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Synthesis, characterization, and catalytic activity of ionic liquids based on biosources

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ABSTRACT

New room-temperature ionic liquids were synthesized from natural and easily available feedstocks (choline hydroxide and amino acids) following an economical and green route in which the only by-product was water. They were successfully applied as catalysts for the Knoevenagel test reaction between benzaldehyde and different active methylene compounds, at room temperature and under solvent-free conditions, to produce α,β-unsaturated carbonyl compounds, exhibiting good conversions and high selectivities. The catalytic role of cholinium and aminoacetate ions in the Knoevenagel condensation is discussed.

Room-temperature ionic liquids (RTILs) are increasingly attracting attention due to their unique characteristics: low vapor pressure, non-flammability, high thermal and chemical stability, possibility of recycling, good solubility for a wide spectrum of compounds even gases, and high suitability for modifications.[1] Based on these properties, ionic liquids (ILs) have emerged as a novel class of compounds to be used in many fields, namely electrochemistry, organic synthesis and catalysis,[2,1a,b] metal recovery from solutions,[3] and carbon dioxide capture.[4] Even so, concerns have risen over the potential toxicity as well as the low biodegradability of most of the currently employed ILs.[5] To overcome these drawbacks some ionic liquids have already been synthesized from renewable, non-toxic biosources,[6] thus meeting with one of the main principles of green chemistry.[7] Among these sources, natural products (amino acids, vitamins, etc.) with an interesting molecular diversity have the potential to be converted into ILs by means of green procedures, such as simple ion exchange and/or acid–base reactions.[8] Natural amino acids were first used in 2005 by Fukumoto et al. for the synthesis of 1-ethyl-3-methylimidazolium-based ILs.[8a] Since then, many ionic liquids in which the forming anion comes from a natural product (amino acid) have been prepared.[9]

In this work, five new RTILs were prepared by using only renewable, non-toxic natural products (choline hydroxide as the source for the cation and amino acids for the different anions) by a straightforward synthetic procedure and without expensive chemical modifications (Scheme 1).

The Knoevenagel condensation is one of the most widely used C–C bond forming reaction in the synthesis of important intermediates for fine chemicals, such as α,β-unsaturated carbonyl compounds from active methylene and carbonyl compounds (Scheme 2).[10] Particularly, the use of methylene malonic esters leads to several important key industrial and pharmacological products.[11,12] Traditionally, ammonia, primary or secondary amines, and their salts are employed as catalysts.[13] In recent years efforts have been focused on the search for new catalysts,[14] including ionic liquids.[15–17] Moreover, in the production of fine chemicals, the development of environmentally friendly catalysts has attracted a growing interest.[7]

The catalytic properties of the RTILs prepared in this work were tested in the Knoevenagel condensation under solvent-free conditions between benzaldehyde and different methylene compounds such as ethyl cyanoacetate (**1**) ($pK_a = 9$), ethyl acetoacetate (**2**) ($pK_a = 10.7$), diethyl malonate (**3**) ($pK_a = 13.3$), or ethyl bromoacetate (**4**) ($pK_a = 16.5$) in a batch reactor at room temperature (Scheme 3). The pK_a value determines the minimum basicity demanded by the reactant to run the condensation reaction.

According to the ^1H and $^{13}C\{^1H\}$ NMR data, the synthesized RTILs are pure compounds with no remains of the choline hydrox-

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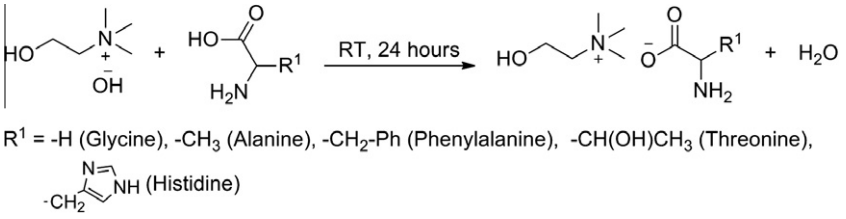
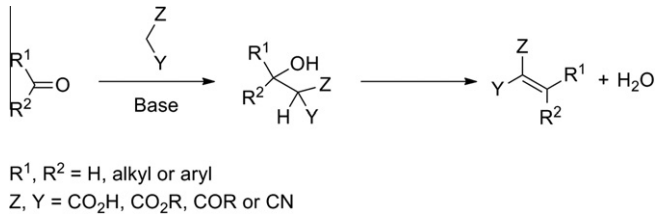
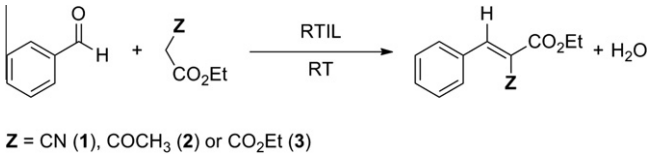


Scheme 1. RTILs synthesis.



Scheme 2. Knoevenagel condensation between carbonyl and active methylene compounds.



Scheme 3. Knoevenagel condensation of benzaldehyde with activated methylene compounds in the presence of the RTILs.

ide or amino acids used as feedstocks. Changes in the chemical shifts were especially significant for the aminoacetate ions as a consequence of the ionic liquid formation. As an example, the ^{1}H NMR spectrum of the [Chol][Ala] shows a doublet at 1.23 ppm and a quadruplet at 3.32 ppm corresponding to the CH_3 and CH of the alaninate anion; those in the free amino acid appearing at 1.48 ppm and 3.78 ppm, respectively.

Results of the TGA analysis are given in Table 1. All the RTILs show decomposition temperatures below 180 °C which are between those of choline hydroxide and the corresponding amino acid. No relationship between the cation size and the decomposition temperature was found for these RTILs. Previous studies in the literature on the synthesis/characterization of this type of ILs are limited to those prepared from choline hydroxide and proline ([Chol][Pro]), which shows a similar decomposition temperature (159 °C).[18]

Results of the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate (pK_a = 9) are given in Table 2. Conversions ranging from 57% at 60 min up to 74% after 3 h of reaction time were achieved with only 1% of catalyst loading. Based on ^{1}H NMR data, the *E*-stereoisomer was found to be the sole reaction product. Since the selectivity to the Knoevenagel product was 100% in all the cases, conversions are also the product yields.

Table 1
Decomposition temperature of the RTILs

RTIL	Decomposition temperature (°C)
[Chol][Ala]	152
[Chol][Gly]	148
[Chol][Phe]	166
[Chol][Thr]	171
[Chol][His]	128

In the condensation of benzaldehyde and ethyl acetoacetate (pK_a = 10.7) (Table 3), [Chol][Ala] showed the highest activity at shorter reaction times (5 h); while [Chol][Gly] exhibited the lowest. For longer reaction times (24 h), a maximum activity value up to 57% was afforded by [Chol][Thr] and up to 55% by [Chol][Gly]. Predictably, the use of ethyl acetoacetate as a methylene precursor promotes side reactions, including self condensation, that lessen the selectivity toward the Knoevenagel product.[19]

Selectivities to Knoevenagel product of 100% were found for the reaction between benzaldehyde and diethylmalonate (pK_a = 13.3) (Table 4). However, noticeable differences in the final conversions among the synthesized RTILs were observed for this reactant. Thus, a conversion value of 60.5% was achieved after 7 h of the reaction by using the most active [Chol][Ala], whereas that corresponding to [Chol][His] amounted to only 19%.

The RTILs were also tested in the reaction of benzaldehyde and ethyl bromoacetate (pK_a = 16.5) (Table 5). Results were very limited both in terms of the overall yields and the selectivity. For these particular reactants, the formation of the corresponding epoxide (Darzens reaction) competes strongly with the Knoevenagel condensation, under the current experimental conditions.[20] Nevertheless, the best result was obtained for [Chol][Gly] with a 36% selectivity toward the condensed product and 6% of overall yield.

The efficiency of the RTILs presented in this work compares reasonably well with the previous results obtained using task-specific ILs.[15–17] Besides the already stressed advantage of their low toxicity as well as biodegradability, the [Chol][Aminoacetate] liquids exhibit significant differences to other basic ILs employed in Knoevenagel condensation reactions. Although specific mechanisms have been scarcely discussed, most approaches to the design of new task-specific ILs for this reaction are focused on the enhancement of their basic strength. Thus, the best performing IL reported so far for Knoevenagel condensations is, to our knowledge, a strong base such as [C_4mim][OH]. The prominent relevance of the $[OH]^-$ ion in that particular system was pointed out, with the replacement of the IL anion leading to the deactivation of the catalyst.[15b]

In principle, the aminoacetate anions of the RTILs reported here were expected to be the reaction promoters through the formation of a stabilized enolate anion by abstraction of the proton from the methylene group of the malonic ester (Scheme 4).[21] However, the RTIL synthetic route depicted in Scheme 1 might be reversed as water is produced in the Knoevenagel reaction (Schemes 2 and 4), thus leading to significant amounts of choline hydroxide. This latter compound has demonstrated its catalytic activity in aldol condensations.[22] Therefore, it was decided to test the efficiency of [Chol][OH] in the Knoevenagel condensation to better elucidate a plausible mechanism for the reactions under study. Results are also included in Tables 2–5.

Overall, the performance of [Chol][OH] was rather limited, its efficiency decreasing as the basicity demand of the methylene compound increases. The ability of [Chol][OH] in transferring effectively $[OH]^-$ to the reaction medium seems much lower than that of [C_4mim][OH].[15b] This is somehow surprising since [Chol][OH] is also considered to be a strong base. On the other hand, the catalytic

Table 2
Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate ($pK_a = 9$)[a] versus reaction time

Time[b]	Yield[c] (%)					
	[Chol][Ala]	[Chol][Phe]	[Chol][Thr]	[Chol][Gly]	[Chol][His]	[Chol][OH]
15	63.7	50.3	60.1	63.5	13.7	42.0
30	64.3	54.5	61.0	65.3	19.0	46.8
60	65.8	57.1	63.8	68.0	65.4	53.8
120	66.2	65.5	66.0	70.1	72.5	66.2
180	72.5	70.0	66.6	73.7	74.2	68.1

[a] Benzaldehyde 14 mmol, ethyl cyanoacetate 14 mmol, 1% of RTIL, room temperature.
[b] Minutes.
[c] 100% selectivity to Knoevenagel product.

Table 3
Knoevenagel condensation between benzaldehyde and ethyl acetoacetate ($pK_a = 10.7$)[a] versus reaction time

Time[b]	Conversion (%) [selectivity to Knoevenagel product (%)]					
	[Chol][Ala]	[Chol][Phe]	[Chol][Thr]	[Chol][Gly]	[Chol][His]	[Chol][OH]
5	45.4 [67.2]	29.7 [87.5]	29.4 [91.2]	7.2 [90.3]	34.5 [86.7]	16.8 [46.4]
7	51.0 [71.9]	38.1 [82.7]	44.0 [90.1]	17.6 [64.2]	37.4 [81.0]	17.0 [46.0]
24	52.5 [76.4]	52.8 [68.2]	57.4 [90.8]	55.1 [72.6]	48.6 [76.7]	23.1 [39.8]

[a] Benzaldehyde 9 mmol, ethyl acetoacetate 9 mmol, 2% RTIL, room temperature.
[b] Hours.

Table 4
Knoevenagel condensation between benzaldehyde and diethyl malonate ($pK_a = 13.3$)[a] versus reaction time

Time[b]	Yield[c] (%)					
	[Chol][Ala]	[Chol][Phe]	[Chol][Thr]	[Chol][Gly]	[Chol][His]	[Chol][OH]
2	38.9	27.6	20.3	33.9	1.0	3.0
4	51.3	39.5	27.8	45.6	17.9	4.7
7	60.5	54.7	32.1	52.0	19.0	5.9

[a] Benzaldehyde 7 mmol, diethyl malonate 7 mmol, 10% RTIL, room temperature.
[b] Hours.
[c] 100% selectivity to Knoevenagel product.

Table 5
Knoevenagel condensation between benzaldehyde and ethyl bromoacetate ($pK_a = 16.5$)[a] versus reaction time

Time[b]	Conversion (%) [selectivity to Knoevenagel product (%)]					
	[Chol][Ala]	[Chol][Phe]	[Chol][Thr]	[Chol][Gly]	[Chol][His]	[Chol][OH]
7	7.2 [3.0]	13.5 [3.0]	3.5 [3.0]	6.1 [36.0]	6.3 [0.0]	0.0 [0.0]

[a] Benzaldehyde 7 mmol, ethyl bromoacetate 7 mmol, 10% RTIL, room temperature.
[b] Hours.

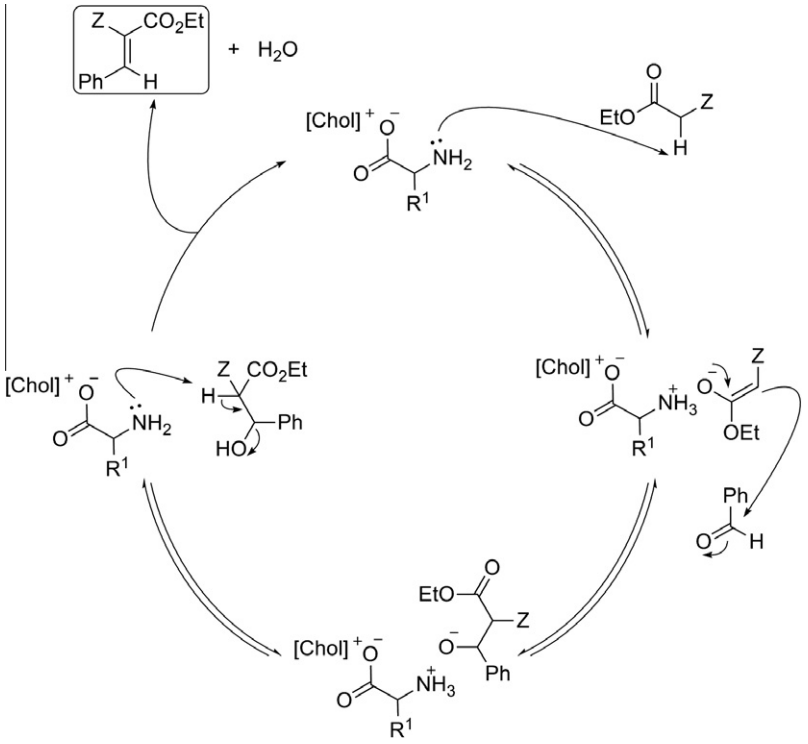
efficiency of the [Chol][OH] IL was very similar to that reported for the task-specific ionic liquid [H_3N^+–CH_2–CH_2–OH][Acetate] having a weak basic character.[15a]

Nevertheless, [Chol][OH] could only compete with the RTILs as a catalyst in the reaction between benzaldehyde and ethyl cyanoacetate ($pK_a = 9$) (Table 2).

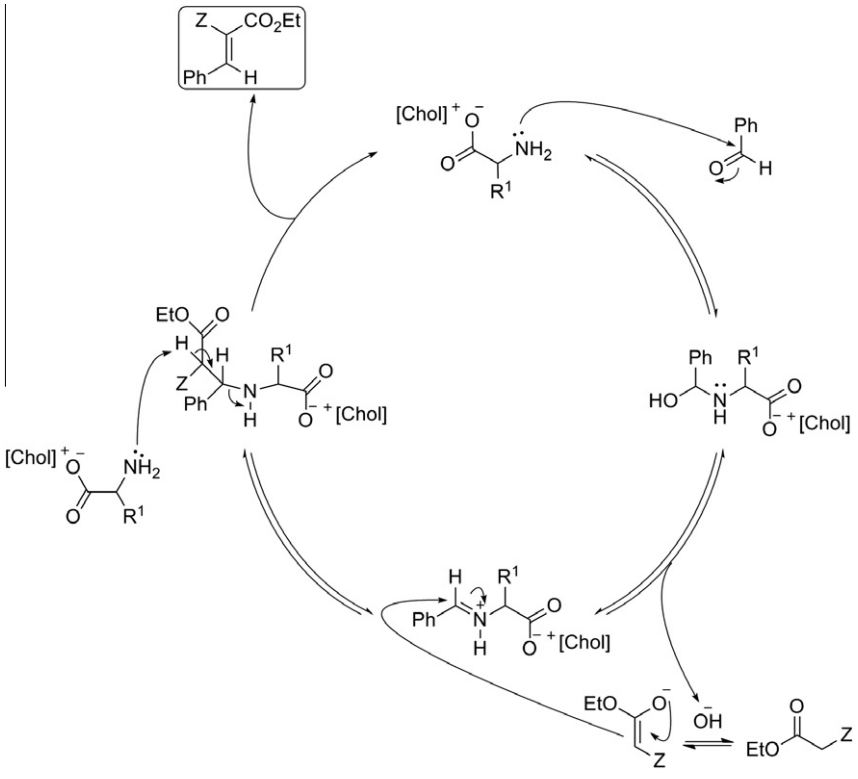
The series of RTILs tested in this work allow one to get a further insight into the possible mechanisms of the reaction. Since the pK_a of the $–NH_2$ group of the aminoacetates under consideration spans an interval of approximately one pK_a unit in the following order:[23] 9.1 ([Phe], [His]) < 9.6 ([Gly], [Ala]) < 10.4 [Thr], the whole series of RTILs appears to have enough basic strength ($pK_a \geqslant 9$) to abstract the proton from the methylene group of ethyl cyanoacetate (Scheme 4). Therefore, no significant conversion differences between the RTILs tested were found after 3 h (Table 2). Even so, it is worth noticing the differences in yields observed for [Chol][Phe] and particularly for [Chol][His] at low reaction times. This can be understood in terms of steric hindrance of the two bulky side chains of these two amino acids (Scheme 1).

Basic strength would also explain the good performance of [Chol][Thr] in the condensation between benzaldehyde and ethyl acetoacetate ($pK_a = 10.7$) (Table 3). However, for the rest of RTILs bearing $–NH_2$ groups of lower pK_a, the mechanism depicted in Scheme 5 would help to understand the relatively good results obtained. This plausible mechanism has been proposed to explain the efficiency in the Knoevenagel condensation reaction of relatively weak bases with limited proton abstraction ability, especially when high pK_a-demanding methylene compounds are considered.[24,25] It envisages the formation of hemiaminal intermediates which are strong electrophiles, by addition of the amine group to the carbonyl group of the benzaldehyde. The same path should be followed when the pK_a demand increases to 13.3 (Table 4). In this case, the efficiency of the catalysts does not correlate at all with the pK_a of their $–NH_2$ group.

Obviously, this mechanism would co-exist with that described in Scheme 4 for relatively low pK_a-demanding reactions. The three methyl groups attached to the nitrogen atom of the $[Chol]^+$ ion should restrict their activating ability through a mechanism similar



Scheme 4. Mechanism of the Knoevenagel condensation between benzaldehyde and methylene compounds [Z = CN (**1**)] in the presence of the RTILs, for low pK_a demanding reactions.



Scheme 5. Alternative mechanism of the Knoevenagel condensation between benzaldehyde and methylene compounds [Z = $COCH_3$ (**2**), CO_2Et (**3**)] in the presence of the RTILs, for high pK_a demanding reactions.

to that of Scheme 5, that is, [Chol][OH] catalytic activity in this reaction would be limited by its capacity to abstract a proton from the methylene group of the malonic ester. Finally, although the different experimental conditions limit a direct comparison, the [Chol][Aminoacetate] RTILs render better efficiencies than those previously reported when using amino acids as promoters for

Knoevenagel reactions in different media, including ILs.[24,26,27] This might be explained on the basis of the stabilization of different reaction intermediates by the cholinium counterion (Schemes 4 and 5).

New RTILs were synthesized from bio-renewable, economic, and easily available feedstocks. Their synthesis was carried out by a green route in which the only by-product was water. All of the synthesized RTILs were successfully tested as catalysts for the Knoevenagel condensation between benzaldehyde and three different active methylene compounds affording good conversions and high selectivities, running at room temperature. This might avoid the use of low biodegradable imidazolium or imidazolium-derivate compounds suggested so far as catalysts for this reaction. The aminoacetate part of the RTILs was identified as the promoter of the condensation reactions through two different mechanisms, depending on the pK_a demand of the malonic ester.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.060.

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