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Betainium-based ionic liquids catalyzed multicomponent Hantzsch reactions for the efficient synthesis of acridinediones†

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In this study, a series of betainium-based ionic liquids with various anions have been synthesized and their catalytic performances for the Hantzsch reactions have been investigated. It is shown that these ionic liquids have high selectivity for the one-pot production of acridinediones through Hantzsch reactions under mild conditions, and betainium lactate has the highest catalytic activity. This ionic liquid catalyst is very cheap and easy to prepare; the catalytic procedure is very simple and the catalyst can be recycled and reutilized. In addition, the biocompatibility of the raw material of these ionic liquids suggests that this catalytic system may have great industrial potential applications.

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 catalyst 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] Brønsted acidic imidazolium ionic liquids,[15] triethylbenzylammonium chloride,[16] sulfonic acid functionalized silica,[17] $Zn(OAc)_2 \cdot 2H_2O$ 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] $CeCl_3 \cdot 7H_2O$ in ionic liquid[25] 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 reactions[29] 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 carboxyl acid group on the betainium cation has stronger 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

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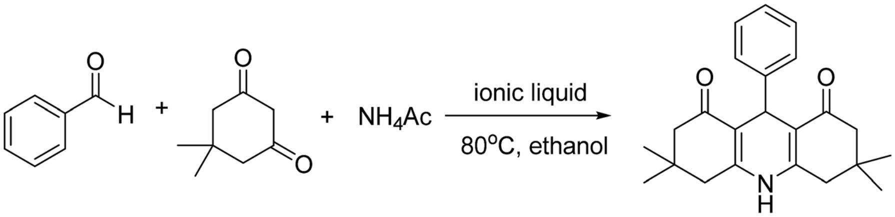
Table 1 Catalytic performances of different ionic liquids on the synthesis of acridinediones



Entry[a]	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][H_2PO_4]	3	70
8	[Choline][Lac]	4	25 (50[c])
9	[Choline][H_2PO_4]	4	25 (45[c])

[a] 0.5 mmol benzaldehyde, 1 mmol 5,5-dimethyl-1,3-cyclohexanedione, 0.75 mmol NH_4Ac 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.

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 (H_2PO_4), were synthesized and their catalytic performances were investigated using the reaction among benzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione and NH_4Ac 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 H_2PO_4 were also used in the model reactions. The results were collected in Table 1. It can be seen that although anhydrous betain and lactic acid can promote this reaction, the ionic liquids have high catalytic activity and ionic liquids with betanium cations have higher chemo-selectivity for the one-pot Hantzsch reactions, whereas the ionic liquids with cholinium cations prefer to produce the two component reaction product between benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione. The ionic liquid with betanium cation and lactate anion, [Hbet][Lac], has the highest catalytic activity and selectivity.

Table 2 Influence of the solvent on the model reaction

Entry[a]	Solvent	Time (h)	Yield[b] (%)
1	MeOH	3	55
2	EtOH	3	90
3	CH_3CN	3	70
4	H_2O	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 NH_4Ac 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[a]	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 NH_4Ac 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.

Table 4 Influence of reaction temperature on the model reaction

Entry	T (°C)	Time	Yield[a,b] (%)
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 NH_4Ac 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.

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 NH_4Ac smoothly to give the target compounds with good to excellent isolated yields. An allyl aldehyde like cinnamaldehyde, heteroaromatic aldehydes like pyridylaldehyde and furfuraldehyde could also be converted to the corresponding acridinediones with excellent isolated yields within 3 hours.

The reusability of the ionic liquids was also investigated using the reaction between 4-methoxy-benzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione and NH_4Ac as a model system, and the results are illustrated in Fig. 1. It was shown that after five cycles the catalytic activity had a negligible decrease, suggesting the excellent recyclability of this ionic liquid in Hantzsch reactions.

The plausible reaction mechanism was proposed and is illustrated in Fig. 2. The hydrogen bond donor ability of the ionic liquid may increase the enol (**1b**) content in the keto–enol equilibrium of dimitone. The C=O of the aldehyde was polarized by the formation of hydrogen bonds with the carboxyl group on the cation of the ionic liquid, which was then attacked by **1b** to form intermediate **4** and then dehydrated to **5**. NH_4OAc was decomposed to NH_3 and CH_3COOH, and NH_3 attacked enol **1b** to form intermediate **6**. The intermediate **6** reacted with **5** to form the product **3**.

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; ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AV-400 instrument with $CDCl_3$ as solvent.

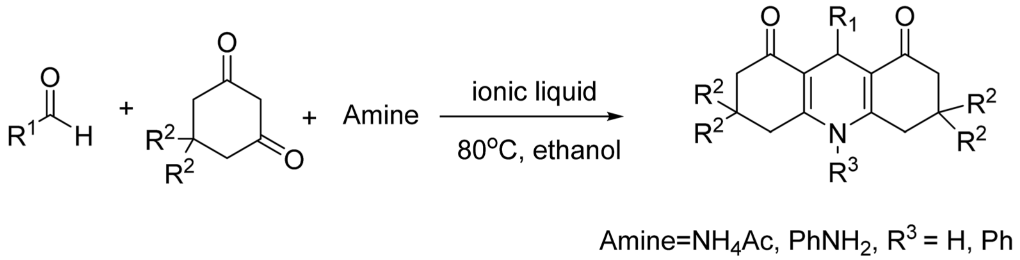
Synthesis of betainium ionic liquids

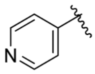
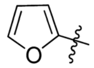
0.1 mol carboxyl acid dissolved in 10 ml methanol was drop-wise added to the 100 ml flask containing 0.1 mol anhydrous betain in

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

Entry	Catalyst	Solvent/condition	Time	Yields	Ref.
1	L-Proline	H_2O, reflux	3 h	84	18
2	MSI_3PW	$BMINTf_2$, 90 °C	4 h	98	20
3	CdO	Solvent free, 120 °C	8 min	92	14
4	Glycol, NaOAC	H_2O, microwave	10 min	78–94	11
5	Cellulose sulfuric	Solvent free, 100 °C	5 h	80	23
6	CAN	PEG-400, 50 °C	4–8 h	91	24
7	Triethylbenzylammonium chloride	Solvent free, 85 °C	20 min	85	16
8	[CMIM][CF_3COO]	H_2O : EtOH (1 : 1), 80 °C	1.5 h	85	17
9	$CeCl_3\cdot 7H_2O$	[Bmim][BF_4], 100 °C	3 h	87	25
10	$NiFe_2O_4$@SiO_2–FHS	Solvent free, 80 °C	15–30 min	90	26

Table 6 [Hbet][Lac] catalyzed synthesis of acridinedione derivatives



Entry	R^1	R^2	Amine	Time (h)	Yield[a] (%)	Mp (°C) (obs)	Mp (°C) (lit)
1	C_6H_5	CH_3	NH_4Ac	3	90	272	277–278 (ref. 31)
2	$4\text{-}NO_2C_6H_4$	CH_3	NH_4Ac	8	85	268–270	261–262 (ref. 32)
3	$3\text{-}NO_2C_6H_4$	CH_3	NH_4Ac	8	80	298–300	287–289 (ref. 31)
4	$4\text{-}BrC_6H_4$	CH_3	NH_4Ac	5	85	>300	330–332 (ref. 33)
5	$4\text{-}CH_3OC_6H_4$	CH_3	NH_4Ac	3	96	>300	275–277 (ref. 8)
6	$4\text{-}HOC_6H_4$	CH_3	NH_4Ac	3	95	>300	>300 (ref. 31)
7	$4\text{-}CH_3C_6H_4$	CH_3	NH_4Ac	3	90	>300	270–275 (ref. 8)
8	$4\text{-}CF_3C_6H_4$	CH_3	NH_4Ac	3	95	258–260	>300 (ref. 8)
9	$4\text{-}ClC_6H_4$	CH_3	NH_4Ac	3.5	85	302–303	300–301 (ref. 34)
10	$4\text{-}FC_6H_4$	CH_3	NH_4Ac	3.5	85	246–248	275–276 (ref. 16)
11	$3\text{-}ClC_6H_4$	CH_3	NH_4Ac	3.5	85	290	283–285 (ref. 8)
12	$4\text{-}OH\text{-}3\text{-}CH_3OC_6H_3$	CH_3	NH_4Ac	8	90	300	295–298 (ref. 8)
13	$2\text{-}ClC_6H_4$	CH_3	NH_4Ac	6	87	290–292	263–264 (ref. 8)
14	$C_6H_4CH{=}CH$	CH_3	NH_4Ac	1	88	217	—
15		CH_3	NH_4Ac	1	95	248–250	—
16		CH_3	NH_4Ac	3	95	292	—
17	C_6H_5	H	NH_4Ac	3	95	310	279–281 (ref. 17)
18	$4\text{-}CH_3OC_6H_4$	H	NH_4Ac	3	92	>300	306–308 (ref. 17)
19	$4\text{-}HOC_6H_4$	H	NH_4Ac	3	85	>300	305–307 (ref. 17)
20	$4\text{-}CH_3C_6H_4$	H	NH_4Ac	2	95	300	—
21	$4\text{-}ClC_6H_4$	H	NH_4Ac	3	95	300	298–299 (ref. 17)
22	$4\text{-}CH_3OC_6H_4$	CH_3	$PhNH_2$	3	80	290–292	291–293 (ref. 19)
23	$3\text{-}NO_2C_6H_4$	CH_3	$PhNH_2$	3	75	281–283	281–283 (ref. 19)
24	$4\text{-}ClC_6H_4$	CH_3	$PhNH_2$	3	75	237–239	243–245 (ref. 19)

[a] Isolated yield.

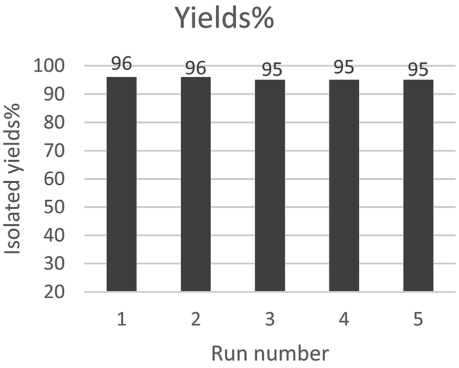


Fig. 1 Recyclability of ionic liquid catalyst.

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

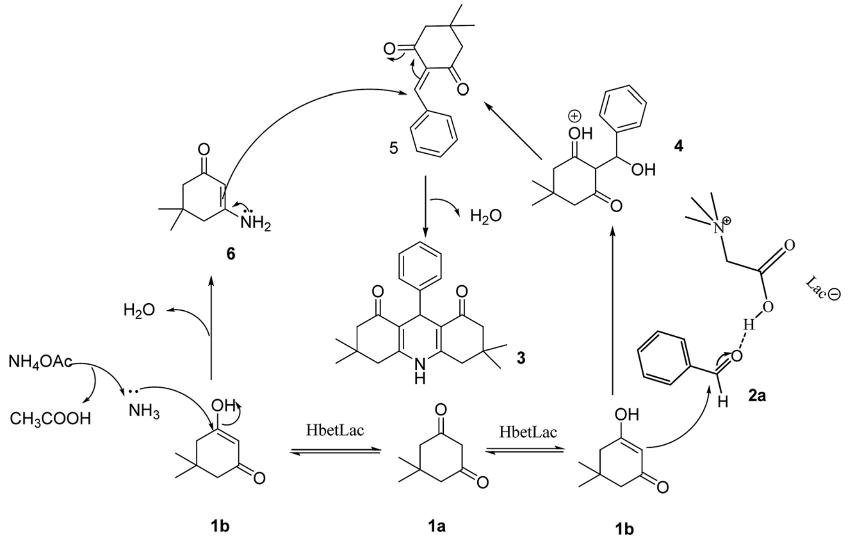
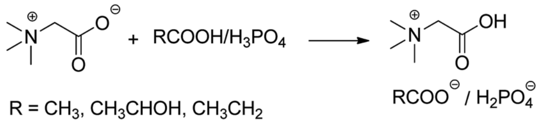


Fig. 2 The plausible reaction mechanism for the ionic liquid catalyzed Hantzsch reactions.



Scheme 1 Synthesis of the betainium ionic liquids.

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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