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ARTICLE

2-Pyrrolidinecarboxylic Acid Ionic Liquid Catalyzed Knoevenagel Condensation

SONG Hongbing, YU Yinghao, CHEN Xuewei, LI Xuehui*, XI Hongxia

School of Chemistry and Chemical Engineering, Pulp and Paper Engineering State Key Laboratory of China, South China University of Technology, Guangzhou 510640, Guangdong, China

Abstract: The pyrrolidinecarboxylic functionalized ionic liquid, 1-butyl-3-methylimidazolium-(S)-2-pyrrolidinecarboxylic acid salt ([bmim][Pro]), was prepared using an improved procedure. α,β-Unsaturated carbonyl compounds were selectively synthesized and high yields (88%─97%) were obtained at room temperature in aqueous media when [bmim][Pro] was used as the catalyst for the Knoevenagel reaction between a methylene compound and an aldehyde or ketone. [bmim][Pro] was reused six times without loss of catalytic activity. The catalytic mechanism is briefly discussed.

Key words: proline; ionic liquid; catalysis; Knoevenagel condensation

The Knoevenagel condensation reaction is one of the most important reactions in organic synthesis for carbon-carbon bond formation [1]. In recent years, there has been growing interest in it for the synthesis of important intermediates or products for perfumes, pharmaceuticals, calcium antagonists, and polymers [2–4]. This reaction is catalyzed by bases [5,6], acids [7], and catalysts containing acidic or basic sites [8]. Basic microporous titanosilicate ETS-10 [9], modified polyacrylamide containing amino functional groups [10], and rare earth exchanged NaY zeolite [11] have been employed in solution and under solvent-free conditions with variable yields. However, the use of hazardous and carcinogenic solvents and difficulty in catalyst recovery are incompatible with green chemistry. Therefore, an environmental benign process for this reaction is desired.

Ionic liquids (ILs), especially for those derived from natural products [12], are catalysts and potential alternatives to volatile and hazardous organic solvents for a variety of important reactions [13,14]. Amino acids are good candidates for the development of novel functional ILs due to the varied structures and functionalities of their groups [15,16]. Chiral ILs derived from natural amino acids or amino acid esters have been used as catalysts in the asymmetric Michael addition reaction [17], Diels-Alder reaction [18], and Aldol reaction [19]. Proline is a common amino acid without a hydrogen on the amide group. It cannot act as a hydrogen bond donor, but is a hydrogen bond acceptor. Therefore, proline and its derivatives are often used as asymmetric catalysts in organic reactions. For example, chiral pyrrolidines derived from L-proline and its derivates were successfully used as highly enantioselective organocatalysts [20–22]. In this work, a new route for the synthesis of 1-butyl-3-methylimidazolium-(*S*)-2-pyrrolidinecarboxylic acid ionic liquid ([bmim][Pro]) was developed and its catalytic properties for the Knoevenagel condensation reaction of a methylene compound with aldehyde in water were investigated. It gave high yields (88%–97%) and selectivity (100%), and was recyclable.

1 Experimental

1.1 Reagents

N-methylimidazole and *n*-butyl chloride (purity ＞99%) were purchased from Acros Organics. L-proline and other reagents (AR grade) were purchased from Guangdong Guanghua Chemical Factory Co., Ltd. All reagents were used

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*Corresponding author. Tel/Fax: +86-20-87114707; E-mail: cexhli@scut.edu.cn
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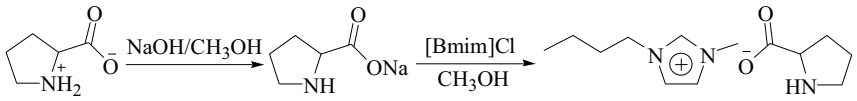


Scheme 1. Synthesis of [bmim][Pro] ionic liquid.

as received without further purification.

1.2 Preparation and characterization of [bmim][Pro]

[bmim]Cl was synthesized by a reported procedure [23]. [bmim][Pro] was prepared in two steps (Scheme 1). First, the neutralization reaction between L-proline (50 mmol, 5.76 g) and sodium hydroxide (50 mmol, 2.00 g) was carried out in 10 ml methanol under mild stirring at 25 °C for 4 h, after which the water and methanol were evaporated to get the L-proline sodium salt (Na[Pro]). Second, anion exchange between [bmim]Cl (50 mmol, 8.74 g) and Na[Pro] (50 mmol, 6.85 g) was carried out in methanol at 25 °C for 4 h, after which the precipitate (NaCl) was removed by filtration and the resulting solution was evaporated to give the colorless and transparent oily liquid [bmim][Pro] (11.53 g, 91%).

The structure of the [bmim][Pro] ionic liquid was characterized by IR, ^{1}H NMR and ^{13}C NMR as follows. ^{1}H NMR (400 MHz, DMSO) δ 0.85 (t, J = 7.2 Hz, 3H), 1.21 (q, 2H), 1.37 (m, 1H), 1.45 (m, 1H), 1.57 (m, 1H), 1.72 (m, 3H), 2.87 (m, 1H), 3.01 (s, 1H), 3.12 (s, 1H), 3.60 (s, 1H), 3.83 (s, 3H), 4.14 (t, J = 7.2 Hz, 2H), 7.71 (s, 1H), 7.79 (s, 1H), 9.54 (s, 1H). ^{13}C NMR (400 MHz, DMSO) δ 13.7, 19.2, 26.5, 31.6, 31.9, 36.1, 47.5, 48.9, 63.1, 122.7, 124.0, 137.6, 177.0. IR (KBr): 3406, 2962, 2220, 1579, 1390, 1169, 623 cm^{-1}.

1.3 Procedure for Knoevenagel condensation

In a typical experiment, benzaldehyde (10 mmol, 1.06 g) and malononitrile (10 mmol, 0.66 g) were simultaneously transferred into a 25 ml round-bottomed flask equipped with a magnetic stirrer, and then the ionic liquid catalyst [bmim][Pro] (10 mol% of benzaldehyde, 0.253 g) and water (10 ml) were added. The reaction mixture was stirred at room temperature for 20 min, and then the solid product was filtrated and washed with water (10 ml × 3). After drying, 1.47 g 2-benzylidene malononitrile was obtained with 95% of yield. This was also characterized by ^{1}H NMR, ^{13}C NMR, and IR. The reaction is highly stereo-selective and gave only the *E*-isomer.

2 Results and discussion

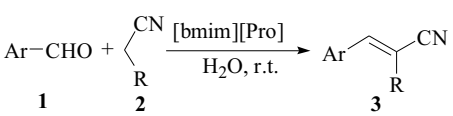
2.1 The advantages of the new synthesis route of [bmim][Pro] ionic liquid

The synthesis of [bmim][Pro] has been described previously [24]. In that procedure, onium hydroxide was first prepared and then neutralized by the natural amino acid L-proline. However, the preparation of onium hydroxide is time consuming and it is difficult to purify onium hydroxide because of the strong hydrogen bonds between water and onium hydroxide, which is also sensitive to the CO_2 in air [25]. Thus, we developed here a simple and efficient method for the preparation of the required task-specific ionic liquid from L-proline. In our procedure, the neutralization of L-proline with sodium hydroxide takes place quickly and the subsequent anion exchange avoids the use of the unstable CO_2-sensitive hydroxide intermediate. The advantages of this approach include high yield, good controllability, short reaction time, and simple operation.

2.2 Knoevenagel condensation catalyzed by [bmim][Pro]

The [bmim][Pro] ionic liquid was then tested as the catalyst for the Knoevenagel condensation reaction of aromatic aldehydes with malononitrile or ethyl cyanoacetate under different reaction conditions (Scheme 2). Excellent product yields were obtained in a short time using water at room temperature as the medium. The results are summarized in Table 1.

The reaction between benzaldehyde and malononitrile in aqueous medium gave the product 3a with 95% yield in 20 min, and benzaldehyde reacted with ethyl cyanoacetate to give the product 3b with 88% yield in 40 min (Table 1). 3c (97%) and 3d (93%) were obtained in 20 min when furfuraldehyde was reacted with malononitrile and ethyl cyanoacetate, respectively. The condensation product (3e) was obtained with moderate yield (90%) in 20 min. Moreover, it was clear that the reactions between furfuraldehyde and malononitrile/ethyl



Scheme 2. Knoevenagel condensation catalyzed by [bmim][Pro].

Table 1 Yields from Knoevenagel condensation with different substrates

Product	Aldehyde	R	Time (min)	Yield[a] (%)
3a	benzaldehyde	CN	20	95
3b	benzaldehyde	COOEt	40	88
3c	furfural	CN	20	97
3d	furfural	COOEt	20	93
3e	4-hydroxybenzaldehyde	COOEt	20	90

Reaction conditions: 10 mmol reactants, 1 mmol [bmim][Pro], 10 ml H_2O, 25 °C.

[a]Refer to the pure isolated products characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopic data.

cyanoacetate achieved much higher yield than those of the reactions between benzaldehyde and malononitrile/ethyl cyanoacetate. In addition, malononitrile was more reactive than ethyl cyanoacetate with the same aromatic aldehyde because the electron withdrawing ability of the substituent CN group is stronger than that of the carbonyl group, that is, the methylene group of malononitrile was more reactive than that of ethyl cyanoacetate and reacted more readily with aromatic aldehydes, which is consistent with a precious report [26].

The isolated products were also characterized by ^{1}H NMR, ^{13}C NMR, and IR as follows.

3a (Table 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 4.39 (q, 2H), 7.51 (t, J = 7.2 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.99 (d, J = 7.6 Hz, 2H), 8.26 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.19, 62.73, 103.03, 129.26, 131.05, 133.28, 155.00, 162.48. IR (KBr): 2980, 2220, 1730, 1600, 1440, 1300, 1260, 1200, 1090, 1010, 768, 683, 582, 482 cm^{-1}.

3b (Table 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, J = 8.0 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.91 (d, J = 7.6 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.20, 62.68, 102.96, 129.21, 131.00, 133.28, 155.13, 163.25. IR (KBr): 3032, 2222, 1591, 1448, 1215, 957, 756, 677, 617, 517 cm^{-1}.

3c (Table 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 4.35(q, 2H), 6.66(q, 1H), 7.39 (d, J = 4.0 Hz, 1H), 7.75(d, J = 1.6 Hz, 1H), 8.01 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.14, 62.89, 98.82, 113.84, 115.31, 121.71, 139.46, 148.52, 149.04, 162.57. IR (KBr): 3420, 3130, 3040, 2990, 2220, 1920, 1720, 1620, 1540, 1460, 1370, 1260, 1020, 760, 588 cm^{-1}.

3d (Table 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (q, 1H), 7.37 (d, J = 3.6 Hz, 1H), 7.51 (s, 1H), 7.80 (d, J = 1.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 30.85, 112.50, 113.69, 114.36, 123.20, 142.98, 148.09, 149.41. IR (KBr): 3043, 2226, 1606, 1455, 1294, 1149, 1020, 937, 766, 582 cm^{-1}.

3e (Table 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 4.35 (q, 2H), 6.95 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 8.8 Hz, 2H), 8.16 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.09, 62.51, 98.92, 116.37, 123.97, 133.93, 154.77, 161.33, 163.21. IR (KBr): 3325, 3024, 2226, 1714, 1587, 1443, 1284, 1205, 1171, 843, 515 cm^{-1}.

Table 2 Effect of recycling on the reaction

Recycle time	Isolated yield[a] (%)
1	95
2	94
3	92
4	89
5	87
6	84

Reaction conditions: 10 mmol furfural, 10 mmol ethyl cyanoacetate, 1 mmol [bmim][Pro], 10 ml H_2O, 25 °C, 20 min.
[a]Refer to isolated pure product **3a**, unless stated otherwise.

2.3 Recycle of [bmim][Pro]

It is well known that a notable advantage of an IL as a catalyst is its recyclability. After product filtration and water evaporation, the catalyst was reused for the reaction. [bmim][Pro] IL was successfully recycled six times without a decrease in activity. All the reactions were completed in 20 min and yields of 84%–95% were obtained (Table 2).

2.4 Mechanism of Knoevenagel condensation catalyzed by [bmim][Pro]

An IL derived from natural L-proline can behave as an anion and it has been proposed that the L-proline functional group acts as a "microaldolase" that facilitates the reaction steps including the formation of the imine intermediate and the carbon-carbon bond [27]. Hence, a mechanism (Fig. 1) can be proposed where the L-proline anion acts as an organocatalyst with the acceptor role of the corresponding iminium interme-

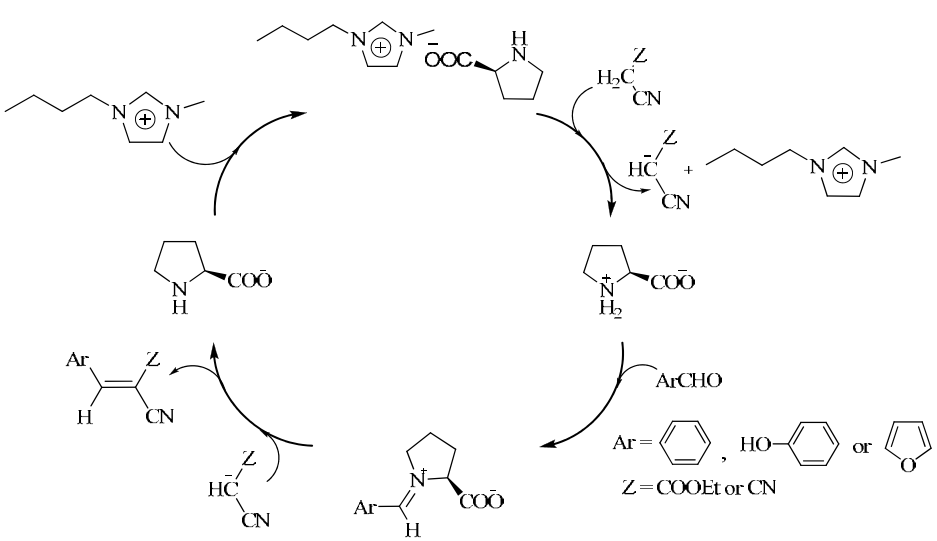


Fig. 1. Mechanism for Knoevenagel condensation catalyzed by [bmim][Pro].

diate. When the L-proline anion reacts with a methylene group, an intermediate is formed that can react with the aldehyde, and the resulting aldol undergoes a subsequent base-induced elimination.

3 Conclusions

The synthesis of [bmim][Pro] developed is simple and efficient. [bmim][Pro] is an environmentally friendly catalyst for the Knoevenagel condensation reaction in aqueous solution at room temperature, in which aldehydes were reacted with methylene compounds. It gave 88%–97% isolated product yields under mild conditions. The significant features of this process include high yields, mild reaction conditions, short reaction time, high yields, and ease of product isolation. [bmim][Pro] was recycled six times without loss of activity. A reaction mechanism was proposed.

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