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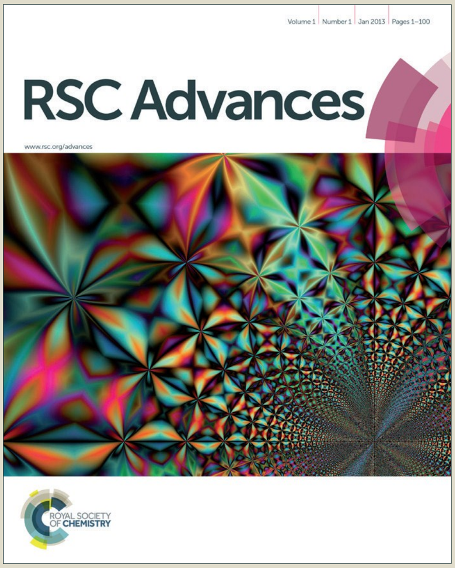

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ARTICLE

Lewis acidic ionic liquids of crown ether complex cations: preparation and applications in organic reactions

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A range of Lewis acidic ionic liquids composed of crown ether complex cations were designed, synthesised and characterised by Raman, MS, FT-IR, thermogravimetric differential thermal analysis (TGA-DSC) and elemental analysis. These Lewis acidic ionic liquids were utilized as catalysts to prepare 2-phenyl-1H-benzo[d]imidazole using same amount of aldehyde and o-phenylenediamine under atmosphere and 1-benzyl-2-phenyl-1H-benzo[d]imidazole using two equivalent of aldehyde and one equivalent of *o*-phenylenediamine in argon. These ionic liquids were also found to be good catalysts to synthesize bis(indolyl)methane derivatives under mild conditions. In addition, the plausible mechanisms of above reactions in the presence of ionic liquids as catalysts were suggested and discussed.

Introduction

In the past decades, ionic liquids (ILs) have attracted much attention in the area of organic reactions[1] due to their special features, such as negligible vapour pressure, not flammable, high ionic conductivity, good tunable solubility, excellent thermal and chemical stability.[2-5] Nowadays, researchers are attracted by the ‘air and water stable’ ionic liquids, but the investigation and application of the Lewis acidic ionic liquids are still the main spotlight.[6] In the early 1950s, the $[AlCl_4]^-$anion was paired with suitable cations to get the first record Lewis acidic ionic liquids or molten salts.[7] Since then a lot of similar anions have been exploited such as $[FeCl_4]^-$, $[ZnCl_3]^-$ and so on.[8]

To extend the ILs family, our group defined a novel type of ionic liquid containing crown ether complex cations with various anions that were utilized to catalyse various organic reactions.[9-12] Recently, a Calix[4]arene-chelated potassium salt was also reported as efficient catalyst for organometallic reactions,[13] which was similar to our ILs. Pursuant to our previous study, a series of Lewis acidic crown ether complex cations ionic liquids were devised, synthesized and applied to Friedel-Crafts alkylation reaction[14,15] and the synthesis of benzimidazole derivatives.

The benzimidazole derivatives are well known as their various biological and pharmaceutical activities.[16-18] Although different catalysts have been reported for the synthesis of these heterocycles,[19-21] tedious workup procedures, drastic reaction conditions, low yields, co-occurrence of several side reactions have limited their practical applications. Therefore, new methods are necessary to be developed. Herein, new IL of $[18\text{-}C\text{-}6K][FeCl_4]$ was utilized to prepare benzimidazole derivatives as an efficient catalyst.

Bis(indolyl)methane derivatives are well known for their vast biological activity, and many methods of their synthesis have been reported such as Lewis acids, Brønsted acids, and ionic liquids.[22-24] Herein, new IL of $[18\text{-}C\text{-}6K][FeCl_4]$ showed an excellent catalytic efficiency in the reaction of aldehyde and indole to give bis(indolyl)methane derivatives.

Experimental

Materials and methods

All commercially available reagents were used without further purification unless otherwise indicated. Reactions were monitored by thin layer chromatography (TLC). All yields were isolated products after purification, and column chromatography and recrystallization purifications were carried out. Products were analysed and characterized by using Varian 300/400 spectrometer using DMSO-d_6 as an internal standard solvent for ^{1}H-NMR and ^{13}C-NMR measurements. Infrared spectra were collected on a Nicolet NEXUS670 FT-IR spectrometer using a KBr pellet. MS (ESI) was carried out on a Bruker APEX II mass spectrometer. Raman spectra were collected on in Via Raman microscopy system using a laser wavelength of 628 nm. Melting points were performed using a TGA/DSC/NETZS CH STA449C instrument heated from 30-800^{o}C (heating rate of 10^{o}C/min, under N_2).

Preparation of Lewis acidic ionic liquid of crown ether complex cations

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Following our previous study, we attempted to prepare a novel type of Lewis acidic ionic liquids. The inorganic potassium or sodium chlorine salt (10 mmol) was mixed with 18-crown-6 (10mmol, 2.6432 g) or 15-crown-5 (10 mmol, 2.2026 g) in water (15 mL). The mixture was stirred for 12h at the room temperature. After completion of the reaction, the excess water was evaporated under reduced pressure. Then, the solid and $AlCl_3/FeCl_3·6H_2O/ZnCl_2$ (10 mmol) were refluxed in ethanol. After stirring for 12h, the solvent was removed under reduced pressure. The residue was dried in vacuum to generate the desired product in 100% yield (Fig. 1).

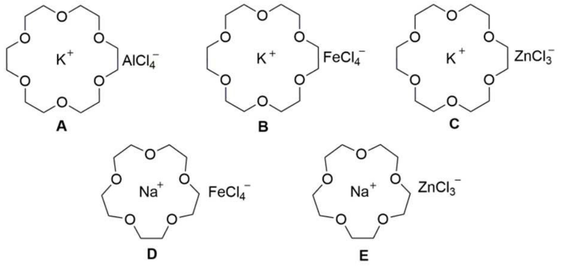

Fig. 1. The structures of Lewis acidic crown ether complex cation ionic liquids.

General procedure for synthesis of 1-substituted benzimidazole derivatives

The catalytic reactions were performed with arylaldehyde (1 mmol), 1,2-phenylenediamine (1.0 mmol) and ionic liquid (0.05 mmol) in ethanol (5 mL). The mixture was stirred for a proper time in air at room temperature monitoring the reaction progress by TLC. After completion of the reaction, the mixture was evaporated under reduced pressure to get the crude product, which was purified by column chromatography using petroleum ether/ethyl acetate/dichloromethane (2:1:1) as eluent to give pure target product.

General procedure for synthesis of 1,2-disubstituted benzimidazole derivarives.

The reactions were carried out with arylaldehydes (2 mmol), 1,2-phenylenediamine (1.0 mmol) and ionic liquid (0.05 mmol) in ethanol (5 mL). The mixture was stirred for a certain time in argon atmosphere at room temperature. After completion of the reaction, the mixture was evaporated under reduced pressure to get crude product, which was then purified by column chromatography using petroleum ether/ethyl acetate/dichloromethane (2:1:1) as eluent to yield pure product.

Typical procedure for the synthesis of bis-indolylmethanes derivarives

The portion of indole (2.0 mmol), arylaldehydes (1.0 mmol), methanol (5 mL) and ionic liquid (0.1 mmol) were added to a 10 mL round-bottom flask equipped with a magnetic stir bar at room temperature. After completion of the reaction monitoring by TLC, water (10 mL was added to the mixture and extracted with CH_2Cl_2 (3×10mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the desired product, which was then purified by flash column chromatography.

Results and discussion

It is important to identify the anion speciation of Lewis acidic ionic liquids. Raman/ESI-MS was then used to authenticate the formation of anion (Fig. 2) since their symmetric structures. The Raman spectra of the five ILs are appearance in the range of 200-500 cm^{-1} and are consistent with the literature report.[25-27] According to the principle of Raman spectra, the Stockes line is attributed to the symmetric stretching vibration of metal chloride clusters. The stockes lines of triangle structure of $ZnCl_3^-$ that has a weak interaction with cation are appeared at 287 cm^{-1} in both **C** and **E** ILs. The stockes lines of tetrahedron structure of $FeCl_4^-$ that has a strong interaction with cation are appeared at 335 and 341cm^{-1} in **B** and **D**, respectively. The obtained ionic liquids were in high purity and given sharp melting points. The melting points of the ILs are in the range of 91-158 °C (Table 1) and significantly lower than that of homologous metal chlorates due to the difference of ions in ILs. Moreover, the good thermodynamic stabilities were demonstrated by TGA-DSC analysis, in which their decomposed points are in the range of 205-280 °C (Table 1). All the ionic liquids exhibit relatively lower melting point that match our new definition about ionic liquids.[9]

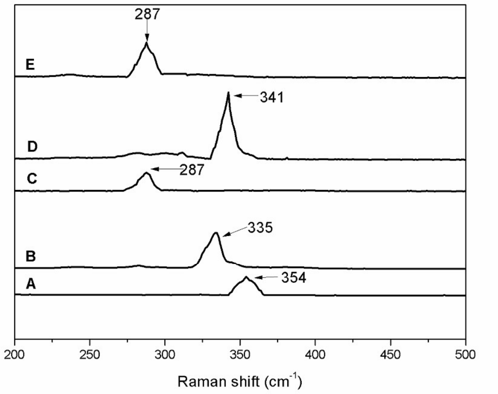

Fig. 2. Raman spectra of five Lewis acidic ILs.

Currently, Lewis acidic ionic liquids are of immense diversity in application, such as acting as catalysts in synthesis chemistry, providing transitional improvements in electroplating, supplying new gas scrubbing processes and preparing of new inorganic semiconductor materials. Similarly, our Lewis acidic ionic liquids of crown ether complex cations also showed efficient catalytic ability in organic reactions.

Table 1. The properties of new Lewis acidic ILs.

Entry	ILs	Colour	M.p.(°C)[a]	T_d(°C)[a]
1	A	White	120	210
2	B	Green	109	233
3	C	White	91	280
4	D	Green	117	205
5	E	White	158	218

[a] All melting points and decomposed temperatures (T_d) were measured by XT-4 instrument and also determined by TGA-DSC, heating at 10 °C min^{-1} under N_2.

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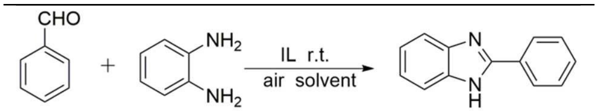
In this paper, we wish to use the ILs as catalysts for the preparation of benzimidazole derivates. With this purpose in mind, we firstly choose *o*-phenylenediamine (1.0 mmol) and benzaldehyde (1.0 mmol) as the model substrates in order to synthesize benzimidazole under different reaction conditions. Fortunately, [18-C-6K][$FeCl_4$] (**B**) can initiate the desired reaction to proceed efficiently in air atmosphere, solely producing 2-phenyl-1H-benzo[d]imidazole in 90% yield (Table 2, entry 2). For comparison, low yields of products could be afforded under the same reaction conditions in the presence of [18-C-6K][$AlCl_4$], [18-C-6K][$ZnCl_3$], [15-C-5Na][$FeCl_4$], and [15-C-5Na][$ZnCl_3$], respectively (Table 2, entries 1, 3-5). Then, the solvent effect was also investigated. The results show that protonic solvents give better yield (Table 2, entries 6, 10, 2) than aprotic solvent under similar conditions (Table 2, entries 7-9). Thus, 82% yield can be obtained by using **B** as catalyst in ethanol within 1 hour (Table 2, entry 10).

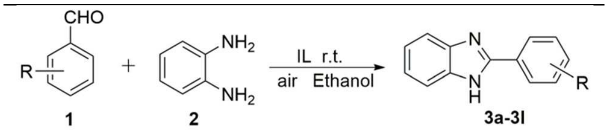
Table 2. Catalyst screening and optimization of reaction conditions[a]



Entry	IL	Solvent	Time (h)	Yield[b] (%)
1	**A**	CH_3CH_2OH	4	78
2	**B**	CH_3CH_2OH	2	90
3	**C**	CH_3CH_2OH	4	62
4	**D**	CH_3CH_2OH	2	56
5	**E**	CH_3CH_2OH	4	64
6	**B**	CH_3OH	2	73
7	**B**	THF	2	72
8	**B**	CH_2Cl_2	2	70
9	**B**	CH_3CN	2	69
10	**B**	CH_3CH_2OH	1	82

[a] Reaction conditions: Benzaldehyde (1 mmol), 1, 2-phenylenediamine (1 mmol), catalysts (10 mol %), solvent (5 ml). [b] Isolated yield.

Table 3. The synthesis of 1-substituted benzimidazole derivatives[a].



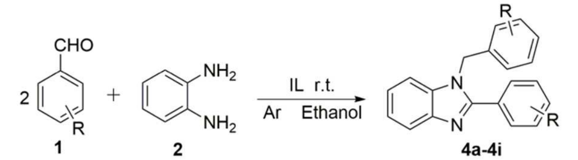
Entry	-R	Product	Time (h)	Yield[b] (%)
1	H	**3a**	2	90
2	4-NO_2	**3b**	2	99
3	2-NO_2	**3c**	2	67
4	3-NO_2	**3d**	2	99
5	4-Cl	**3e**	2	85
6	2-Cl	**3f**	2	88
7	2,4-Cl	**3g**	2	92
8	4-CH_3	**3h**	2	85
9	3-OCH_3	**3i**	2	94
10	2-OCH_3	**3j**	2	72
11	2-OH	**3k**	2	86
12	4-OH	**3l**	2	57

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), catalysts(**B**, 10 mol %), ethanol (5 ml). [b] Isolated yield.

Under the optimized conditions, the scope of reaction was investigated, in which, *o*-phenylenediamine was reacted with various aldehydes to generate corresponding products. The results were summarized in Table 3. The substituted benzaldehydes with electro-withdrawing groups show better activity (Table 3, entries 2,4,7) than that with electron-donating groups (Table 3, entries 4,10,12) owing to the more electron positive of carbon in carbonyl. Even 2- Nitrobenzene formaldehyde with large steric hindrance can also react with *o*-phenylenediamine to produce target product in moderate yield under this reaction conditions (Table 3, entry 3).

Surprisingly, when two equivalent of benzaldehyde (2.0 mmol) reacted with one equivalent of *o*-phenylenediamine (1.0 mmol) in argon atmosphere at room temperature, 1-benzyl-2-phenyl-1H-benzo[d]imidazoles were obtained in high yield without any by-product (Table 4). The synthesis of 1,2-disubstituted benzimidazoles were also investigated with five kinds of Lewis acidic ionic liquids (Table 4, entries 1-5). [18-C-6K][$FeCl_4$] (**B**) was still good choice for obtaining 1,2-disubstituted benzimidazoles in ethanol at the room temperature. To further extend the scope of this reaction, the aromatic aldehydes possessing different substituents were applied in this reaction. We found that the benzaldehydes with electron-donating groups or weak electron-withdrawing groups could react with *o*-phenylenediamine to generate desired 1,2-disubstituted benzimidazoles (Table 4, entries 6-13) and the benzaldehydes with strong electron-withdrawing groups showed no reactivity because the corresponding intermediate is too stable to dehydrate (*vide infra*).

Table 4. The synthesis of 1,2-disubstituted benzimidazole derivatives[a].



Entry	IL	R	Product	Time(h)	Yield[b] (%)
1	**A**	H	**4a**	4	70
2	**B**	H	**4a**	2	87
3	**C**	H	**4a**	3	71
4	**D**	H	**4a**	2	82
5	**E**	H	**4a**	3	72
6	**B**	2-OCH_3	**4b**	2	72
7	**B**	2-Cl	**4c**	2	80
8	**B**	3-CH_3	**4d**	2	69
9	**B**	3-OH	**4e**	2	59
10	**B**	2,4-Cl	**4f**	2	67
11	**B**	2,5-OCH_3	**6g**	20	97
12	**B**	2-OCH_3	**6h**	30	99
13	**B**	2,4-Cl	**6i**	60	95

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), catalysts 10 mol %, ethanol (5 ml). [b] Isolated yield.

For understanding the difference of the syntheses of 1-substituted benzimidazole and 1,2-disubstituted benzimidazole, a possible mechanism is carefully proposed in Fig. 3. It can be seen that the amino-groups of reactant are

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activated by cations of ILs and the aldehydes are activated simultaneously by anions of ILs, which accelerate the rates of reactions. When the imines of intermediate (**i**) was formed by the activated reactants, a key zwitterionic-type intermediate (**ii**) of cyclization was easily produced by the aid of IL. After 1,3-H shift of (**ii**), the most important intermeiate (**iii**) was generated. When the air was involved in the reaction, the intermediate (**iii**) was oxidized and dehydrated to yield 1-substituted benzimidazole, which is similar to the literature[28]. In the argon atomosphere, the intermediate (**iii**) stablized in protonic solvent could react continuously with excess benzaldehyde to produce another zwitterionic-type intermediate (**iv**). When the proton reacts with (**iv**), the intermediate (**v**) was formed via a dehydration process. Finally the 1,2-disubstituted benzimidazole can be obtained by an intramolecular rearrangement and deprotonation.

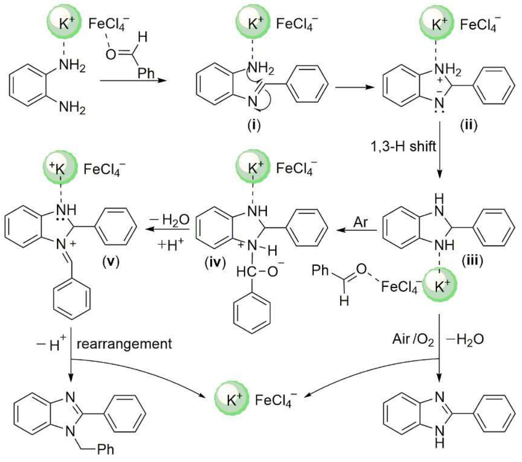
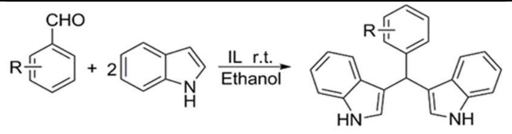


Fig. 3. Proposed mechanism for the reaction of o-phenylenediamine and benzaldehyde in the presence of ILs

Table 5. The synthesis of bis(indolyl)alkyane.[a]



1 **5** **6a-6i**

Entry	IL	R	Product	Time(min)	Yield[b] (%)
1	**A**	H	**6a**	120	76
2	**B**	H	**6a**	60	99
3	**C**	H	**6a**	120	81
4	**D**	H	**6a**	100	87
5	**E**	H	**6a**	120	74
6	**B**	4-NO_2	**6b**	150	90
7	**B**	2-NO_2	**6c**	50	98
8	**B**	4-Cl	**6d**	40	97
9	**B**	4-OH	**6e**	50	99
10	**B**	4-CH_3	**6f**	50	98
11	**B**	2,5-OCH_3	**6g**	20	97
12	**B**	2-OCH_3	**6h**	30	99
13	**B**	2,4-Cl	**6i**	60	95

[a]Reaction conditions: **1** (1 mmol), **5** (2 mmol), catalyst (10%), ethanol (5 ml). [b] Isolated yield.

It is well known that Friedel–Crafts alkylation reaction is one of the most powerful methods to synthesize optically functionalization of aromatic compounds. This reaction is carried out between an aromatic substrate and an acyl component in the presence of an acid catalyst. Herein, a series of Lewis acidic ionic liquid were utilized to synthesize bis(indolyl)alkyane with indole and aldehyde. The results are summarized in Table 5. Among the ILs, [18-C-6K][$FeCl_4$] showed the best activity in ethanol (Table 5, entry 2 *vs* 1, 3-5). To extend the scope of this reaction, various substituted benzaldehydes were reacted with indole to generate the corresponding products under the optimal reaction conditions. Fortunately, all reactions proceeded smoothly and generated target products in high yield in a proper time. It is clear to see that the benzaldehydes with electron-donating groups show better yield in short reaction time (Table 5, entries 9-12) than that with electron-withdrawing groups (Table 5, entries 6-8, 13).

Finally, the probable mechanism of the synthesis of bis(indolyl)methanes reaction was proposed (Fig. 4). First, the anion $[FeCl_4]^-$ activates the carbonyl group of the aldehyde while a molecule of indole attacks the aldehyde to generate intermediate **I**. After loss of H_2O to afford intermediate **II**, and then another molecule of indole reacts with intermediate **II** toward intermediate **III**. Accompanying with leaving of cation $[18\text{-C-}6K]^+$, the bis(indolyl)methane **6a** is finally formed. Meanwhile, the catalyst of ionic liquid [18-C-6K][$FeCl_4$] is regenerated for the next catalytic cycle.

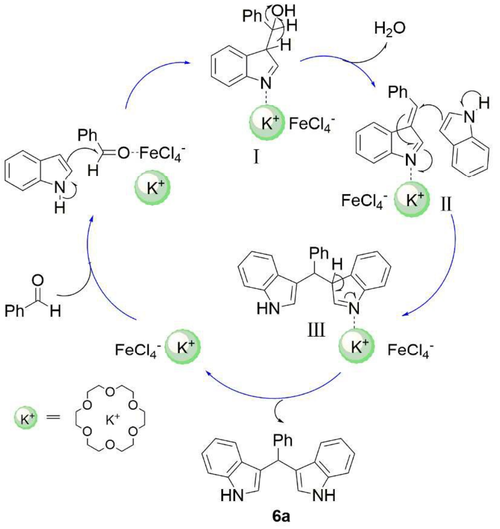


Fig. 4. Proposed mechanism for the reaction of indole and benzaldehyde in the presence of ILs.

Conclusions

In summary, we designed and synthesized five new Lewis acidic ionic liquids of crown ether complex cations that were applied to the synthesis of benzimidazole derivatives as catalysts. By controlling reaction conditions, various substituted products could be obtained in high yield under mild reaction conditions. Furthermore, these new ionic liquids

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also showed good catalytic abilities for the synthesis of bis(indolyl)alkyanes. Their excellent catalytic activities might be attributed to the Lewis acidity of metal complex anions and crown ether alkali cations that can activate substrates and stabilize intermediates, which were revealed in the proposed mechanisms. Further investigation on other applications of these type ionic liquids is on the way in our laboratory.

Acknowledgments

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