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# Activated hydrotalcites as catalysts for the synthesis of chalcones of pharmaceutical interest

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#### Abstract

The Claisen–Schmidt condensation between benzaldehyde and acetophenone has been carried out in the presence of calcined-rehydrated hydrotalcites as solid-base catalysts. The rehydration method and the effect of the water content as well as the chemical composition of the rehydrated Al–Mg mixed oxides have been studied. The results showed that an Al–Mg mixed oxide with an Al/(Al + Mg) molar ratio of 0.25 with a water content of 35 wt% was the optimum catalyst which gives excellent activity for this type of condensation. This optimized catalyst has been applied to the synthesis of several chalcones with antiinflammatory, antineoplasic, and diuretic pharmacological activities achieving in all cases excellent activity and selectivity to the corresponding chalcones. A comparative study in the homogeneous phase using KOH as base catalyst showed that the rehydrated Al–Mg mixed oxides can compete with the conventional KOH when the reaction is performed at higher reaction temperatures. This behavior is not attributed to a lower intrinsic activity of the active sites on the solid, but to the small concentration of accessible active sites existing on the rehydrated sample. © 2003 Elsevier Inc. All rights reserved.

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### 1. Introduction

The Claisen–Schmidt (CS) condensation between acetophenone and benzaldehyde derivatives is a valuable C–C bond-forming reaction which allows  $\alpha$ ,  $\beta$ -unsaturated ketones called chalcones to be obtained. Chalcones belong to the flavonoid family which are synthesized in plants performing diverse physiological functions such as attractants of pollinators, UV protectors, and insect repellents. They have found numerous applications as pesticides, photoprotectors in plastic, solar creams, food additives, and a plethora of interesting biological activities (antimalarial [1], antiinflammatory [2], cytotoxic [3], anticancer [4], diuretic, and choleretic [5,6]) have been reported.

Traditionally, the Claisen–Schmidt condensation is carried out at 323 K using 10–60% of alkaline hydroxides or sodium ethoxide over a period of 12–15 h [6]. It is widely accepted that there is a need to develop clean and economical processes, where the use of noxious substances and the gen-

\* Corresponding author. *E-mail address:* acorma@itq.upv.es (A. Corma). eration of wastes can be avoided. The generation of wastes can be important in the synthesis of fine chemicals and pharmaceuticals, and they consist primarily of inorganic salts such as sodium chloride, sodium sulfate, and ammonium sulfate formed in the reaction or in subsequent neutralization steps. The replacement of liquid by solid-base catalysts for the production of fine chemicals not only allows easy separation and recycling of the catalyst from the reaction mixture, but for many bimolecular reactions heterogeneous catalysts can give better selectivity than homogeneous catalysts.

The use of basic solids, such as potassium carbonates [7], barium hydroxides [8–10], alumina [11], MgO [12], calcined hydrotalcites [13,14], and natural phosphates modified with sodium nitrate [15] or with KF [16], has received much attention over the last years as potential catalysts for Claisen–Schmidt condensations.

Solid-base catalysts, such as alkali-exchanged zeolites [17], sepiolites [18], organic resins [19], magnesium aluminum mixed oxides derived from hydrotalcites [20], and more recently, aluminophosphates oxinitrides (ALPON) [21] which can cover a wide range of basic strengths, have been used at the laboratory scale for different organic reactions. Among them, calcined hydrotalcites are the most promising candidates for performing aldol condensations [22].

Hydrotalcites, Mg<sub>6</sub>Al<sub>2</sub>(OH)<sub>16</sub>CO<sub>34</sub>H<sub>2</sub>O, are hydrated aluminum-magnesium hydroxides of lamelar structure, in which the excess of positive charge, originating from the  $Mg^{2+}-Al^{3+}$  substitution, is compensated by interlayer anions such as carbonate anions. Its structure resembles that of brucite, Mg(OH)<sub>2</sub>, where the magnesium cation is octahedrally coordinated by hydroxyl ions. Calcination over 800 K decomposes reversibly the hydrotalcite into a high surface area mixed magnesium-aluminum oxide which presents basic sites that are associated to structural hydroxyl groups as well as strong Lewis basic sites associated to  $O^{2-}Mn^+$ acid-base pairs [23-25]. Calcined hydrotalcites are able to catalyze aldol condensations such as the self-condensation of acetone [26], acetaldehyde [27], the condensation of formaldehyde and benzaldehyde with acetone [14,28], and the Claisen-Schmidt condensation to obtain chalcones and flavanones [13,14]. However, it has been reported recently that the catalytic activity of calcined hydrotalcites can be enhanced by rehydration at room temperature under exclusion of  $CO_2$  [29]. This treatment results in the restoration of the original layered structure where the compensating anions in the interlayer are OH<sup>-</sup>. Although little is known up to now about the nature and number of active Brönsted basic sites and the mechanism involved, this material is able to catalyze aldol condensations such as the self-condensation of acetone [30], benzaldehyde with acetone [14,29], citral with acetone or methyl ethyl ketone [31], Knoevenagel condensations [32], and Michael additions [33].

Concerning the Claisen-Schmidt condensation between acetophenone and benzaldehyde, only one example of the use of calcined-rehydrated hydrotalcites as basic catalyst has been reported in the literature. The condensation was carried using dimethylformamide as a solvent, at 273 K and in the presence of a calcined hydrotalcite sample that was rehydrated with a flow of nitrogen saturated with water for 6 h. Under these reaction conditions it was possible to achieve about 80% yield of chalcone after 3 h of reaction time [34]. However, a "green" process would tend to avoid the use of organic solvents. Along this line we have shown that it is possible to prepare flavonoids using calcined hydrotalcites as base catalysts in the absence of solvent at temperatures between 423 and 443 K [13]. In the present work we have attempted to optimize the activation of double-layered materials as basic catalysts using the condensation between benzaldehyde and acetophenone as a reaction test. The knowledge acquired from this study has been used for the synthesis of chalcones with different chemical structures, which exhibit anticancer and anti-inflammatory activity [35,36]. Finally, the synthesis a commercial product called Vesidryl (2',4,4'-trimethoxychalcone) using the optimized solid-base catalysts has been carried out successfully. This product is of pharmacological interests because of its diuretic and choleretic properties [5].

### 2. Experimental

# 2.1. Catalysts

Al-Mg hydrotalcites were prepared from gels produced by mixing two solutions: solution A containing 3 - x mol of  $Mg(NO_3)_2 \cdot 6H_2O$  and x moles of  $Al(NO_3)_3 \cdot 9H_2O$  in the (Al + Mg) concentration of 1.5 mol/L for a ratio x/3:0.25and 0.33, solution B containing of 6 + x mol of NaOH and 2 mol of Na<sub>2</sub>CO<sub>3</sub> dissolved in the same volume of the solution A. Both solutions are coadded at a rate of 1 mL/min under a vigorous mechanical stirring at room temperature. The product was left at 333 K for 12 h. The hydrotalcite formed was filtered and washed until the pH of the filtrate was 7. The resultant solid was dried at 333 K for 12 h. The hydrotalcite was activated by calcination at 723 K in a dry nitrogen flow. The temperature was raised at a rate of 2 °C/min to reach 723 K and was maintained at this temperature for 6 h. The solid was then cooled until room temperature and used.

Rehydration of calcined hydrotalcites (HTc) was carried out by two different methods: rehydration at room temperature under a flow of nitrogen gas (40 mL/min) saturated with water vapor for different times (HTc-R series) and by directly adding different amounts of water on the calcined hydrotalcite just before reaction (HTc-A series).

The KF/Al<sub>2</sub>O<sub>3</sub> sample with a 40 wt% of KF was purchased from Aldrich.

X-ray diffraction measurements were recorded with a Philips X'PERT (PN 3719) diffractometer (Cu-K<sub> $\alpha$ </sub> radiation provided by a graphite monochromator) equipped with an automatic variable divergence slit and working in the constant irradiated area mode.

Chemical analyses of the samples were performed by atomic absorption after disintegration of the solids.  $N_2$  and Ar adsorption/desorption isotherms were performed at 77 and 87.3 K, respectively, in an ASAP 2010 apparatus from Micromeritics, after pretreating the samples under vacuum at 673 K overnight (for the calcined hydrotalcites) and at 393 K (for the calcined-rehydrated hydrotalcites). The BET surfaces were obtained using the BET methodology. The physicochemical characteristics of the samples are summarized in Table 1.

Table 1			
Main physicochemical	characteristics	of the	catalysts

1 5		2	
Catalyst	Al/ (Al + Mg)	Surface area BET (m <sup>2</sup> /g)	Average pore diameter (Å)
HTc(0.25)	0.25	245	103
HTc(0.33)	0.33	220	103
HTc-R(0.25) <sup>a</sup>	0.25	46	266
HTc-A(0.25) <sup>b</sup>	0.25	30	277

<sup>a</sup> Rehydrated for 18 h at room temperature under a flow of nitrogen saturated with water vapor (40 mL/min) (35 wt% of water content).

<sup>b</sup> Rehydrated by directly adding 35 wt% of water on the calcined hydrotalcite.

### 2.2. Reaction procedure

Typically, a mixture of benzaldehyde (17.76 mmol), acetophenone (14.8 mmol), and the catalyst was added in a three-necked-bottom flask equipped with a condenser system. The resultant suspension was heated up to the required temperature under vigorous stirring in an oil bath equipped with an automatic temperature control system. Samples were taken at regular time periods and analyzed by gas chromatography (GC) using a FID detector and a Tracer-wax column (15 m × 0.32 mm × 0.25 µm).The response factors were calculated for each reactive agent from pure samples. Reaction products were identified by GC-MS (Hewlett-Packard 5988 A) and by <sup>1</sup>H NMR spectroscopy (Varian VXR-400S, 400 MHz).

#### 2.3. Synthesis of Vesidryl in the homogeneous phase

Typically 2.36 mmol of KOH in 2 mL of hydroalcoholic solution (50%) was added to a mixture of anisaldehyde (10.5 mmol) and 2,4-dimethoxyacetophenone (10.5 mmol), and the mixture was stirred at 298 K. Samples were taken at regular time periods and analyzed by gas chromatography. After a 6-h reaction time, the catalyst was neutralized with an aqueous solution of hydrogen chloride, and the aqueous layer was extracted two times with dichloromethane. The organic layer was dried with anhydrous sodium sulfate. After solvent evaporation, the organic residue was weighed and analyzed by GC and <sup>1</sup>H RMN.

### 3. Results and discussion

The Claisen–Schmidt condensation between acetophenone (1) and benzaldehyde (2) (Scheme 1) was first carried out at 423 K, in the absence of solvent and in the presence of 10 wt% of either a calcined hydrotalcite (HTc(0.25)) or the corresponding rehydrated sample (HTc-R(0.25) for 24 h. With this last catalyst the reaction gives *trans*-chalcone (3), and the mechanism generally accepted involves the formation of the anion of acetophenone followed by its attack to the carbonyl group of benzaldehyde. The yield of chalcone versus time obtained is displayed in Fig. 1 and compared with that obtained using the calcined hydrotalcite precursor as catalyst. Neither benzyl alcohol nor benzoic acid were observed in the reaction products with either of the two catalysts, indicating that the Cannizaro reaction does not take place under these conditions.



Scheme 1.



Fig. 1. Yield of chalcone **3** versus reaction time obtained in the condensation between acetophenone and benzaldehyde at 423 K in the presence of 24-h rehydrated hydrotalcite (HTc-R(0.25)) ( $\bigcirc$ ) and calcined hydrotalcite (HTc(0.25)) ( $\square$ ).

As can be observed in Fig. 1, there is a clear improvement in the catalytic activity when the calcined hydrotalcite is rehydrated, while the selectivity to chalcone is the same on the two catalysts. This increase in activity due to rehydration has been attributed to the presence of  $OH^-$  anions which present Brönsted basicity and therefore high activity in aldol-type reactions [29].

The high activity exhibited by the calcined-rehydrated hydrotalcite allows a decrease of the reaction temperature and, in order to select the most appropriate, the condensation between acetophenone and benzaldehyde was carried out at 303, 323, 343, and 373 K, using 15% of HTc(0.25) sample which was rehydrated for 24 h.

In Fig. 2, yields of chalcone (**3**) versus time at different reaction temperatures are presented. These results show that using a rehydrated hydrotalcite it is possible to reduce the reaction temperature to 323 K, achieving under these conditions practically total conversion after a 2-h reaction time.

From this study it was possible to calculate the apparent activation energy of 39.80 kJ/mol which is very similar to that reported previously in the literature using solid-base ca-



Fig. 2. Influence of the temperature on the yield of chalcone **3** in the presence of 24-h rehydrated hydrotalcite (HTc-R(0.25)), at 303 ( $\Box$ ), 323 ( $\bigcirc$ ), 343 ( $\diamondsuit$ ), and 373 ( $\times$ ).



Fig. 3. Powder X-ray diffraction patterns of hydrotalcite after synthesis, calcination, and rehydration for different periods of time.

talysts [9,14], as well as for other condensations of this type in the homogeneous phase [37], indicating that the reaction was not limited by either external or internal diffusion on the solid catalyst.

# *3.1. Influence of the water content of calcined-rehydrated hydrotalcites*

Since water is also a product in the Claisen–Schmidt condensation it is of interest to study the influence of the water content in the rehydrated sample on the rate of reaction. Thus, we have studied the influence of the rehydration time, and consequently the influence of the amount of water content over the calcined hydrotalcite, on activity and selectivity. Owing to the fact that water reacts with the catalyst surface activating the basic sites and that water is also a reaction product, a maximum in activity for an optimum water content of the catalyst should be expected. Indeed an excess of water on the catalyst surface could cause, besides the poisoning of the active basic sites, the shifting of the reaction equilibrium toward the formation of reagents.

The study was carried out starting from the HTc(0.25) sample. Equivalent amounts of this catalyst were rehydrated at room temperature in the absence of any CO<sub>2</sub> for 6, 12, 18, 24, and 48 h in a stream of nitrogen saturated with water vapor at 295 K. The X-ray diffraction patterns of hydrotalcites after synthesis, calcination, and rehydration for different periods of time are presented in Fig. 3. It can be observed that the layered crystalline structure of hydrotalcite is de-

Table 2

Claisen–Schmidt condensation between benzaldehyde (18.5 mmol) and acetophenone (14.8 mmol) using calcined HTc(0.25) (15 wt%) with different amounts of water content at 323 K

Rehydration time (h)	Water content (wt%)	$r_0 \times 10^4 \; (\text{mol}/(\text{min g}))$	Yield (%) to <b>3</b> (1 h)	
0	0	0.28	4	
6	20	1.9	47	
12	25	2.7	64	
18	35	5.2	82	
24	47	4.0	73	
48	82	3.1	50	

stroyed during calcination at 723 K, and it is converted in a mixed oxide of the Mg(Al)O type. The original layered structure is restored to a large extent by rehydration of the calcined solid, giving a meixnerite-like structure where the weak base carbonate anions have been replaced by the strong Brönsted OH<sup>-</sup> sites. Moreover, a strong decrease in surface area from 245  $m^2/g$  after calcinations to 46  $m^2/g$  after 18 h of rehydration is observed, as a consequence of the closure of micropores and mesopores by agglomeration of platelets [38]. These different rehydrated hydrotalcites were tested at 323 K using a benzaldehyde/acetophenone ratio of 1.2. In Table 2 the initial rate of formation of chalcone per gram of HTc(0.25) as a function of the water content and the yield of chalcone after 1 h of reaction time are reported. As we can observe, the activity of the calcined sample (mixed oxide) is very low, but activity and yield of chalcone increase when increasing the amount of water added until reaching a maximum for 35 wt% of water (18 h of rehydration), after which the activity decreases progressively when increasing the water added. After this maximum we can suppose that there is an excess of water on the catalyst surface that negatively affects the active sites and the reaction equilibrium.

### 3.2. Influence of the rehydration methodology

At this point it is seen that the most active HTc-R sample has 35% of water content. However in order to achieve this level of catalyst activation a lengthy (18 h) rehydration treatment was needed when following the reported procedure [29]. With the aim of finding a faster and easy workup rehydration procedure we have studied the possibility of activating the HTc samples by a simple water addition on the freshly calcined hydrotalcite. Then, in a given amount (15 wt%) of HTc(0.25) sample, different amounts of water were dropped just before the addition of reagents (HTc-A(0.25) series).

The results of initial rate versus water content of the samples are displayed in Fig. 4. As one can observe, when the percentage of water content is low (20 and 25%) there is a difference in the initial activity between the samples rehydrated with a stream of nitrogen saturated with water (HTc-R(0.25)) and the samples rehydrated by directly dropping the water on them (HTc-A(0.25)) that are more active. This result could indicate that by treating at short times the



Fig. 4. Influence of water content (wt%) of the calcined hydrotalcite (HTc(0.25)) on the initial rate of formation of chalcone **3** at 323 K in the presence of HTc-R series ( $\bullet$ ) and HTc-A series ( $\bigcirc$ ).

calcined hydrotalcite with nitrogen saturated with water vapor, a low reconstruction degree of the hydrotalcite could be achieved, which means a low density of available OH<sup>-</sup> sites and therefore lower catalytic activity. On the other hand, the water directly dropped on the catalyst reacts instantly with the most accessible oxygen anions at the surface, generating Brönsted basic sites that could be easily accessible to acetophenone reagent. However, for values of water content equal or higher than 35%, both series (HTc-R(0.25) and HTc-A(0.25)) exhibit similar behavior, achieving the maximum activity for the same value of water content which corresponds to 35 wt%. In fact, when the kinetic behavior of the two most active samples rehydrated following both methods are compared (Fig. 5) we can see that they display the same activity, achieving a 98% yield of chalcone after 4 h of reaction time. These results are in good agreement with the X-ray diffraction patterns of both samples that show the same reconstruction level.

For comparison purposes, another rehydration methodology of hydrotalcites which has been previously reported [38] was carried out. Thus, the HTc(0.25) sample was immersed in CO<sub>2</sub>-free water (100 mL/g) and stirred under an argon atmosphere for 1 h at room temperature. After filtration under inert atmosphere, the catalyst was thoroughly washed with



Fig. 5. Yield of chalcone versus reaction time when Claisen–Schmidt condensation was carried out at 323 K in the presence of 18-h rehydrated hydrotalcite (35 wt%) (HTc-R(0.25)) ( $\bullet$ ), and calcined hydrotalcite with 35 wt% water added (HTc-A(0.25)) ( $\odot$ ).

ethanol and dried under an argon flow at room temperature. After this treatment, the solid (called as HTc-I(0.25) sample) had a water content of 40 wt%. The results of activity obtained with the HTc-I(0.25) sample for the Claisen–Schmidt condensation were compared with those obtained using a HTc-A(0.25) sample prepared by adding 40 wt% of water, and we found that after 2 h of reaction time the HTc-A sample gives 92% of chalcone, whereas the HTc-I sample achieves 72%.

From these results we can conclude that the hydrotalcite activation method by in situ dropping the water to the mixed oxide allows us to achieve a high yield and selectivity of chalcone at very reasonable reaction times and temperatures, showing that this is an interesting alternative to the use of other rehydration methods reported previously for the activation of hydrotalcites.

# 3.3. Influence of the chemical composition of the rehydrated hydrotalcite catalyst

In order to study the influence of the chemical composition of hydrotalcite catalyst on the activity and selectivity to chalcone, we prepared a second hydrotalcite sample with an Al/(Al + Mg) ratio of 0.33 (HTc(0.33)), and after calcination and rehydration, its activity for the Claisen–Schmidt condensation between acetophenone and benzaldehyde was compared with that obtained with the rehydrated HTc(0.25) sample. The reaction was carried out with 7 wt% of catalyst, at 323 K and both catalyst samples were activated by adding 35 wt% of water just before reaction. In Fig. 6 it is possible to see that for the same amount of water content, the hydrotalcite sample with a lower Al/(Al + Mg) ratio displays a superior activity.

Owing to the fact that the number of compensating hydroxyl groups increases when increasing the Al/Mg ratio in the meixnerite-like form, it could be expected in principle, that with the sample with a higher Al/Mg ratio, the amount of water content giving the maximum catalytic activ-



Fig. 6. Influence of the Al/(Al + Mg) ratio on the yield of chalcone **3** when the condensation was carried out using HTc(0.25) ( $\bigcirc$ ) and HTc(0.33) ( $\square$ ) with 35% water added, respectively.



Fig. 7. Influence of water added (wt%) to HTc(0.33) on yield of chalcone **3**; ( $\bigcirc$ ) 34 wt%; ( $\times$ ) 43 wt%; ( $\square$ ) 60 wt%; ( $\diamondsuit$ ) 77 wt%.

ity should be shifted toward higher values than those found for the sample with lower Al/Mg ratios. Indeed, when the influence of water content of the HTc(0.33) on the catalytic activity was studied, we found (Fig. 7) that for this sample 60 wt% of water was necessary to be added in order to achieve the best catalytic activity. In any case, the catalytic activity is lower than that of the HTc-A(0.25) with the optimum level of rehydration (35 wt% of water). These results indicate that, as in the case of calcined hydrotalcites, the basicity of the regenerated OH<sup>-</sup> hydrotalcites strongly depends on their chemical composition. These results are in good agreement with those previously reported for the condensation of benzaldehyde and acetone [39] and

Table 3

Synthesis of chalcone derivatives using a regenerated hydrotalcite by the addition of water<sup>a</sup>

isophorone isomerization [40], where the authors found a maximum activity for a calcined-rehydrated hydrotalcite with an Al/(Al + Mg) ratio of 0.25.

# 3.4. Preparation of chalcones with biological activity using calcined-rehydrated hydrotalcites

Recently, chalcone derivatives are attracting important attention due to the numerous pharmacological studies concerning their anti-AIDS, anti-inflammatory, anticancer, and antibacterial activity. Moreover, they are important intermediates in much pharmaceutical synthesis. Thus, the knowledge acquired in the previous part of the work was extrapolated here to prepare a variety of recently reported chalcones that present anticancer [35] and anti-inflammatory [36] activity (see Table 3).

The condensations were carried out at different reaction temperatures using a HTc-A(0.25) with a 35 wt% of water content and, when it was possible, in the absence of solvent (Table 3). No by-products coming from ketone selfcondensation or Cannizaro's reaction were detected, achieving maximum selectivity in all cases. The activity shown by the basic catalyst for these condensations, as well as the yield of chalcone derivative obtained for each substrate, is well correlated with the acidity of the  $\alpha$ -hydrogen of the corresponding alkyl aryl ketone (Fig. 8) and/or with the positive charge density bearing on the carbon in the carbonyl group of the aromatic aldehyde. Thus, the  $\beta$ -diketone (entry 4) gives the bests results, achieving a 93% yield of chal-

Entry	Aldehyde	Alkyl aryl ketone	Chalcone derivative	$T(\mathbf{K})$	Vield (%)	Selectivity (%)
1	O O			333	87 (2 h)	99
2	o U	° () ()		333	68 (2 h)	99
3	O U			333 373 393	26 (7 h) 60 (7 h) 88 (7 h)	99 99 99 99
4	O I I I I I I I I I I I I I I I I I I I			298 <sup>b</sup> 333 <sup>b</sup>	95 (7 h) 93 (1 h)	99 99
5	N O		N O	333 373	45 (7 h) 75 (4 h)	99 99

<sup>a</sup> Reaction conditions: ketone (10 mmol); aldehyde (10 mmol), using HTc(0.25), (10 wt%) with 35 wt% of water ((HTc-A(0.25) sample). Reactions were carried out in absence of solvent except for entry 4.

<sup>b</sup> 10 mL of CH<sub>2</sub>Cl<sub>2</sub> as a solvent.



Fig. 8. Positive charge density of the  $\alpha$ -hydrogen of different alkyl aryl ketones versus their corresponding initial rates of condensation with benzaldehyde; tetralone ( $\bullet$ ); acetophenone ( $\blacksquare$ ), and 1,3-indandione ( $\blacktriangle$ ).

cone at 333 K after a 1-h reaction time, whereas in order to achieve a good yield for the condensation of benzaldehyde with the tetralone (entry 3) it was necessary to increase the temperature to 393 K. When benzaldehyde was substituted by 2-pyridil carboxyaldehyde (entry 5) a decrease in activity was observed. This behavior must be correlated with the lower positive charge density bearing on the carbon of the carbonyl group in the 2-pyridil derivative (+0.30) with respect to benzaldehyde (+0.33). Finally, it is interesting to note the different yield obtained for acetophenone and acetonaphthone (entries 1 and 2) despite the fact that the acidity of the  $\alpha$ -hydrogens at the methyl group should be the same for both reactants. In fact, an additional experiment carried out in the homogeneous phase using KOH as catalyst showed that both molecules have the same reactivity (Fig. 9). Therefore, we must conclude that the differences in conversion obtained with these two reactants on the solid catalyst are not related to differences of intrinsic reactivity of the molecules, but should be related to geometrical constraints for adsorption on the catalyst surface. Perhaps the most bulky acetonaphthone has lesser accessibility to the active sites than acetophenone, for this reason decreasing the final yield to the corresponding chalcone derivative.

Finally, we have tested the activity of the rehydrated hydrotalcite for preparing Vesidryl. As we said above, Vesidryl (2',4,4'-trimethoxychalcone) (6) (Scheme 2) is a chalcone with a pharmaceutical interest owing to its choleretic and diuretic properties. This compound is obtained by Claisen–Schmidt condensation between 2,4-dimethoxyacetophenone (4) and 4-methoxybenzaldehyde (5) under base catalysis and more specifically using KOH as catalyst. With the aim of



Fig. 9. Yield of Claisen–Schmidt condensation between benzaldehyde with acetophenone ( $\blacktriangle$ ) and acetonaphthone ( $\times$ ) versus reaction time using (KOH) as homogeneous catalyst. Reaction conditions: 10 mmol aldehyde, 10 mmol aryl ketone in 5 × 10<sup>-4</sup> mol of KOH in 2 mL of ethanol at 298 K.

applying the catalyst optimized in this work for the synthesis of Vesidryl, the reaction between **4** and **5** was carried out using a HTc(0.25) sample, which was activated in situ by the addition of 35 wt% of water. The reaction was performed in the absence of solvent, using 12 wt% of catalyst and 353 K.

In Table 4 the results obtained with this calcined-rehydrated hydrotalcite are compared with those obtained with a homogeneous base and other heterogeneous catalysts such as KF/alumina, and the calcined hydrotalcite precursor.

Results in Table 4 show that KF/alumina and rehydrated hydrotalcite are the most active solid-base catalysts. However, rehydrated hydrotalcite exhibiting Brönsted basic sites gives higher selectivity to Vesidryl (99%) than the former (62%) and is much more active than the calcined sample. The high activity of KF-alumina was expected considering the high activity shown by this material in Michael additions or aldol condensations [41] that require strong basicities. In fact, with this catalyst it was possible to achieve 90% conversion of dimethoxyacetophenone (4) within 1 h

 Table 4

 Synthesis of Vesidryl on different catalysts

Entry	Catalyst	Catalyst (wt%)	Time (h)	Т (К)	Yield of <b>6</b> (%)	Selectivity to 6 (%)
1	HTc-A(0.25)	12	2	353	57	99
2	HTc(0.25)	12	4	393	20	99
3	KF/Al <sub>2</sub> O <sub>3</sub>	12	1	353	56	62
4	KOH	4	2	353	77	99
5	KOH	0.2	6	393	6	100
6	КОН	57	4	298	90	98



2', 4'4-trimethoxy chalcone



Fig. 10. Yield of Vesidryl versus reaction time when the condensation was performed using a HTc-R(0.25) sample with 35 wt% water content at 373 K  $(\bigcirc)$  and 408 K  $(\square)$ .

of reaction time. However, the presence of strong basic sites should be responsible for its low selectivity to Vesidryl (6), due to the consecutive Michael addition of the acetophenone derivative of the Vesidryl. The results from Fig. 10 show that it is possible to achieve more than 90% yield of Vesidryl with 99% selectivity within 4 h, on the rehydrated hydrotalcite when the reaction temperature is increased to 408 K.

For comparison purposes, the reaction was also performed in the homogeneous phase using a strong conventional base (KOH). In this case, the amount of base used was the equivalent in moles to the amount of Al content in the rehydrated hydrotalcite, and at 353 K, a good conversion to Vesidryl was observed (Table 4, entry 4). However, when the amount of KOH was decreased 20-fold, which corresponds to the theoretical 5% accessible Brönsted basic sites existing in the rehydrated hydrotalcite [42], the Claisen–Schmidt condensation did not occur at 353 K in the time periods studied, and only when the temperature was increased to 393 K, 6% of chalcone was detected after a 6-h reaction time (entry 5). These results agree with those recently reported by Roelofs et al. for the self-condensation of acetone using regenerated hydrotalcites as catalysts, where they concluded that the activation of calcined hydrotalcites by rehydration implies not only the incorporation of OH<sup>-</sup> as an interlayer anion, but the calcination-rehydration process of the layered double hydroxide precursor gives rise the formation of an irregular structure which leads to an increase of the basic strength of the OH<sup>-</sup> near the edges of HT platelets. This is responsible of the high activity exhibited by the materials in aldol condensation reactions [43]. Finally, from Table 4, we can see that working with KOH as catalyst it is possible to obtain a good yield of Vesidryl working at room temperature (entry 6). However in this case a high concentration of base should be used, with the corresponding negative effects on product separation and catalyst neutralization and disposal.

### 4. Conclusions

We have seen that partially regenerated hydrotalcites prepared by fast rehydration of the calcined mixed oxides are active and selective catalysts for CS condensations. Optimized rehydrated catalysts required an optimum amount of water added, which is a function of the chemical composition Al/(Al + Mg) ratio of the precursor.

The optimized hydrotalcite catalysts can successfully be applied to the synthesis of chalcones with anti-inflammatory, anticancer, and diuretic pharmacological activities. These solid catalysts can only compete with the conventionally used KOH when the former are used at higher reaction temperatures. This is not due to a lower intrinsic activity of the active sites in the rehydrated hydrotalcite, but to the small amount of the active sites accessible to the reactants in the solid catalyst. It becomes evident to us that delaminated hydrotalcites or hydrotalcites with smaller crystallites should be prepared in which the number of accessible active sites would be larger.

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