Introduction

Multicomponent reactions (MCRs) have received a great deal of attention in organic synthesis and combinatorial chemistry due to their wide supplement of molecular diversity and high atom economic efficiency.1,2 Although MCRs can provide high throughput generation of organic compounds, often in a one-pot strategy, they still suffer from the utilization of excessive reagents and toxic solvents, harsh reaction conditions and long reaction time. Therefore, appropriately selected catalysts or reaction medium for special MCRs plays a critical role towards the development of green processes. Ionic liquids which are composed of organic cations and organic or inorganic anions have been widely used in organic synthesis and catalysis in the past two decades.3–6 The ability to remain a liquid under a wide range of temperatures, negligible vapor pressure and facile functionalization of ionic liquids make them attractive alternatives as the reaction medium or catalyst for MCRs, and numerous MCRs have been performed efficiently with the help of acidic or basic ionic liquids, acting as both reaction media and catalysts.7,8

Acridinediones are an important class of heterocyclic compounds found in much complex compounds that exhibit antimalarial, antibacterial, anticancer and antimicrobial activities.9,10 Moreover, some of their derivatives have been used as laser dyes and photoinitiators.11 The multicomponent Hantzsch reaction is an efficient method for the synthesis of acridinediones using aldehydes, dimedones and different nitrogen sources like urea, methyl amine, aniline or ammonium acetate as starting materials. The reported catalysts include amberlyst-15,12 silica-supported polyphosphoric acid,13 CdO nanoparticles,14 Bronsted acidic imidazolium ionic liquids,15 triethylbenzylammonium chloride,16 sulfonic acid functionalized MCM-41, ZnO,17 Zn(OAc)2·2H2O or proline,18 cetyl trimethyl ammonium bromide (CTAB),19 heteropolyacid functionalized ionic liquid,20 p-sulfonic acid calix[4]arene,21 acetate acid,22 cellulose sulfuric acid,23 ceric ammonium nitrate (CAN) in PEG,24 CeCl3·7H2O in ionic liquid25 or ferric hydrogen sulfate supported on silica-coated nickel ferrite nanoparticles.26 However, almost all of these catalyst systems have limitations, such as the use of hazardous solvents, prolonged reaction time, expensive reagents, a tedious or high cost catalyst preparation procedure, and the impossibility to recycle the catalyst. Thus, it is still necessary to develop efficient methods for the synthesis of acridinediones using low cost and reusable catalysts.

In our previous study, we have developed a series of hydroxyl functionalized task-specific ionic liquids used to catalyze organic reactions with aldehydes, including Knoevenagel reactions,27 Biginelli reactions,28 Pechmann reactions29 and Domino Knoevenagel-Michael reactions.30 In those studies, we found that the C=O group of the aldehyde could be activated by the hydrogen-bond donor groups on the cations of ionic liquids, and increasing the hydrogen-bond donor ability benefits their catalytic activities. In this study, a series of ionic liquids based on a betainium cation was synthesized. It is known that the C=O group of the aldehyde could be activated by the hydrogen-bond donor ability than that of the hydroxyl group, and therefore the ionic liquids based on betainium are expected to show stronger activation ability towards C=O. Then, we...
investigated the catalytic activities of these synthesized betainium-based ionic liquids on the multicomponent Hantzsch reactions. The results showed that various aryl aldehydes with electron withdrawing or electron donating groups, heterocyclic aromatic aldehydes and allyl aldehyde could react smoothly with dimedone and ammonium acetate under mild conditions to give the target acridinediones in good to excellent isolated yields. Moreover, the betainium-based ionic liquids are easy to prepare and the raw materials like anhydrous betain and acetate acids are both biocompatible and very cheap. In addition, their ability to be reused in this catalytic procedure, further supports their use as a greener catalyst for the synthesis of acridinediones through one-pot Hantzsch reactions.

### Results and discussion

#### Different catalytic performances of the ionic liquids

A series of ionic liquids based on betainium cation (Hbet) with different anions, such as lactic (Lac), acetate (Ac), propionate (Pr) and dihydrogen phosphate (H2PO4), were synthesized and their catalytic performances were investigated using the reaction among benzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione and NH4Ac as a model. For the sake of comparison, anhydrous betain, lactic acid and the ionic liquids based on cholinium cation with anions such as Lac and H2PO4 were also used in the model reactions. The results were collected in Table 1.  

| Entry | Catalyst | Reaction time (h) | Yield (b) (%) |
|-------|----------|------------------|---------------|
| 1     | —        | 3                | Trace         |
| 2     | Betain   | 3                | 50            |
| 3     | HLac     | 3                | 35            |
| 4     | [Hbet][Lac] | 3            | 90            |
| 5     | [Hbet][Ac] | 3             | 75            |
| 6     | [Hbet][Pr] | 3              | 65            |
| 7     | [Hbet][H2PO4] | 3              | 70            |
| 8     | [Choline][Lac] | 4           | 25 (50\(^\circ\)) |
| 9     | [Choline][H2PO4] | 4          | 25 (45\(^\circ\)) |

\(^{a}\) 0.5 mmol benzaldehyde, 1 mmol 5,5-dimethyl-1,3-cyclohexanedione, 0.75 mmol NH4Ac and 0.15 mmol ionic liquid were mixed with 1 ml ethanol, and heated at 80 °C for the desired reaction time. \(^{b}\) Isolated yields. \(^{c}\) The yield for the product of benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione.

### Table 2. Influence of the solvent on the model reaction

| Entry | Solvent | Time (h) | Yield (b) (%) |
|-------|---------|----------|---------------|
| 1     | MeOH    | 3        | 55            |
| 2     | EtOH    | 3        | 90            |
| 3     | CH3CN   | 3        | 70            |
| 4     | H2O     | 3        | Trace         |
| 5     | Solventless | 3    | Trace         |
| 6     | [Hbet][Lac] | 3       | 55            |

\(^{a}\) 0.5 mmol benzaldehyde, 1 mmol 5,5-dimethyl-1,3-cyclohexanedione, 0.75 mmol NH4Ac and 0.15 mmol ionic liquid were mixed with 1 ml solvent, and then heated at 80 °C for the desired reaction time. \(^{b}\) Isolated yields.

### Table 3. Influence of the catalyst amount on the model reaction

| Entry | Catalyst amount (mol%) | Time | Yield (b) (%) |
|-------|------------------------|------|---------------|
| 1     | 0                      | 6 h  | Trace         |
| 2     | 5                      | 3 h  | 55            |
| 3     | 10                     | 3 h  | 75            |
| 4     | 30                     | 3 h  | 90            |
| 5     | 50                     | 3 h  | 90            |
| 6     | 100                    | 3 h  | 90            |

\(^{a}\) 0.5 mmol benzaldehyde, 1 mmol 5,5-dimethyl-1,3-cyclohexanedione, 0.75 mmol NH4Ac and corresponding amount of ionic liquid were mixed with 1 ml ethanol, and then heated at 80 °C for the desired reaction time. \(^{b}\) Isolated yields.
The influences of solvent, catalyst amount and reaction temperature

The influences of solvent, catalyst amount and reaction temperature were investigated using the model reaction. It can be seen from Table 2 that solvents have a significant effect on the catalytic performances of ionic liquids and ethanol is the proper solvent. The results in Table 3 showed that the increase of the ionic liquid amount from 0 to 30 mol% was beneficial to the reaction, but further increasing the amount to 100 mol% had a negligible effect. Therefore, 30 mol% [Hbet][Lac] based on aldehyde was selected as the optimal catalyst amount. Then, the influence of the reaction temperature on the model reaction was investigated under the catalysis of the optimized amount of ionic liquid, and the results are given in Table 4. It is clear that 80 °C is the most favorable reaction temperature. Table 5 has also collected the reaction conditions of the other reported catalytic systems.

Next, the substrate tolerance of this catalyst for the synthesis of acridinediones through Hantzsch reactions was investigated using different aldehydes under optimized conditions, and the results are displayed in Table 6. It is evident that various aromatic aldehydes with electron donating or electron withdrawing substituent groups could react with 5,5-dimethyl-1,3-cyclohexanedione and NH₄Ac smoothly to give the target compounds with good to excellent isolated yields. An allyl aldehyde like cinnamaldehyde, heteroaromatic aldehydes could be converted to the corresponding acridinediones with good to excellent isolated yields. The operation and work-up procedures were very simple and no column chromatography purification was needed. In addition, this ionic liquid catalyst is very cheap, easy to prepare, and its raw materials such as anhydrous betain and lactic acid are highly biocompatible and biodegradable, which make the preparation and utilization procedures more safe and green.

**Conclusion**

The biocompatible ionic liquid [Hbet][Lac] was found to be an efficient and reusable catalyst for the Hantzsch reactions under mild conditions. Various aromatic aldehydes, allyl aldehyde and heteroaromatic aldehydes could be converted to the corresponding acridinediones with good to excellent isolated yields. The operation and work-up procedures were very simple and no column chromatography purification was needed. In addition, this ionic liquid catalyst is very cheap, easy to prepare, and its raw materials such as anhydrous betain and lactic acid are highly biocompatible and biodegradable, which make the preparation and utilization procedures more safe and green.

**Experimental**

**Chemical and instrument**

All of the reagents purchased were of AR grade and used without further purification. Melting points were detected with a XTC-1 Microscopic Melting Point Measurer (Sichuan University Instrument Factory) without correction; ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker AV-400 instrument with CDCl₃ as solvent.

**Synthesis of betainium ionic liquids**

0.1 mol carboxylic acid dissolved in 10 ml methanol was drop-wise added to the 100 ml flask containing 0.1 mol anhydrous betain in

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### Table 4 Influence of reaction temperature on the model reaction

| Entry | T (°C) | Time | Yield \(\%\) |
|-------|--------|------|-------------|
| 1     | r.t.   | 3 h  | —           |
| 2     | 40     | 3 h  | Trace       |
| 3     | 50     | 3 h  | 30          |
| 4     | 80     | 3 h  | 90          |
| 5     | 100    | 3 h  | 90          |

\(a\) 0.5 mmol benzaldehyde, 1 mmol 5,5-dimethyl-1,3-cyclohexanedione, 0.75 mmol NH₄Ac and 30 mol% of ionic liquid were mixed with 1 ml ethanol, and then heated at corresponding reaction temperature for the desired reaction time. \(b\) Isolated yields.

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### Table 5 The comparison of the performance of various catalyst on the model reaction

| Entry | Catalyst                          | Solvent/condition | Time | Yields |
|-------|----------------------------------|-------------------|------|--------|
| 1     | l-Proline                        | H₂O, reflux       | 3 h  | 84     |
| 2     | MSL/PW                           | BMINTf₂, 90 °C    | 4 h  | 98     |
| 3     | CdO                              | Solvent free, 120 °C | 8 min | 92     |
| 4     | Glycol, NaOAC                    | H₂O₂ microwave    | 10 min | 78–94 |
| 5     | Cellulose sulfuric               | Solvent free, 100 °C | 5 h  | 80     |
| 6     | CAN                              | PEG-400, 50 °C    | 4–8 h | 91     |
| 7     | Triethylbenzylammonium chloride  | Solvent free, 85 °C | 20 min | 85     |
| 8     | [CMIM][CF₃COO]                   | H₂O : EtOH (1 : 1), 80 °C | 1.5 h | 85     |
| 9     | CeCl₃·7H₂O                       | [Bmim][BF₄] , 100 °C | 3 h  | 87     |
| 10    | NiFe₂O₄@SiO₂–FHS                 | Solvent free, 80 °C | 15–30 min | 90     |

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10 ml methanol under stirring. The solution was stirred at room temperature for 24 h to complete the reaction, and then the methanol was removed at 50 °C to get the target ionic liquids with white solid or pale yellow liquid status (Scheme 1).

**General procedures for the synthesis of 1,8-dioxodecahydroacridines**

In a 10 ml round bottom flask, the mixture of aromatic aldehyde (0.5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol), ammonium acetate (0.75 mmol) and [Hbet][Lac] (30 mol%) in ethanol (1 ml) was stirred at 80 °C for the desired time. The process of reaction was monitored using TLC (the solvent for the TLC is the mixture of ethyl acetate and petroleum ether (b.p. 60–90 °C)). After completion of the reaction, the mixture was gradually cooled to room temperature and ice water was added

| Entry | R¹ | R² | Amine | Time (h) | Yield (%) | Mp [°C] (obs) | Mp [°C] (lit) |
|-------|----|----|-------|----------|------------|---------------|---------------|
| 1     | C₆H₅ | CH₃ | NH₄Ac | 3        | 90         | 272           | 277–278 (ref. 31) |
| 2     | 4-NO₂C₆H₄ | CH₃ | NH₄Ac | 8        | 85         | 268–270       | 261–262 (ref. 32) |
| 3     | 3-NO₂C₆H₄ | CH₃ | NH₄Ac | 8        | 80         | 298–300       | 287–289 (ref. 31) |
| 4     | 4-BrC₆H₄ | CH₃ | NH₄Ac | 5        | 85         | >300          | 330–332 (ref. 33) |
| 5     | 4-CH₃OC₆H₄ | CH₃ | NH₄Ac | 3        | 95         | >300          | 275–277 (ref. 8) |
| 6     | 4-HOC₆H₄ | CH₃ | NH₄Ac | 3        | 95         | >300          | >300 (ref. 31) |
| 7     | 4-CH₃C₆H₄ | CH₃ | NH₄Ac | 3        | 95         | >300          | 270–275 (ref. 8) |
| 8     | 4-CF₃C₆H₄ | CH₃ | NH₄Ac | 3        | 95         | >300          | >300 (ref. 34) |
| 9     | 4-ClC₆H₄ | CH₃ | NH₄Ac | 3.5      | 85         | 302–303       | 300–301 (ref. 34) |
| 10    | 4-FClC₆H₄ | CH₃ | NH₄Ac | 3.5      | 85         | 246–248       | 275–276 (ref. 16) |
| 11    | 3-CNC₆H₄ | CH₃ | NH₄Ac | 3.5      | 85         | 290           | 283–285 (ref. 8) |
| 12    | 4-OH-3-CH₃OC₆H₃ | CH₃ | NH₄Ac | 8        | 90         | 300           | 295–298 (ref. 8) |
| 13    | 2-ClC₆H₄ | CH₃ | NH₄Ac | 6        | 87         | 290–292       | 263–264 (ref. 8) |
| 14    | C₆H₄CH=CH | CH₃ | NH₄Ac | 1        | 88         | 217           | —             |
| 15 | | | | | | |
| 16 | | | | | | |
| 17 | C₆H₅ | H | NH₄Ac | 3 | 95 | 310 | 279–281 (ref. 17) |
| 18 | C₆H₄CH₃ | H | NH₄Ac | 3 | 95 | >300 | 306–308 (ref. 17) |
| 19 | 4-CH₃OC₆H₄ | H | NH₄Ac | 3 | 85 | >300 | 305–307 (ref. 17) |
| 20 | 4-CH₃C₆H₄ | H | NH₄Ac | 2 | 95 | 300 | — |
| 21 | 4-ClC₆H₄ | H | NH₄Ac | 3 | 95 | 300 | 298–299 (ref. 17) |
| 22 | 4-CH₃OC₆H₄ | CH₃ | PhNH₂ | 3 | 80 | 290–292 | 291–293 (ref. 19) |
| 23 | 3-NO₂C₆H₄ | CH₃ | PhNH₂ | 3 | 75 | 281–283 | 281–283 (ref. 19) |
| 24 | 4-ClC₆H₄ | CH₃ | PhNH₂ | 3 | 75 | 237–239 | 243–245 (ref. 19) |

Isolated yield.
under stirring, and then the product could be isolated as solid precipitate. The solid product was filtered and washed using ice aqueous ethanol solution (1 : 1 in volume) or recrystallized in ethanol to get the pure products.

**Reutilization of the ionic liquid**

The reusability of [Hbet][Lac] was investigated from the reaction between p-methoxybenzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione and ammonium acetate as a model. After the completion of the reaction, ice water was added to the reaction mixtures. The solid product was filtered and the catalyst [Hbet][Lac] was recovered from the filtrate. The containing water was evaporated, and then the ionic liquid was dried in vacuum at 50 °C for 12 h. The recovered ionic liquid can then be reused for additional runs without activation.

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