Molecular Sieves in Ionic Liquids as an Efficient and Recyclable Medium for the Synthesis of Imines

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Abstract: A great variety of imines were efficiently isolated in high yields from the reaction of aldehydes and amines in ionic liquids. The ionic liquids could be recovered and reused for at least five cycles without loss in the yields being a useful alternative to dichloromethane or diethyl ether, which are the commonly used solvents for this reaction.

Key words: ionic liquids, imines, green chemistry

Imines or Schiff bases are important intermediates in organic synthesis.[1] The formation of these compounds from the reaction of aldehydes and primary amines is usually carried out in ethereal or chlorinated organic solvents, which are volatile, flammable and toxic. Thus, the search for green reaction media to perform organic reactions is a matter of much concern.[2] In this respect, ionic liquids, specially those obtained from quaternary ammonium cations and weak coordinating anions, play an important role.[3]

Among the known ionic liquids, those derived from dialkylimidazolium cations have received special attention since their chemical and physical properties can be finely tuned for a range of applications by varying the alkyl chains or anions.[3] Indeed, they are considered as environmentally friendly substitutes for volatile organic solvents, because of some important characteristics such as: low vapor pressure, ability to act as catalysts, chemical and thermal stability, nonflammability, high ionic conductivity and a wide electrochemical potential window.[3] For these reasons, ionic liquids have found increasing applications in organic synthesis recently.[4]

There are some recent reports of imines formation in ionic liquids in the literature. However, in these studies the imines were formed in situ and subsequently used without being isolated, for example, in Diels–Alder[5] and asymmetric Mannich-type reactions[6] as well as in three-component coupling reactions.[7] Thus, no systematic study has been conducted so far towards the synthesis and isolation of imines in ionic liquids.

In this work we describe the use of molecular sieves in ionic liquids as an efficient and recyclable system for the synthesis of several imines.[8] The ionic liquids used were prepared according to known procedures[9] and are shown in Figure 1. The choice for these compounds resides on the fact that they can be easily obtained and have been used in a variety of organic reactions with very good results,[10] which are summarized in Table 1.

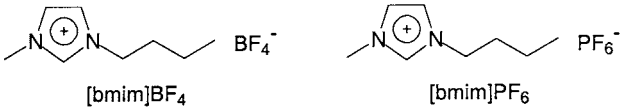

Figure 1 Employed ionic liquids

Aliphatic, aromatic and heteroaromatic aldehydes and amines were investigated. The reactions were run at room temperature and the crude imines were smoothly obtained in excellent yields in all cases without the need for purification. Slower reaction rates were obtained when tryptamine was used probably due to its low solubility in the ionic liquids (Table 1, entries 1, 7 and 8).

In order to compare the reaction rates in ionic liquids with conventional solvents, some reactions were carried out in CH_2Cl_2 (Table 2). We found out that the use of 4 Å molecular sieves as water scavenger had little effect in the yields but lowered the reaction times in [bmim]PF_6 as compared to the reactions run in CH_2Cl_2 (compare entries 1, 5, 6, 8–10 and 13, Table 2). On the other hand, no effect of this kind was observed in [bmim]BF_4 (entries 4, 12, Table 2), which might be due to the differences in solubility of water in these two ionic liquids[3d] and the formation of different polarity regions.[11]

The products were easily separated from the ionic liquids by simple extraction with diethyl ether and were usually obtained in high purity (>90% by ^{1}H NMR) requiring no purification for further uses. The remaining system containing the ionic liquid and molecular sieves, was then dried by heating under vacuum for 30 minutes.[12]

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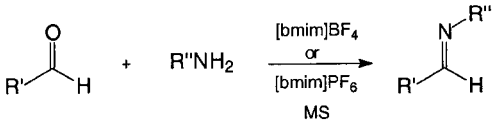
Table 1 Experimental Conditions and Results of the Reactions between Aldehydes and Amines in Ionic Liquids[13,14]



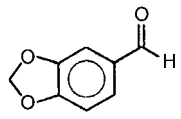
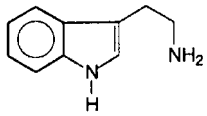
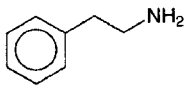
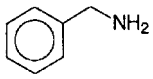
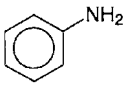
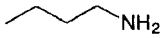
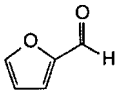
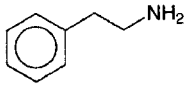
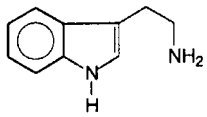
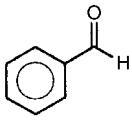
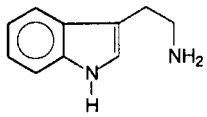
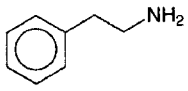
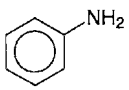
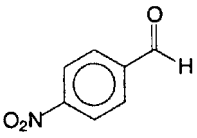
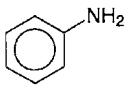
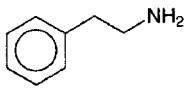
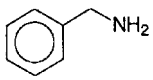
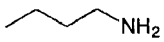
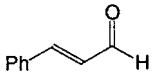
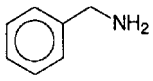
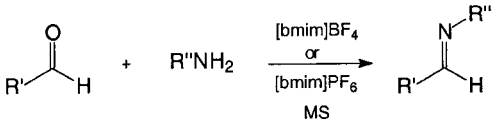
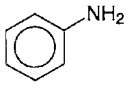
Entry	Aldehyde	Amine	Ionic liquid	Time (min)	Yield (%)
1			[bmim]BF_4	300	89
2			[bmim]BF_4	30	95
3			[bmim]PF_6	15	98
4			[bmim]PF_6	15	96
5			[bmim]PF_6	150	93
6			[bmim]PF_6	120	90
7			[bmim]BF_4	240	90
8			[bmim]BF_4	300	95
9			[bmim]BF_4	180	90
10			[bmim]PF_6	180	94
11			[bmim]PF_6	20	95
12			[bmim]PF_6	20	91
13			[bmim]PF_6	120	88
14			[bmim]PF_6	120	85
15			[bmim]PF_6	50	89

Table 1 Experimental Conditions and Results of the Reactions between Aldehydes and Amines in Ionic Liquids[13,14] (continued)



Entry	Aldehyde	Amine	Ionic liquid	Time (min)	Yield (%)
16			[bmim]PF_6	15	95

[a] Reactions carried out without molecular sieves.

The reaction of benzylamine and piperonal was used to evaluate the possibility of recycling this system. In this sense, after the reaction end the product was extracted with Et_2O and a new charge of reagents was added. The results are shown in Table 3. As depicted in Table 3, it is evident that the system still retains high conversion after repeating the recycling procedure up to 4 times.

It is important to note that no residual ionic liquid in the ether layer or any organic product in the ionic liquids was detected by ^1H NMR analysis.

In summary, imines could be efficiently prepared and isolated under mild conditions by the reaction of aldehydes and amines in ionic liquids in the presence of molecular sieves. These reaction media proved to be useful alternatives to organic solvents in this reaction due to the simplicity of the reaction and workup procedures combined with the possibility of its easy recovery and reuse.

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Table 2 Effect of the Use of Molecular Sieves in the Synthesis of Imines in Different Solvents

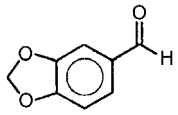
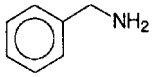
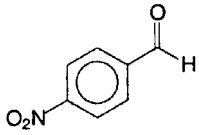
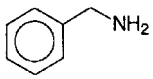
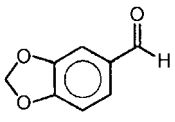
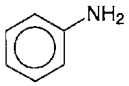
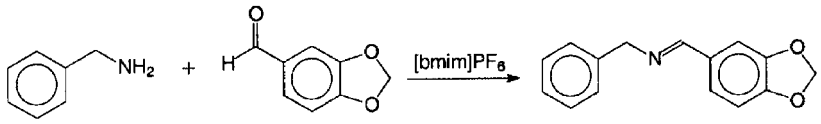
Entry	Aldehyde	Amine	4 Å MS	Solvent	Time (min)	Yield (%)
1			Yes	[bmim]PF_6	15	98
2			No	[bmim]PF_6	45	96
3			Yes	[bmim]BF_4	15	95
4			No	[bmim]BF_4	10	93
5			Yes	CH_2Cl_2	45	91
6			Yes	[bmim]PF_6	120	88
7			No	[bmim]PF_6	330	91
8			Yes	CH_2Cl_2	180	83
9			Yes	[bmim]PF_6	15	96
10			No	[bmim]PF_6	25	97
11			Yes	[bmim]BF_4	80	89
12			No	[bmim]BF_4	80	91
13			Yes	CH_2Cl_2	30	94

Table 3 Recovery and Reuse of the Ionic Liquid Phase Containing Molecular Sieves in the Synthesis of Imines



Entry	Cycle	Time (min)	Yield (%)
1	1	15	98
2	2	15	98
3	3	15	96
4	4	15	96
5	5	15	96

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(8) Part of this work has been presented at the *X Brazilian Meeting on Organic Synthesis*, August, **2003**, São Pedro, SP, Brazil.

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(12) It was found in the reaction between piperonal and benzylamine that it is not really necessary to heat the ionic liquid under vacuum to recover its activity. It was still active even after 3 runs only by removing the solvent under vacuum.

(13) **Typical Experimental Procedure:** A solution of aldehyde (1 mmol) and amine (1 mmol) in [bmim]BF_4 or [bmim]PF_6 (0.5–1.0 mL) containing 4 Å molecular sieves was stirred at r.t. until no starting material has left as confirmed by TLC. The reaction was then extracted with Et_2O (3 × 5 mL) by simple decantation. The combined organic phases were concentrated at reduced pressure to furnish the crude product. The recovered ionic liquid containing molecular sieves was dried at 60–-70 °C under vacuum (0.1 mm Hg) for 0.5 h.

(14) All the compounds gave satisfactory spectroscopic data.