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Supported choline hydroxide (ionic liquid) as heterogeneous catalyst for aldol condensation reactions

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Choline hydroxide was used as a basic catalyst for aldol condensation reactions to produce new C–C bonds between several ketones and aldehydes. Choline supported on MgO exhibits higher TOF values than other well known basic catalysts in these reactions.

It is an exciting challenge to find new solid Brønsted-type basic catalysts able to perform with high activities and selectivities condensation reactions for the synthesis of pharmaceutical and fine chemicals. These reactions are indeed known to be catalysed by Brønsted sites and industrially are carried out in the homogeneous phase with KOH or NaOH.[1] The use of these kinds of bases has numerous disadvantages such as waste production, corrosion and no catalyst recovery. In recent years, different solid base catalysts, such as hydrotalcites have been in the spotlight for a large number of reactions. They have emerged as heterogeneous catalysts, and have been used as precursors in the self-aldol condensation of acetone,[2] benzaldehyde–acetone condensation,[3] synthesis of flavanones[4] and the condensation of citral and ketones, into pseudoionones, which are precursors for vitamin A.[5] Ionic liquids have a large nature of physical and chemical properties which make them useful for different applications, mainly as solvents in homogeneous catalysis.[6] They are composed of organic cations and inorganic or organic anions. The resulting salts are non volatile, thermally and chemically stable and their miscibility can be altered by varying the alkyl chain length of the cation or the nature of the anions.[7] Most of common ionic liquids are based in neutral 1,3-dialkylimidazolium cations, and $[PF_6]^-$ or $[BF_4]^-$ anions, and are used in catalytic applications.[8] They are also good solvents for transition metal complexes, and can be recycled easily. They have been used as solvents for several reactions involving C–C bond formation, such as Michael additions,[9] Knoevenagel condensations[10] or aldol reactions.[11] Recently, a process[12] for the synthesis of aldol condensation products is described with the use of a neutral ionic liquid medium comprising an imidazolium cation together with a basic catalyst, KOH (Fig. 1). This shows that a hydroxylated ionic liquid would act as a basic catalyst. Therefore, in this communication we report, for the first time, the activity of choline hydroxide (CH) (Fig. 2). Moreover, a heterogeneous catalyst has been tentatively performed by impregnation of CH on MgO support (CHMgO). The activity of this new catalyst was compared to other well known ones, such as rehydrated hydrotalcites (HT*reh*), MgO and NaOH. Several condensation reactions of a variety of carbonyl compounds were carried out by using these catalysts.†

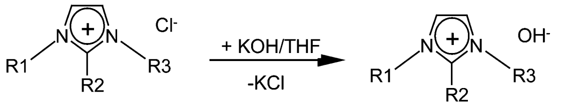
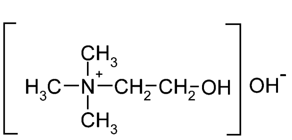


Fig. 1 Basic ionic liquid derived from an imidazolium salt.



$$\left[H_3C-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}-CH_2-CH_2-OH \right] OH^-$$

Fig. 2 Choline hydroxide molecule.

Most of the obtained products are interesting in pharmacological and flavour and fragrance industries. The results are summarised in Table 1. The two isomers of citral (neral and geranial) (entry 1) can be converted (93%) in one hour to the corresponding pseudoionone PS (2 isomers) with excellent selectivity, when using CH. After 1 hour of reaction, and comparing the amount of OH^- for CH (4.4 mmol OH^-), CHMgO (1.1 mmol OH^-) and a classical solution of NaOH (2.2 mmol OH^-), better results are obtained for CHMgO. The self-aldol condensation of acetone (entry 2) was carried out at 1 °C to avoid the dehydrated product; the thermodynamic equilibrium to diacetonealcohol was achieved only in 0.4 hours for the CHMgO catalyst. At 2.5 h of reaction time, citral can be coupled to 2-butanone (entry 3), for the synthesis of methyl-pseudoionones with a high conversion around 90%, and a selectivity of 94% using both CH and CHMgO as catalysts. When comparing to HT*reh* (35 mmol OH^-, around 35 times higher than in CHMgO), only a 57% of conversion is obtained. A TOF value around 70 times higher is obtained for CHMgO than for HT*reh*. The formation of two different carbanions in the 2-butanone molecule results in the production of four products (iso- and n-methyl PS isomers from neral and geranial). Higher conversions and selectivities are obtained in the production of benzylideneacetone (entry 4) from the aldol condensation between acetone and benzaldehyde with CH, CHMgO with respect to MgO. Besides, CHMgO shows the highest activity (a TOF five times higher than for CH), indicating that there is a synergic effect between choline and MgO. However, at total conversion (0.10 h of reaction) and due to the production of dibenzylideneacetone, the selectivity to benzylideneacetone decreases to around 77% because of the double attack of acetone to two benzaldehyde molecules. From the condensation (entry 5) of benzaldehyde **1** and 2′-hydroxyacetophenone **2**, (see also Fig. 3) 2′-hydroxychalcone **3** is produced and directly isomerised to flavanone **4**. After 2.5 hours of reaction, 99% of the 2′-hydroxyacetophenone was condensed to benzaldehyde. Selectivity is expressed as 2′-hydroxychalcone together with its flavanone isomer. When the reaction begins, high yields of the two products are achieved, but for longer times, selectivity is drastically reduced from 90% at a conversion level of 56% to 58% when the conversion of 2′-hydroxyacetophenone is complete. This fact can be explained due to the formation of other by-products, mainly, product **5**. This major side reaction occurs through the condensation of flavanone and the remaining benzaldehyde.

For the synthesis of jasminaldehyde (entry 6), both catalysts, CH and CHMgO, lead to excellent conversions in a relatively short time and selectivities around 84%. The undesired product comes from the self-condensation of heptanal to form 2-n-pentyl-2-nonenal, but it could be inhibited to some extent by maintaining a low concentration of heptanal relative to benzaldehyde in the reaction mixture, or by a slow addition of heptanal. The results from the condensation of piperonal (heliotropine) with propionaldehyde (entry 7) show that a conversion of 79% can be achieved in 5 hours, and a selectivity of 85% to the main product (methylenedioxyphenyl methacrolein). A complete piperonal conversion is

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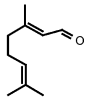
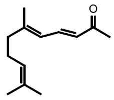
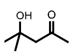
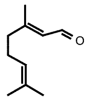
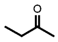
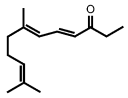
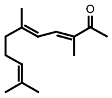
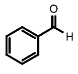
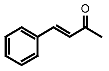
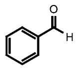
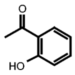
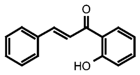
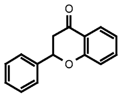
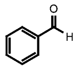
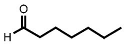
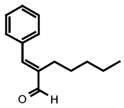
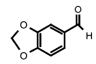
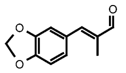
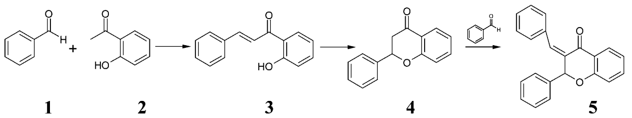
Table 1 Condensation reactions catalysed by choline hydroxide or MgO-supported choline[a]

Entry	Substrate	Ketone	Products	Catalyst	Time (h)	X(%)[b]; (TOF(S^{-1})[i])	Selectivity (%)
1				CH	1	93.3(15.7)	98.2
				CHMgO	1	94.2(66.8)	95.5
				NaOH[c]	1	80.1(29.2)	87
2[e]				CHMgO	0.4	23(14.25)	90
3			 	CH	2.5	90.2(17.8)	94.3
				CHMgO	2.5	90.6(82.3)	94.2
				HTreh[d]	2.5	57.0(1.2)	94.0
4				CH	0.03	28.2(14.57)	89.7
				CHMgO	0.03	39.1(80.7)	90.2
				MgO	4.0	30.3	88.2
5			 	CH	2.5	99.4(2.5)	58.2
6[f]				CH	1.9	95.8(19.7)[g]	83.7
				CHMgO	1.0	87.2(72.6)[g]	84
7[h]				CH	5	78.8(1.2)	85.2

[a] Reaction conditions: ratio ketone/substrate 4.4, T = 60 °C, CH = 0.5 ml (4.43 mmol OH$^-$), CHMgO = 0.125 ml (1.11 mmol OH$^-$) on 1g MgO; [b] X = Conversion of substrate; [c] Solution of NaOH (2.21 mmol OH$^-$); [d] Rehydrated HT ($\approx$35 mmol OH$^-$); [e] Carried out at 1 °C; [f] Ratio ketone/substrate (heptanal/benzaldehyde) = 0.23; [g] Conversion of heptanal; [h] Ratio ketone/substrate (propanal/piperonal) = 2, T = 30 °C; [i] Initial TOF (mmol substrate per mmol OH$^-$·S)·10^3.



1 **2** **3** **4** **5**

Fig. 3 Condensation of 2′-hydroxyacetophenone and benzaldehyde.

achieved at 7 h of reaction but a selectivity of 76% is obtained to the main product; a by-product involving the self-condensation of propanal, 2-methyl-2-pentenal, is also present. The formation of this by-product could be also avoided by a slow addition of propanal. An advantage for this reaction is that the expected product of cross-condensation has a lower solubility in methanol than heliotropine and it can be separated without by-products.

In conclusion, a new basic catalyst involving an ionic liquid (choline hydroxide) has been developed. In addition, higher performances can be obtained when choline is immobilised on a support (MgO)(heterogeneous catalyst), giving higher TOF values for several aldol condensation reactions between ketones and aldehydes. This fact opens new opportunities and alternatives of great interest for new base-catalysed reactions.

Notes and references

† Choline hydroxide was impregnated on MgO (70 m^2 g^{-1}). The reactions were performed in a 100 ml batch reactor under argon, for avoiding CO$_2$. For a typical experimental procedure, to a stirred solution of substrate and ketone were added choline hydroxide (0.5 ml) or choline (0.125 ml) supported on MgO (1 g). The flask was maintained at the desired temperature. Samples were analysed by gas chromatography (GC) using internal standard. This work was financially supported by the Ministerio de Ciencia y Tecnología of Spain (REN2002-04464-CO2-01) and Destilaciones Bordas S.A.

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