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Base Catalysis for Fine Chemicals Production: Claisen–Schmidt Condensation on Zeolites and Hydrotalcites for the Production of Chalcones and Flavanones of Pharmaceutical Interest

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Chalcones and flavanones of commercial interest have been obtained with high yields and selectivities using solid base catalysts derived from hydrotalcites. The Al/(Al + Mg) ratio and hydrotalcite crystallite size are important parameters controlling catalyst activity. These catalysts give better results than acid- (HY) or alkaline-exchanged Y zeolites. An optimized hydrotalcite shows excellent catalytic properties for the synthesis of 2′,4,4′-trimethoxychalcone (Vesidryl), a product of pharmacological interest. The reactivity of substituted acetophenones and benzaldehyde follows the Hammet correlation. In addition to electronic effects, geometrical effects can also play a role in the reactivity of substituted acetophenones and benzaldehyde.

INTRODUCTION

Flavonoids are biosynthetic compounds which play an important role in preserving the health of plants against infections and parasites. Although much attention has been paid to the biosynthesis of flavonoids (1), it is not fully understood. However, it is accepted that the intermediate compounds for flavonoid synthesis are the isomers chalcone and flavanone (2). Industrially, they have found applications in pharmacology and as photoprotectors. In this way, a large number of chalcones have interesting antineoplastic, spasmolytic, diuretic, choleretic, antibiotic, bacteriostatic, and bactericidal properties (3–5). Also, the high UV–visible extinction coefficients of some chalcones make them useful as photoprotectors in plastic, solar creams, and food additives.

The synthesis of the basic structure of the flavonoids (Scheme 1), i.e., 2′-hydroxychalcone, has been carried out by different procedures, but the most general one is based on the Claisen–Schmidt condensation between substituted 2-hydroxyacetophenones and substituted benzaldehyde to give α,β unsaturated ketones (Scheme 2). The reaction is normally carried out at 50°C using 10–60 wt% of alkaline hydroxides or sodium ethoxide as catalysts over a period of 12–15 h (1, 6).

Other base catalysts, such as magnesium *t*-butoxide (7), potassium carbonates (8), and barium hydroxides either dehydrated (9) or activated by ultrasound (10, 11), have also been used for this synthesis.

The synthesis of chalcones can also be catalyzed by acid catalysts such as HCl (12), $AlCl_3$ (13), BF_3 (14), phosphorus oxychloride (15), borax (16), aluminium oxide (17), titanium (IV) chloride (18), and zeolites (19).

In this work the Claisen–Schmidt condensation of a series of substituted acetophenones and benzaldehydes has been carried out on a series of environmentally friendly base catalysts of increasing basicities. Their catalytic behavior has also been compared with that of an acid zeolite catalyst.

EXPERIMENTAL

Materials

A CsNaX zeolite was prepared by repeated exchange of a NaX zeolite (13X) with an aqueous solution of CsCl (0.5 *M*) at room temperature. The CsNa sepiolite was prepared starting from a sodium form of sepiolite (20) and carrying out the ion exchange using an aqueous solution of CsCl at room temperature. The final sepiolite contained 1.7 and 6.3 wt% of Cs and Na, respectively, as determined by atomic absorption.

The hydrotalcites were prepared from gels produced by mixing a solution of $Mg(NO_3)_2$ and $Al(NO_3)_3$ (1.5 *M* in (Al + Mg) and Al/(Al + Mg) atomic ratios of 0.20, 0.25, and 0.33) with a solution containing Na_2CO_3 (1 *M*), and the NaOH necessary to obtain pH's of 13 and 10. The resultant gels were aged at different temperatures for 18 h and then filtered and washed until pH = 7 (Table 1). After the solids were dried at 80°C for 12 h, the hydrotalcites were calcined in air at 450°C for 18 h in order to obtain Mg–Al mixed oxides, which were used as the base catalysts. A MgO sample was prepared following the proce-

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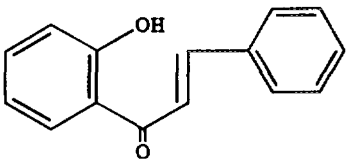


SCHEME 1

dure previously reported (21). The characteristics of the resultant catalysts are given in Table 2.

An acid HY zeolite was prepared from a NaY (SK-40) zeolite by NH_4^+ exchange followed by deep calcination at 550°C. This procedure was repeated three times in order to reduce the Na^+ content of the sample. The final HY zeolite has a framework Si/Al ratio of 5.2, 0.15 wt% of Na_2O, and 90% crystallinity.

Reaction Procedure

Base catalysis. Solvent-free mixture of the corresponding acetophenone (7 mmol) and benzaldehyde (8 mmol) was heated at 150°C in a batch glass reactor with stirring. When the reaction temperature stabilized, the catalyst (5 wt%) was added and the reaction started. From this moment, samples were taken at intervals. The reaction products were analyzed by GC–MS and ^1H-NMR spectroscopy (Varian 360 EM spectrometer). The catalyst present in each sample was always washed with CH_2Cl_2 and the extracted products were also analyzed and included in the mass balance. The course of the reaction was followed by using a Hewlett–Packard 5890 flame ionization detector and a 25-m capillary column coated with 5% cross-linked phenylmethylsilicone.

Acid catalysts. The zeolite catalyst (10 wt%) was activated in the reactor at 150°C and 1 Torr for 2 h. After this, a mixture of the corresponding acetophenone (7 mmol) and benzaldehyde (8 mmol) dissolved in dichloromethane (25 ml) was added at room temperature, and the dichloromethane was evaporated in vacuum. The resultant mixture was rapidly heated at 150°C and the same procedure as above was followed.

TABLE 1

Characteristics of the Synthesis Gels and Crystallization Conditions of the Hydrotalcites

Sample	Gel composition	pH	Crystallization temperature (K)
C-10	$2Mg:1Al:2Na_2CO_3:7\ NaOH$	13	583
C-12	$2Mg:1Al:2Na_2CO_3:5NaOH$	10	583
C-13	$2.25Mg:0.75Al:2Na_2CO_3:6.75NaOH$	13	353
C-14	$2.25Mg:0.75Al:2Na_2CO_3:6.75NaOH$	13	585

Note. In all cases the crystallization time was 18 h.

RESULTS AND DISCUSSION

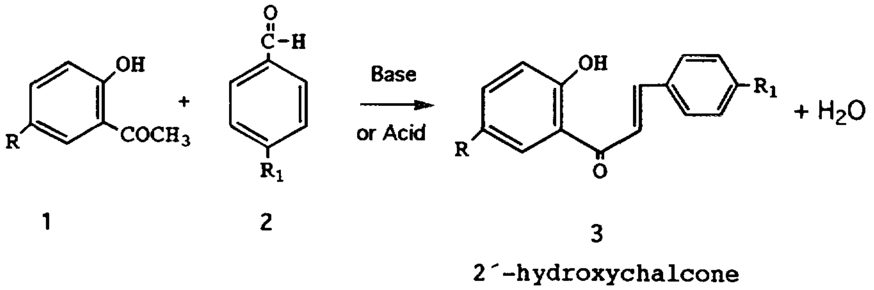
The preparation of 2′-hydroxychalcone (**3**) and its flavanone isomer (**4**) is the first reaction step in the Claisen–Schmidt condensation of 2-hydroxyacetophenone (**1**) and benzaldehyde (**2**) to give *trans*-2′-hydroxychalcone (**3**) (Scheme 2). When an acid catalyst is used, the reaction starts with the attack of a proton on the

TABLE 2

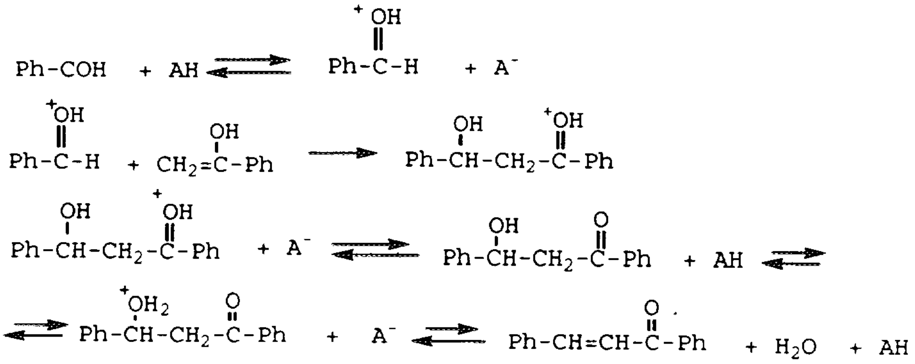
Composition and Surface Area of the Calcined Basic Catalysts Determined by N_2 Physisorption and Following the BET Procedure

Sample	Al/(Al + Mg)	BET surface area (*S*) ($m^2\ g^{-1}$)	Crystallite size (nm)
XNaCs		650	—
Cs–sepiolite		160	—
C-10	0.30	173	400
C-12	0.33	162	400
C-13	0.25	214	<50
C-14	0.25	196	400
MgO	—	199	not measured

Note. Crystallite size was determined by SEM.

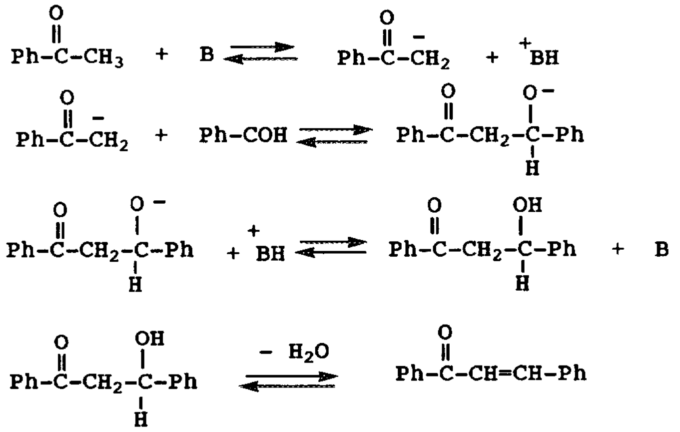


SCHEME 2



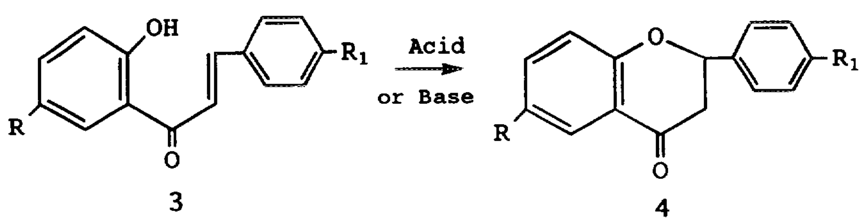
SCHEME 3

carbonyl group of the benzyaldehyde followed by the attack of this on the enolic form of the acetophenone (Scheme 3). In the case of base-catalyzed Claisen–Schmidt condensation, the mechanism generally accepted involves formation of the anion of acetophenone, followed by its attack on the carbonyl group of benzaldehyde (Scheme 4). By either the acid- or the base-catalyzed route, if the reaction conditions and the substituents present in the aromatic nucleus are suitable, the chalcone formed can cyclize to give the corresponding flavanone isomer (1, 6) (Scheme 5).



SCHEME 4

When the reaction between 2-hydroxyacetophenone **1a** and benzaldehyde **2a** was carried out using an HY zeolite, which was shown to be able to protonate carbonyl groups (22), the reaction occurred (Table 3), and a relatively high selectivity to flavanone **(4a)** was observed. However, when zeolite NaX and a sepiolite were partially exchanged with Cs (Table 2) in order to produce base catalysts, their activity was very low (Table 3). This is not surprising, taking into account that the acidity of the hydrogens in the methyl group of the acetophenone corresponds to a pK_a = 15.8, and it has been demonstrated previously (23) that in the exchanged CsNaX, and Cs sepiolite catalysts, most of the basic sites are able to abstract protons with pK_a ~ 10.7 and ~13.3, respectively. It is apparent from this that a catalyst with stronger basic sites should be used. It has been shown (24) that zeolites containing an excess of Cs over the exchange capacity are strong base catalysts and therefore they can probably carry out the reaction successfully. However, they have to be handled in an inert atmospheric in order to avoid the formation of carbonates. Moreover, in some cases, the presence of water can also be harmful for these catalysts. Owing to this, we thought that a base catalyst derived from Mg–Al hydrotalcite, which is strong enough to abstract the proton from the methyl group in a molecule such as acetophenone (pK_a = 15.8) (25, 26), could be adequate to carry out this reaction in a selective way. Results from Table 3 clearly show that



3
2′-hydroxychalcone

4
flavanone

SCHEME 5

TABLE 3

Catalytic Activity of Different Catalysts for the Condensation of 2-Hydroxyacetophenone (1a) and Benzaldehyde (2a) in the Presence of Air at 150°C, 5 wt% Catalyst, and 1 h Reaction Time

Catalysts	Total conversion (X) (mol %)	Yield (%) 3	Yield (%) 4	Initial rate (r_0) (mol h^{-1})[a]	r_0/S (mol m^{-2} h^{-1})	X/S (mol g m^{-2})
XNaCs	1	0.7	0.3	—	—	—
SpCs	2	1.4	0.6	—	—	—
HY-102[b]	12	3	9	—	—	—
C-13	78	50	28	146	0.68	0.36
C-14	60	42	18	56	0.28	0.30
OMg	40	27	13	21	0.10	0.20

[a] r_0 is the overall initial rate (r_0**3** + r_0**4**).
[b] 10 wt%.

the Mg–Al hydrotalcite-derived catalyst is active for carrying out the desired reaction and its activity is much higher than that of the acid catalysts. The lower activity of the acid catalyst may be due to the protonation of the acetophenone carbonyl group in competition with that of benzaldehyde. This would result in a decrease of the amount of intermediates able to produce the desired product.

Influence of the Chemical Composition and Crystal Size of the Hydrotalcite Catalyst

It is known that the base properties of calcined hydrotalcite depend on the Al/(Al + Mg) ratio (27). When the amount of Al increases, the total number of basic sites decreases, but the proportion of the stronger ones increases (28). Thus, for any base-catalyzed reaction, a maximum in activity should occur for an optimum Al/(Al + Mg) ratio. This optimum will depend on the base strength needed to activate the particular reactant. Thus the higher the basicity needed, the higher will be the Al/(Al + Mg) ratio for which the maximum in activity will be found.

In order to find the optimum for the reaction studied here, catalyst samples with Al/(Al + Mg) ratios ranging from zero (MgO) to 0.33 were prepared, and their activities per unit surface area have been plotted in Fig. 1. It can be seen there that a maximum in activity occurs for Al/(Al + Mg) between 0.25 and 0.30.

In the case of $Mg_6Al_2O_9$ solid base materials formed by the controlled calcination of hydrotalcites, it appears that the active surface sites include hydroxide groups and a range of O^{2-}–Mg^{+2} acid–base pairs (29). The basicity of the Lewis sites associated to framework oxygens depends on their coordination. Thus those oxygens located in corners of the crystal should have a stronger basicity than the oxygens located either on edges or on crystal faces. If this is so, one may expect to modify the relative populations of those by modifying the crystallite size of the hydrotalcites. Results from Table 3 show that the sample with larger crystals shows lower activity per unit surface area than sample C-13, which was synthesized with the same chemical composition but with smaller crystallites. These results indicate that the stronger base sites, which are those related to the oxygens with a low coordination number, play an important role in this reaction.

It should be noted (Fig. 2) that although sample C-13 gives a higher conversion than C-14 for short reaction times, for longer times the differences are practically negligible. This, together with the fact that the conversion of both samples remains unchanged after ~2 reaction time, indicates that these catalysts become poisoned during the reaction, and also that the more active catalyst deacti-

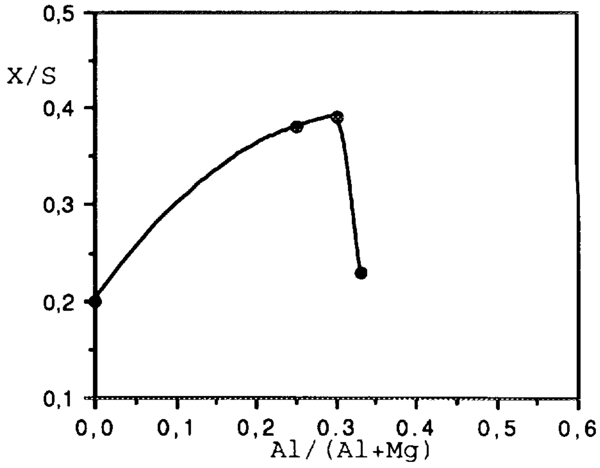


FIG. 1. Influence of the Al/(Al + Mg) ratio of the starting hydrotalcite on the overall conversion per unit surface area (X/S) for the condensation reaction between **1a** and **2a**.

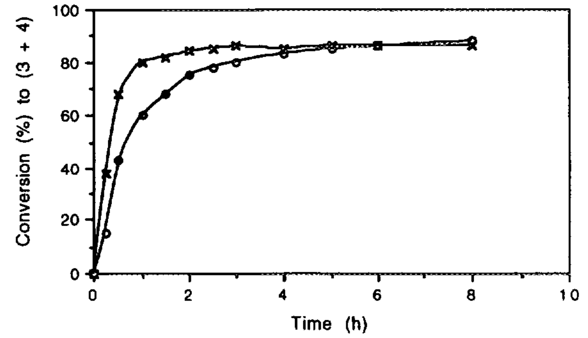


FIG. 2. Claisen–Schmidt condensation between **1a** and **2a** on calcined hydrotalcites with different crystal sizes (C-13(×), C-14(O)) at 150°C, in the presence of air and 5 wt% catalyst.

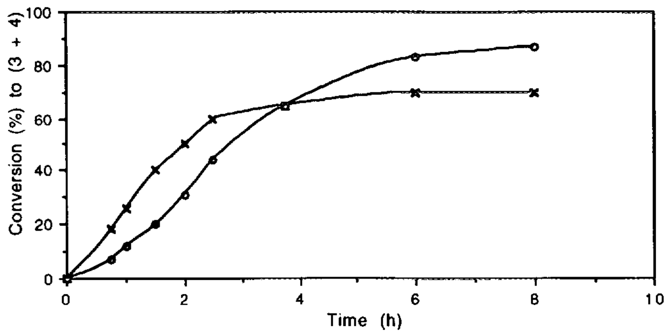


FIG. 3. Claisen–Schmidt condensation between **1a** and **2a** on calcined hydrotalcites with different crystal sizes (C-13(×), C-14(O)) at 120°C, in the presence of air and 5 wt% catalyst.

vates faster. This can be better seen when the reaction is carried out at a lower temperature (Fig. 3). When the catalyst used in the reaction was analyzed by IR, it was observed that magnesium benzoate was formed on its surface. This indicates that benzoic acid should be formed during the reaction, and that it becomes adsorbed on the catalyst, neutralizing basic sites. The fact that no benzylic alcohol was detected in the reaction mixture strongly suggests that benzoic acid is not formed through a Cannizzaro reaction, but probably by direct oxidation of benzaldehyde. In order to check this, an experiment was carried out with benzaldehyde and hydrotalcite (2.5 wt%) at 150°C. After 20 h of reaction, 60% of the benzaldehyde was transformed into benzoic acid, while only 1% benzylic alcohol was found. These results suggest that benzoic acid is formed by oxidation of benzaldehyde with air. If this is so, a lower catalyst deactivation should be obtained if the reactor is flushed with an inert gas. To check this, the reaction was carried out at 120°C on the C-13 catalyst in the presence of argon. Under these experimental conditions the conversion increased with time, reaching 97% after 22 h. However, when the reaction was performed under the same reaction conditions but in the presence of air, the conversion was 70% and remained unchanged with increasing reaction time after 7 h.

The regenerability of the poisoned catalysts was studied and it was found that, after calcination at 450°C for 3 h, full initial activity was recovered.

Influence of the Nature of the Reactant

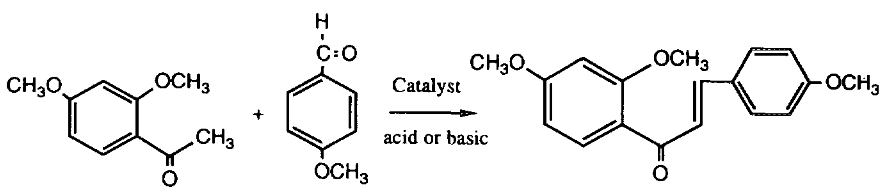
The Claisen–Schmidt condensation was carried out using substituted acetophenone and benzaldehyde derivatives. Results from Table 4 show that the presence of electron acceptor groups in the aromatic ring of benzaldehyde increases the reaction rate in proportion to the value of the Hammet constant. Meanwhile, the presence of electron donor groups decreases the reaction rate. It should be noted that any of the reactants with substituent groups in either of the two aromatic rings gives a lower conversion than the unsubstituted reactants. This can hardly be explained by means of electronic effects; geometric effects related to diffusional problems or geometrical restrictions on the adequate adsorption configuration, due to the present of larger groups such as NO_2, Cl, and OCH_3, have to be claimed (11).

TABLE 4

Catalytic Activity of Hydrotalcite C-13 for the Condensation of 2-Hydroxyacetophenone (1a–e) and Benzaldehyde Derivatives (2a–e) in the Presence of Air at 150°C, 5 wt% Catalyst, and 1 h Reaction

	R	*R*^{1}	Total conversion (*X*) (mol %)	Yield (%) 3	Yield (%) 4	Initial rate (r_0) (mol h^{-1})^a	r_0/S (mol m^{-2} h^{-1})	*X*/*S* (mol g m^{-2})
a	H	H	78	50	28	146	0.68	0.36
b	H	NO_2	61	16	45	77	0.35	0.28
c	H	Cl	35	27	8	36	0.16	0.16
d	H	OCH_3	17	7	10	17	0.08	0.07
e	OCH_3	H	23	16	7	25	0.11	0.10

[a] r_0 is the overall initial rate ($r_0 3 + r_0 4$).



Vesidryl (5)
(2′,4′,4-trimethoxychalcone)

SCHEME 6

Preparation of Vesidryl

In order to show a practical application of the catalyst optimized for these type of reactions, the synthesis of Vesidryl (2′,4,4′-trimethoxychalcone), **5** (Scheme 6), has been carried out on C-13 hydrotalcite at 150 and 170°C reaction temperatures. This product is of pharmacological interest owing to its diuretic and choleretic properties.

Results from Table 5 show that high conversions and selectivities of the desired product can be obtained. Conversion is much higher on the hydrotalcite catalyst than on an HY zeolite, in agreement with the results given above. The high conversions and excellent selectivities to Vesidryl obtained using calcined hydrotalcites as catalysts open new possibilities for these materials in the production of chalcones and flavanones of pharmacologic interest.

CONCLUSIONS

It has been shown that Mg–Al hydrotalcites are active and selective catalysts in the production of chalcones and flavanones of commercial interest through a Claisen–Schmidt reaction.

An optimum in activity was found for samples with Al/(Al + Mg) molar ratios of 0.25–0.30. It is thought that smaller crystallites are more active than larger crystals, indicating that the stronger basic sites, probably those occupied by oxygens at corners, play an important role in this reaction. Deactivation of the catalyst occurs. This is probably due to the neutralization of basic sites by benzoic acid formed by oxidation of benzaldehyde, which occurs when the reaction is carried out in the presence of air; hence the reaction is better under an inert atmosphere.

The activity of substituted benzophenone and benzaldehyde follows the Hammet correlation, showing the influence of electronic effects. However, geometrical factors may also play a role in the case of substituted acetophenones and benzaldehyde. Finally, it has been shown that under mild reaction conditions, and using an optimized hydrotalcite as catalyst precursor, the formation of Vesidryl can be catalyzed with high yield and selectivity.

TABLE 5

Conversion of Vesidryl (5) under Different Reaction Conditions in the Presence of Air

Catalysts	Catalyst wt (%)	T(°C)	Vesidryl (**5**) yield (%)[a]	Initial rate (r_0) (mol h^{-1})	r_0/S (mol m^{-2} h^{-1})
HY-102	10	150	15	—	—
C-13	5	150	55	7	0.032
C-13	5	170	85	16	0.074

[a] 20 h Reaction time in the presence of air.

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