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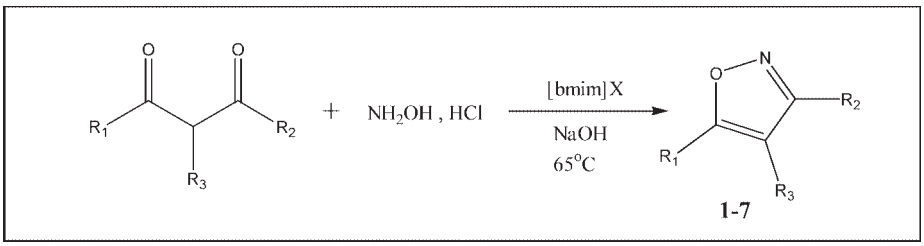

An efficient one-pot synthesis of 3,5-disubstitueted isoxazoles from β-diketones in room temperature ionic liquids (ILs) is described. Compared with the classical reaction conditions, this new synthetic method is environmentally friendly and has the advantages of recyclability of IL and very good to excellent yields.

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INTRODUCTION

Synthesis of substituted isoxazole derivatives is particularly important because a lot of compounds containing the isoxazole ring system are known to have a variety of biological activities in pharmaceutical and agricultural areas [1]. Their range of uses includes medicinal, herbicidal, fungicidal, pesticidal applications, dyes, insulating oils, and lubricants. Since Claisen's report in 1891 [2], many methods have been developed for the preparation of substituted isoxazoles which can generally be divided into two synthetic routes. The first involves the condensation reaction of a hydroxylamine with a carbonyl compound and provides easy access to 3,5-disubstituted isoxazoles [1]. The second route involves the 1,3-dipolar cycloaddition of a nitrile oxide with an alkyne. In this transformation, nitrile oxides react intermolecularly with monosubstituted alkynes to again give a preponderance of 3,5-disubstituted isoxazoles [3] and furoxan is a significant byproduct.

Room temperature ionic liquids (ILs) have been the subject of considerable interest as new, nonvolatile, and environmentally friendly alternatives to conventional organic solvents. They are salts of organic cations and a variety of anions [4–7]. ILs are compatible with several organic transformations [8–10], they readily immobilize several catalysts in their native form [11,12] or the supported catalysts [13]. They have been found to alter the outcome of chemical reactions in a dramatic fashion [14], thus forming a new paradigm in organic synthesis.

In continuation of our recent interest to use ILs, water or solventless systems as green reaction mediums [15], we report herein the synthesis of isoxazole derivatives in reusable imidazolium-based ILs using NaOH as base Scheme 1.

A typical reaction of dibenzoylmethane with hydroxyl-amine was carried out in the IL, [bmim]Br, at ambient conditions to form 3,5-diphenyl isoxazole. However, at room temperature, reaction does not proceed further to afford the product even in trace amounts. Consequently, the reaction was carried out at higher temperatures and optimum results were obtained at 65°C (75%).

For further optimization, several ILs based on butylmethylimidazolium salts [bmim]X with varying anions were screened for the typical reaction of dibenzoil-methane with hydroxylamine at 65°C for complete conversions as monitored by TLC to afford 3,5-diphenyl isoxazole. The results are recorded in Table 1. Evidently, $[bmim]BF_4$ was found to be superior in terms of yield (83%) and reaction time (5 h) when compared with other ILs.

Consequently, all further reactions with other β-diketones were conducted by using $[bmim]BF_4$ as the reaction medium Table 2. Acetylacetone and 2,4-hexanedione were mostly recovered unchanged. All the products were fully characterized by M.P., ^{13}C NMR, ^{1}H

Scheme 1

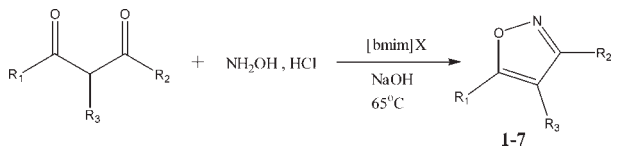

Table 1

Synthesis of 3,5-diphenyl isoxazole in [bmim]X at 65°C.

Entry	Ionic liquid	Time (h)	Yield[a] (%)
1	[bmim]Br	5	75
2	[bmim]BF_4	5	83
3	[bmim]Cl	5	72
4	[bmim]ClO_4	5	70
5	[bmim]PF_6	5	72

[a] Isolated yield after column chromatography.

NMR, and the values [16] were in agreement with those reported in literature.

Recycling of the IL was carried out for the reaction of β-diketone and hydroxylamine hydrochloride following an extremely straightforward protocol. After complete reaction and workup the residue containing IL was dissolved in EtOAc, filtered through a filter paper, dried over Na_2SO_4, and the solvent was removed on a rotary evaporator. The IL was further vacuum dried at 0.1 mmHg for 1 h and used for two more runs under identical conditions as for run 1. The results gained are shown in Table 3. It can be seen that a slight reduction in yield was observed in runs carried out using ''old'' IL, and furthermore the products obtained were of the same purity as in the first run.

In conclusion, a novel method for the one-pot synthesis of the biologically active isoxazoles has been developed by the reaction of β-diketone and hydroxylamine hydrochloride in the IL [bmim]Br in excellent isolated yields. The solvent IL was recovered almost entirely and recycled successfully. The moderate reaction conditions, easy workup procedure and recyclability of the nonvolatile IL make this an environment friendly method amenable for scaleup.

EXPERIMENTAL

All of the melting points are uncorrected and were determined with a Stuart scientific apparatus. Infrared spectra were recorded in KBr and were determined on a PerkinElmer FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ as solvent and TMS as internal standard. All solvents and chemicals were of research grade and were used as obtained from Merck. The imidazolium-based ILs investigated were prepared according to the procedure reported in the previous literature [17].

Table 2

Preparation of 3,5-disubstituted isoxazoles in [bmim]BF_4.

					Melting point (°C)		
Product number	R_1	R_2	R_3	Time (h)	Found	Reported	Yield[a] (%)
1	Ph	Ph	H	5	138–142	140-141 [18]	83
2	Ph	Me	H	6.2	65–68	67 [19]	78
3	Ph	Ph	Me	5.5	121–123	–	78
4	Ph	4-$NO_2C_6H_4$	H	6	223–227	226–228 [20]	78
5	Ph	4-ClC_6H_4	H	6	170–177	172–178 [21]	81
6	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	H	5.5	169–174	172–175 [21]	75
7	4-$MeOC_6H_4$	4-ClC_6H_4	H	5.5	207–211	210 [20]	73

[a] Isolated yield after column chromatography.

Table 3

Ionic liquid recycling for the reaction of β-diketone and hydroxylamine hydrochloride.

	Cycle 1		Cycle 2		Cycle 3	
Ionic liquid	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
[bmim]Br	5	80	6	78	7	76
[bmim]BF_4	5	83	6	80	7	79
[bmim]Cl	5	72	6	70	7	69
[bmim]ClO_4	5	70	6	68	7	65
[bmim]PF_6	5	72	6	71	7	67

[a]Isolated yields of 3,5-diphenylisoxazole.

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[16] General procedure for compounds (**1–7**): A mixture of β-diketone (1 mmol), hydroxylamine hydrochloride (1.1 mmol), and NaOH (1 mmol) was heated in 2 mL [bmim]BF_4 at 65°C for appropriate time (Table 1). The completion of reaction was monitored by TLC using (EtOAc/petroleum 1:8) as eluent. After completion of the reaction, the mixture was extracted with Et_2O (15 mL × 3). The Et_2O layers were collected and concentrated in vacuum. Then the crude mixture was purified by column chromatography using (HEX/EtOAc 9:1) on silica gel to afford corresponding isoxazoles. $C_{15}H_{11}NO$ (**1**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, 4H, Ph), 7.34 (m, 6H, Ph), 6.43 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 147.1, 136.9, 127.9, 127.0, 126.1, 98.3; *Anal*. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; O, 7.23. Found: C, 81.40; H, 4.98; N, 6.30; O, 7.32. $C_{10}H_9NO$ (**2**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, 2H, Ph), 7.34 (m, 3H, Ph), 6.46 (s, 1H, CH), 2.25 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 146.1, 136.4, 127.9, 127.7, 126.0, 98.4, 17.3. $C_{16}H_{13}NO$ (**3**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, 4H, Ph), 7.36 (m, 6H, Ph), 2.35 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9, 149.1, 138.4, 129.9, 129.0, 128.2, 96.4, 19.3; *Anal*. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95; O, 6.80. Found: C, 81.66; H, 5.54; N, 5.93; O, 6.87. $C_{15}H_{10}N_2O_3$ (**4**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, 2H, Ph), 7.44–7.49 (m, 5H, Ph), 7.44 (d, 2H, Ph), 6.33 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9, 158.9, 152.7, 150.1, 146.6, 142.6, 138.4, 129.9, 129.2, 127.2, 99.7. $C_{15}H_{10}ClNO$ (**5**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, 2H, Ph), 7.38–7.5045 (m, 5H, Ph), 7.44 (d, 2H, Ph), 6.46 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 158.9, 151.7, 149.1, 144.5, 140.9, 137.4, 128.0, 127.0, 125.2, 98.0. $C_{16}H_{12}N_2O_4$ (**6**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, 2H, Ph), 7.34–7.50 (m, 4H, Ph), 7.25 (d, 2H, Ph), 6.35 (s, 1H, CH), 4.32 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 157.9, 151.7, 149.1, 145.5, 140.6, 136.4, 128.9, 128.0, 126.2, 98.4. $C_{16}H_{12}ClNO_2$ (**7**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, 2H, Ph), 7.30–7.45 (m, 4H, Ph), 7.25 (d, 2H, Ph), 6.32 (s, 1H, CH), 4.35 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8, 158.1, 152.5, 150.1, 146.5, 139.6, 136.0, 126.9, 126.9, 127.2, 100.1; *Anal*. Calcd. for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; Cl, 12.41; N, 4.90; O, 11.20. Found: C, 67.21; H, 4.20; Cl, 12.37; N, 4.88; O, 11.34.

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