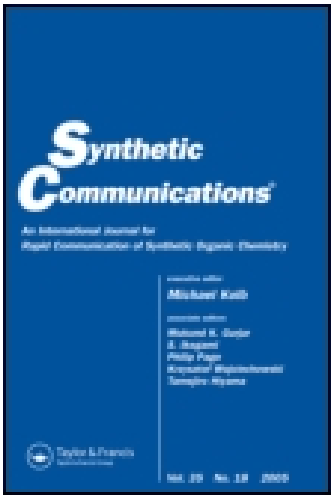

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Efficient Synthesis of Quinoxalines in the Ionic Liquid 1-*n*-Butylimidazolium Tetrafluoroborate ([Hbim]BF_4) at Ambient Temperature

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Pune, India

Abstract: Quinoxaline derivatives have been synthesized in excellent yields using an ionic liquid (IL) (viz., 1-*n*-butylimidazolium tetrafluoroborate) as a reaction medium as well as promoter from various 1,2-diketones and aryl-1,2-diamines. The process is general for the synthesis of quinoxaline derivatives from aromatic as well as aliphatic-1,2-diketones. The advantages of the present method are ambient reaction temperature, simplicity of operation, high yields of products, the recyclability of the IL, and ecofriendly nature of the reaction medium.

Keywords: Aryl-1,2-diamines, 1,2-diketones, ionic liquid (IL), quinoxalines

INTRODUCTION

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles and have shown a broad spectrum of biological activities.[1,2] The quinoxaline ring moiety constitutes part of various antibiotics such as echinomycin, levomycin, and actinoleutin,[3] which are known to inhibit growth of Gram-positive bacteria. They have been reported for their applications in pharmaceuticals[4,5] and have also been used as building blocks for the synthesis of organic semiconductors.[6,7] They are also well known for their applications in efficient electroluminescent materials[8]

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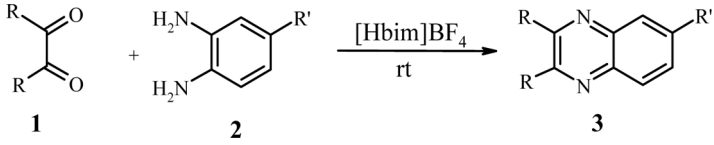
and as building blocks for the synthesis of anion receptors,[9] cavitands,[10] dehydroannulenes,[11] and DNA-cleaving agents.[12]

By far the most common method of synthesis relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h, giving 34–85% yields.[13] Numerous methods are available in the literature for the synthesis of quinoxaline derivatives including the Bi-catalyzed oxidative coupling of epoxides and ene-1,2-diamines,[14] solid-phase synthesis on Synphase™ lanterns,[15] cyclization of a-arylimino oximes of α-dicarbonyl compounds under reflux in acetic anhydride,[16] condensation of *o*-phenylenediamines and 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation,[17] iodine-catalyzed cyclocondensation of 1,2-dicarbonyl compounds and substituted *o*-phenylenediamines in dimethyl sulfoxide (DMSO)[18] and CH_3CN,[19] and cerium ammonium nitrate (CAN)-catalyzed cyclocondensation reaction between 1,2-dicarbomyl compounds and 1,2-diamines.[20] Recently, Heravi et al. reported the synthesis of quinoxaline derivatives catalyzed by $CuSO_4 \cdot 5H_2O$ in water and Zn[(L)proline] in HOAc.[21]

However, most of the existing methodologies suffer from disadvantages such as use of volatile organic solvents, use of catalyst, use of expensive and detrimental metal precursors, critical product isolation procedures that limit their use under the aspect of environmentally benign processes. Thus, to replace these critical reaction conditions and limitations, the development of a new synthetic process for the synthesis of quinoxaline derivatives would be highly desirable. In recent times, room-temperature ionic liquids (RTILs) have shown great promise as attractive alternatives to conventional solvents. They possess the unique advantages of high thermal stability, negligible vapor pressure, immiscibility with a number of organic solvents, and recyclability.[22] As part of our ongoing program to develop more efficient methods for the synthesis of biologically active heterocycles[23] using environment friendly solvents such as an ionic liquid (IL), we herein report the synthesis of 2,3-disubstituted quinoxaline derivatives from 1,2-diketone and aryl-1,2-diamines in the IL, 1-*n*-butylimidazolium tetrafluoroborates as reaction medium as well as promoter.

RESULTS AND DISCUSSION

In the beginning, a model reaction was carried out by condensing benzil with 1,2-diaminobenzene in the IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4). When a mixture of benzil and 1,2-diaminobenzene was stirred in [Hbim]BF_4 at room temperature, it afforded the desired product 2,3-diphenyl-quinoxaline **3a** in 96% yield in just 20 min (Scheme 1).



Scheme 1. Synthesis of quinoxaline derivatives in $[Hbim]BF_4$.

To optimize the reaction conditions, ILs based on 1-*n*-butylimidazolium [Hbim] cations with varying anions were screened for this model reaction at room temperature for 2 h to afford 2,3-diphenyl-quinoxaline **3a**, and the results are summarized in Table 1. It is evident from the result that among the screened ILs, $[Hbim]BF_4$ the best by virtue of its inherent Brønsted acidity conferred by the most acidic –NH hydrogen [chemical shift δ ppm = 14.6].

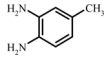
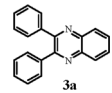
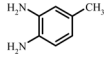
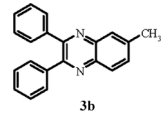
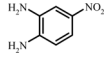
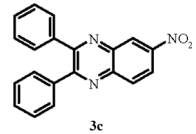
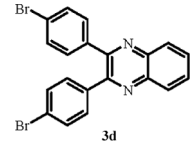
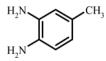
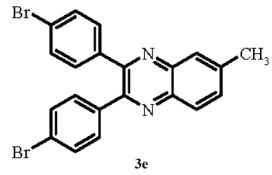
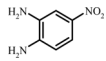
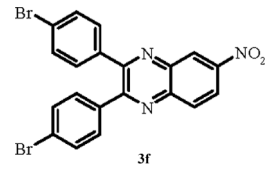
Consequently, all further studies were carried out using $[Hbim]BF_4$ as a reaction medium as well as promoter for the synthesis of various quinoxaline derivatives. To investigate the scope and generality of this process, a series of aryl-1,2-diketone **1** and substituted 1,2-diaminobenzene **2** was subjected to condensation using IL as reaction media. The process tolerates well both electron-donating as well as electron-withdrawing substituents on 1,2-diaminobenzene and afforded the quinoxaline derivatives in excellent isolated yields. The applicability of the methodology is further successfully extended for the synthesis of substituted quinoxalines by performing the reaction with aliphatic-1,2-diketone and 1,2-diaminobenzene. When aliphatic-1,2-diketone such as 1,2-cyclohexandione and 3,4-hexanedione were subjected to condensation with 1,2-diaminobenzene, reactions were smoothly completed in short reaction times (10–15 min) and afforded the corresponding 2,3-dialkyl-quinoxaline derivatives in good isolated yields. However, the yields are relatively lower than 2,3-diaryl-quinoxalines. On reviewing the literature on quinoxaline synthesis, it was observed that very few methods have been reported for the synthesis of 2,3-dialkyl-quinoxalines. It was noteworthy that our process is equally applicable for both aromatic-1,2-diketone as well as for aliphatic-1,2-diketone (Table 2, Entries 9–12).

Table 1. Synthesis of 2,3-diphenyl quinoxaline **3a** in different ILs

Entry	ILs	p*Ka*[a]	–NH proton δ ppm	Yield[b] (%)
1	$[Hbim]ClO_4$	−11	11.83	62
2	[Hbim]Br	−9	12.17	79
3	[Hbim]Cl	−7	12.22	88
4	$[Hbim]BF_4$	0.5	14.59	96

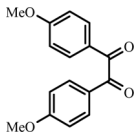
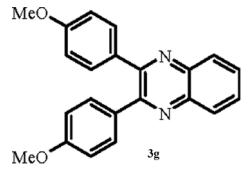
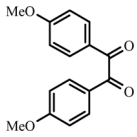
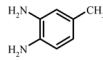
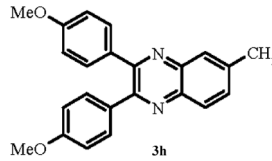
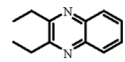
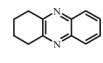
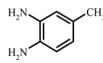
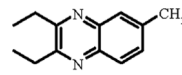
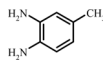
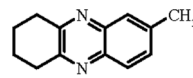
[a]The p*Ka* values of the parent acid of the anions.
[b]Isolated yield after column chromatography.

Table 2. Synthesis of quinoxalines (3a–l) in $[Hbim]BF_4$

Entry	Diketone **1**	1,2-Diamine **2**	Quinoxalines **3**	Time (min)	Yield[a] (%)	Mp (°C)
1			 **3a**	20	96	128–129 (126–127[21a])
2			 **3b**	15	95	117–118 (116–117[21a])
3			 **3c**	15	96	193–194 (193–194[21a])
4			 **3d**	20	94	194–195
5			 **3e**	25	92	185–186
6			 **3f**	25	89	188–190

(*Continued*)

Table 2. Continued

Entry	Diketone 1	1,2-Diamine 2	Quinoxalines 3	Time (min)	Yield[a] (%)	Mp (°C)
7			 **3g**	20	91	152–153 (151–152[21a])
8			 **3h**	40	96	126–127 (125–127[21a])
9			 **3i**	10	78	51–52
10			 **3j**	15	69	94–95
11			 **3k**	15	75	41–42
12			 **3l**	10	71	84–85

[a]Isolated yield after column chromatography.

The efficacy of the ILs to promote these heterocyclization reactions was correlated with the basicity of the anions as well as –NH proton chemical shifts of the ILs. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield (Table 1). This correlation was also evident when the yield of **3a** was compared with –NH proton chemical shifts of the ILs indicative of the Brønsted acidities of the [Hbim] ILs (Table 1). The IL [Hbim]BF_4 has most efficiently promoted this heterocyclization reaction by virtue of its inherent Brønsted acidity conferred by the most acidic –NH hydrogen [chemical shift δ ppm = 14.6].

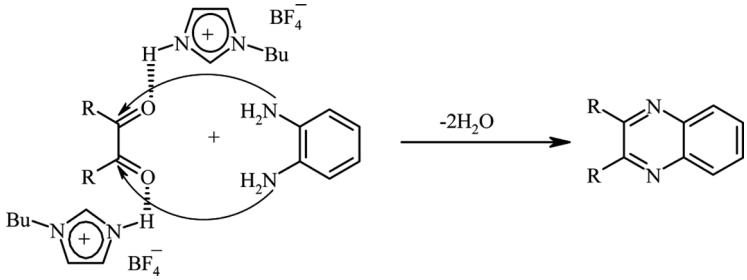
The reaction procedure is very simple and easy to carry out. A mixture of 1,2-diketone and 1,2-diaminobenzenes in IL was stirred at ambient temperature until completion of the reaction. On completion, the reaction mixture was diluted with water, and the product was extracted using an innocuous solvent such as ethyl acetate. The organic layer was separated from the aqueous phase and evaporated under reduced pressure to afford the crude quinoxalines, which were further purified by column chromatography. All the products were characterized by their melting point, IR, elemental analyses, and ^1H and ^{13}C NMR spectroscopy. For known compounds, the values were in good agreement with those reported in the literature. The aqueous layer containing the IL was subjected to distillation at 80 °C under reduced pressure (10 mm Hg) for 4 h to remove water, leaving behind the IL in almost complete recovery. The IL thus recovered was further used three times for the typical reaction of benzil and 1,2-diaminobenzene without any loss in yield and purity.

Plausible Mechanism

Based on these observations, the following probable mechanism may be postulated for this reaction as shown in Scheme 2. The role of the IL may be postulated in terms of some Brønsted acidity of the –NH proton of the imidazolium cation, leading to its interaction with the carbonyl oxygen atom of 1,2-diketone, thereby increasing the polarization and promoting the cyclocondensation reaction.

CONCLUSION

In conclusion, we have developed a simple, convenient, and efficient method for the synthesis of quinoxaline derivatives from various



Scheme 2. Plausible mechanism for the synthesis of quinoxalines.

1,2-diketones and 1,2-diaminobenzene using the IL 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) as a reaction medium as well as promoter under mild reaction conditions at room temperature. The process is general for the synthesis of quinoxaline derivatives from aromatic as well as aliphatic-1,2-diketones. The advantages of the present procedure are simplicity of operation, short reaction times, high yields of products, and complete recyclability of the reaction medium.

EXPERIMENTAL

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-200 spectrometer in $CDCl_3$ using TMS as the internal standard. Infrared (IR) spectra were recorded with ATI Mattson RS-1 FTIR spectrometer using KBr pellets. Elemental analyses were obtained using a flash EA 1112 Thermofinnigan instrument. Melting points were recorded in an open capillary on a Buchi Melting-Point B-540 apparatus. All solvents and chemicals were of research grade and were used as obtained from Merck and Lancaster. Column chromatography was performed using silica gel (60 to 120-mesh size).

General Procedure for the Synthesis of Quinoxaline Derivatives

A mixture of 1,2-diketone **1** (1 mmol) and aryl-1,2-diamine **2** (1.1 mmol) in [Hbim]BF_4 (2 mL) was stirred at room temperature for the appropriate time mentioned in Table 2. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was diluted with water and extracted using ethyl acetate (3×10 mL). The combined organic layer was dried over

anhydrous magnesium sulfate and evaporated under reduced pressure to obtain the crude product, which was further purified by column chromatography using petroleum ether–ethyl acetate (5:95 ratio) to obtain the pure 2,3-disubstituted-quinoxaline derivatives **3**.

Characterization Data for New Quinoxaline Derivatives

2,3-Bis(4-bromophenyl)quinoxaline (**3d**)

White solid; mp 194–195 °C; IR (KBr): υ_{max} 3019, 1589, 1343, 1216, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.36–7.42 (m, 4H, ArH), 7.47–7.53 (m, 4H, ArH), 7.76–7.81 (q, $J = 6.40$ & 3.45 Hz, 2H, ArH), 8.12–8.17 (q, $J = 6.40$ & 3.45 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 123.6, 129.1, 130.3, 131.3, 131.6, 137.5, 141.1, 151.8. Anal. calcd. for $C_{20}H_{12}Br_2N_2$ (440): C, 54.58; H, 2.75; N, 6.36. Found: C, 54.67; H, 2.84; N, 6.48.

2,3-Bis(4-bromophenyl)-6-methylquinoxaline (**3e**)

White solid; mp 185–186 °C; IR (KBr): υ_{max} 3019, 2974, 1619, 1589, 1484, 1342, 1215, 1073, 979, 833, 757, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.61 (s, 3H, CH_3), 7.34–7.40 (m, 4H, ArH), 7.46–7.51 (m, 4H, ArH), 7.59–7.64 (dd, $J = 8.58$ & 1.88 Hz, 1H, ArH), 7.91 (s, 1H, ArH), 8.01–8.05 (d, $J = 8.58$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.9, 123.4, 123.5, 127.9, 128.6, 131.3, 131.5, 132.7, 137.7, 139.6, 141.0, 141.2, 150.9, 151.6. Anal. calcd. for $C_{21}H_{14}Br_2N_2$ (454): C, 55.54; H, 3.11; N, 6.17. Found: C, 55.41; H, 3.21; N, 6.32.

2,3-Bis(4-bromophenyl)-6-nitroquinoxaline (**3f**)

Faint yellow solid; mp 188–190 °C; IR (KBr): υ_{max} 3019, 1618, 1588, 1528, 1344, 1216, 1129, 1072, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.39–7.45 (m, 4H, ArH), 7.49–7.54 (m, 4H, ArH), 8.22–8.27 (d, $J = 9.14$ Hz, 1H, ArH), 8.47–8.53 (dd, $J = 9.14$ & 2.48 Hz, 1H, ArH), 8.99–9.00 (d, $J = 2.48$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 123.6, 124.6, 124.7, 125.4, 130.7, 131.3, 131.8, 136.4, 136.5, 139.8, 143.3, 147.9, 154.0, 154.6. Anal. calcd. for $C_{20}H_{11}Br_2N_3O_2$ (485): C, 49.52; H, 2.29; N, 8.66. Found: C, 49.41; H, 2.17; N, 8.81.

2,3-Diethylquinoxaline (**3i**)

White solid; mp 51–52 °C; IR (KBr): υ_{max} 3064, 2974, 2875, 1607, 1487, 1459, 1397, 1283, 1046, 757, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ

1.37–1.44 (t, $J = 7.51$ Hz, 6H, CH_3), 2.99–3.10 (q, $J = 7.51$ Hz, 4H, CH_2), 7.62–7.67 (q, $J = 6.30$ & 3.50 Hz, 2H, ArH), 7.97–8.02 (q, $J = 6.30$ & 3.50 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.4, 28.2, 128.3, 128.5, 140.9, 157.1. Anal. calcd. for $C_{12}H_{14}N_2$ (186): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.53; H, 7.67; N, 14.89.

1,2,3,4-Tetrahydrophenazine (**3j**)

Pale yellow solid; mp 94–95 °C; IR (KBr): υ_{max} 3019, 2948, 2868, 1592, 1565, 1487, 1340, 1215, 1213, 928, 826, 756, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.03 (s, 4H, CH_2), 3.15 (s, 4H, CH_2), 7.62–7.67 (q, $J = 6.40$ & 3.45 Hz, 2H, ArH), 7.93–7.98 (q, $J = 6.40$ & 3.45 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.6, 33.0, 128.1, 128.8, 141.0, 153.9; Anal. calcd. for $C_{12}H_{12}N_2$ (184): C, 78.23; H, 6.57; N, 15.21. Found: C, 78.11; H, 6.70; N, 15.29.

2,3-Diethyl-6-methylquinoxaline (**3k**)

White solid; mp 41–42 °C; IR (KBr): υ_{max} 2974, 2876, 1623, 1563, 1459, 1377, 1240, 1046, 964, 829, 755, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35–1.43 (t, $J = 7.48$ Hz, 6H, CH_3), 2.54 (s, 3H, CH_3), 2.96–3.07 (q, $J = 7.48$ Hz, 4H, CH_2), 7.45–7.50 (dd, $J = 8.60$ & 1.92 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 7.85–7.89 (d, $J = 8.52$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.4, 12.5, 21.5, 28.1, 28.2, 127.3, 127.8, 130.7, 138.7, 139.3, 140.9, 156.1, 156.9. Anal. calcd. for $C_{13}H_{16}N_2$ (200): C, 77.96; H, 8.05; N, 13.99. Found: C, 77.83; H, 7.93; N, 14.15.

1,2,3,4-Tetrahydro-7-methylphenazine (**3l**)

Brown solid; mp 84–85 °C; IR (KBr): υ_{max} 3018, 2947, 2867, 1622, 1495, 1454, 1215, 934, 817, 756, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.98– 2.05 (m, 4H, CH_2), 2.54 (s, 3H, CH_3), 3.09–3.16 (m, 4H, CH_2), 7.45–7.50 (dd, $J = 8.60$ & 1.88 Hz, 1H, ArH), 7.72 (s, 1H, ArH), 7.81–7.86 (d, $J = 8.60$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.6, 22.7, 32.9, 33.0, 127.0, 127.6, 131.0, 139.0, 139.4, 141.1, 152.9, 153.7. Anal. calcd. for $C_{13}H_{14}N_2$ (198): C, 78.75; H, 7.12; N, 14.13. Found: C, 78.63; H, 7.33; N, 14.04.

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