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Functional ionic liquid from biorenewable materials: synthesis and application as a catalyst in direct aldol reactions

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Abstract—A new room temperature ionic liquid (IL) (2-hydroxyethyl)-trimethyl-ammonium (*S*)-2-pyrrolidinecarboxylic acid salt ([Choline][Pro]) has been synthesized from biorenewable and nontoxic raw materials (choline chloride and L(−)-proline) in a simple and relative green route. The IL has been demonstrated to be the efficient catalyst of the direct aldol reactions between ketones and aromatic aldehydes in water at room temperature. The aldol products can be obtained with good yields and the IL in aqueous phase can be separated easily and reused.

1. Introduction

Green chemistry that possesses the spirit of sustainable development was booming in the 1990s,[1] and has attracted more and more interest in the 21st century. Large amounts of organic solvents are used in chemical processes, many of which are volatile, flammable, and toxic. The use of non-hazardous and renewable materials is one of the most important goals of green chemistry.[2] Room temperature ionic liquids (ILs), which are organic salts with a melting point lower than 100 °C, have attracted much attention in recent years.[3] ILs have some unusual properties, such as negligible vapor pressure, nonflammability, high thermal stability, wide liquid temperature range, and strong solvent power for both organic and inorganic substances. In addition, the structure of ILs can be designed and modified to achieve desired properties. Recently, some functional (or task-specific) ILs have been synthesized and applied in different fields.[4] For example, ILs with acidic groups have been used in Fischer esterification, alcohol dehydrodimerization, pinacol rearrangement,[5] and Mannich reactions.[6] The ILs with basic groups have been utilized in Markovnikov addition,[7] Michael addition,[8] absorption of CO_2, and SO_2.[9,10] Employment of the ILs with metal ion-ligating groups in extraction of metal ion and organometal catalysis has been studied.[11,4a] Utilization of the ILs with organocatalyst fragments in small organic molecular catalysis has also been investigated.[12]

With the increasing concerns about the environmental protection, synthesis of ILs from renewable raw materials through a green chemistry procedure is desirable. Some ILs have been synthesized using renewable materials.[13] Many kinds of natural products have the potential to be converted into ILs through relative green methods such as simple ion exchange and acid–base reactions directly.[14] Among the biorenewable materials, choline chloride and proline are very attractive in the synthesis of ILs. Choline based-ILs (including eutectic liquids) have been used not only as solvents or catalysts in organic synthesis,[15] but also as solvents and templates in preparation of novel polymorphous materials.[15a,16] As a commonly used organocatalyst, the catalytic performance of proline in ILs has been studied for different reactions.[17] ILs functionalized by proline have been synthesized and applied to catalyze organic reactions. For example, the nitrogen atom of proline was transformed into several kinds of ammoniums that acted as cations of ILs;[14b,c] The carboxyl group of proline was converted into anions of ILs;[14a,d] The proline moiety was covalently linked with the imidazolium cation of ILs, and these ILs were used as organocatalysts in Michael additions[12a] and aldol reactions.[18]

Keywords: Ionic liquid; Green chemistry; Choline; Proline; Aldol reaction.
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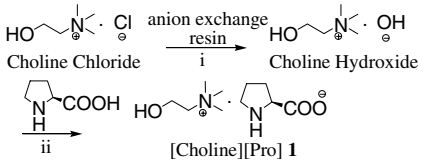
In this Letter, we report a new IL (2-hydroxyethyl)-trimethyl-ammonium (*S*)-2-pyrrolidinecarboxylic acid salt ([Choline][Pro]) **1** that is composed of choline cations and proline anions, which can be synthesized simply by ion exchange and neutralization. The feature of this IL is that both cation and anion are from renewable materials. Our further study has demonstrated that the IL **1** is a very efficient catalyst for direct aldol reactions, and can be reused easily in aqueous solution.

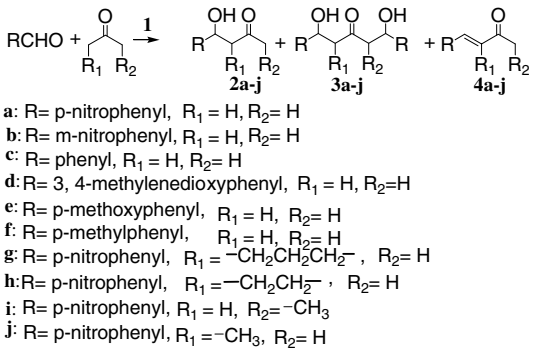
2. Results and discussion

The route to prepare the new IL (2-hydroxyethyl)-trimethyl-ammonium (*S*)-2-pyrrolidinecarboxylic acid salt ([Choline][Pro]) **1** is shown in Scheme 1, which is similar to that used to synthesize imidazolium-based IL with amino acids.[14a] Choline chloride was first converted to choline hydroxide aqueous solution through the column of 717 anion-exchange resin. The aqueous solution was neutralized with L(−)-proline to obtain the IL [Choline][Pro] **1** that is a light-yellow oil at room temperature.[19] The total yield of **1** is 95.0% and the density is 1.13 g/cm^3 at 25.0 °C. The thermal stability of **1** was studied using thermogravimetric analysis (TGA, NETZSCH STA 409 PC/PG) in N_2 at a heating rate of 10 °C /min, which shows that the decomposition temperature (T_{dec}) of **1** is 159.7 °C.

The aldol reaction as a useful C–C bond-forming reaction catalyzed by organocatalysts had been studied extensively.[20] We first applied [Choline][Pro] **1** to catalyze the direct aldol reaction of acetone with *p*-nitrobenzaldehyde, and the results are shown in Table 1. When **1** was used as the catalyst in solvent-free conditions at room temperature, the reaction was completed in a very short time (Table 1, entries 1–3). Especially,

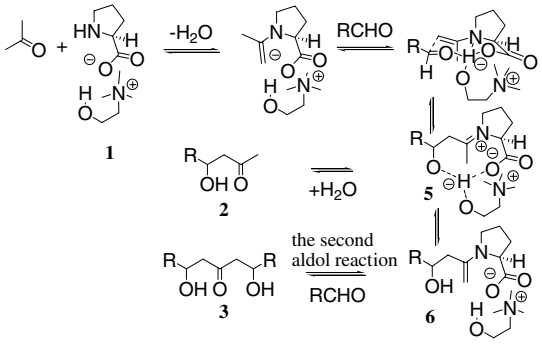


Scheme 1. Schematic illustration of the synthesis of IL [Choline][Pro] **1**. Reagents and conditions: (i) 717 anion-exchange resin, water as eluent, rt; (ii) L(−)-proline (1.05 equiv), rt, 48 h (95% yield of two steps).



Scheme 2. The aldol reactions catalyzed by [Choline][Pro] **1**.

when 30 mol % of **1** was used, the reaction could be finished in 1 min. The aldol products were the normal product **2a** and the second aldol product **3a** (Scheme 2), and there was no dehydrated product **4a** detected by isolation or direct ^{1}H NMR spectroscopy of the crude products. When the amount of **1** was reduced from 30 mol % to 5 mol %, the total yield of the aldol products **2a** and **3a** decreased from 84.4% to 75.6% and the reaction took 3 h to complete (Table 1, entries 2 and 3). In the solvent-free condition the ratio of **2a** and **3a** was about 1:1. The proposed mechanism of forming **3a** is shown in Scheme 3, which is similar to the one described by Peng and Jiang.[21] Intermediate **5** could be converted in two ways: one would form product **2** and another would form intermediate **6** that could undergo the second aldol condensation to provide product **3**.



Scheme 3. The proposed mechanism of the aldol reaction catalyzed by [Choline][Pro] **1** in solvent-free condition.

Table 1. Direct aldol reaction of 4-nitrobenzaldehyde and acetone at room temperature

Entry	IL (mmol)	4-Nitrobenzaldehyde (mmol)	Acetone (mmol)	Water (mL)	Time (min)	Yield[a] (%)		
						2a	**3a**	**2a + 3a**
1	0.3	1	2	—	10	53.3	29.0	82.3
2	0.3	1	10	—	1	40.8	43.6	84.4
3	0.05	1	10	—	180	36.4	29.2	75.6
4	0.3	1	10	1	5	90.2	7.6	97.8
5	0.1	1	10	1	10	89.7	9.9	99.6
6	0.05	1	10	1	15	90.2	9.2	99.4
7	0.05	1	5	1	20	82.2	13.5	95.7

[a] Isolated yield.

In order to improve the yield and selectivity of **2a**, the reaction was conducted in water.[22] One of the reasons was that water was required in the step from intermediate **5** to product **2**. The concentration of water, which was just produced by the reaction between acetone and **1** in solvent-free conditions (Scheme 3) was much lower than the concentration of water, which was used as the solvent. Therefore, the rate of converting **5** to **2** should be increased in water. As expected, the yield of **2a** was increased to 90.2%, and the total yield of **2a** and **3a** reached 99.6% when water was used as solvent (Table 1, entries 4 and 5). The reaction was still fast, although it was slower than that under the solvent-free condition. Decreasing the amount of **1** from 30 mol % to 5 mol % slowed down the reaction rate considerably (Table 1, entries 4–6), and the reaction could be finished with similar yields within 15 min instead of 5 min, which indicated that the IL **1** was very efficient for the reaction. Moreover, increasing the equivalents of acetone (Table 1, entries 6 and 7) improved the reaction rate and chemoselectivity.

In addition, the phase states at different reaction stages were observed carefully and the pictures are shown in Figure 1. There were two phases, the oily product phase and aqueous phase, in the system after the reaction was completed. Therefore, using water as the solvent made the separation easier. More importantly, IL can be recycled more easily because IL existed in the aqueous phase. In this work we tested the reusability of the aqueous phase that contained the IL. The aqueous solution was used directly for the next run after separation and extraction of the products, and the results are listed in Table 2. There was no obvious decrease in yields after the aqueous phase was recycled three times.

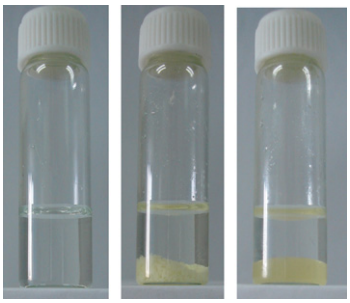


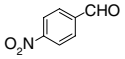
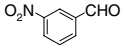
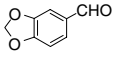
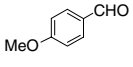
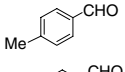
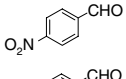
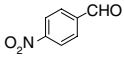
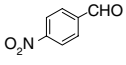
Figure 1. The photographs of the model reaction in water (Table 1, entry 4) at different stages. From left to right: aqueous solution of [Choline][Pro] and acetone; the powder of 4-nitrobenzaldehyde added into the aqueous solution; the oil phase of products appeared under the aqueous phase after the reaction.

Table 2. The recycling of [Choline][Pro] aqueous solution in direct aldol reaction of 4-nitrobenzaldehyde with acetone

Runs	Time (min)	Yield (%)		
		2a	**3a**	**2a + 3a**
1[a,b]	5	90.2	7.6	97.8
2[c]	5	90.2	5.3	95.5
3[c]	5	91.9	4.8	96.7
4[c]	6	89.4	7.3	96.7

[a] The condition of the first run was the same as that for entry 4 in Table 1.
[b] Isolated yield.
[c] Determined by ^{1}H NMR without isolation.

Table 3. Direct aldol reactions of aromatic aldehydes and ketones

Entry	Ketone	Aldehyde	Products	Time	Yield[a] (%)			
					2 (*anti*:*syn*)	**3**	**4**	**2 + 3 + 4**
1			**2a**, **3a**	15 min	90.2	9.2	—	99.4
2			**2b**, **3b**	10 min	88.9	11.0	—	99.9
3			**2c**, **4c**	12 h	80.4	—	8.0	88.4
4			**2d**, **4d**	5.5 h	55.1	—	10.5	65.6[b]
5			**2e**, **4e**	24 h	36.0	—	26.5	62.5[c]
6			**2f**, **4f**	21 h	70.0	—	23.4	93.4
7			**2g**	4 h	97.9(2:1)	—	—	97.9
8			**2h**	1.5 h	97.8(1:2)	—	—	97.8
9			**2i**/**2j**	0.5 h	60.4/38.6[e]	—	—	99.0

The reaction conditions: [Choine][Pro] **1** (0.05 mmol), ketone (10 mmol), aldehyde (1 mmol), water (1 mL), and room temperature.
[a] Entries 1–5 are isolated yields, entries 5–9 are determined by ^{1}H NMR spectroscopy without isolation.
[b] 30.6% piperonaldehhyde was recycled.
[c] 37.3% *p*-methoxybenzaldehyde was recycled.
[d] 2 mmol cyclopentanone was used.
[e] The yield of **2i** is 60.4%, the yield of **2j** is 38.6%.

It was expected that chiral IL **1** should introduce optical activities into the products. Unfortunately, the enantiomeric excess values were less than 10% in both aqueous and solvent-free cases.

Direct aldol reactions of different aromatic aldehydes and ketones catalyzed by **1** in water were also studied, and the results are summarized in Table 3. The results indicated that not only reactive aromatic aldehydes bearing electron-withdrawing groups but also benzaldehyde, *p*-methylbenzaldehyde, piperonaldehyde, and *p*-methoxybenzaldehyde could reach good to moderate yields. For the reactions with reactive aromatic aldehydes, almost 100% conversion of the aromatic aldehydes was achieved in 10–240 min and the dehydrated products were not detected by isolation or ^{1}H NMR spectroscopy of the crude products (Table 3, entries 1, 2, 7, 8, and 9). When the direct aldol reaction was conducted with less reactive aromatic aldehydes, there were no second aldol products, but dehydrated products **4** were obtained (Table 3, entries 3–6). For the reactions of benzaldehyde and *p*-methylbenzaldehyde, the total yields were good and the reaction rates were relatively fast (Table 3, entries 3 and 4). In addition, when cyclohexanone, cyclopentanone, and butanone were reacted with *p*-nitrobenzaldehyde, only products **2** were formed (Table 3, entries 7–9).

3. Conclusions

A new functional IL [Choline][Pro] **1** has been synthesized from choline chloride and L(−)-proline, which is a successful example of preparing IL completely from biorenewable nontoxic raw materials through a simple and green route. The IL can be used to catalyze direct aldol reactions between a variety of ketones and aromatic aldehydes efficiently in water. The aldol reactions catalyzed by this IL can be finished in a very short time with good yields, and there is no dehydrated product produced in most cases. The reaction mixtures separate into an aqueous phase and an organic phase after reaction. After simple separation and extraction, the IL-containing aqueous phase can be reused without any obvious decrease in activity. We expect that this green IL would have the potential for other applications.

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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.2007.06.051.

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19. *Procedures to prepare ionic liquid (2-hydroxyethyl)-trimethyl-ammonium (S)-2-pyrrolidinecarboxylic acid salt [Choline][Pro]* (**1**): Choline chloride (5.02 g, 36.0 mmol) was converted into choline hydroxide aqueous solution though the column of 717 anion-exchange resin. In this step, the eluate was collected until its pH value was 9, using water as the eluent. Then L(−)-proline (4.35 g, 37.8 mmol) was added into the above aqueous solution. The mixture was stirred at room temperature for 48 h, and then water was removed under vacuum at 50 °C to obtain a light-yellow oil. Acetonitrile (10 mL) and methanol (10 mL) were added into the oil to precipitate the excess proline. The mixture was filtered to remove the excess proline. The filtrate was evaporated to remove the solvent to give a light-yellow liquid. The obtained product was dried under vacuum for 2 days at 60 °C. The total yield was 95.0%. ^{1}H NMR (300 MHz, D_2O) δ (ppm): 1.64–1.69 (m, 3H), 2.01–2.05 (m, 1H), 2.67–2.75 (m, 1H), 2.94–3.00 (m, 1H), 3.10 (s, 9H), 3.40–3.47 (m, 3H), 3.95 (d, $J = 3.5$Hz, 2H); ^{13}C NMR (75 MHz, D_2O) δ (ppm): 25.0, 30.6, 45.9, 53.8, 55.5, 61.5, 67.4, 181.6; $[\alpha]_D^{20}$ −35.2 (*c* 2.0, H_2O).
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22. *General procedures of conducting direct aldol reactions*: The desired amounts of IL [Choline][Pro] and ketone (10 mmol) were dissolved in water (1 mL), and aromatic aldehyde (1 mmol) was added into the aqueous solution. The reaction mixture was stirred at room temperature until that the TLC showed that the aldehyde disappeared completely. An oil phase appeared under the aqueous layer. The oil phase was separated directly from the aqueous phase. Then the aqueous phase was extracted with ethyl acetate (2 × 2 mL). The extract was combined with the oil phase, and dried with anhydrous magnesium sulfate. The crude product was obtained after removing the solvent under vacuum. The product was identified by ^{1}H NMR.