A SIMPLE N-SUBSTITUTION OF PYRROLE AND INDOLE USING BASIC IONIC LIQUID [BMIM][OH] AS CATALYST AND GREEN SOLVENT

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Abstract – In basic ionic liquids, 1-methyl-3-butylimidazolium hydroxide, [BMIm][OH], pyrrole and indole replaced the halogen atom of an alkyl halide to give the corresponding N-substituted pyrrole and indole in excellent yield. Benzenesulfonyl chloride, p-methylbenzenesulfonyl chloride and benzoyl chloride reacted similarly with pyrroles to afford the N-substituted pyrroles in quantitative yield.

INTRODUCTION

The development of simple, efficient and green synthetic methods for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. The synthesis and reaction of pyrroles and indoles have been a topic of research interests for over a century because a number of their derivative occur in nature and possess a variety of important biological activities. N-Substituted pyroles and indoles are usually obtained by the reaction of pyrrolyl and indolyl anion with the appropriate alkylating agents. N-Substitution of pyrroles and indoles can be achieved by use of various strong bases such as BuLi, NaNH2, NaH in various solvents, for example, acetone, DMSO, DMF, and THF etc, in order to generate the anion, which reacts as a nucleophile. The use of these strong bases may limit the processes, because the experimental work can be laborious and time consuming, requiring special care to avoid hydrolysis. So, some improvement of classical methods has been made by using bases such as potassium, sodium hydroxide in hexamethylposphoric triamide, potassium hydroxide in dimethyl sulfoxide, ionic liquids, polyethene glycols or their dialkyl ethers. Moreover, phase transfer procedures have been developed by use of potassium hydroxide or potassium tert-butoxide in the presence of crown ethers as PTC. However, these methods were some limited by the
harsh reaction, relatively long reaction time, low yield and using toxic solvent or catalysts. Therefore, the development of a mild, efficient, and highly regioselective N-substitution of pyrrole and indole is still urgent.

Room temperature ionic liquids have attracted increasing attention as the green, high-tech reaction media,\textsuperscript{17-18} while it has also been reported that ionic liquids containing imidazolium cations can act as media in some organic reactions not only for the facilitation of catalyst recovery but also for the acceleration of the reaction rate and improvement of selectivity.\textsuperscript{19-20} Numbers of ionic liquids containing stable acidic\textsuperscript{21} or neutral anions\textsuperscript{22} have been developed and successfully applied to catalyze many types of reaction, such as oligomerization,\textsuperscript{23} hydrogenation,\textsuperscript{24} regioselective alkylation,\textsuperscript{25} Friedel–Crafts reactions,\textsuperscript{26} dimerization of alkenes,\textsuperscript{27} Diels–Alder reactions,\textsuperscript{28} Michael addition reactions,\textsuperscript{29} cross-coupling reactions\textsuperscript{30} and some enzymic reactions.\textsuperscript{31} Relevant reports about ionic liquids containing stable basic anions, however, were relatively scarce: supported choline hydroxide has been used as a basic catalyst for aldol condensation reactions,\textsuperscript{32} while the basic ionic liquid [bmIm][OH] has been successfully applied to catalyze Michael addition reactions,\textsuperscript{33} Markovnikov addition reactions,\textsuperscript{34} Knoevenagel condensation reactions.\textsuperscript{35} Our recent interest has been in the development of new synthetic method using basic ionic liquids as catalyst and green solvent. As part of a program to investigate the range of organic reactions possible in basic ionic liquids, we examined the reactions of N-substitution of pyrrole and indole (Scheme 1), which would provide a efficient synthetic method of N-substituted pyrroles and indoles.

![Scheme 1](image)

\begin{center}
\textbf{RESULTS AND DISCUSSION}
\end{center}

First, we found that in the presence of [bmIm][OH], the reaction of pyrrole with methyl iodide, could proceed smoothly at 30 °C in 84 % yield (Table 1, Entry 1). In a similar fashion, the reactions of pyrrole with a variety of halogen derivatives were investigated. We found that the reaction is general and applicable to primary alkyl halides containing iodide, bromide and chloride (Table 1, Entries 1-7). For secondary bromide, the yield is also good (Table 1, Entry 2). When allyl bromide is employed as the alkylating agent, N-allylpyrrole can be produced in quantitative yield (Table 1, Entry 5), and in those reported procedures,\textsuperscript{36} a mixture of C- and N-allylpyrroles was obtained, even C-alkylated material predominates over N-alkylated material.\textsuperscript{36} In order to explore the generality of the method developed for the N-substitution of pyrrole, we tried the reaction of pyrrole with benzenesulfonyl chloride, p-methylbenzenesulfonyl chloride and benzoyl chloride, and the N-substituted pyrroles were obtained in quantitative yields (Table 1, Entries 8-10).
On the basis of these results, we exploited our method to indole. We found that the N-alkylation of indole can also be performed with high yield in basic ionic liquids [bmIm][OH] (Table 1, Entries 11-15).

All the products gave satisfactory mp., IR and $^1$H NMR data which were consistent with the literature data.

The present method has many obvious advantages, compared to those reported in literature, including highly regioselective, the generality, the higher yield, being environmentally more benign. [bmIm][OH] plays double roles of catalyst and solvent. Firstly, amines exhibited higher nucleophilicity in ionic liquids than in organic solvents. On the other hand, the hydroxide anion of the ionic liquid [bmIm][OH] might assist in the formation of nucleophilic anions generated from amines, which should increase the nucleophilicity of amines further, as has been demonstrated by a $^{13}$C NMR experiment. 

In conclusion, we have demonstrated that the N-substitution of pyrrole and indole can effectively be performed in the basic ionic liquids [bmIm][OH] with high yield, which provides a simple and efficient method for the synthesis of the N-substituted pyroles and indoles.

**Table 1.** The N-substitution of pyrrole and indole in basic ionic liquids [bmIm][OH]$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>RX</th>
<th>Reaction condition</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pyrrole</td>
<td>MeI</td>
<td>2 h, 30 °C</td>
<td>$N$-methylpyrrole (a)</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>i-PrBr</td>
<td>2 h, 30 °C</td>
<td>$N$-i-propylpyrrole (b)</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>n-BuBr</td>
<td>1 h, 60 °C</td>
<td>$N$-butylpyrrole (e)</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>n-BuCl</td>
<td>2 h, 60 °C</td>
<td>$N$-butylpyrrole (c)</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>CH$_2$=CHCH$_2$Br</td>
<td>1 h, 60 °C</td>
<td>$N$-allylpyrrole (d)</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>C$_6$H$_5$CH$_2$Br</td>
<td>1 h, 60 °C</td>
<td>$N$-benzylpyrrole (e)</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>C$_6$H$_5$CH$_2$Cl</td>
<td>1 h, 60 °C</td>
<td>$N$-benzylpyrrole (e)</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>C$_6$H$_5$SO$_2$Cl</td>
<td>1 h, 60 °C</td>
<td>$N$-phenylsulfonylpyrrole (f)</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>p-MeC$_6$H$_5$SO$_2$Cl</td>
<td>1 h, 60 °C</td>
<td>$N$-$p$-Methylbenzenesulfonylpyrrole (g)</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>indole</td>
<td>C$_6$H$_5$COCl</td>
<td>1 h, 30 °C</td>
<td>$N$-benzoylpyrrole (h)</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>MeI</td>
<td>1 h, 30 °C</td>
<td>$N$-methyldihydroindole (i)</td>
<td>92</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>EtBr</td>
<td>1 h, 30 °C</td>
<td>$N$-ethylindole (j)</td>
<td>95</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>n-PrBr</td>
<td>1 h, 30 °C</td>
<td>$N$-propylindole (k)</td>
<td>96</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>n-BuBr</td>
<td>1 h, 30 °C</td>
<td>$N$-butylindole (l)</td>
<td>94</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>C$_6$H$_5$CH$_2$Cl</td>
<td>1 h, 30 °C</td>
<td>$N$-benzylindole (m)</td>
<td>97</td>
</tr>
</tbody>
</table>

$^a$ All reactions were run with pyrrole or indole (2 mmol), RX (3 mmol) in basic ionic liquid [bmIm][OH] (2 mL).

$^b$ Isolated yield.

**EXPERIMENTAL**

Melting points were determined on digital melting point apparatus and were not corrected. Infrared
spectra were recorded on a VECTOR22 (Bruker). Nuclear magnetic resonance spectra were recorded on AVANCE DMX 200 (Bruker) spectrometer. The ionic liquids, 1-methyl-3-butylimidazolium hydroxide, [bmIm][OH], was synthesized according to reported procedures. The other materials are commercially available and were used without further purification.

General procedure
A mixture of pyrrole or indole (2 mmol), alkyl halide (3 mmol), and [bmIm][OH] (2 mL) was stirred for 1-2 h at 30-60 °C (reaction conditions given in Table 1). The reaction mixture was extracted with Et2O (3×5 mL). The combined ether extracts were evaporated under reduced pressure and the resulting crude products were separated by the preparative thin-layer chromatography on silica gel using a mixture of AcOEt and petroleum ether as developer to give the corresponding pure product.

Spectroscopic data:

N-Methylpyrrole (a): Oil. IR (Film): 2943, 2907, 2810, 1508, 1386, 1327, 1286, 1088, 1061, 968, 819, 723, 665, 606 cm⁻¹. ¹H NMR (CDCl₃): δ = 6.41 (d, J = 2.4 Hz, 2H), 6.10 (d, J = 2.4 Hz, 2H), 3.61 (s, 3H).

N-i-Propylpyrrole (b): Oil. IR (Film): 2955, 2812, 1510, 1419, 1386, 1375, 1286, 1088, 1059, 968, 819, 722, 663 cm⁻¹. ¹H NMR (CDCl₃): δ = 6.59 (d, J = 2.4 Hz, 2H), 6.15 (d, J = 2.4 Hz, 2H), 3.76 (m, J = 7.2 Hz, 1H), 1.72 (d, J = 7.2 Hz, 6H).

N-Butylpyrrole (c): Oil. IR (Film): 3117, 2967, 1566, 1465, 1498, 1282, 1115, 1090, 718 cm⁻¹. ¹H NMR (CDCl₃): δ = 6.60 (d, J = 2.4 Hz, 2H), 6.17 (d, J = 2.4 Hz, 2H), 3.81 (t, J = 6.8 Hz, 2H), 1.70 (m, 2H), 1.27 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

N-Allylpyrrole (d): Oil. IR (Film): 3118, 2966, 1498, 1282, 1090, 717 cm⁻¹. ¹H NMR (CDCl₃): δ = 6.57 (d, J = 2.4 Hz, 2H), 6.12 (d, J = 2.4 Hz, 2H), 5.62-6.06 (m, 1H), 4.84-5.29 (m, 2H), 4.42 (m, 2H).

N-Benzylpyrrole (e): Oil. IR (Film): 3117, 3018, 2918, 1656, 1494, 1452, 1208, 1065, 775, 745, 718 cm⁻¹. ¹H NMR (CDCl₃): δ = 7.24 (m, 3H), 7.08 (m, 2H), 6.65 (d, J = 2.6 Hz, 2H), 6.17 (d, J = 2.6 Hz, 2H), 4.96 (s, 2H).

N-Phenylsulfonyl pyrrole (f): mp 90 °C (lit., mp 89.5 °C). IR (KBr): 3076, 1576, 1454, 1393, 1061, 730, 621 cm⁻¹. ¹H NMR (CDCl₃): δ = 7.2-8.3 (m, 9H).

N-p-Methylbenzenesulfonyl pyrrole (g): mp 105 °C (lit., mp 104.5 °C). IR (KBr): 3077, 2957, 1574, 1454, 1393, 1059, 859 cm⁻¹. ¹H NMR (CDCl₃): δ = 7.3-8.4 (m, 8H), 2.42 (s, 3H).

N-Benzoylpyrrole (h): Oil. IR (KBr): 3075, 1698, 1601, 1455, 724 cm⁻¹. ¹H NMR (CDCl₃): δ = 7.94 (d, J = 6.8 Hz, 2H), 7.65 (m, 1H), 7.51 (m, 2H), 7.12 (d, J = 2.2 Hz, 2H), 6.21 (d, J = 2.2 Hz, 2H).

N-Methylindole (i): Oil. IR (neat): 3054, 2943, 1513, 1476, 1330, 1316, 1243, 763, 740, 712 cm⁻¹. ¹H NMR (CDCl₃): δ = 7.66 (dd, J = 8.4, 1.0 Hz, 1H), 7.38 (dd, J = 8.4, 0.8 Hz, 1H), 7.26 (m, 1H), 7.14 (dd, J = 8.4, 0.8 Hz, 1H).
N-Ethylindole (j): Oil. \(^{14}\) IR (neat): 3054, 2978, 2933, 1512, 1462, 1314, 1222, 740, 695 cm\(^{-1}\). \(^{1}H\) NMR (CDCl\(_3\)): δ = 7.66 (dd, \(J = 7.6, 1.0\) Hz, 1H), 7.39 (d, \(J = 8.4\) Hz, 1H), 7.14–7.16 (m, 2H), 6.53 (dd, \(J = 5.6, 2.4\) Hz, 1H), 4.20 (q, \(J = 7.2\) Hz, 2H), 1.50 (t, \(J = 7.4\) Hz, 3H).

N-Propylindole (k): Oil. \(^{14}\) IR (neat): 3054, 2965, 2933, 1511, 1463, 1315, 762, 739 cm\(^{-1}\). \(^{1}H\) NMR (CDCl\(_3\)): δ = 7.71 (dd, \(J = 7.6, 1.0\) Hz, 1H), 7.42 (d, \(J = 8.4\) Hz, 1H), 7.30 (m, 1H), 7.16–7.20 (m, 2H), 6.57 (dd, \(J = 5.6, 2.4\) Hz, 1H), 4.25 (t, \(J = 7.2\) Hz, 2H), 1.54 (m, 2H), 1.00 (t, \(J = 7.4\) Hz, 3H).

N-Butylindole (l): Oil. \(^{14}\) IR (neat): 3056, 2957, 2931, 1559, 1512, 1316, 762, 738, 715 cm\(^{-1}\). \(^{1}H\) NMR (CDCl\(_3\)): δ = 7.72 (dd, \(J = 7.6, 1.0\) Hz, 1H), 7.45 (d, \(J = 8.4\) Hz, 1H), 7.30 (m, 1H), 7.16–7.22 (m, 2H), 6.59 (dd, \(J = 5.6, 2.4\) Hz, 1H), 4.20 (t, \(J = 7.6\) Hz, 2H), 1.90 (m, 2H), 1.45 (m, 2H), 1.04 (t, \(J = 7.4\) Hz, 3H).

N-Benzylindole (m): mp 42-43 °C (lit., \(^{14}\) mp 41–42 °C). IR (KBr): 3003, 2981, 2142, 1465, 1343, 1203, 1094, 1024, 765, 735, 642 cm\(^{-1}\). \(^{1}H\) NMR (CDCl\(_3\)): δ = 7.62–7.37 (m, 4H), 7.31–7.16 (m, 5H), 6.96 (d, \(J = 2.8\) Hz, 1H), 6.64 (d, \(J = 2.8\) Hz, 1H), 5.30 (s, 2H).

ACKNOWLEDGEMENTS

This work was financially supported by the Project of NSFC (20862001), NCET and Top Academic Leaders of JiangXi Province, the Science Foundation of JiangXi Province (2008GZH0055), the Science and Technology Foundation of the Education Department of JiangXi Province (GJJ09259).

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