Ionic Liquid Mediated Rapid Synthesis of 3-Substituted Pyrazoles

Chandrashekhar G Devkate1*, Khandu D Warad2, Mahendra B Bhalerao3, Digambar D Gaikwad3 and Mohammad Idrees M Siddique4

1Department of Chemistry, Indraraj Arts, Commerce and Science College Sillod, Aurangabad, India
2Department of Chemistry, Dr Babasaheb Ambedkar Marathwada University, Aurangabad, India
3Department of Chemistry, Govt College of Arts and Science, Aurangabad, India
4Department of Chemistry, Government of Institute Science, Nagpur, India

ABSTRACT

A simple, highly efficient and environmentally friendly method for the synthesis 3-substituted pyrazoles by one pot condensation reaction of substituted cinnamaldehydes and tosylhydrazide in ionic liquid, 1-Butyl-3-methylimidazolium tetrafluoroborate. This method was developed by screening of different imidazolium-based ionic liquids. The reaction system exhibited tolerance with various functional groups and gives good to excellent yields. 

Keywords: Ionic liquid; Pyrazole; N-Tosylhydrazine

INTRODUCTION

Pyrazoles are well known five-membered nitrogen-containing heterocyclic compounds possessing diverse bioactivities, such as analgesic agent, platelet aggregation inhibitors, and nonsteroidal anti-inflammatory agents. The pyrazole based compounds are widely used in the development of medicaments [1] and in agrochemicals [2]. They are also useful intermediates for many industrial products [3], [4]. Consequently, pyrazoles have attracted much attention due to their wide uses and various procedures for their synthesis have been developed [5-8]. As reported in the literature, the synthetic methods toward substituted pyrazoles include: (a) Condensation of α,β-unsaturated carbonyl compounds with hydrazines, which is widely used method [9-15]. Literature survey reveals that there are various methods have been developed for the syntheses of pyrazoles [16]. However, it is found that in the most of the synthetic routes, the organic solvents have been used. Generally, these reactions require longer time for completion and the yields of the product are low to moderate. Among the popular procedures for pyrazole synthesis, hydrazine hydrate is applied as a predominant nitrogen source; nevertheless, most of these transformations are dependent on a large excess amount of hydrazine hydrate and oxidant or base. In 1987, Shechter et al. published the early report in which only 1.1 equiv of tosyl hydrazide with unsaturated ketone was used as nitrogen source for the preparation of 1H-cyclooctapyrazoles [17-21]. Then, a remarkable number of novel 1H-pyrazole synthesis using substituted hydrazides, especially sulfonyl hydrazides as nitrogen transfer reagents have been reported. In 2011, Yu and co-workers established a highly efficient and eco-friendly protocol for the preparation of substituted 1H-pyrazoles by a one-pot condensation reaction of α,β-unsaturated carbonyl compounds with tosyl hydrazide promoted by stoichiometric tetrabutylammonium bromide in water [22]. Many of the reported methods for the Knorr synthesis of pyrazoles suffer from drawbacks, such as the use of organic solvent and unrecoverable catalyst, harsh reaction conditions [23] and long reaction times [24]. Ionic liquids (ILs) has attracted the attention on scientific community in the last decade, due to their particular properties and their applications in Organic Synthesis [25-27], catalysis [28-30], biocatalysis [31,32], liquid-liquid separations [33-34], extraction [35-38] and dissolution (cellulose in microwave [39] and petroleum asphaltene in microwave [40]) processes, nanomaterials synthesis [41], polymerization reactions [42,43] and electrochemistry [44,45]. ILs are an excellent alternative to substitute volatile organic solvents

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in more environmental friendly technologies (“green technologies”). ILs attracted the attention of the researchers due to their very low vapor pressures, thermal and chemical stability, ability to act as catalyst, and non-flammability and non-corrosives properties.

EXPERIMENTAL SECTION

General considerations
All reagents and catalyst purchased from commercial sources were used as received. The solvents ionic liquids wasprepared by reported procedure [46] and used. All reactions were carried out in oven-dried glassware and were magnetically stirred. FTIR spectra were taken on F.T.Infra-Red Spectrophotometer Model RZX (Perkin Elmer) and 

1H and 13C spectra were taken on bruker AVANCE II 400 MHz spectrometer with TMS as internal standard CDCl3 / DMSO as solvent.ESI-Mass spectral data were recorded on Q-TOF Micro Waters (ESI-MS) Spectrometer.

General procedure for the Screening of ionic liquids:
A mixture of Cinnamaldehyde (1) (7.57 mmol) and tosylhydrazine (2) (7.57 mmol) was dissolved in separately in five different imidazolium-based ionic liquids (5 ml) and stirred at room temperature for 30 min. After stirring the reaction mixtures for 30 min., the reaction mass were poured on crushed ice. The obtained solids were filtered, washed with water and dried. The crude compounds were crystallized using DMF-Ethanol. Then for every seven different aldehydes the procedure was repeated. After screening the imidazolium-based ionic liquids, it was found that 1-Butyl-3-methylimidazolium tetrafluoroborate was a suitable and novel medium for carrying the cyclocondensation leading to title products with excellent yields (Table 1, entry 3). The advantage of 1-Butyl-3-methylimidazolium tetrafluoroborate is that, it is stable, easily synthesized, cost effective, and recyclable.

Table 1: Screening of ionic liquids to search a suitable medium for one pot synthesis of phenyl pyrazoles (3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic liquids</th>
<th>Time (min.)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-Butyl-3-methylimidazolium hexafluorophosphate</td>
<td>30</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>1-Butyl-3-methylimidazolium Chloride</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>1-Butyl-3-methylimidazolium tetrafluoroborate</td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>1-Ethyl-3-methylimidazolium tetrafluoroborate</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>1-Ethyl-3-methylimidazolium Chloride</td>
<td>30</td>
<td>56</td>
</tr>
</tbody>
</table>

*Reaction conditions: A mixture of Cinnamaldehyde (1) (7.57 mmol) and tosylhydrazine (2) (7.57 mmol) was dissolved in ionic liquids (5 ml) and stirred at room temperature for 30 min; 

General procedure for the synthesis of 3-substituted Pyrazoles (3a-g)
A mixture of cinnamaldehydes (1a-g) (7.57 mmol) and tosylhydrazine (2) (7.57 mmol) was dissolved in ionic liquid, 1-Butyl-3-methylimidazolium tetrafluoroborate (5 ml) and stirred at room temperature for 30 min. After stirring the reaction mixture for 30 min., the reaction mass was poured on crushed ice. The obtained solid was filtered, washed with water and dried. The crude compound was crystallized using DMF-Ethanol.

Scheme: One pot synthesis of substituted phenyl pyrazoles (3a-g) using 1-Butyl-3-methylimidazolium tetrafluoroborate

**Compound 3c:** white solid, FTIR cm⁻¹: 3164 (N-H str.), 1535 (C=N str., Pyrazolyl), 1047 (C-O str.); ¹H-NMR (400 MHz, DMSO): δ 3.76 (s, 3H, -OCH₃), 6.64 (d, 1H, Ar-H, J = 8 Hz), 7.27 (t, 1H, Ar-H, J = 8 Hz), 7.38 (d, 1H, Ar-H, J = 8 Hz), 7.43 (s, 1H, Ar-H), 7.63 (s, 2H, Pyrazolyl), and 13.02 (s, 1H, N-H) ppm; ¹³C-NMR (100 MHz, DMSO): δ 159.58, 133.87, 129.59, 117.65, 112.90, 110.50, 101.98, 54.81 ppm; MS (ESI, m/z): calcd for C₁₀H₁₀N₂O (M + H⁺) 174.0793; found: 175.1162.
Table 2: One pot synthesis of phenyl pyrazoles (3a-g), carried in 1-Butyl-3-methylimidazolium tetrafluoroborate

<table>
<thead>
<tr>
<th>Compound</th>
<th>R’</th>
<th>Product</th>
<th>Yield</th>
<th>M. P. (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>-H</td>
<td><img src="Image" alt="Structure" /></td>
<td>90</td>
<td>78-82</td>
</tr>
<tr>
<td>3b</td>
<td>p-Me</td>
<td><img src="Image" alt="Structure" /></td>
<td>93</td>
<td>76-78</td>
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<tr>
<td>3c</td>
<td>m-OMe</td>
<td><img src="Image" alt="Structure" /></td>
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<td>90-91</td>
</tr>
<tr>
<td>3d</td>
<td>p-F</td>
<td><img src="Image" alt="Structure" /></td>
<td>88</td>
<td>101-103</td>
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<tr>
<td>3e</td>
<td>p-Cl</td>
<td><img src="Image" alt="Structure" /></td>
<td>90</td>
<td>100-104</td>
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<tr>
<td>3f</td>
<td>m-Br</td>
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<td>87</td>
<td>71-75</td>
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<tr>
<td>3g</td>
<td>p-NO₂</td>
<td><img src="Image" alt="Structure" /></td>
<td>62</td>
<td>194-195</td>
</tr>
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</table>

RESULTS AND DISCUSSION

The titled compounds have been synthesized by one pot synthesis by using readily available starting materials, such as cinnamaldehyde (1a-g) and p-toluenesulfonyl hydrazide (TsNHNH₂) (2). The ionic liquid, 1-Butyl-3-methylimidazolium tetrafluoroborate was prepared and used immediately. The reactions were carried out at room temperature for 30 min. The progress of the reaction was monitored by TLC. Various cinnamaldehydes (1a-g) could give target pyrazoles through the same action with excellent yields (3a-g).
CONCLUSION

In conclusion, we have developed a simple, highly efficient, and environmentally friendly method for the synthesis of 3-substituted-1H-pyrazoles in ionic liquid, 1-Butyl-3-methylimidazolium tetrafluoroborate. The reaction system exhibits tolerance with various functional groups, and gives desired product in good to excellent yields. Moreover, the present reaction process provides a potential for the large-scale synthesis of 3-substituted-1H-pyrazoles. Further studies on the biological activities of the products and application of this methodology to other interesting pyrazole derivatives are underway in our laboratory.

REFERENCES

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