Short Time One-Spot Synthesis of 2, 4, 5-Trisubstituted-Imidazoles Using Morpholinium Hydrogen Sulphate as Green and Reusable Catalysts

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Abstract

Morpholinium hydrogen Sulphate as Brønsted acidic ionic liquid was used as an efficient and reusable catalyst for the one-pot synthesis of 2,4,5-trisubstituted imidazoles that achieved by three component cyclocondensation of 1,2-dicarbonyl compound, aromatic or aliphatic aldehyde and ammonium acetate under thermal solvent-free conditions. The key advantages of this process are cost effectiveness of catalyst, reusability of catalyst, easy work-up and purification of products by non-chromatographic methods, excellent yields and very short time reactions. Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity.

Keywords: 2, 4, 5-triaryl imidazoles, Morpholinium Hydrogen Sulphate, Reusable Catalysts

1. Introduction

Multicomponent reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation (Bora et al, 2003). The developing of new MCRs (Sadek et al, 2012) and improving known multi-component reactions are an area of considerable current interest. One such reaction is the synthesis of imidazoles. Naturally occurring substituted imidazoles, as well as synthetic derivatives thereof, exhibit wide ranges of biological activities, making them attractive compounds for organic chemists (Sharma et al, 2008). They act as inhibitors of p38 MAP kinase (Vikrant et al, 2012) B-Raf kinase (Takle et al, 2006) transforming growth factor b1 (TGF-b1) type 1 activin receptor-like kinase (ALK5) (Khanna et al, 1997) cyclooxygenase-2 (COX-2)( Lange et al, 2005) and biosynthesis of interleukin-1 (IL-1) (Gallagher et al, 1995). Appropriately substituted imidazoles are extensively used as glucagon receptors (de Loszlo et al, 1999) and CB1 cannabinoid receptor antagonists (Eyers et al, 1998) modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) (Newman et al, 2000) antibacterial (Antolini et al, 1999) and antitumor (Wang et al, 2002) agents and also as pesticides (Veisi et al, 2012). Recent advances in green chemistry and organometallic catalysis has extended the application of imidazoles as ionic liquids (Chowdhury et al, 2007) and N-heterocyclic carbenes (Kuhl, 2007).

Ionic liquid (IL) technology offers a new and environmentally benign approach toward modern synthetic chemistry. Ionic liquids have interesting advantages such as extremely low vapour pressure, excellent thermal stability, reusability, and talent to dissolve many organic and inorganic substrates (Ohno, 2008). Ionic liquids have been successfully employed as solvents and catalyst for a variety of reactions (Rogers et al, 2002; Sheldon et al, 2007; Wasserscheid & Welton, 2008 and Freemantle, 2009), which promise widespread applications in industry and organic syntheses.
We report here a simple, mild and efficient method for the preparation of the 2,4,5-triazylimidazoles using morphinolium hydrogen sulphate as Brønsted acidic ionic liquid catalyst that considered as efficient and reusable catalyst. The procedure reported herein is not cumbersome; consequently, the methodology represents a good addition to the list of methods available for the synthesis of highly substituted imidazoles.

2. Experimental

2.1. Chemicals and Instruments

All reagents were purchased from Merck and Aldrich and used without further purification. Spectra IR and 1H NMR and 13C NMR spectra) were recorded on SHIMADZU FT-IR-8400s and Bruker (300-MHz) spectrophotometers respectively. The purity of the substances and the progress of the reactions were checked on TLC and melting points.

2.2. General Procedure for Preparation of Ionic Liquid

Morpholine (20 mmol) was added into a 150 ml three necked flask with a magnetic stirrer. Then equimolar concentrated sulfuric acid (98 wt.%) was added drop wise slowly into the flask at 0 °C then stirring at 80 °C for 12 hours. The mixture was washed with diethyl ether three times to remove non-ionic residues and dried in vacuum by recrystallisation from ethanol. All of the solid product was consequently the methodology represents a good addition to the list of methods available for the synthesis of highly substituted imidazoles.

2.3. General Procedure for Preparation of 2,4,5-trisubstituted Imidazoles

Benzoil (5 mmol), aldehyde (5 mmol), and ammonium acetate (20 mmol) were added to morpholinium hydrogen Sulphate (0.4 g, 2 mmol) in an oil bath at room temperature as in Scheme 1. The resulting mixture was heated to 100 °C as in Scheme 1. The resulting mixture was washed with diethyl ether three times to remove non-ionic residues and dried in vacuum by a rotary evaporator to obtain the viscous clear diethyl ammonium hydrogen Sulphate (Xie et al, 2008 and Shaterian & Ranjbar, 2011).

3. Spectral and Analytical Data

12,4,5-Triphenyl-1H-imidazole (1a): MP. 271-272 °C. FTIR (KBr, cm⁻¹): 3434(NH), 2993, 2470, 1638(C=C), 1510(C=N); 1H NMR (300 MHz, DMSO-d₆): 12.7 (s, 1H), 8.1 (d, J=47.8 Hz, 2H), 7.1-7.9 (m, 13H, arom.); 13C NMR (300 MHz, DMSO-d₆): d 146, 136, 135.4, 130.8, 130, 129, 128.75, 128.3, 127.5, 127, 125.6.

2-2-(4,5-Diphenyl-1H-imidazol-2-yl)-phenol (1b): MP. 204-205 °C. FTIR (KBr, cm⁻¹): 3596 (OH), 3432(NH), 2998, 2465, 1636(C=C), 1216; 1H NMR (300 MHz, DMSO-d₆): 8.6 - 6.95 (d, 2H, j=7.4), 6.98-7.01 (d, 1H, J = 8.05), 7.17-7.23 (m, 10H, arom.), 12.74 (br.s. 1H); 13C NMR (300 MHz, DMSO-d₆): 146.0, 136.0, 130.08, 130.0, 129.0, 128.9, 128, 128.2, 127.6, 126.7, 125.6.

4-(4,5-Diphenyl-1H-imidazol-2-yl)-phenol (1c): MP: 268-269 °C. FTIR (KBr, cm⁻¹): 3590 (OH), 3454 (NH), 3284, 3064, 1701(C=C), 1283; 1H NMR (300 MHz, DMSO-d₆): d 12.20 (s, 1H, NH), 7.92 (d, J=8.4 Hz, 2H), 7.52-7.29 (m, 10H), 6.80 (d, J=48.4 Hz, 2H); 13C NMR (300 MHz, DMSO-d₆): 157.6, 146.65, 127.12, 125.7, 124.3, 121.9, 114.75, 112.85, 98.55, 95.46 ppm.

2-(2-Nitrophenyl)-4,5-diphenyl-1H-imidazole (1h): MP. 271-272 °C. FTIR (KBr, cm⁻¹): 3410, 3061, 1614, 1490, 1179, 1028, 761; 1H NMR (300 MHz, DMSO-d₆): δ=12.52 (s, 1H), 8.03 (dt, J=8.80 Hz, 2.0 Hz, 2H), 7.70-7.10(m, 10H), 7.03 (dt, J=8.8 Hz, 2.0 Hz, 2H), 3.81 (s, 3H); 13C NMR (300 MHz, DMSO-d₆): 158.32, 154.09, 136.01, 134.62, 131.85, 127.4, 117.4, 111.85, 30.00 ppm.

2-(4,4-diphenyl-1H-imidazol-2-yl)-phenol (1e): MP 256–259 °C. FTIR (KBr, cm⁻¹): 3447, 3061, 1614, 1501; 1H NMR (300 MHz, DMSO-d₆): d 12.31 (s, 1H, NH), 7.92 (d, J=48.4 Hz, 2H), 7.7-7.11 (m, 10H, arom.), 6.80 (d, J=48.4 Hz, 2H), 2.97 (s, 6H (CH₃)₃); 13C NMR (300 MHz, DMSO-d₆): 154.46, 145.64, 137.4, 135.08, 131.85, 127.4, 126.38, 125.55, 117.4, 111.85, 30.00 ppm.

2-(3,4-Dimethoxyphenyl)-4,5-diphenylimidazole (1f): MP 218-219 °C. FTIR (KBr, cm⁻¹): 3381(NH), 3062(C-H), 3002, 2960, 1593 (C=N), 1512, 1265, 1023, 765. 1H NMR (300 MHz, DMSO-d₆): 7.9-8.2 (m, 10H, arom.); 13C NMR (300 MHz, DMSO-d₆): 55.78, 55.747, 115.722, 112.294, 122.146, 123.772, 126.430, 126.696, 128.29, 129.107, 129.35, 129.90, 131.35, 131.467, 134.943, 136.733, 147.904, 148.931, 149.769 ppm.

2-(4-Nitrophenyl)-4,5-diphenylimidazole (1g): MP 199–201°C. FTIR (KBr, cm⁻¹): 3421(NH), 2928, 1596(C-H), 1515, 856; 1H NMR (300 MHz, DMSO-d₆): 7.00-8.52 (m, 14H, arom.), 11.7(s. br., NH); 13C NMR (300 MHz, DMSO-d₆): 124.165, 126.659, 126.862, 128.568, 129.631, 130.341, 131.103, 131.345, 134.737, 137.891, 148.069, 145.633, 147.460 ppm.

2-(2-Nitrophenyl)-4,5-diphenylimidazole (1h): MP 199-201°C. FTIR (KBr, cm⁻¹): 3421 (NH), 2928, 1596 (C-N), 1515, 1345, 856; 1H NMR (300 MHz, DMSO-d₆): d 12.10 (br. s., 1H, NH), 7.9-8.2 (m, 14H, arom.); 13C NMR (300 MHz, DMSO-d₆): 118.5, 122.0, 124.0, 125.4, 126.1, 128.2.
126.9, 127.0, 128.4, 129.7, 130.6, 136.1, 141.0, 147.0. 

C{subscript:21}H_{13}N_{3}O_{2}.

hydrogen Sulphate (0.4 g, 2 mmol), as catalyst produces 2,4,5-trisubstituted imidazoles under solvent free

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\text{Scheme 1. Morpholinium Hydrogen Sulphate as Brønsted Acidic Ionic Liquid for Synthesis of 2, 4, 5-trisubstituted Imidazoles}
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\[
\text{Table 1. Synthesis of 2, 4, 5-trisubstituted Imidazoles via a One-Pot Pseudo four Component Reaction in the Presence of Morpholinium Hydrogen Sulphate as Brønsted Acidic Ionic Liquid Under Thermal Solvent-Free Condition at 100 °C}
\]

<table>
<thead>
<tr>
<th>No.</th>
<th>Aldehydes (R)</th>
<th>Yield (%)</th>
<th>R.T. (min)</th>
<th>M.P. (°C)</th>
<th>M. Wt. (g)</th>
<th>M. Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>C{subscript:6}H_{5}</td>
<td>98</td>
<td>20</td>
<td>271-272</td>
<td>296.37</td>
<td>C{subscript:21}H_{16}N_{2}</td>
</tr>
<tr>
<td>B</td>
<td>2-OHC{subscript:6}H_{4}</td>
<td>95</td>
<td>15</td>
<td>204-205</td>
<td>312.36</td>
<td>C{subscript:21}H_{16}N_{2}O</td>
</tr>
<tr>
<td>C</td>
<td>4-OHC{subscript:6}H_{4}</td>
<td>96</td>
<td>15</td>
<td>267-269</td>
<td>312.36</td>
<td>C{subscript:21}H_{16}N_{2}O</td>
</tr>
<tr>
<td>D</td>
<td>4-CH{subscript:3}OC{subscript:6}H_{4}</td>
<td>96</td>
<td>15</td>
<td>230-232</td>
<td>326.39</td>
<td>C{subscript:22}H_{18}N_{2}O</td>
</tr>
<tr>
<td>E</td>
<td>4-(CH{subscript:3})<em>{2}NC{subscript:6}H</em>{4}</td>
<td>94</td>
<td>30</td>
<td>256-258</td>
<td>339.43</td>
<td>C{subscript:23}H_{18}N_{3}</td>
</tr>
<tr>
<td>F</td>
<td>3,5-CH{subscript:3}OC{subscript:6}H_{4}</td>
<td>96</td>
<td>25</td>
<td>222-224</td>
<td>356.42</td>
<td>C{subscript:23}H_{20}N_{2}O</td>
</tr>
<tr>
<td>G</td>
<td>4-NO{subscript:2}C{subscript:6}H_{4}</td>
<td>94</td>
<td>20</td>
<td>241-242</td>
<td>341.36</td>
<td>C{subscript:21}H_{15}N_{2}O</td>
</tr>
<tr>
<td>H</td>
<td>2-NO{subscript:2}C{subscript:6}H_{4}</td>
<td>95</td>
<td>25</td>
<td>230-231</td>
<td>341.36</td>
<td>C{subscript:21}H_{15}N_{2}O</td>
</tr>
</tbody>
</table>

4. Results and Discussion

As a result of the versatile biological activities of substituted imidazoles numerous classical methods for the synthesis of these compounds have been reported (Breslow, 1995; Pozharskii et al, 1997; Freedman & Lescalzo, 2009 and Shaterian et al, 2011). In a typical procedure, benzil or benzoin, aldehydes and ammonium acetate are condensed in the presence of strong protic acid such as H{subscript:3}PO{subscript:4} (Shaterian et al, 2011), H{subscript:2}SO{subscript:4} (Shaterian & Oveisi, 2009), HOAc (Shaterian et al, 2009) as well as organo catalyst in HOAc (Freemantle, 2009) under reflux conditions. These homogeneous catalysts present limitations due to the use of corrosive reagents and the necessity of neutralization of the strong acid media. In addition, the synthesis of these heterocycles in polar organic solvents such as ethanol, methanol, acetic acid, DMF and DMSO lead to complex isolation and recovery procedures.

First report, the condensation reaction of benzil or benzoin (5 mmol), aldehyde (5 mmol) and ammonium acetate (20 mmol) in the presence of ionic liquid, diethyl ammonium hydrogen Sulphate (0.4 g, 2 mmol), as catalyst produces 2,4,5-trisubstituted imidazoles under solvent free conditions at 100 °C.

The stoichiometric amount of ammonium acetate in the preparation of 2,4,5-trisubstituted imidazoles is two. We can prepare 2,4,5-trisubstituted imidazoles using two equivalents of ammonium acetate but we observed in our experiment and other published papers, if we use inexpensive and available ammonium acetate having more than two equivalents, the reaction will show better results. Thus, a slight excess of the ammonium acetate was found to be advantageous and hence the molar ratio of benzil or benzoin to ammonium acetate was kept at 1:4. The efficiency and versatility of the ionic liquid as catalyst for the preparation 2,4,5-trisubstituted imidazoles were demonstrated by the wide range of substituted and structurally diverse aldehydes to synthesize the corresponding products in high to excellent yields (Table 2).

The presence of electron donating groups (Scheme 2) on the aromatic aldehyde resulted in the corresponding products in low yields and the reaction was sluggish, however the presence of electron withdrawing groups afforded the corresponding 2,4,5-trisubstituted imidazoles

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in shorter reaction time with higher yields. Also, benzil in comparison with benzoin gives corresponding products in shorter reaction time.

The Brønsted acidic ionic liquid catalyst used here is efficient and reusable catalyst. The procedure reported herein is not cumbersome; consequently, the methodology represents a good addition to the list of methods available for the synthesis of highly substituted imidazoles.

5. Conclusion

In conclusion, we report a simple, mild and efficient method for the preparation of the 2, 4, 5-triarylimidazoles.

Acknowledgement

Table 2. Comparison of the Efficiency of Various Catalysts with Diethyl Ammonium Hydrogen Sulphate in the Synthesis of 2, 4, 5-Trisubstituted Imidazoles

<table>
<thead>
<tr>
<th>No.</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>InCl$_3$·3H$_2$O</td>
<td>MeOH/R.T</td>
<td>492</td>
<td>76</td>
<td>Sharma et al, 2008</td>
</tr>
<tr>
<td>2</td>
<td>KH$_2$PO$_4$</td>
<td>Reflux in EtOH</td>
<td>60</td>
<td>89</td>
<td>Joshi et al, 2010</td>
</tr>
<tr>
<td>3</td>
<td>Yb(OPf)$_3$</td>
<td>C10F18/80 °C</td>
<td>360</td>
<td>80</td>
<td>Shaterian et al, 2011</td>
</tr>
<tr>
<td>4</td>
<td>Zr(acac)$_4$</td>
<td>Reflux in EtOH</td>
<td>120</td>
<td>95</td>
<td>Khosropour, 2008</td>
</tr>
<tr>
<td>5</td>
<td>L-proline</td>
<td>Methanol/60 °C</td>
<td>540</td>
<td>87</td>
<td>Samai et al, 2009</td>
</tr>
<tr>
<td>6</td>
<td>[Hbim]BF$_4$</td>
<td>100 °C</td>
<td>60</td>
<td>94</td>
<td>Qasim et al, 2011</td>
</tr>
<tr>
<td>7</td>
<td>NiCl$_2$·6H$_2$OAl$_2$O$_3$</td>
<td>Reflux in EtOH</td>
<td>90</td>
<td>89</td>
<td>Siddiqui et al, 2005</td>
</tr>
<tr>
<td>8</td>
<td>N-methyl-2-pyrrolidonium hydrogen Sulphate</td>
<td>100 °C</td>
<td>60</td>
<td>98</td>
<td>Shaterian &amp; Ranjbar, 2011</td>
</tr>
<tr>
<td>9</td>
<td>Morpholinium hydrogen Sulphate</td>
<td>100 °C</td>
<td>15-30</td>
<td>98</td>
<td>Present work</td>
</tr>
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</table>

Scheme 2. Mechanism of Condensation Reaction between Benzil, Benzaldehyde, and Ammonium Acetate in the Presence of Morpholinium Hydrogen Sulphate as Brønsted Acidic Ionic Liquid
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References


