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Pyrrole synthesis in ionic liquids by Paal–Knorr condensation under mild conditions

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Abstract—Paal–Knorr condensation of 2,5-hexandione with primary amines was successfully carried out in ionic liquids. Through investigating different ionic liquids, different reaction times, the reaction, using ionic liquids as solvent, exhibited simple product isolation procedure, improved yields and exclusive selectivity and the mild conditions and the avoidance of using toxic catalysts are also its special features. Recovery and reuse of ionic liquid are also satisfactory.

Room temperature ionic liquids, especially those based on the 1-alkyl-3-methylimidazolium cation, have given a promise as attractive alternative to conventional solvents. Besides their special characteristics,[1] they can even not only promote some organic reactions,[2] but also provide the chemoselectivity to some reaction processes[3] and simple and convenient isolation of product in catalytic reactions.[4] In our continuing effort to utilize ionic liquids as an environmentally attractive media, for the synthesis and catalysis processes, we have some interests in the organic reactions participated by some nitrogen-containing compounds because their rate could be evidently accelerated by ionic liquids.[5]

Most recently, Paal–Knorr condensation has experienced a rekindled interest in the synthetic chemistry for the preparation of pyrrole, pyrazoles and their derivatives, as naturally occurring organic compounds and intermediates for pharmaceutical industry. Various acidic materials, such as zeolite,[6] $Ti(OPr^i)_4$,[7] Al_2O_3,[8] *p*-TSA,[9] layered zirconium phosphate and zirconium sulfophenyl phosphonate,[10] as well as the microwave technology[11] have been used to promote these condensations. However, some of them often involve the use of excess amounts of acids because they can be trapped by nitrogen in this condensation, or hazard organic solvents, tedious workup, large amounts of solid catalysts,[6] may not be the preferred choices in view of green chemistry. Hence, an efficient and mild Paal–Knorr condensation is needed for contemporary chemical synthesis. Herein, we wish to report our preliminary results on the synthesis of pyrroles from γ-diketone and primary amines in ionic liquids at ambient temperature.

Initial experimentation was undertaken in $[BMIm]BF_4$ ionic liquid. Two conditions were used: one in which the reaction had gone to completion, was to obtain the yields as far as it can achieve; the other was terminated before completion, so that the conversion of aniline after a certain period was observed. When using diethyl ether as extractant, the pyrrole product and unreacted aniline could be recovered with thoroughly mass balances as assessed using nitrobenzene as external standard, however, cyclohexane and hexane were failed.

In conventional systems, an excess of amine usually has to be used in order to promote the condensation.[10] From a recent atom-economical standpoint, the use of nearly equimolar amounts of substrates is strongly required. Thus we have initially treated aniline with equimolar 2,5-hexandione in ionic liquids as well as in organic solvents to compare their efficiency and the results are presented in Figure 1.

In these ionic liquids, it can be seen that the initial rate of these reactions is very high as 70–91% aniline conversion was obtained in the 1 h, especially in [BMIm]I, 86% of aniline was consumed within 30 min and the

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Keywords: Paal–Knorr; Ionic liquid; 2,5-Hexandione; Primary amine; Pyrrole.

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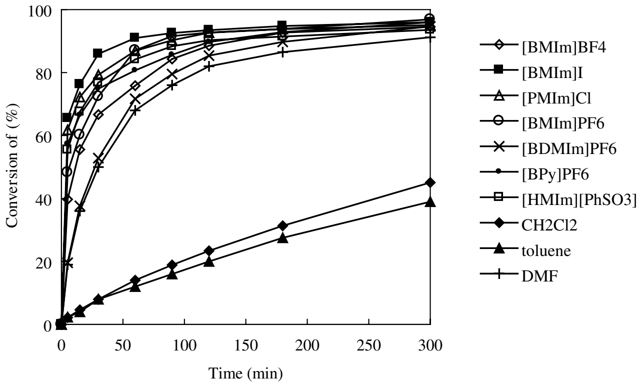
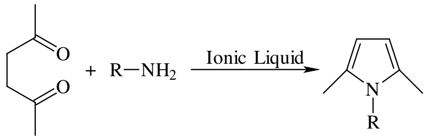


Figure 1. Paal–Knorr condensation of aniline with 2,5-hexandione to compare the efficiency of ionic liquids and organic solvents.



Scheme 1. Synthesis of N-substituted-2,5-dimethylpyrrole in some ionic liquids.

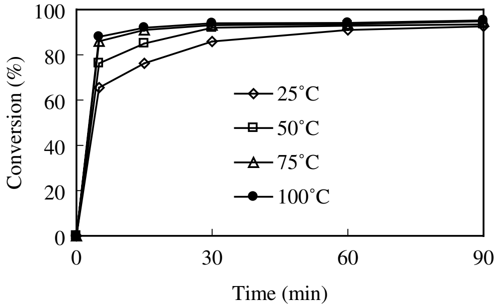


Figure 2. The effect of temperature on the Paal–Knorr condensation of aniline with 2,5-hexandione in [BMIm]I ionic liquid.

Table 1. Pyrroles derivatives produced from Paal–Knorr condensation in [BMIm]I (via Scheme 1)

Entry	R	Time (min)	Yield (%)[a]
1	*n*-Propyl	30	96
2	*n*-Heptyl	30	95
3	*iso*-Propyl	30	96
4	*t*-Butyl	60	97
5	Cyclohexyl	60	95
6	Benzyl	30	99
7	Phenyl	180	96 (94)[b]
8	Tolyl	180	94
9	*p*-Nitrophenyl	180	93
10	*p*-Methoxyphenyl	180	95
11	2-Pyridinyl	180	85

[a] GC yield.

[b] Yield of *N*-phenyl-2,5-dimethylpyrrole obtained in the ionic liquid of having been reused three times.

product exclusively is *N*-phenyl-2,5-dimethylpyrrole. It is noteworthy that Figure 1 shows the maximum conversions of aniline, obtained in all the tested ionic liquids within 5 h, are all greater than 94%. To determine whether the ionic liquid was an essential factor to realize the high conversions of this condensation, the same reaction (Scheme 1) was carried out in traditional solvents. As a result, the Paal–Knorr condensations were sluggish in CH_2Cl_2 and toluene, and the conversions only reached 45% and 39%, respectively, after 5 h reaction. But the result in nitrogen-containing solvents, such as DMF was better. It is worthy to note that aniline has a relatively low activity for this reaction, in order to obtain the yield as high as possible in the traditional systems,[10] even more than 24 h has to be used, which reproducibly indicated the effectiveness of ionic liquids for Paal–Knorr pyrrole synthesis.

Having established the best solvent [BMIm]I, we started to study the effect of temperature on the Paal–Knorr condensation of aniline with 2,5-hexandione and the results are presented in Figure 2. When the reaction temperature was raised, maximum yield was reached soon: for a 25 °C rise in temperature, the reaction time can be halved until 75 °C. Because the 1.5 h of reaction time, which is comparable with the conventional systems, is sufficient to complete this condensation under room temperature, the reaction was ultimately carried out at 25 °C to meet the requirement of minimization of energy consumption, which is one of the principles of green chemistry.

Having these results in hand, other amines have been subjected to the above-mentioned optimized conditions, and the results are listed in Table 1. It is evident that our methodology is reasonably general and can be applied to several amines. It is well known that the reactivity of aliphatic amines is more potent compared with that of aromatic amines, thus aliphatic amines give higher yields or shorter reaction times that are generally observed in other systems.[6] It is gratifying that labile functionality such as methoxy and nitro groups are tolerated under this reaction condition.

The recycle process was investigated starting with fresh [BMIm]I and aniline. After the reaction was completed (monitored by GC), the ionic liquid was recycled and reused in the next cycle with the same substrate. To our delight, the ionic liquid could be reused three times without losing activity.

In summary, Paal–Knorr condensation of 2,5-hexandione with an amine was successfully achieved in ionic liquids. Compared with classical methods, the reaction using ionic liquids as solvent has exhibited simple product isolation procedure, improved yields and exclusive selectivity. Other advantages are the accelerated reaction rate, mild conditions and avoidance of using toxic catalysts. Recovery and reuse of ionic liquids are also satisfactory, which demonstrates the cost efficiency and green aspect of our methodology.

A representative procedure as follows: Aniline (1 mmol) and 2,5-hexandione (1 mmol) were dissolved into 1.5 g [BMIm]I ionic liquid in a 50 mL round bottom flask equipped with a magnetic stirer, and the mixture was heated at room temperature for 3 h with vigorous stirring. After the reaction, the content was extracted with ethyl ether (5 mL × 3). The GC/MS analysis of the combined organic extractant indicated the formation of *N*-phenyl-2,5-dimethylpyrrole.

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