts are listed in Table 1. The X-ray diffraction patterns of Li^+- and Cs^+-montmorillonites show the usual behavior of well-ordered montmorillonite. The only important difference observed between the different samples is that the pattern of Cs^+-exchanged sample shows a 001 reflection peak less intense and wider than those of natural, Na^+- and Li^+-montmorillonites. This effect is usual in Cs^+-exchanged clays, being due to the low structure factor of these samples and, sometimes, to a loss of crystallinity [20].

The chemical composition of the samples was studied by AA. The analyses listed in Table 1, show the alkali metal content.

The cation exchange capacity (CEC) of this clay was 117 meq/100 g of dry montmorillonite. Table 1 show a value of 127 meq/100 g CEC for the Cs^+-M. Taking into account the precision of the methods used, these two values, 117 and 127 meq/100 g, respectively are similar. Thus, the CEC value is within the experimental error of the measurements.

4.2. Michael addition reactions

The regiospecific addition of purines precursors of guanines is usually carried out within room temperature and 50°C using K_2CO_3/DMF as basic catalyst [2].

In the present work the condensation of imidazole and ethyl acrylate (Scheme 1) has been carried out under mild experimental conditions and in absence of any solvent, using the microwave irradiation to accelerate the process.

Under our experimental conditions, we have found that *N*-substituted derivative **A** is selectively obtained when ethyl acrylate is added to imidazole. The mass spectrum of the reaction product (MS m/s: 168 (M^+), 122, 95, 81(100), 68, 54, 41) confirms that compound **A** is the only product generated.

In this study some reaction parameters, such as irradiation time, irradiation power, and the amount of catalyst have been investigated in order to know their influence on the conversion and selectivity of the reaction. In addition, the reaction temperatures during the microwave irradiation were measured and complementary conventional heating experiments were carried out for comparison.

4.3. Effect of the amount of catalyst

The influence of the amount of montmorillonite used has been studied during the Michael addition of ethyl acrylate to imidazole using 0.05, 0.1 and 0.2g of the catalyst samples (Li^+-M and Cs^+-M). Besides, in order to investigate the possible influence of the irradiation powers and times on the results obtained with a determined amount of catalyst, the corresponding experiments were carried out.

The conversion values obtained with both montmorillonites are shown in Table 2. The product **A** is the only one obtained in all cases, with conversion values comprised between 5 and 75%, depending on the microwave power employed and irradiation time.

It is observed, in general, that for a determined amount of catalyst, the amount of **A** increases with the irradiation time.

Fig. 1 as an example, shows the effect of the amount of catalyst in the Michael addition at 450 W for 1, 3, and 5 min of irradiation, using Li^+ and Cs^+ montmorillonites.

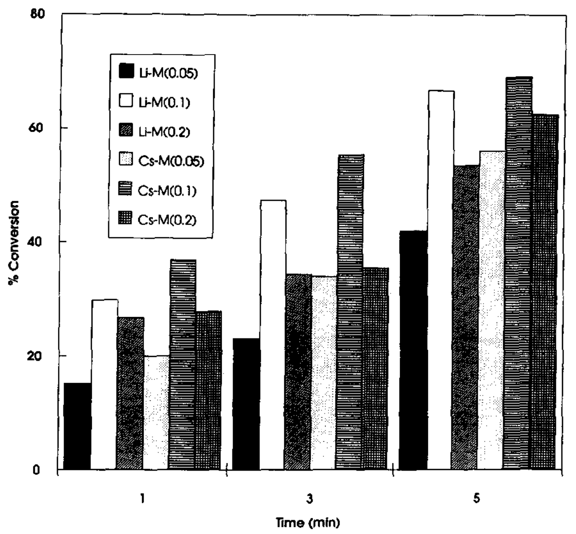


Fig. 1. Effect of the amount of catalyst in the Michael addition of imidazole and ethyl acrylate at 450 W.

It can be observed that, at all the reaction times studied, the highest values of **A** are obtained for 0.1 g of catalyst and 850 W during 5 min. This behaviour is observed for both montmorillonites employed, and at all the irradiation times studied. It can be said that the combined effect of the catalyst amount, irradiation power and amount of catalysts, determines the most suitable conditions for the production of **A**.

On the other hand, in order to know if the reaction takes place in absence of a catalyst, a blank experiment with only the reactants was carried out at 850 W for 5 min, which are, respectively, the highest irradiation power and time used in the rest of experiments with catalysts. A value of 27% conversion to **A** was obtained (it can be due to the effect of the microwave irradiation), in contrast to the 75%

Table 2
Michael addition of imidazole (2.5 mmol) and ethyl acrylate (2.5 mmol) using 0.1 g of Li^+- and Cs^+-Montmorillonite, respectively, in different reaction conditions

Catalyst	Conversion values (%) power								
	150 W			450 W			850 W		
	1 min	3 min	5 min	1 min	3 min	5 min	1 min	3 min	5 min
Temp. (°C)	28	33	35	38	48	51	41	57	75
Li^+-M	5.5	41.5	50.2	29.8	47.4	66.7	39.7	64.8	72.3
Cs^+-M	8.6	49.1	54.4	36.9	55.3	69.1	48.1	73.8	74.5

Table 3
Michael addition of imidazole (2.5 mmol) and ethyl acrylate (2.5 mmol) using 0.1 g of Li^+- and Cs^+-montmorillonite, respectively, using conventional heating activation

Temperature (°C)	Time (min)	Conversion (%)	
		Li^+-M	Cs^+-M
35	1	0.0	0.0
	3	0.0	0.0
	5	0.0	0.0
	15	15.4	17.9
	30	33.1	35.5
50	1	0.0	0.0
	3	0.0	0.0
	5	5.1	9.1
	15	27.3	31.5
	30	56.2	62.4
75	1	0.0	0.0
	3	15.2	26.2
	5	27.3	41.1
	15	46.1	58.6
	30	76.0	82.2

value obtained with Cs^+-montmorillonite for the same time and power, results which combine the effect of the microwave and the basic strength of the catalyst.

Table 2 summarizes the temperatures attained at the times and microwave powers of irradiation used for the catalytic runs. The condensation reaction under thermal activation were carried out at 35°C, 50°C and 75°C which are the temperatures attained under microwave irradiation at 150 W, 450 W and 850 W, respectively. The results of the runs under thermal activation are presented in Table 3. Comparison with Table 2 evidences that the microwave activation performs much better than thermal activation since higher conversion levels are reached in less time, even when no stirring can be provided for the runs under microwave irradiation.

4.4. Influence of the type of alkali cation in the montmorillonite

The effect of the alkali cation in the catalyst has been studied carrying out several microwave irradiation experiments at different times, for a fixed power and amount of catalyst. As a representative example, the results obtained with 0.1 g of each montmorillonite at a power of 850 W are shown (Fig. 2).

It can be observed that at the lowest and middle times (1 and 3 min), the Cs^+-M gives higher yields than the Li^+-M, but at longer times, quite similar values (around 75%) are obtained for both alkaline montmorillonites. These results, together with those given in Table 2, suggest that our Cs^+-M is a more active catalyst than the Li^+-M, probably because it has a higher basic strength. When the irradiation is longer the influence of this factor leads to similar results for both Li^+- and Cs^+-samples.

4.5. Effect of the microwave irradiation power

The effect of the power of the microwave irradiation has also been studied. Powers of 150, 450, and 850 W have been selected to carry out the condensation of imidazole and ethyl acrylate at different experimental conditions. As an example, Fig. 3A and B show the results obtained when Li^+-M (0.1 g) and Cs^+-M (0.1 g) were used as catalysts, respectively.

From these results, it can be said that the reactivity increases with the microwave irradiation power, being the order of activity 150 < 850 W, and getting values of 75% for the highest

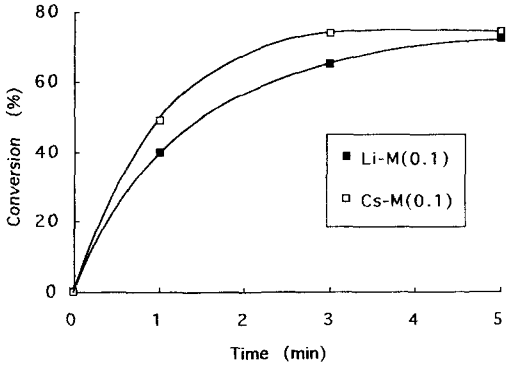


Fig. 2. Influence of the alkali cation in the Michael addition of imidazole and ethyl acrylate at 850 W and using 0.1 g of montmorillonite.

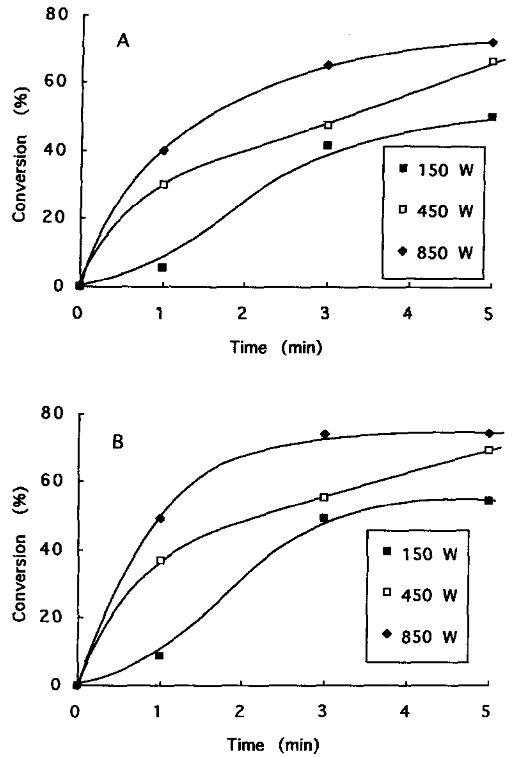


Fig. 3. Effect of the irradiation power in the Michael addition of ethyl acrylate and imidazole using (A) Li-montmorillonite (0.1 g) and (B) Cs-montmorillonite (0.1 g).

power, which is approximately 1.6 times higher than that yield by the lowest power. Under the highest power of irradiation the activity is highest, but tends to level off at 5 min. This may be indicative of an excessive heating of the montmorillonite, which would lead to a partial dehydration of the clay. The same order of activity was observed for other amounts of catalyst.

Additional investigation was done to explore the potential and selective heating of the reactants and the montmorillonite. The rate enhancement of the reactions was confirmed in our system when they were promoted by microwave irradiation. We have observed that the montmorillonite absorbs the microwave radiation and that the presence of montmorillonite in the mixture improves the heating of the system. This absorption may account for a better activation of the active sites of the alkali exchanged montmorillonites.

5. Conclusions

Michael addition between imidazole and ethyl acrylate can be performed in absence of any solvent, under mild microwave irradiation using alkali exchanged montmorillonites as base catalysts. Under these experimental conditions, the formation of environmental hazardous residues is avoided. It has been found that the alkaline exchanged montmorillonites are active and very selective catalysts for the Michael additions of imidazole and ethyl acrylate. Both montmorillonites (the Li^+- and Cs^+-samples) present enough basic strength to accelerate the reaction. It can be also concluded that, in general, under our experimental conditions, the reactivity increases with the irradiation power and irradiation time, giving the highest values of the condensation product when 0.1 g of catalyst are used. Values of 75% of conversion with 100% of selectivity are obtained in only 5 min of reaction.

All these results show the great utility of microwave irradiation (combined with the use of a base catalyst) in this type of Michael additions, which yields excellent results of reactivity under easy experimental conditions and in a very short time.

This method can be extended to the preparation of other *N*-substituted purines which serve as precursors in the primary route to pharmaceutically important acyclic nucleoside analogues with anti-viral properties.

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