Novel DBU-based hydroxyl ionic liquid for efficient Knoevenagel reaction in water
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1. Introduction
Owing to the unique chemical and physical properties, ionic liquids (ILs) have received much attention for applications as solvent alternatives (1, 2). In general, pyridinium and imidazolium ionic liquids bearing simple alkyl appendages were widely used (3). Changes in IL physical properties such as viscosity, hydrophobicity and polarity have been accomplished by altering the length of the alkyl groups on the rings (4, 5). More recently, some other heterocyclic molecules with functional side chains were used in the preparation of ionic liquids, and many functional ILs were synthesized and utilized as catalysts for different reactions (6), the study of structure–property relationship of functional ionic liquid and their basic properties have aroused renewed interest (7, 8).

The Knoevenagel reaction is one of the most important reactions in organic synthesis for carbon–carbon bond formation (9, 10), both the acid catalyst and the base catalyst can catalyze this reaction (11–15). Under the action of acid catalyst or base catalyst, the protonation of carbonyl oxygen or dehydrogenation of activated methylene played an important role, improvements in these areas will facilitate the reaction. In our early work, the protic ionic liquid HMTA–AcOH has been developed and used in the Knoevenagel condensation reactions (16). For the good catalytic effect, we proposed an acid–base catalytic mechanism, the HMTA–AcOH both capture the active methylene proton and provide proton to the carbonyl group, thus facilitating the reaction. Soon afterwards, the [Et3NH][HSO4] (17), [Dabco–H][AcO] (18), [DBU–H][AcO] (19), [DBU][Lac] (20) and pyrrolidinium base protic ionic liquids (21) were used one after another in the Knoevenagel condensation reaction. These results further confirm the high efficiency of the Knoevenagel reaction comes from the convenience of proton transfer. In an early report, Cheng disclosed hydroxyl ionic liquid (HIL) as novel support for the Baylis–Hillman catalyst (22), the HIL-bound quinuclidine showed better catalytic activity than its non-hydroxyl ionic liquid analogs. This beneficial effect of HIL was ascribed to the presence of hydroxyl group in the side chain of the quinuclidine, which can accelerate the transfer of proton via activation of hydrogen bonds. Based on the catalytic effect of hydrogen bond on the Morita-Baylis–Hillman reaction and the stabilizing effect of ionic liquid on the reaction intermediate, we speculate that the hydrogen bond between the carbonyl group and the solvent or catalyst may accelerate Knoevenagel reaction, and the hydroxyl ionic liquid may exert...
good facilitation to the Knoevenagel reaction. To meet our research interesting and improve the Knoevenagel reaction, \( N \)-(2-Hydroxy-ethyl)-pyridinium chloride \([\text{HyEtPy}]\text{Cl}\) was synthesized and applied in the Knoevenagel condensation reaction \((23)\). Although some good catalytic effects have been achieved, it is necessary to further explore the application of other hydroxyl ionic liquids in the Knoevenagel reaction. In continue our research interests, three ionic salts based on DBU (Scheme 1) were synthesized and applied in the Knoevenagel reaction. From Table 1, the ionic salt \( 1\)-(2-hydroxy-ethyl)-DBU bromide \([\text{HyEtDBU}]\text{Br}\) showed higher catalytic activity than its non-hydroxyl counterparts \([\text{EtDBU}]\text{Br}\) and \([\text{BuDBU}]\text{Br}\), and excellent yield 99% of the object product was achieved after only one minute. Herein, we would like to reveal the structure–property relationship of functional ionic liquid and present the catalytic application of the hydroxyl ionic liquid \([\text{HyEtDBU}]\text{Br}\) in the Knoevenagel reaction.

2. Materials and methods

2.1. Materials and products

All chemicals were purchased from commercial suppliers and were used without further purification. For the NMR spectra of all products, see Supporting Information.

2.2. Methods

\(^1\)H and \(^13\)C NMR were recorded on a Bruker Avance DPX 400 spectrometer at 400 and 100 MHz in DMSO-\(d_6\) or CDCl\(_3\), respectively. Chemical shifts were reported in parts per million (\(\delta\)), relative to the internal standard of tetramethylsilane (TMS). Melting points were determined using WRS-1B digital melting point meter and were not corrected.

2.3. Preparation and characterization of the ionic salts

2.3.1. \( 1\)-(2-Hydroxyethyl)-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepinium bromide

To a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (15.2 g, 0.1 mol) in ethyl acetate (15 mL) was added 2-bromoethanol (7 mL, 0.1 mol), and the mixture was refluxed for 2 h, the crude product \([\text{HyEtDBU}]\text{Br}\) was formed. Then the crude product was purified by the recrystallization with 15 mL ethyl acetate, and the residual solvent was removed in vacuum to give the product \([\text{HyEtDBU}]\text{Br}\) (27 g, 97%) as a white crystal. m. p. 115.6°C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 6.82 (s, 1H), 3.59–3.49 (m, 6H), 3.22 (d, \(J = 5.6\) Hz, 2H), 2.78 (d, \(J = 9.6\) Hz, 2H), 1.88 (t, \(J =\) 5.6 Hz, 2H), 1.61 (d, \(J = 17.1\) Hz, 8H); \(^13\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 165.74, 63.15, 54.47, 53.83, 48.40, 37.87, 31.79, 28.59, 26.41, 23.83, 19.41.

2.3.2. \( 1\)-Ethyl-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepinium bromide

The synthesis of \([\text{EtDBU}]\text{Br}\) followed similar procedure as that of \([\text{HyEtDBU}]\text{Br}\). With 24.9 g of \([\text{EtDBU}]\text{Br}\) (95%) was obtained as a white crystal solid. m. p. 109.8°C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 3.71 (dd, \(J = 29.6, 7.6\) Hz, 2H), 3.63–3.44 (m, 6H), 2.92 (d, \(J = 8.8\) Hz, 2H), 1.97–1.85 (m, 2H), 1.61 (d, \(J = 7.4\) Hz, 6H), 1.09 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 165.74, 63.15, 54.47, 53.83, 48.40, 37.87, 31.79, 28.59, 26.41, 23.83, 19.41.

2.3.3. \( 1\)-Butyl-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepinium bromide

The synthesis of \([\text{BuDBU}]\text{Br}\) followed similar procedure as that of \([\text{HyEtDBU}]\text{Br}\). With 27.2 g of \([\text{BuDBU}]\text{Br}\) (94%) was
obtained as a pale yellow solid. m. p. 85.2°C; 1H NMR (400 MHz, DMSO-d6) δ 3.67 (d, J = 7.7 Hz, 2H), 3.51 (dd, J = 15.0, 7.7 Hz, 6H), 2.92 (d, J = 8.5 Hz, 2H), 1.93 (t, J = 6.5 Hz, 2H), 1.62 (d, J = 7.8 Hz, 6H), 1.48 (dt, J = 15.0, 7.7 Hz, 2H), 1.34–1.21 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); 13C NMR (101 MHz, DMSO-d6) δ 166.29, 54.38, 53.36, 48.96, 47.02, 30.80, 28.07, 27.69, 25.91, 23.26, 20.11, 19.50, 14.17.

2.4. General procedure for Knoevenagel condensation reaction

To a stirred mixture of 10 mmol aldehyde and 12 mmol ethyl cyanoacetate in 4.0 g [HyEtDBU]Br-H2O (1 ml H2O and 3 g [HyEtDBU]Br) at room temperature was added 10 mmol DABCO. The formation of the product was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was diluted with saturated brine (30 mL) and the product solidified from the reaction mixture. The crude product was purified by recrystallization from ethanol and no column purification was followed. After that, the product was further characterized by 1H NMR and 13C NMR, the NMR spectra of all products are given in the Supporting Information (SI).

3. Results and discussion

In general, halogenated ionic salts are easy to prepare by one step reaction of halogenated hydrocarbon with substituted pyridine or imidazole, but are rarely used as solvents for organic reactions because they are mostly solid at room temperature (24, 25). Recently, based on the development of green chemistry, water was used to prompt the organic reactions and some excellent results were obtained (26, 27). To our knowledge, halogenated ionic liquids have a good solubility in water, and it is easy to get a homogeneous system by mixing them with water. Based on this point, the halogenated ionic salt [HyEtDBU]Br containing hydroxyl group was prepared by one step reaction of DBU with 2-bromothanol. When mixed it with water and used the water-ionic liquid composite system in the Knoevenagel reaction of 4-chloro-benzaldehyde with ethyl cyanoacetate, to our surprise, after only one minute, the target product was achieved at 99% yield, and the reaction process is very simple and the pure products are obtained by filtration and recrystallization only. In order to explore better reaction conditions, the effects of other bases, hydroxy-free ionic liquids and the amount of water were further investigated, and the experimental results are summarized in Table 1. As therein revealed, in the presence of three different solid bases, DABCO, HMTA and K2CO3, the organic base showed better effect, and the high yield 99% and the short reaction time one minute were obtained when the base DABCO was used (Table 1, entry 1). Interestingly, in the absence of base, the [HyEtDBU]Br prompted Knoevenagel reaction of 4-chloro-benzaldehyde with ethyl cyanoacetate works very well, and the 93% yield was achieved after 26 min (Table 1, entry 3). The reasons for this may be attributed to two factors: (i) the activation of the hydrogen bond to the carbonyl group facilitates the attack of the nucleophile; and (ii) nitrogen atom in ionic liquid [HyEtDBU]Br showed a certain weak alkalinity, which promoted the conversion of ethyl cyanoacetate to carbanion. To reveal the structural-effect relationship of the ionic salts, Two other ionic salts with similar structures ([EtDBU]Br and [BuDBU]Br) were synthesized and used in the same reaction (Table 1, entries 5, 6). Among all three ionic salts based on DBU, the hydroxyl ionic salt [HyEtDBU]Br provided the best result with respect to reaction time and yield of the product (Table 1, entry 1). By comparing the structures of three ionic liquids, we believe that the hydroxyl group in ionic salt [HyEtDBU]Br should play an important role in the process of the catalytic reaction, and the [HyEtDBU]Br may serve as a protic additive to promote the Knoevenagel reaction. Further optimization of reaction conditions revealed that the amount of H2O also affect the reaction, when the amount of water reaches 25% (Table 1, entry 1), the best reaction result (yield 99%, 1 min) is got, with the increase or reduce the amount of water, the reaction time significantly longer and the yield also dropped (Table 1, entries 7–10). Although water is added at 4 or 5 mL, the high reaction yields 91 and 90 were also obtained after 4 h, one milliliter of water is still the best. After careful observation to the reaction phenomena, we noticed that the change in water content will change the polarity of the composite solvent system, thus affecting the solubility of the raw material and further affecting the reaction. When the ratio of water to ionic salt is 1:3, and the amount of water added is 1 mL, the raw material is completely dissolved, and the reaction effect is the best (Table 1, entry 1). When 4 or 5 mL water was added (Table 1, entries 11, 12), the aggregation of raw material with product decreased, and lower aggregation provided slightly better result in terms of reaction yield. In general, the results of Table 1 showed that the [HyEtDBU]Br-H2O composite system (mH2O: mionic salt = 1:3) is most suitable for the Knoevenagel reaction, in the presence of DABCO, the best yield and the shortest reaction time was obtained (Table 1, entry 1).

To further evaluate the scope and limitation of this methodology, we extended our studies to the reaction of ethyl 2-cyanoacetate with a variety of structurally diverse aromatic aldehydes under the optimized
conditions, and the results are shown in Table 2. In short reaction time (1 min–4.5 h), a variety of aromatic aldehydes bearing electron donating or withdrawing groups reacted favorably with ethyl 2-cyanoacetate, and the desired products were given in excellent yields (92–99%). It is notable that the electron-rich 4-hydroxy benzaldehyde, which is usually quite an inert substrate, could provide a fairly good yield (96%, Entry 7). We think the reason may be attribute to the hydrogen bond between the hydroxyl group in the ionic liquid and the hydroxyl group on the aromatic aldehyde, the presence of hydrogen bond weakens the conjugation of hydroxyl group with benzene ring, and facilitates the nucleophilic addition of reactive methylene group to aldehyde. There is a common reaction phenomenon that the reaction yields of aromatic aldehydes bearing electron-withdrawing groups (NO2 and CN) are slightly higher than aldehydes bearing electron-donating (OCH3 and OH) substituents. Interestingly, when ter-ephthalaldehyde was used as substrate, two aldehyde group all reacted with ethyl 2-cyanoacetate, and excellent yield 94% of dual Knoevenagel adduct was obtained (Entry 9). When we try to get the product that only one aldehyde group participated in the reaction by changing the amount of the ethyl 2-cyanoacetate, the results are very poor. To our delight, heteroaryl aldehyde and steric-hindrance aldehydes, also give the corresponding adducts with a fairly good yields (Table 2, entries 10–12).

In general, the recyclability of the catalyst is a very important factor. To clarify this issue, the recyclability of the composite system ([HyEtDBU]Br-H2O) was investigated and the Knoevenagel reaction of 4-chlorobenzaldehyde with ethyl cyanoacetate was selected as a model. After completion of the reaction, owing to the product precipitates out directly, the composite system ([HyEtDBU]Br-H2O) could be easily recycled by filtering the product from the mixture. The filtrate containing water, [HyEtDBU]Br and DABCO could be directly reused for the next cycle, and the recovered composite system [HyEtDBU]Br-H2O was used at least eight times almost without reduction of the reaction yields. During the cycle, after the first reaction was completed, we noticed that a small amount of DABCO also precipitated out with the product, which led to a slightly longer

Table 2. Knoevenagel condensation of aldehydes with ethyl cyanoacetate.

| Entry | RCHO       | Product | Time | mp (°C) (lit. mp) | Yield(%) |
|-------|------------|---------|------|------------------|----------|
| 1     |            |         | 0.5 h| 50.8–51.3 (50–52) (28) | 97       |
| 2     |            |         | 1.5 h| 81.8–82.5 (81–82) (29) | 95       |
| 3     |            |         | 1 h  | 97.8–98.1 (94–96) (29) | 98       |
| 4     |            |         | 1 min| 92.8–93.2 (92–94) (30) | 99       |
| 5     |            |         | 0.5 h| 168.7–169.4 (168–169) (31) | 98       |
| 6     |            |         | 3 h  | 170.2–170.8 (168–169) (32) | 99       |
| 7     |            |         | 3 h  | 171.5–171.8 (170–171) (28) | 96       |
| 8     |            |         | 0.5 h| 82.6–82.9 (81–82) (19) | 97       |
| 9c    |            |         | 1.5 h| 199.8–200.3 (199–200) (33) | 94       |
| 10    |            |         | 1 h  | 96.6–97.2 (93–94) (34) | 93       |
| 11    |            |         | 0.5 h| 81.6–82.0 (81.5–82) (35) | 93       |
| 12    |            |         | 4.5 h| 187.8–188.3 (187) (36) | 92       |

*General reaction conditions: [HyEtDBU]Br (3 g), H2O (1 mL), DABCO (10 mmol), aldehyde (10 mmol), ethyl cyanoacetate (12 mmol).
*bRefers to work-up yield.
*cEthyl cyanocetate (22 mmol).
reaction time in the later cycle, but almost no change in the reaction yield. In the following study, we try to change the treatment method of the reaction to further explore the reliability of cyclic reaction. When the reaction was over, we used ethyl acetate to extract the reactants, and the rest of the ionic liquid and water was directly used in the next cycle. When 4-chlorobenzaldehyde, ethyl cyanoacetate and DABCO were added to the recycled composite system ([HyEtDBU]Br-H2O) for repeating the reaction, the result showed that the reaction yield and reaction time were almost the same as the first reaction. The recovered [HyEtDBU]Br-H2O was used at least eight times almost without change of reaction times and yields.

A plausible mechanism for the formation of Knoevenagel adduct in the presence of [HyEtDBU]Br-H2O-DABCO composite system is depicted in Scheme 2. As can be seen from Scheme 2, the hydrogen bonding interactions between the hydroxyl group of the [HyEtDBU]Br and the carbonyl group of the aldehyde may increase the electrophilicity of the carbon atom of the carbonyl group, which make the nucleophilic addition easier. After the addition product is formed, IL-OH further migrate proton through the formation of six-membered ring, in which IL-OH may act as a shuttle to transfer the proton from the C-position to the alkoxide of intermediate. In the final stage of dehydration, protonated DABCO may act as a proton donor and facilitate the elimination of H2O. Based on these reasons, the Knoevenagel adducts are quickly formed. In summary, hydroxyl ionic liquids and the catalyst DABCO play an important role in the Knoevenagel reaction.

4. Conclusion

In summary, three ionic liquids based on DBU were prepared and the structure–property relationship of them was further explored. Due to the hydrogen bond effect and alkalinity, the ionic liquid [HyEtDBU]Br shows excellent catalytic effects on the Knoevenagel condensation and a recyclable protic-ionic-liquid solvent–catalyst system, [HyEtDBU]Br-H2O-DABCO, was developed and used in the Knoevenagel condensation reaction of aromatic aldehydes with ethyl 2-cyanoacetate. At room temperature, the Knoevenagel condensation preceded very well, short reaction time (1 min~4.5 h) and high reaction yields (92%~99%) were obtained. Furthermore, the solvent–catalyst system [HyEtDBU]Br-H2O can be recycled eight times without significant loss of catalytic activity. After completion of the reaction, the desired products can be obtained by simple filtration and recrystallization. This procedure offers some significant advantages including simple operation, excellent yield, short reaction time and recyclability of the solvent-catalyst system, which makes the present protocol practical for the preparation of multifunctional Knoevenagel condensation products.

Disclosure statement

No potential conflict of interest was reported by the authors.

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