Ionic Liquid Promoted Multicomponent Reaction: A Good Strategy for the Eco-Compatible Synthesis of Functionalized Pyrroles

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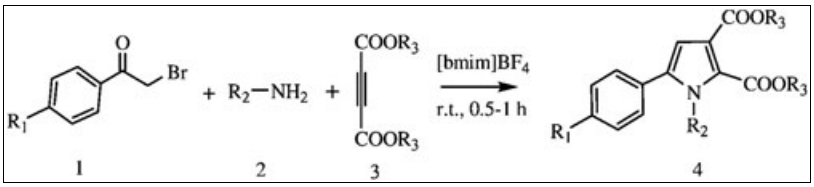

Task specific [bmim]BF_4 was found to be reusable, alternative, and effective reaction media for multicomponent synthesis of highly functionalized pyrroles. Generality of the procedure was established by synthesizing various pyrroles from wide range of aromatic/aliphatic amine, phenacyl bromide, and electrophilic alkynes by utilizing this protocol without any acid or metal catalyst. Ecocompatibility, short reaction time, excellent yield, recyclability of [bmim]BF_4, low cost, easy work-up, and mild reaction conditions are additional advantages of the procedure in the context of sustainable and green chemistry.

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INTRODUCTION

Pyrroles are common structural motif in variety of natural products [1], biologically active compounds [2], and several drugs [3]. They also play major role in the synthetic building blocks [4], pharmacophore [5], and various kind of functional material [6]. In addition, pyrroles find application as promising organic semiconductor [7] and valuable intermediates [8] in organic synthesis. Consequently, they appear to be molecular scaffolds of considerable interest for synthetic organic chemist. Syntheses of pyrroles include classical Hantzsch reaction [9], Knorr reaction [10], and Paal–Knorr condensation reaction [11]]. Recently, new approaches based on the multicomponent coupling [12] and cycloisomerization of alkyne and allene containing substrates catalyzed by a transition metal [13] have been developed and have drawn extensive and enduring attention. Despite numerous diverse approaches toward the synthesis of polysubstituted pyrroles development of an easy, efficient, environmentally benign synthetic method still remains an attractive goal.

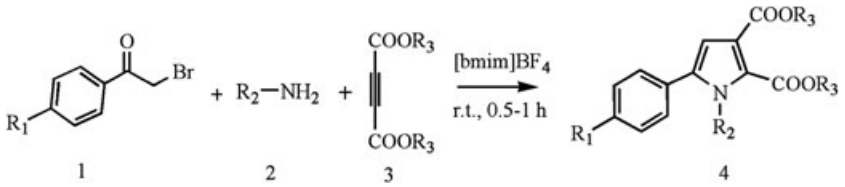
The quality and efficiency of organic synthesis now-a-days is measured not only by the parameters like yields and selectivity but also by the parameters like reaction time, cost, and availability of the starting material as well as source of energy. Multicomponent, one-pot reactions [14] have emerged as an efficient and powerful tool in advance synthetic organic chemistry. Multicomponent reactions leading to the preparation of the libraries of the small organic molecules is a rapidly evolving area of research. MCRs have ability of formation of complex molecule in single operation, multiple bonds forming capability and ability to carry out reaction involving toxic intermediates without exposure of these intermediates to environment has been proved without doubt. Recently, much attention have been devoted toward ionic liquid due to their inherent features such as nonvolatility, low inflammability, high thermal stability, ability to dissolve large number of organic and inorganic compounds, easy reusability [15], etc. Capacity of the ionic environment to generate internal pressure and to promote the association of reactant in solvent cavities renders them excellent media for multicomponent one-pot reactions. Recently, various organic transformations have been reported using [bmim]BF_4 as a catalyst as well as reaction media [16].

As part of our endeavors for the design and development of simple and green methodology for the synthesis of biodynamic heterocycle [17], we wish to describe herein a multicomponent, one-pot, pyrrole synthesis by using [bmim]BF_4 as reaction medium without any catalyst (Scheme 1).

RESULT AND DISCUSSION

To optimize the reaction condition and to study the scope of the reaction were tried using different traditional solvents ethanol, THF, CH_3CN, DCM, and ionic liquid, without any catalyst. Another factor was the reaction temperature. The experiments were run from r.t. to reflux. We found that the reaction does not proceed at all. Although the $FeCl_3$ catalyzed reaction of aniline and phenacyl bromide in halogenated solvent is reported [18] to give the desired product with longer reaction time (16–20 h). But when the

Scheme 1. Synthesis of functionalized pyrroles using [bmim]BF_4 at r.t.



reaction was carried out in ionic liquid [bmim]BF_4 proceeds smoothly, quantitatively and completed within 0.5–1.0 h at room temperature. This observation clearly indicated that in the present reaction conditions the ionic liquid plays the dual role of solvent and promoter. Ionic environment generated internal pressure which promoted the association of reactants in ionic liquid cavities as well as enhance the bond forming transformations. Thus, the reaction in [bmim]BF_4 is advantageous, because of its operational simplicity, and it can be reused in subsequent reactions. After the completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 20 mL) and residual ionic liquid were activated at 85°C under vacuum for an hour. The recycled ionic liquid was used for four times for the same reaction, and we found no substantial loss in activity.

With the optimized condition in hand various derivatives of phenacyl bromide, aliphatic/aromatic amine, and DEAD/DMAD were used to explore the generality and reproducibility of this protocol; results are summarized in Table 1.

On the basis of the results obtained above, a plausible mechanism of this reaction is illustrated in Scheme 2. α,β-unsaturated *N*-arylamine formed *in situ* from aromatic/aliphatic amine and DEAD/DMAD, was not isolated but it on nucleophilic substitution with α-bromoketone and subsequent intramolecular dehydrative cycloaddition afforded highly functionalized pyrroles. Presence of electron releasing group on 1 and/or 2 accelerated the nucleophilic addition as well as nucleophilic substitution and hence promoted the formation of product and enhance yield of the product. But the electron withdrawing group in 1 and/or 2 retarded the overall rate of formation of product and yield of the product.

CONCLUSION

In summary, ionic liquid are used as efficient and useful reaction medium for the synthesis of polysubstituted pyrroles. Compared with the conventional method, above protocols offer several advantages like higher yield, shorter reaction time, ecocompatible reaction condition, operational simplicity, efficient recovery, and recyclability of [bmim]BF_4.

EXPERIMENTAL

Melting points were determined into an open glass capillary method and are uncorrected. All chemicals used were of reagent grade and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz on a Broker AVANCE DPX FT spectrometer in $CDCl_3$ using TMS as an internal reference. Mass spectra were determined on a JEOL sx-102 (FAB) mass spectrometer at 70 eV. Elemental

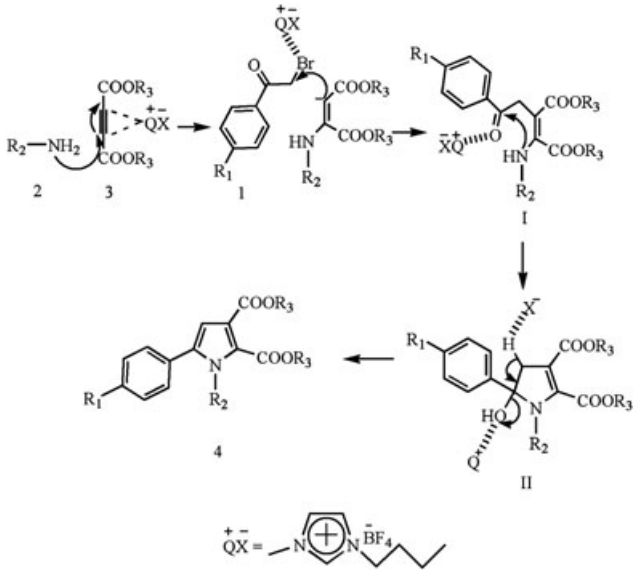
Table 1

Synthesis of functionalized pyrroles[a] using ionic liquid [bmim]BF_4.

Entry	Product	R_1	R_2	R_3	Time (min)	Yield[b] (%)
1	**4a**	H	C_6H_5	C_2H_5	60	87
2	**4b**	H	C_6H_5	CH_3	70	86
3	**4c**	CH_3	C_6H_5	C_2H_5	65	90
4	**4d**	CH_3	C_6H_5	CH_3	60	93
5	**4e**	OCH_3	ClC_6H_4	C_2H_5	75	92
6	**4f**	OCH_3	ClC_6H_4	CH_3	70	92
7	**4g**	NO_2	C_6H_5	C_2H_5	80	85
8	**4h**	NO_2	C_6H_5	CH_3	65	85
9	**4i**	NO_2	$CH_3C_6H_4$	C_2H_5	75	86
10	**4j**	NO_2	$CH_3C_6H_5$	CH_3	75	86
11	**4k**	CH_3	ClC_6H_4	C_2H_5	65	92
12	**4l**	CH_3	ClC_6H_4	CH_3	63	92
13	**4m**	H	C_2H_5	CH_3	55	90
14	**4n**	H	CH_3	CH_3	50	90

[a]Reaction condition: α-halo-ketone (1.05 mmol), aniline (1 mmol), and DEAD/DMAD (1 mmol) in [bmim]BF_4 at rt.
[b]Isolated yield.

Scheme 2. Plausible mechanism for ionic liquid promoted synthesis of functionalized pyrroles.



analysis was executed using a Coleman automatic C, H, and N analyzer. The progress of the reaction was monitored by TLC (Merk silica gel).

General procedure. A mixture of aniline (1 mmol) and α-halo-ketone (1.05 mmol) in [bmim]BF_4 (2 mL) was added DEAD (1 mmol) dropwise and stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated brine solution and dried (anhyd. Na_2SO_4) and concentrated under vacuum and the resulting crude product was directly charged on a silica gel (Merck, 60–120 mesh) column and eluted with 5–10% ethyl acetate/*n*-hexane to afford the corresponding pure product. The residual ionic liquid was dried under vacuum and reused. All the products were prepared by following the same procedure and characterized mass and NMR.

Spectral data compounds 3a-n.

1,5-Diphenyl-1H-pyrrole-2,3-dicarboxilic acid diethyl ester (4a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 8 Hz, 3 H), 1.27 (t, *J* = 8 Hz, 3 H), 4.18 (q, *J* = 8 Hz, 2 H), 4.31 (q, *J* = 8 Hz, 2 H), 7.02 (s, 1 H), 7.22–7.54 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.4, 61.7, 62.1, 122.6, 123.5, 124.8, 126.4, 127.5, 128.3, 133.6, 140.3, 160.4, 167. MS (ESI): *m*/*z* = 364 $[M + H]^+$. Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.78; H, 5.65; N, 3.93.

1,5-Diphenyl-1H-pyrrole-2,3-dicarboxilic acid dimethyl ester (4b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3 H), 3.84 (s, 3 H), 6.98 (s, 1 H), 7.57–7.24 (m, 10 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 53.2, 55.4, 124.1, 125.8, 126.9, 127.2, 128.1, 128.8, 132.8, 161.5, 167.7. MS (ESI): *m*/*z* = 336 $[M + H]^+$. Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.52; H, 5.22; N, 4.24.

1-Phenyl-5-tolyl-1H-pyrrole-2,3-dicarboxilic acid diethyl ester (4c). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23, (t, *J* = 8 Hz, 3 H), 1.33 (t, *J* = 8 Hz, 3 H), 2.32 (s, 3H), 4.22 (q, *J* = 8 Hz, 2 H), 4.34 (q, *J* = 8 Hz, 2 H), 7.1 (s, 1 H), 7.25–7.58 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 14.7, 21.1, 61.9, 62.4, 122.4, 123.7, 125.1, 126.7, 127.2, 128.5, 133.2, 140, 160.1, 167.2. MS (ESI): *m*/*z* = 378 $[M + H]^+$. Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.14; H, 5.62; N, 3.94.

1-Phenyl-5-tolyl-1H-pyrrole-2,3-dicarboxilic acid dimethyl ester (4d). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.77 (s, 3 H), 3.89 (s, 3 H), 7.14 (s, 1 H), 7.25–7.55 (m, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8, 53.2, 54.1, 124.6, 126.1, 127.4, 127.9, 128.6, 129, 133, 161.7, 167.5. MS (ESI): *m*/*z* = 336 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.27; H, 5.32; N, 4.09.

1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1H-pyrrole-2,3-dicarboxylic acid diethyl ester (4e). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 8, 3H), 1.31 (t, *J* = 8, 3H), 3.75 (s, 3H), 4.24 (q, *J* = 8, 2H), 4.32 (q, *J* = 8, 2H), 6.88–6.90 (d, *J* = 6Hz, 2H), 7.16 (s, 1H), 7.22–7.37 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 13.2, 57.1, 61.5, 61.2, 112.3, 112.9, 116.7, 118.4, 121.3, 124.2, 124.8, 128.7, 129.1, 129.8, 130.1, 140.1, 158, 163, 167.9. MS (ESI): *m*/*z* = 428 $[M + H]^+$. Anal. Calcd for $C_{23}H_{22}ClNO_5$: C, 64.56; H, 5.18; N, 3.27. Found: C, 64.68; H, 5.25; N, 6.48.

1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1H-pyrrole-2,3-dicarboxylic acid dimethyl ester (4f). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.95 (s, 2H), 4.12 (s, 2H), 6.86–6.89 (d, *J* = 6Hz, 2H), 7.18 (s, 1H), 7.21–7.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 57.1, 58.6, 112.5, 112.2, 116.5, 118.1, 121.8, 124.5, 124.4, 128.1, 129.3, 130, 130.7, 140.1, 159.2, 163.4, 170. MS (ESI): *m*/*z* = 400 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}ClNO_5$: C, 63.08; H, 4.54; N, 3.50. Found: C, 63.15; H, 4.38; N, 3.55.

5-(4-Nitrophenyl)-1-phenyl-1H-pyrrole-2,3-dicarboxylic acid diethyl ester (4g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 8, 3H), 1.27 (t, *J* = 8, 3H), 4.21 (q, *J* = 8, 2H), 4.32 (q, *J* = 8, 2H), 7.11 (s, 1H), 7.36–7.41 (m, 2H), 7.45 (m, 2H), 7.63 (d, *J* = 9, 2H), 8.24 (d, *J* = 9, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 13.7, 60.9, 61.1, 121.2, 122, 122.8, 123.7, 126.5, 128.4, 129.1, 129.5, 138.9, 140, 157.4, 160.2, 166.6. MS (ESI): *m*/*z* = 409 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.64; H, 4.83; N, 6.94.

5-(4-Nitrophenyl)-1-phenyl-1H-pyrrole-2,3-dicarboxylic acid dimethyl ester (4h). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3 H), 3.86 (s, 3 H), 7.05 (s, 1 H), 7.33–7.38 (m, 2 H), 7.42–7.52 (m, 3 H), 7.61 (d, *J* = 9 Hz, 2 H), 8.26 (d, *J* = 9 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.3, 51.4, 120.7, 122.3, 124.1, 125.5, 126.3, 128.2, 128.7, 129.1, 138.4, 140.2, 146.7, 160.12, 166.5. MS (ESI): *m/z* = 381 $[M + H]^+$. Anal. Calcd for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.24; N, 7.37. Found: C, 63.11; H, 4.32; N, 7.35.

5-(4-Nitrophenyl)-1-(4-tolyl)-1H-pyrrole-2,3-dicarboxylic acid diethyl ester (4i). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, *J* = 8 Hz, 3 H), 1.33 (t, *J* = 8 Hz, 3 H), 2.42 (s, 3 H), 4.18 (q, *J* = 8 Hz, 2 H), 4.34 (q, *J* = 8 Hz, 2 H), 7.04 (s, 1 H), 7.11–7.27 (m, 4 H), 7.60 (d, *J* = 8.0 Hz, 2 H), 8.22 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 13.6, 22.7, 61.5, 61.8, 123.2, 123.4, 126.2, 126.5, 127.8, 128, 130.2, 139.3, 147.2, 160.2, 166.1. MS (ESI): *m/z* = 423 $[M + H]^+$. Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.47; H, 5.21; N, 6.65.

5-(4-Nitrophenyl)-1-(4-tolyl)-1H-pyrrole-2,3-dicarboxylic acid dimethyl ester (4j). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3 H), 3.63 (s, 3 H), 3.86 (s, 3 H), 7.04 (s, 1 H), 7.05–7.35 (m, 4 H), 7.61 (d, *J* = 9 Hz, 2 H), 8.23 (d, *J* = 9 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 52.2, 123.2, 123.4, 125.3, 125.8, 127.4, 128.5, 128.9, 130.2, 130.7, 139.4, 146.7, 161.4, 167.2. MS (ESI): *m/z* = 395 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 63.85; H, 4.68; N, 7.17.

1-(4-Chloro-phenyl)-5-p-tolyl-1H-pyrrole-2,3-dicarboxylic acid diethyl ester (4k). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 8 Hz, 3 H), 1.33 (t, *J* = 8 Hz, 3 H), 2.42 (s, 3 H), 4.21 (q, *J* = 8 Hz, 2 H), 4.31 (q, *J* = 8 Hz, 2 H), 7.06 (s, 1H), 7.12–7.37 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 13.7, 21.2, 58.5, 61.1, 112.4, 118.1, 121.7, 124.2, 124.8, 126, 129.4, 130, 133.2, 138.2, 138.9, 159.6, 167. MS (ESI): *m/z* = 412 $[M + H]^+$. Anal. Calcd for $C_{23}H_{22}ClNO_4$: C, 67.07; H, 5.38; N, 5.13. Found: C, 67.15; H, 5.45; N, 5.07.

1-(4-Chloro-phenyl)-5-p-tolyl-1H-pyrrole-2,3-dicarboxylic acid dimethyl ester (4l). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.74 (s, 3 H), 3.83 (s, 3 H), 7.01 (s, 1 H), 7.19–7.42 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 50.2, 51.8, 112.5, 118.2, 121.6, 123.4, 124.2, 124.7, 126.9, 127.3, 129.4, 133.5, 138.1, 138.7, 158.9, 166.8. MS (ESI): *m/z* = 384 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}ClNO_4$: C, 65.71; H, 4.73; N, 5.13. Found: C, 65.82; H, 4.67; N, 5.08.

1-Ethyl-5-phenyl-1H-pyrrole-2,3-dicarboxylic acid dimethyl ester (4m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (t, *J* = 8 Hz, 3 H), 3.75 (s, 3H), 3.85 (s, 2H), 3.89 (s, 3H), 6.84 (s, 1H), 7.18–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 33.5, 50.1, 110.2, 126.1, 127.0, 128.7, 129.6, 136.9, 159.4, 167.2. MS (ESI): *m/z* = 288 $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 65.82; H, 5.84; N, 4.97.

1-Methyl-5-phenyl-1H-pyrrole-2,3-dicarboxylic acid dimethyl ester (4n). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (s, 3 H), 3.75 (s, 3H), 3.78 (s, 3H), 3.91 (s, 2H), 6.86 (s, 1H), 7.24–7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 49.3, 50.1, 110.6, 115.7, 127.1, 128.7, 129.4, 136.8, 159.6, 167.4. MS (ESI): *m/z* = 274 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.82; H, 5.53; N, 5.13. Found: C, 65.71; H, 5.59; N, 5.17.

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