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Synthesis of *N*-alkylimidazolium salts and their utility as solvents in the Beckmann rearrangement

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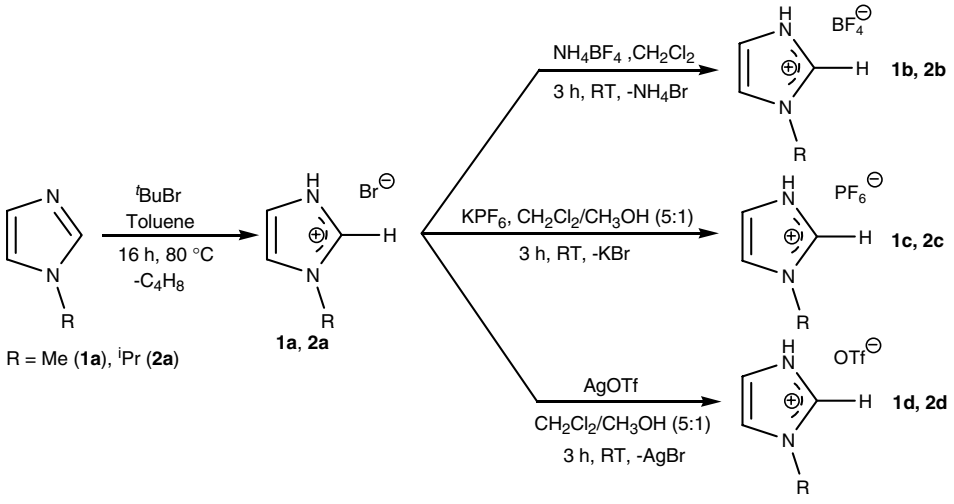
Abstract—Six different room temperature ionic liquids (RTILs) based on *N*-methyl or *N*-isopropyl imidazolium cations with counteranions, such as BF_4^-, PF_6^-, and OTf^-, have been synthesized by exchanging the counteranions of the corresponding *N*-methyl or *N*-isopropylimidazolium bromides using appropriate salts such as NH_4BF_4, KPF_6, and AgOTf. Catalytic amounts of these ionic liquids (ILs) have been used as the reaction medium for the Beckmann rearrangement of oximes to amides in the presence of PCl_5. A moderate to good conversion of oximes to amides in all the six ILs was observed.

The conversion of ketoximes to amides is known as the Beckmann rearrangement and is an important method for the synthesis of various N-substituted amides. Amides, in general, are potential precursors for the synthesis of various natural products as well as synthetic intermediates for medicinal drugs and materials. For instance, ε-caprolactam, has been synthesized industrially through Beckmann rearrangement of cyclohexanone oxime.[1,2] In general, these reactions are carried out in Brønsted acids, such as H_2SO_4 and $SOCl_2$, at high



Scheme 1. Synthesis of *N*-alkylimidazolium salts.

Keywords: *N*-Methylimidazolium bromide; *N*-Isopropylimidazolium bromide; Room temperature ionic liquids (RTILs); Anion exchange; Reaction medium; Beckmann rearrangement; ε-Caprolactam.
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temperatures (130 °C).[3] However, a large amount of NH_4OH is necessary to neutralize the acid, which leads to the formation of $(NH_4)_2SO_4$ as a byproduct. Thus, to avoid corrosion and generation of waste, an alternative, mild route is required and hence Beckmann rearrangements were studied both in organic liquids and in vapor-phase media. Vapor-phase processes have been carried out using solid catalysts such as metal oxides, zeolites and clays at high temperatures close to 300 °C. During these experiments a large amount of coke formation leading to deactivation of the catalysts was observed.[4] A few examples of solvent-free organo catalyzed Beckmann rearrangements have been reported.[5] Beckmann rearrangements in liquid-phase using catalysts such as sulfamic acid, cyanuric chloride, lanthanide triflate, BOP-Cl [bis(2-oxo-3-oxazolidinyl)phosphinic chloride] and $RuCl_3$ in organic solvents such as DMF and acetonitrile, as well as in supercritical water, have been carried out.[6] An advantage of this method is that a high conversion of oximes with very good selectivity has been observed. Although several conversions of oximes to the corresponding amides have been studied, a mild and environmentally benign route for the conversion of cyclohexanone oxime to ε-caprolactam as well as the separation of this product from the reaction mixture is difficult to achieve.

Recently RTILs have been widely used as *green* solvents for various organic syntheses.[7] Deng et al. and others have carried out the Beckmann rearrangements of oximes to amides using Lewis acidic RTILs based on *N*,*N*′-dialkylimidazolium salts or *n*-butylpyridinium tetrafluoroborate in the presence of PCl_5, P_2O_5, or H_3BO_3 as catalyst, which showed high conversions and selectivity, especially for ε-caprolactam.[8] However, the separation of ε-caprolactam from the reaction mixture was difficult due to its recombination with the Lewis acidic RTILs.[8d] One of the advantages of imidazolium based RTILs is the possibility of tuning the physical and chemical properties with respect to the substituent on the nitrogen centers of the imidazolium cations as well as the counteranions. Recent studies have also indicated that the solubility of the imidazolium salts in polar solvents depends upon the nature of the counteranions, which play an important role.[9] The key would be to design a suitable ionic liquid, which is soluble in water, but immiscible with organic solvents, so that the organic products can be extracted using organic solvents. Compared to Lewis acidic ionic liquids, the solubility of Brønsted acidic ionic liquids in water would be greater and hence the latter would be the better choice of solvent to separate the products from the reaction mixtures. Recently, it has been demonstrated that Brønsted acidic RTILs based on *N*-alkylimidazolium salts have been successfully used as reaction media, which promote reactions without the need of any additional catalyst and the final products were separated using simple extraction. Examples include protection of carbonyls as ketals/acetals, preparation of 2,4,5 triarylimidazoles, esterification reactions, and the synthesis of β-enaminones.[10] Further, the use of a caprolactum-based ionic liquid shows better conversion of cyclohexanone oxime and moderate to good isolated yields of

Table 1. Spectral values for ILs **1b–d** and **2a–d**

	Physical state	^{1}H NMR[a] (ppm)					^{13}C NMR[a] (ppm)						[M–X]$^{+}$[b] *m/z*	Yield[c,d] (%)
		2-C*H*	4-C*H*	5-C*H*	N–C*H*$_3$	C*H*(CH$_3$)$_2$	CH(C*H*$_3$)$_2$	2-*C*	4-*C*	5-*C*	N–*C*H$_3$	*C*H(CH$_3$)$_2$	C*H*(CH$_3$)$_2$		
1b	Colorless liquid	9.12	7.69	7.64	3.85	—	—	136.7	124.0	120.7	36.4	—	—	83.0532	94
1c	Colorless liquid	9.09	7.69	7.65	3.86	—	—	135.8	123.1	119.8	35.4	—	—	83.0529	92
1d	Colorless semisolid	9.45	7.88	7.76	3.68	—	—	134.0	120.3	120.0	35.7	—	—	83.0533	89
2a	Light brown liquid	9.41	7.98	7.72	—	4.71	1.45	133.8	120.2	119.7	—	51.8	22.4	111.0804	78
2b	Colorless liquid	9.24	7.90	7.70	—	4.68	1.46	133.9	120.1	119.9	—	51.9	22.4	111.0900	86
2c	Colorless liquid	9.27	7.93	7.71	—	4.69	1.47	133.9	120.1	119.8	—	51.8	22.4	111.0813	93
2d	Colorless semisolid	9.45	7.95	7.68	—	4.67	1.45	133.9	120.3	119.3	—	51.9	22.6	111.0820	89

[a] ^{1}H and ^{13}C NMR spectra were obtained at 400 MHz and 100 MHz, respectively. The spectra were recorded in DMSO-d_6 solution, and the chemical shifts were referenced with respect to tetramethylsilane (^{1}H).

[b] Mass spectrometry was performed in positive ion electrospray mode and methanol was used as the mobile phase.

[c] Isolated yield.

[d] Ionic liquids **1b–d** and **2b–c** were tested with $AgNO_3$ solution; however, the AgBr precipitate was not observed. This indicates the absence of Br^-.

ε-caprolactam were obtained. However, when the same reaction was carried out using *N*-methylimidazolium tetrafluoroborate as catalyst and solvent, the conversion of the cyclohexanone oxime was only 44% with 33% selectivity.[8d]

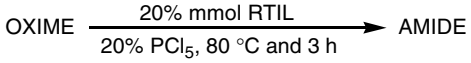
We have synthesized an RTIL based on *N*-methylimidazolium bromide from *N*-methylimidazole and *tert*-butyl bromide.[11] Since we have been interested in studying the utility of ILs as *green* solvents in various organic transformations as well as in the synthesis of coordination polymers; we have prepared six room temperature ionic liquids (RTILs) based on *N*-methyl or *N*-isopropylimidazolium cations with counteranions, including BF_4^-, PF_6^-, and OTf^-. Herein we report the synthesis of *N*-alkylimidazolium salts (**1b–d** and **2a–d**; Scheme 1) and their utility as reaction media in the Beckmann rearrangement in the presence of PCl_5 as catalyst. The solubility of ionic liquids **1b–d** and **2b–d** was very high in polar protic/aprotic solvents but they were immiscible with common organic solvents, which is indeed helpful, especially when recovering the product from the reaction mixture.

N-Alkylimidazolium salts are, in general, prepared by mixing the *N*-alkylimidazole with the corresponding protic acids.[10e] In contrast we have obtained *N*-methylimidazolium bromide by the treatment of commercially available *N*-methylimidazole with *tert*-butyl bromide at elevated temperature. During the reaction, *tert*-butyl bromide releases a molecule of HBr (with evolution of isobutene gas), which further reacts with *N*-methylimidazole, to form *N*-methylimidazolium bromide (**1a**).[12] Following the same method, we also prepared *N*-isopropylimidazolium bromide (**2a**) starting from *N*-isopropylimidazole. Treatment of **1a** and **2a** with salts such as NH_4BF_4, KPF_6, and AgOTf afforded the corresponding *N*-alkylimidazolium salts containing different anions (**1b–d** and **2b–d**; Table 1).[13] The ILs **1b–d** and **2b–d** were soluble in polar protic solvents, including water, methanol, and ethanol (but not in *n*-butanol), and the aprotic solvents, DMSO and DMF; however, they were not soluble in the common organic solvents, toluene, THF, CH_2Cl_2 and $CHCl_3$. ILs **1a** and **2a** were soluble in polar protic, aprotic solvents and also soluble in CH_2Cl_2 and $CHCl_3$.

All the ILs (**1b–1d** and **2a–2d**) were characterized by ^1H and ^{13}C NMR and also by high resolution mass spectrometry (Table 1). In the ^1H NMR, the 2-C*H* proton falls in the range of 9.09–9.47 ppm. Moreover positive ion ESI-MS^+ gave the corresponding cationic ($[M-X]^+$) peak for both *N*-methylimidazolium (**1b–d**) and *N*-isopropylimidazolium (**2a–d**) salts. All the ILs, except **1a** and **2a,** were used as reaction media in the Beckmann rearrangement (Scheme 2).

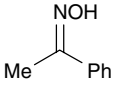
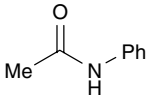
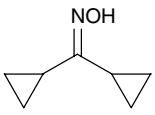
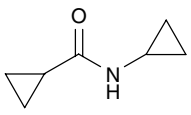
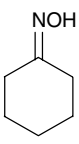
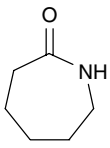
A mixture of PCl_5 (20 mmol %), ionic liquid (20 mmol %) and oxime (2 mmol) was stirred for 3 h at 80 °C under an inert atmosphere.[14] Then water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic phase was separated and the aqueous phase was washed with CH_2Cl_2 (x 3). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum. All the products were characterized by ^1H NMR spectroscopy. The yields were determined from the ^1H NMR spectra, whereas ε-caprolactam was isolated and then crystallized from EtOAc/pet ether (10:1), and its yield calculated (Table 2).

From Table 2, it is evident that good yields of *N*-phenylacetamide were obtained in all the ILs. However, the rearrangement of dicyclopropyl ketoxime in ILs **1c**



Scheme 2. Beckmann rearrangement of oximes in ILs.

Table 2. Beckmann rearrangement of oximes in ILs **1b–d** and **2b–d**

Entry	Reactant	Product[a]	Yield[b] (%)					
			1b	**1c**	**1d**	**2b**	**2c**	**2d**
1			80	74	69	85	83	71
2			31	65	43	54	66	56
3			65[c]	61[c]	42[c]	48[c]	78[c]	31[c]

[a] Products were confirmed by ^1H NMR.
[b] Yields are based on ^1H NMR.
[c] Isolated yield.

and **2c** gave the best product yields compared to the other ILs. The rearrangement of cyclohexanone oxime was also carried out in all the ILs. The yield of ε-caprolactam was high (78%) only when *N*-isopropylimidazolium hexafluorophosphate (**2c**) was used. The isolation of ε-caprolactam was easier from **2c**, which may be due to the high solubility of this IL compared to ε-caprolactam in water. In the other cases, both the IL and ε-caprolactam were highly soluble in water, and hence separation was difficult.

In conclusion, an alternative method for the preparation of *N*-isopropylimidazolium bromide has been reported. The Beckmann rearrangement of three different ketoximes has been investigated using different ILs. The yields were good for the rearrangement of acetophenone oxime in all six ILs, whereas with dicyclopropyl ketoxime and cyclohexanone oxime, good yields were obtained only with *N*-isopropylimidazolium hexafluorophosphate.

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Supplementary data

ESI mass spectra for all ionic liquids are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.051.

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13. *N-Isopropylimidazolium bromide* (**2a**): In a two neck flask, *tert*-butyl bromide (6.85 g, 50 mmol) was added to a toluene (100 mL) solution of *N*-isopropylimidazole (4.41 g, 40 mmol). The resulting mixture was heated to 80 °C for 16 h. The immiscible layers were separated by decanting the toluene and the sticky product was washed with hexane and dried under vacuum.
General procedure for the synthesis of ILs (**1b–d** *and* **2b–d**): Ammonium tetrafluoroborate, potassium hexafluorophosphate, or silver triflate (15 mmol) was added to a solution of **1a** or **2a** (15 mmol) in CH_2Cl_2 (25 mL)/CH_3OH (5 mL). The resulting mixture was stirred at room temperature for 3 h. The solution was cooled to −20 °C, filtered and the volatiles were removed from the filtrate under vacuum to afford the respective ionic liquids.
14. Prior to the Beckmann rearrangement, all the ionic liquids were subjected to vacuum for half an hour to ensure complete removal of water.