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Ionic liquid catalyzed one pot four-component coupling reaction for the synthesis of functionalized pyrroles

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ABSTRACT

A facile and convenient one-pot tandem synthesis of functionalized pyrroles using acidic ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate as a catalyst has been achieved. It involves four-component reaction of amines, aldehydes, 1,3-dicarbonyl compounds and nitroalkane. This method has the advantage of simple and readily available starting materials, low cost, good yields and recyclability of catalyst.

1. Introduction

Pyrroles are an important class of heterocycles found in many natural products [1] and have pharmacological activities [2,3]. It has wide application as antitumor [4], anti-inflammatory [5], antibacterial [6] and antioxidant [7] activities. Moreover, they are widely used in the field of material chemistry [8,9]. Thus, several methods for synthesis of pyrroles have been developed. The commonly used methods are Hantzsch [10,11], Knorr [12–14], Paal–Knorr [15,16] and Clausen Kaas condensation [17] reactions. These classical reactions are very useful but have several drawbacks like multistep synthetic operations, harsh reaction conditions and availability of starting materials. To overcome these problems transition metal [18,19] catalysis and multi-component [20–23] reactions (MCRs) have been developed. MCRs emerged as fast and experimentally simple way of synthesis of complex molecules without the need of isolation and purification of any intermediate which results in minimization of waste, time and cost. Recently functionalized pyrroles have been synthesized via multi component coupling reaction using various catalysts and reagents like Fe(III)-catalyst [24], Pd catalyst [25], iodine [26], heterogenized tungsten complex [27], $NiCl_2$ [27], gluconic acid [29], amberlyst-15 (under ultrasound) [30], nano-$CoFe_2O_4$ supported Mo catalyst [31], $CeCl_3 \cdot 7H_2O$ (under microwave) [32] and nano-$CoFe_2O_4$ supported Sb(III) catalyst [33]. These methods have drawbacks such as use of metal catalyst, tedious workup and long reaction time. In a recent article, Meshram et al. synthesized substituted pyrroles via four-component coupling reaction of amines, aldehydes, 1,3-dicarbonyl compounds and nitroalkane using a huge quantity (5 ml) of ionic liquid $[Hbim]BF_4$ [34] as solvent. Also the authors have not given any clue about the behavior of aromatic amines under the set of reaction conditions described. So, we felt that still there could be a scope of improvement in this reaction so as to overcome the drawbacks of many reported methods using ionic liquid in catalytic amount. More recently, an efficient, mild and green methodology for N-substituted pyrrole derivatives using amberlite IR 120 acidic resin, as a catalyst for Paal–Knorr condensation of 2,5-hexadiene with primary amines under solvent-free condition has also been reported by us [35].

Room temperature ionic liquids are a subject of continuous attention as either solvents or catalysts [36]. Room temperature ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate ($[bmim]HSO_4$) has attracted much attention due to its bronsted acidity, recyclability and efficiency in various organic transformations [37–40]. In continuation with our studies towards exploring the use of $[bmim]HSO_4$ [41–45] we synthesized functionalized pyrroles via one-pot tandem reaction.

2. Experimental

The acidic ionic liquid $[bmim]HSO_4$ was prepared according to our previously reported method in literature [41]. IR spectra were recorded on Perkin Elmer model 1430 spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using Joel 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm with tetramethylsilane as internal standard. Melting points were determined with Sunbeam melting point apparatus and are uncorrected. High resolution mass

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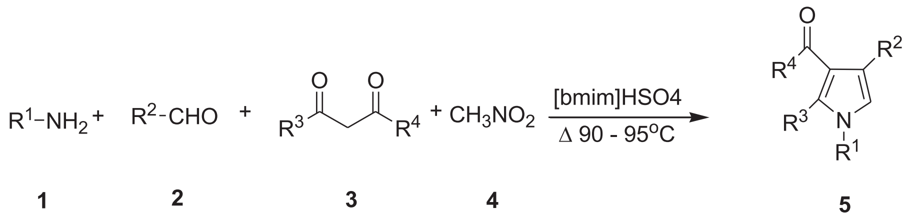

Scheme 1. Synthesis of functionalized pyrroles.

spectra (HRMS) were recorded using Waters Micromass Q-Tf Micro instrument.

2.1. General procedure for the synthesis of functionalized pyrrole derivatives (5)

To a stirred solution of amine **1** (1.0 mmol), aldehyde **2** (1.0 mmol), 1,3-dicarbonyl compound **3** (1.0 mmol) and nitromethane **4** (1.0 mL) were added [bmim]HSO_4 (0.20 mmol) (Scheme 1). The mixture was then heated to 90–95 °C for a set period of time (monitored by TLC) without an inert atmosphere. After completion of the reaction, reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 5 mL) leaving ionic liquid as residue. The combined organic layers were washed with water (2 × 10 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography to afford the desired compound. To recover the catalyst the residual ionic liquid was washed with diethyl ether (5 mL) for 30 min and the ether layer was decanted. The ionic liquid was then dried under vacuum and reused. The formation of known products was related by comparison of melting point, IR and NMR data with literature data. HRMS data for unknown compounds was taken.

2.2. Spectral data for the synthesis of functionalized pyrrole derivatives (5) of three new compounds

1-[4-(4-Hydroxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl] ethanone (5c): Orange solid, mp 170–171 °C. IR (nujol)/υ_{max}cm^{-1}: 3371, 3015, 2926, 1647, 1507, 1406, 1219. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.98 (s, 3H, $-C{=}C(CH_3)$-N), 2.34 (s, 3H, CH_3-C(=O)-), 5.19 (bs, 1H, Ar-OH, D_2O exchangeable), 6.75 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.13 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.25 (d, $J = 6.9$ Hz, 2H, Ar*H*), 7.30–7.43 (m, 3H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.1, 31.0, 115.4, 120.6, 122.6, 126.3, 127.9, 128.2, 129.4, 130.6, 131.4, 135.6, 138.8, 155.4, 198.3 ppm. HRMS: *m/z* calcd for $C_{19}H_{18}NO_2$ (M + 1) 292.1332; found 292.1366.

Table 1
Screening of different catalysts for the preparation of a pyrrole derivative[a].

S.No.	Catalyst(mol%)	Temp(°C)	Time (h)	% Yield[b]
1.	SiO_2 (20)	90–95 °C	14	15
2.	Acidic Al_2O_3 (20)	90–95 °C	14	16
3.	*p*-TSA (20)	90–95 °C	14	25
4.	HCl (20)	90–95 °C	14	12
5.	Amberlist-15 (20)	90–95 °C	24	20
6.	No catalyst	90–95 °C	24	10
7.	[bmim]HSO_4 (15)	Room temp	14	52
8.	[bmim]HSO_4 (15)	90–95 °C	3	79
9.	[bmim]HSO_4 (20)	90–95 °C	3	87
10.	[bmim]HSO_4 (25)	90–95 °C	3	88
11.	[bmim]BF_4 (20)	90–95 °C	3	72
12.	[bmim]I (20)	90–95 °C	3	65

[a] All reactions were carried out using amine (1 mmol), aldehyde (1 mmol) and active methylene compound (1 mmol) with nitromethane (1 mL).
[b] Isolated yield.

1-[4-(3-Bromophenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl] ethanone (5f): Orange sticky liquid. IR (neat)/υ_{max}cm^{-1}: 3055, 2959, 2926, 1723, 1651, 1595, 1504, 1402, 1222. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.01 (s, 3H, $-C{=}C(CH_3)$-N), 2.32 (s, 3H, CH_3-C(=O)-), 6.58 (s,1H, $-C{=}C(H)$-N), 7.16–7.26 (m, 4H, Ar*H*), 7.34–7.46 (m, 5H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.0, 31.2, 120.8, 122.5, 125.0, 126.4, 128.1, 128.3, 129.5, 129.7, 129.9, 132.2, 138.4, 196.3 ppm. HRMS: *m/z* calcd for $C_{19}H_{17}BrNO$ (M + 1) 354.0488; found 354.0512.

1-[1-(4-Hydroxyphenyl)-2-methyl-4-phenyl-1*H*-pyrrol-3-yl] ethanone (5i): Orange solid, mp 155–158 °C. IR (nujol)/υ_{max}cm^{-1}: 3234, 3018, 2922, 1620, 1517, 1410, 1273, 1219. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.00 (s, 3H, $-C{=}C(CH_3)$-N), 2.30 (s, 3H, CH_3-C(=O)-), 4.59 (bs, 1H, Ar-OH, D_2O exchangeable), 6.47 (s, 1H, $-C{=}C(H)$-N), 6.85 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.00 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.16–7.21 (m, 3H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.3, 30.8, 116.3, 121.4, 121.8, 126.5, 127.0, 127.4, 128.3, 129.5, 130.3, 136.1, 136.9, 157.4, 198.7 ppm. HRMS: *m/z* calcd for $C_{19}H_{18}NO_2$ (M + 1) 292.1332; found 292.1239.

3. Results and discussion

It is known that pyrroles can be obtained via Michael reaction of β-enamino ketones or esters and nitroolefins followed via cyclization [24–31,34]. β-Enamino ketones or esters can be obtained from reaction of β-dicarbonyl compounds with amines and nitroolefins can be obtained from reaction of aldehyde and nitroalkane which can be catalyzed by ionic liquids [34,46,47]. So first we examined the reaction of amine **1a**, aldehyde **2b**, active methylene compound **3a** and nitromethane **4** using various catalysts (Table 1). The reactions were carried out at 90–95 °C except for one reaction with [bmim]HSO_4 (entry 6, Table 1) which was carried out at room temperature. The use of SiO_2 (entry 1, Table 1), acidic Al_2O_3 (entry 2, Table 1), *p*-toluenesulfonic acid (*p*-TSA) (entry 3, Table 1), hydrochloric acid (HCl) (entry 4, Table 1) and acidic resin amberlist-15 (entry 5, Table 1) was examined but the product **5b** was isolated only in 11–25% yield. In the absence of a catalyst (entry 6, Table 1) only 10% yield was obtained. The use of acidic ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate ([bmim]HSO_4) (entry 10, Table 1) increased the product yield to 88%. Good yield was obtained using 20 mol% of [bmim]HSO_4 (entry 9, Table 1). On increasing [bmim]HSO_4 to 25 mol% (entry 10, Table 1) no significant improvement in yield was observed while the yield decreased when 15 mol% of [bmim]HSO_4 (entry 8, Table 1) was used or the reaction was carried out at room temperature (entry 7, Table 1). This reaction was also studied in various solvents like dichloromethane, acetonitrile, N,N-dimethylformamide and tetrahydrofuran but the yield of desired product decreased.

Following the optimized reaction conditions, a variety of functionalized pyrroles (**5**) was synthesized (Table 2) in good yields. Both the

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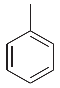
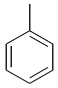
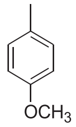
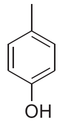
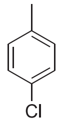
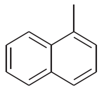
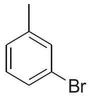
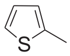
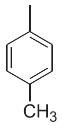
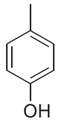
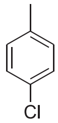
electron rich aromatic aldehydes (Table 2, entries 1–3, 5 and 7) and also weakly electron deficient aromatic aldehydes (Table 2, entries 4 and 6) gave the corresponding pyrroles in good yield. However, in case of a strong electron withdrawing group such as —NO_2 on aromatic aldehydes and using aliphatic aldehydes the yield was not satisfactory and the reaction was not studied further. Similarly electron rich (Table 2, entries 1, 8 and 9) and weakly electron deficient (Table 2, entry 10) aromatic amines gave the corresponding pyrroles in good yield, while in case of nitro anilines no satisfactory yield was obtained. The reaction went well with different dicarbonyl compounds such as acetyl acetone (**3a**), ethyl acetoacetate (**3b**) and methyl acetoacetate (**3c**).

Table 2
Four component coupling synthesis of functionalized pyrrole[a].

S.No.	R^1	Substrate R^2	R^3, R^4	Time (h)	Products	%Yield[b] [Ref]
1.	 **1a**	 **2a**	CH_3, CH_3 **3a**	3	**5a**	90 [24]
2.	**1a**	 **2b**	**3a**	3	**5b**	87 [29]
3.	**1a**	 **2c**	**3a**	3	**5c**	83
4.	**1a**	 **2d**	**3a**	4	**5d**	77 [29]
5.	**1a**	 **2e**	**3a**	6	**5e**	70 [29]
6.	**1a**	 **2f**	**3a**	5	**5f**	70
7.	**1a**	 **2g**	**3a**	2	**5g**	93 [29]
8.	 **1b**	**2a**	**3a**	3	**5h**	89 [29]
9.	 **1c**	**2a**	**3a**	3	**5i**	88
10.	 **1d**	**2a**	**3a**	5	**5j**	68 [29]
11.	**1a**	**2a**	CH_3, OEt **3b**	3	**5k**	95 [29]
12.	**1a**	**2a**	CH_3, OMe **3c**	3	**5l**	91 [29]

[a] All reactions were carried out using amine **1** (1.0 mmol), aldehyde **2** (1.0 mmol), 1,3-dicarbonyl compound **3** (1.0 mmol) and nitromethane **4** (1.0 mL) in the presence of [bmim]HSO_4 (0.20 mmol) at 90–95 °C.

[b] Isolated yield.

Table 3
Reusability of catalyst.

Sr. No.	Run	Yield (%)
1.	1(fresh)	87
2.	2	85
3.	3	81
4.	4	78
5.	5	65

After completely establishing this method for successful conversion of aromatic amines to corresponding pyrroles, we also tried to screen the aliphatic amines and benzyl amines under similar set of conditions as these are more reactive for enaminone [46,47] and pyrrole [34] formations. The expected behavior could not be showed by these substrates and no product was formed in this case. So, we can deduce that this particular ionic liquid is specific towards the reaction of aromatic amines.

A plausible mechanism for the ionic liquid catalyzed tandem reaction was proposed (Scheme 2) in accordance with recent reports from literature [24–31,34].

To investigate the reusability of a catalyst we have taken reaction of amine **1a**, aldehyde **2b**, active methylene compound **3a** and nitromethane **4** as model (Table 3). The residual ionic liquid was washed with diethyl ether and the ether layer was decanted. The ionic liquid was then dried under vacuum and reused. We were able to recycle the ionic liquid thrice, after that there was a sharp decrease in product yield.

4. Conclusions

In conclusion, we have developed an operationally simple, economical and eco-friendly one-pot four-component coupling reaction for synthesis of functionalized pyrroles using an acidic ionic liquid as a powerful and recyclable catalyst. This method has several advantages of high catalytic activity, mild reaction conditions, easily available starting materials, less amount of ionic liquid used and metal free synthesis. Thus, this procedure clearly represents an appealing methodology for the synthesis of functionalized pyrroles.

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Appendix A. Supplementary data

Supporting Information: Experimental details and analytical data of all compounds as well as copy of ^1H NMR and ^{13}C NMR spectra. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molliq.2014.07.038.

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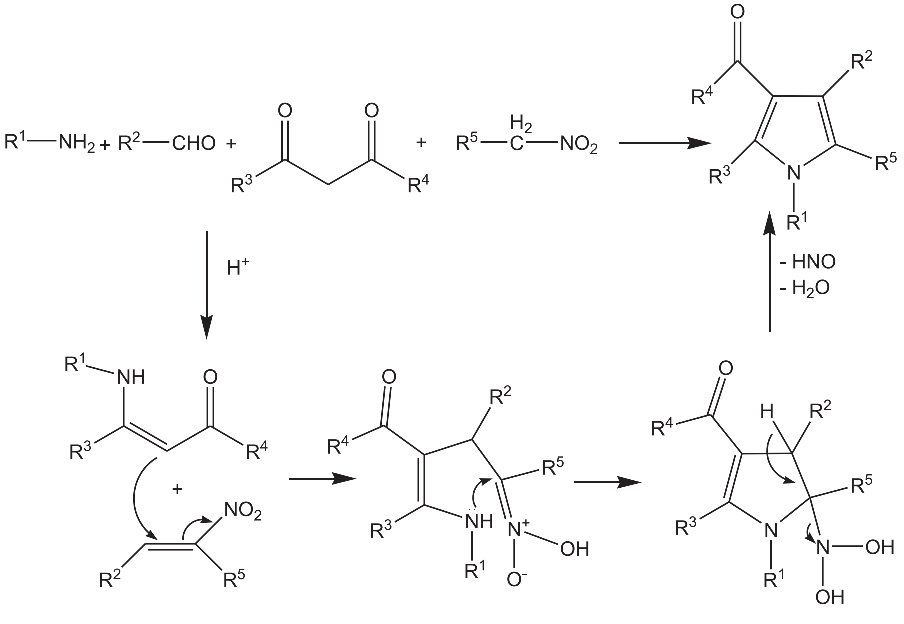

Scheme 2. Plausible mechanism for synthesis of pyrrole derivatives.

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