Sonocatalysis and basic clays. Michael addition between imidazole and ethyl acrylate

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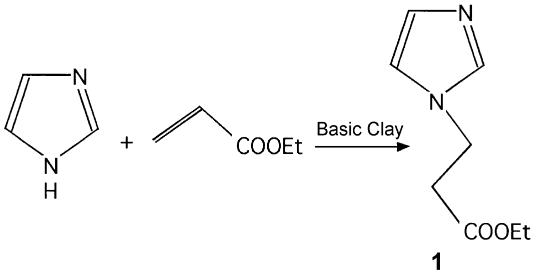
Under ultrasound activation, imidazole was condensed with ethyl acrylate using two basic clays (Li^+ and Cs^+ montmorillonites). The clay catalysts were characterized by chemical analyses, nitrogen adsorption isotherms, and X-ray diffraction. Under sonochemical conditions N-substituted imidazole can be obtained with a high activity and selectivity. The conversion increases with the basicity of the clays and the ultrasonic exposition time. The yield presents a maximum for 0.1 g of Cs^+ montmorillonite after 60 min of sonication.

KEY WORDS: Michael addition; clay catalysts; ultrasound activation; N-substituted imidazole.

1. Introduction

The versatile carbon–carbon bonds forming Michael addition have numerous applications in the synthesis of intermediates in the production of fine chemicals. Many solid base catalysts have been used to obtain the corresponding products [1,2]. The application of new catalytic methods in the fine and specialty chemicals industry has increased in recent years in order to minimize both production cost and waste production [3,4]. Ultrasonic activation induces the rate enhancement of a great number of catalytic reactions in both homogeneous and heterogeneous systems [5] and may afford remarkable yield increases [6]. The chemical effects of ultrasounds have been attributed to the implosive collapse of the cavitation bubbles formed during the interaction between a suitable acoustic wave field and a potentially reacting chemical system. The bubbles are generated at localized points in the liquid mixture. Trapped within a microbubble, the reactant mixture is exposed to a high pressure and temperature, where the molecules fracture forming very reactive species, which react with the surrounding molecules. When the catalyst is a solid material, the ultrasonic effect has several additional benefits [7].

The present paper reports the experimental results obtained in a sonicated heterogeneously catalyzed reaction (Michael addition of imidazole with ethyl acrylate to give exclusively the N-substituted imidazole, compound **1**) on basic clay materials (scheme 1). For comparison, the results obtained under thermal activation are also presented. The influence of several factors during the reaction has been investigated.



Scheme 1. Michael addition between imidazole and ethyl acrylate.

N-substituted imidazoles and their derivatives, obtained for instance through alkylations or Michael additions, are of interest in the pharmaceutical chemistry because of their therapeutic applications [8]. These reactions are generally performed using a liquid base or catalyzed by K_2CO_3/DMF, processes in which hazardous residues are formed. In view of this, the aim of the present study is investigate the effect of the sonication on the Michael addition between imidazole and ethyl acrylate using as heterogeneous catalysts two clay minerals with basic properties.

2. Experimental

2.1. Catalyst preparation and characterization

Montmorillonite from Gador (Almería, in south-eastern Spain) supplied by Minas de Gador was used as raw material. The structural formula of this fraction,

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based on 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 the NH_4^+-exchanged clay, obtained by the Kjeldahl method was 117 meq/100 g based on dry montmorillonite (383 K). The BET 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 had been prepared from natural $<2\,\mu$m 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 were detected, and dried at 323 K. In both cases, Li^+ and Cs^+ cations were in excess with respect to the CEC of the montmorillonite, in the case of Cs^+ about 1.5 times in each exchange, while in the case of Li^+, more difficult to be incorporated to the clay, 3 times the CEC was used in each washing. The samples thus prepared are designed as Li^+-M and Cs^+-M, respectively. The specific areas of the clays 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 clays 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.* [9], which has been applied to a wide range of microporous solids [10,11]. According to this method, the basicity of the montmorillonites increases with the size of the alkaline 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 most basic clay, Cs^+-M.

2.2. Reaction procedure

2.2.1. Conventional heated reactions

An equimolar mixture of the two reactants (2.5 mmol) without any solvent was placed in a batch reactor under stirring, while being heated up to the reaction temperature (303 and 323 K). Then the catalyst was added and the reaction started. Before the reaction, the catalysts were pelletized, crushed and sieved to a particle size within 0.074 and 0.140 mm. The reaction was followed by GC-MS. Previous experiments (modifying the stirring rates, between 1500 and 3000 rpm, and the particle size of the clay (0.074–0.250 mm)), let us confirm that there is no control by external or internal diffusion.

2.2.2. Ultrasonic-induced reactions

Equimolar amounts of the reactants (2.5 mmol) were mixed in a flask without any solvent. The flask was suspended in the ultrasonic bath at the reaction temperature (303 and 323 K). Then, the catalyst was added and the reaction started. An ultrasonic bath (Selecta Ultrasound-H) with a heating system, 40 kHz of frequency and 550 W of power, was used for these experiments. The conversion is expressed in terms of amount of **1** in wt%. The products were isolated by standard procedures and characterized by GC (Konik KNK-3000-HRGC system equipped with a 60 m-long BP1 capillary column) and ^{1}H-RMN in a Bruker (DRX 400) spectrometer, using TMS as internal standard.

3. Results and discussion

3.1. Catalyst characterization

Table 1 shows characterization data of the samples. For the Cs^+-M sample, the sum of Cs^+ and Na^+ is 127 meq per 100 g of clay, close to the CEC of the clay (117 meq per 100 g). It must be noted that the CEC of the clay was measured by the Kjeldahl method over ammonium-exchanged solids, while the cations in the final catalysts were analyzed by atomic absorption, the difference between these two values being within the experimental error. In spite of the three exchange treatments carried out, about one-third of the exchangeable positions remain occupied by Na^+, while the other two thirds have been effectively exchanged by Cs^+.

The X-ray diffraction patterns of Li^+ and Cs^+ montmorillonites are characteristic of a well-ordered montmorillonite. The only important difference observed between the different samples is that the pattern of the 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 [12].

Table 1
Chemical analyses (mmol/100 g of catalyst) and BET surface areas of montmorillonite catalysts.

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

Table 2
Conversion values (%) obtained under ultrasound and thermal activation during the Michael addition reactions between imidazole and ethyl acrylate. Catalysts: Li^+-M and Cs^+-M (0.1 g).

Temperature (K)	Time (min)	Ultrasound		Thermal	
		Li^+-M	Cs^+-M	Li^+-M	Cs^+-M
303	15	30.1	37.0	15.4	17.9
	30	55.3	65.0	33.1	35.5
	60	62.1	77.2	42.3	52.0
323	15	47.3	61.3	27.3	31.5
	30	79.1	85.2	56.2	62.4
	60	89.0	96.7	61.0	73.2

3.2. Michael addition reaction

Ultrasound-assisted addition of imidazole and ethyl acrylate has been carried out under very mild conditions, in dry media, using Li^+-M and Cs^+-M. Under our experimental conditions, the N-substituted derivative **1** is selectively obtained. It was confirmed by the mass spectrum of the reaction product: (MS m/s: 168 (M^+), 122, 95, 81 (100), 68, 54, 41) and ^{1}H-RMN. No other side reactions such as condensation, dimerization or rearrangements in the Michael reaction occurs. By analogy with other type of clays, the classical mechanism of the reaction can be applied [1] and different reaction parameters (*i.e.*, reaction temperature, amount of catalyst, and the type of alkaline promoter on the clay) can be investigated. As a reference, complementary conventional heating experiments were carried out.

3.2.1. Influence of the basicity of the clay in the sonochemical Michael addition reaction

The Michael addition of imidazole and ethyl acrylate was carried out on Li^+-M and Cs^+-M at different temperatures, under ultrasonic activation. As an example, the results obtained at 303 and 323 K are given in table 2.

It can be observed that at any temperature Cs^+-M gives higher yields than the Li^+-M. Under sonochemical activation the activity observed is Li^+-M < Cs^+-M. For longer times, the conversion leads to similar values for both clays.

3.2.2. Influence of the amount of catalyst

The influence of the amount of catalyst has been studied using 0.05 g and 0.1 g of the catalyst under ultrasound activation. The conversion values achieved are shown in figure 1.

The highest values of yield to **1** are obtained for 0.1 g of catalyst after 60 min. Both montmorillonites exhibit this behavior. Conversion values around 77% are obtained at 60 min when Cs^+-M is employed at 303 K. In order to know if the reaction takes place in the absence of any catalyst, a blank reaction was performed at 303 K. A yield of 12% of **1** was obtained after 60 min, in contrast to the 60% and 77% obtained with Li^+-M or Cs^+-M respectively for the same time. So, the combination of the ultrasound waves and the basic strength of the clays results in an important enhancement of the conversion to **1**.

3.2.3. Comparative study between ultrasound activation and conventional thermal activation. Influence of the temperature

The effect of the temperature has been studied during the Michael addition reaction in both ultrasonic and thermal activated reactions using different amounts of Li^+-M and Cs^+-M. As an example, the conversion values achieved at two reaction temperatures using 0.1 g of clay are summarized in table 2.

The comparison between ultrasonic and thermal activation shows that the ultrasound performs much better at any temperature, since higher conversion levels are achieved at the same reaction times. Conversions around 97% are reached in the case of ultrasound activation of Cs^+-M at 323 K, with 100% selectivity to **1**.

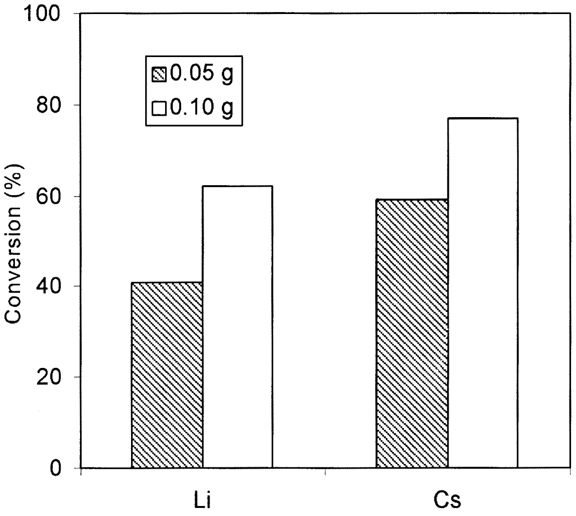

Figure 1. Effect of the amount of catalyst in the ultrasound-activated Michael addition between imidazole and ethyl acrylate at 303 K. Reaction time: 60 min. Catalyst: Cs^+-M.

When this reaction is thermally activated, conversion levels off at ~70%. In general, the conversions obtained under sonochemical activation increase by a factor of 1.4 when the clays are used as catalysts.

4. Conclusions

Under ultrasonic activation, alkaline clays are active and very selective catalysts for Michael addition between imidazole and ethyl acrylate. The sonication exerts a positive effect on the reactivity, enhancing the conversion values if compared with that obtained in a conventional thermally activated reaction system. The highest values of activity are obtained for the Cs^+-M, which presents higher basicity than the Li^+-M. An increase of the amount of the catalyst leads to an increase of the conversion values. All these results show the great utility of sonication (combined with the use of basic clays) in the Michael addition, which yields excellent results under mild conditions. This method can be extended to the preparation of other N-substituted heterocycles, which are important products in the fine chemistry industry.

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