ZnO as an Efficient and Inexpensive Catalyst for One Pot Synthesis of 2, 4, 5-Triphenyl-1H-imidazole Derivatives at Room Temperature

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Abstract: An improved and rapid one pot synthesis of 2,4,6-triphenyl-1H-imidazoles on condensation with benzil, aromatic aldehyde and NH4OAc has been carried out using ZnO as an efficient and inexpensive catalyst in high yield at room temperature. The short reaction time, good yields (60-93%), environmental friendly procedure, mild reaction condition and convenient operation are important advantage of these synthetic methods.

Keywords: Benzil, NH4OAc, Aromatic aldehyde, ZnO, One pot synthesis

Introduction

The importance of imidazoles in biological systems has attracted much interest due to their chemical and biochemical properties. Compounds with imidazole ring system have many pharmacological properties and play an important role in biochemical process\(^1\). The structures of trisubstituted imidazoles are prevalent in natural products and pharmacologically active compounds, such as p38 kinase inhibitor I (SB 203580)\(^2\) and cyclooxygenase-2 (COX-2) inhibitor II, (Figure 1)\(^3\) fungicides and herbicides\(^4\), plant growth regulators\(^5\) and therapeutic agents\(^6\). Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related \(N\)-heterocyclic carbenes (NHC)\(^7,8\).

There are several methods reported in literature for the synthesis of imidazoles such as hetero-cope rearrangement\(^9\), four component condensation of aryglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin\(^10\), reaction of \(N\)-(2-oxo)-amides with ammonium
trifluoroacetate\textsuperscript{11}, 1,2-aminoalcohols in the presence of PCl\textsubscript{5}\textsuperscript{12}, diketones, aldehyde, amine and ammonium acetate in phosphoric acid\textsuperscript{13}, in acetic acid\textsuperscript{14}, organo catalyst in acetic acid\textsuperscript{15} as well as H\textsubscript{2}SO\textsubscript{4}\textsuperscript{16}, DMSO\textsuperscript{17}. Several microwave (MW) assisted syntheses of imidazoles from 1, 2-diketones and aldehydes in the presence of a variety of catalysts have been recently reported. These include MW/silica-gel\textsuperscript{18}, MW/silica-gel/ H-Y\textsuperscript{19}, MW/Al\textsubscript{2}O\textsubscript{3}\textsuperscript{20}, MW/CH\textsubscript{3}COOH\textsuperscript{21}, in DMF\textsuperscript{22}. The condensation of \(\alpha\)-hydroxy ketones with aldehydes and ammonium acetate on solid supported silica gel or alumina in the presence of MW has been reported recently\textsuperscript{23}.

Designing of new specific catalysts and exploring their catalytic activity has caused profound effects in optimizing the efficiency of a wide range of organic synthesis. Development of such catalysts has resulted in more economical and environmentally friendly chemistry through replacing nonselective, unstable, or toxic catalysts\textsuperscript{24}. Surface of metal oxides exhibit both lewis acid and lewis base characters. This is characteristic of many metal oxides, especially TiO\textsubscript{2}, Al\textsubscript{2}O\textsubscript{3}, ZnO, etc. and they are excellent adsorbents for a wide variety of organic compounds and increase reactivity of the reactants\textsuperscript{25}. ZnO is certainly one of the most interesting of metal oxides, because it has surface properties which suggest that a very rich organic chemistry may occur there\textsuperscript{26}.

![Figure 1](image1)

**Figure 1**

Many of the synthetic protocols for imidazoles reported so far suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and often expensive acid catalysts. Moreover, the syntheses of these heterocycles have been usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed off.

![Scheme 1](image2)

**Scheme 1**

<table>
<thead>
<tr>
<th>3a: R = H</th>
<th>3b: R = 4·Me</th>
<th>3c: R = 4·Br</th>
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<tr>
<td>3d: R = 2·Cl</td>
<td>3e: R = 4·Cl</td>
<td>3f: R = 3·NO\textsubscript{2}</td>
</tr>
<tr>
<td>3g: R = 2·OH</td>
<td>3h: R = 4·OMe</td>
<td>3i: R = 4·OH</td>
</tr>
<tr>
<td>3j: R = 3, 4·(OMe)\textsubscript{2}</td>
<td>3k: R = 2·NO\textsubscript{3}</td>
<td>3l: R = 4·NO\textsubscript{2}</td>
</tr>
<tr>
<td>3m: R = 2·F</td>
<td>3n: R = 4·F</td>
<td>3o: R = 2·Me</td>
</tr>
</tbody>
</table>
Experimental
Melting points were recorded in open capillaries with super fit melting point apparatus and were uncorrected. $^1$H NMR spectra were recorded on 300 MHz Bruker FT-NMR spectrometer using tetramethylsilane as internal standard and chemical shifts are reported in $\delta$ units and the coupling constant ($J$) are reported in hertz. $^{13}$C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer. Mass spectra were recorded on Bruker daltonics data analysis 3.4. All chromatographic purification was performed with silica gel (100 - 200 mesh), whereas all TLC (silica gel) developments were performed on silica gel (Merck Kiesel 60F$_{254}$, 0.2 mm thickness) sheets. All reagents and solvents were of commercial quality and were used as supplied unless otherwise stated. Yields reported are isolated yield of the compounds.

General procedure for synthesis of 2,4,5-triphenyl-1H-imidazole derivatives (3a-j)
A mixture of benzil (1 mmol), aldehyde (1 mmol), NH$_4$OAc (5 mmol) and ZnO (5 mol%) in acetonitrile (10 mL) was stirred at room temperature. After completion of the reaction (TLC analysis), it was diluted with water (10 mL) and extracted with dichloromethane (25 mL). The organic layer was dried (Na$_2$SO$_4$), evaporated and purified by chromatography by using chloroform to give the products in 60 - 93% yields.

Selected spectral data of the products
2,4,5-Triphenyl-1H-imidazole (Table 2 entry 1)
Solid; m.p. 267-269 $^\circ$C; IR (KBr) $\nu$ = 3434, 2993, 2470, 1638, 1216 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 12.61 (s, 1H), 7.42 - 8.12 (m, 15H); $^{13}$C NMR (CDCl$_3$): $\delta$ 136.53, 129.14, 128.95, 127.23, 122.14; EIMS: $m/z$ = 296. Anal. Calcd. for C$_{21}$H$_{16}$N$_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.13; H, 5.28; N, 9.35.

4,5–Dipheny-2-p-tolyl-1H-imidazole (Table 2 entry 2)
Solid; m.p. 230-231 $^\circ$C; IR (KBr) $\nu$ = 3405, 3033, 1602, 1493, 1449 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 12.60 (s, 1H), 7.98 (d, 2H, $J$ = 8.4 Hz), 7.20 - 7.56 (m, 12H), 2.23 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 145.53, 137.65, 136.82, 135.24, 131.14, 129.23, 128.65, 128.35, 128.32, 127.65, 127.65, 127.08, 126.43, 125.35, 20.81; EIMS: $m/z$ = 310. Anal. Calcd. for C$_{22}$H$_{18}$N$_2$: C, 85.13; H, 5.83; N, 9.03. Found: C, 85.17; H, 5.85; N, 9.06.

2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 3)
Solid; m.p. 248-250 $^\circ$C; IR (KBr) $\nu$ = 3400, 3060, 1601, 1482, 1450, 1429 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 12.79 (s, 1H), 8.04 (d, 2H, $J$ = 8.4 Hz), 7.68 (d, 2H, $J$ = 8.4 Hz), 7.55 - 7.23 (m, 10H); $^{13}$C NMR (CDCl$_3$): $\delta$ 144.34, 137.34, 134.90, 131.61, 130.83, 129.62, 128.64, 128.33, 128.10, 127.63, 127.13, 126.14, 121.33; EIMS: $m/z$ = 385 (M+1). Anal. Calcd. for C$_{21}$H$_{18}$BrN$_2$: C, 67.21; H, 4.03; Br, 21.29; N, 7.47. Found: C, 67.25; H, 4.08; Br, 21.31; N, 7.45.

2-(2-Chlorophenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 4)
Solid; m.p. 186-188 $^\circ$C; IR (KBr) $\nu$ = 3434, 2993, 2470, 1638, 1216 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 12.5 (s, 1H), 8.03 (dd, 1H, $J$ = 8.7 Hz), 7.58 (d, 2H, $J$ = 8 Hz), 7.47 (dd, 1H, $J$ = 9 Hz), 7.27 - 7.37 (m, 10H); $^{13}$C NMR (CDCl$_3$): $\delta$ 142.25, 130.54, 130.15, 129.67, 128.83, 128.65, 128.47, 127.23, 126.90, 126.51, 125.62, 125.44; EIMS: $m/z$ = 340 (M+1). Anal. Calcd. for C$_{21}$H$_{18}$ClN$_2$: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47. Found: C, 76.27; H, 4.62; Cl, 10.68; N, 8.52.
2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 5)
Solid; m.p. 248-250 °C; IR (KBr) ν = 3405, 3060, 1603, 1484, 1433 cm⁻¹; ¹H NMR (CDCl₃): δ 12.79 (s, 1H), 7.21 - 7.56 (m, 12H), 8.11 (d, 2H, J = 8.8 Hz); ¹³C NMR (CDCl₃): δ 144.33, 137.24, 134.92, 132.54, 130.81, 129.14, 128.73, 128.54, 128.40, 128.31, 128.14, 127.06, 126.55, 126.24; EIMS: m/z = 340 (M+1). Anal. Calcd. for C₂₁H₁₅ClN₂: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47. Found: C, 76.28; H, 4.60; Cl, 10.68; N, 8.50.

2-(3-Nitrophenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 6)
Solid; m.p. 252-254 °C; IR (KBr) ν = 3382, 3064, 1605, 1519, 1348 cm⁻¹; ¹H NMR (CDCl₃): δ 13.10 (s, 1H), 8.96 (t, 1H, J = 2.0 Hz), 8.50 - 8.55 (m, 1H), 8.15-8.25 (m, 1H), 7.78 (t, 1H, J = 8 Hz), 7.24 - 7.60 (m, 10H); ¹³C NMR (CDCl₃): δ 148.36, 143.25, 137.55, 134.52, 131.14, 130.53, 130.32, 129.03, 128.64, 128.30, 128.21, 127.62, 122.55, 119.44; EIMS: m/z = 350. Anal. Calcd. for C₂₁H₁₅N₃O₂: C, 73.89; H, 4.43; N, 12.31; O, 9.97. Found: C, 73.94; H, 4.46; N, 12.29; O, 9.94.

2-(4,5-Diphenyl-1H-imidazol-2-yl)phenol (Table 2 entry 7)
Solid; m.p. 117-119 °C; IR (KBr) ν = 3438, 2985, 2970, 1625, 1226 cm⁻¹; ¹H NMR (CDCl₃): δ 12.62 (s, 1H), 8.03 (dd, 2H, J = 8.7 Hz), 7.59 (d, 2H, J = 8 Hz), 7.49 (s, 1H), 7.27 - 7.34 (m, 10H); ¹³C NMR (CDCl₃): δ 147.62, 133.15, 130.25, 129.53, 128.17, 121.95, 118.56, 116.48; EIMS: m/z = 321 (M+1). Anal. Calcd. for C₂₁H₁₆N₂O: C, 80.75; H, 5.16; N, 8.97; O, 5.12. Found: C, 80.78; H, 5.14; N, 9.02; O, 5.14.

2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 8)
Solid; m.p. 220-222 °C; IR (KBr) ν = 3428, 2983, 2970, 1625, 1226 cm⁻¹; ¹H NMR (CDCl₃): δ 12.52 (s, 1H), 8.03 (d, 2H, J = 8.8 Hz), 7.55 - 7.59 (m, 10H), 6.94 (d, 2H, J = 8.8 Hz), 3.85 (s, 3H); ¹³C NMR (CDCl₃): δ 159.17, 145.75, 132.83, 127.64, 127.45, 126.53, 126.34, 122.73, 113.27, 54.63; EIMS: m/z = 326. Anal. Calcd. for C₂₂H₂₁N₂O: C, 80.96; H, 5.56; N, 8.58; O, 4.90. Found: C, 80.99; H, 5.59; N, 8.56; O, 4.93.

4-(4,5-Diphenyl-1H-imidazol-2-yl)phenol (Table 2 entry 9)
Solid; m.p. 202-204 °C; IR (KBr) ν = 3428, 3215, 1602, 1532 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 12.51 (s, 1H), 7.2 - 7.52 (m, 10H), 6.94 (d, 2H, J = 8.8 Hz), 3.85 (s, 3H); ¹³C NMR (CDCl₃): δ 156.55, 145.46, 129.18, 128.37, 127.93, 126.92, 124.74, 119.08, 116.54, 112.82; EIMS: m/z = 321. Anal. Calcd. for C₂₁H₁₆N₂O: C, 80.75; H, 5.16; N, 8.97; O, 5.12. Found: C, 80.80; H, 5.19; N, 9.03; O, 5.17.

2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 10)
Solid; m.p. 210-212 °C; IR (KBr) ν = 3431, 2987, 2893, 2465, 1636, 1216 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 12.48 (s, 1H), 7.2 - 7.52 (m, 10H), 6.99 (d, 2H, J = 7.8 Hz), 6.89 (d, 2H, J = 7.5 Hz); ¹³C NMR (CDCl₃): δ 150.35, 147.64, 144.82, 129.57, 129.33, 129.30, 129.34, 128.83, 128.81, 127.58, 127.56, 133.14, 124.21, 120.83, 115.81, 112.34, 56.24; EIMS: m/z = 356. Anal. Calcd. for C₂₃H₂₀N₂O₂: C, 77.51; H, 5.66; N, 7.86; O, 8.98. Found: C, 77.56; H, 5.69; N, 7.90; O, 8.94.

Results and Discussion
Having established the advantages of ZnO as catalyst, bearing in mind that solvents can also effect the chemical reaction, we continued to optimize the process by varying the solvents.
such as acetonitrile, THF, ethanol, THF/water (1/1), acetonitrile/water (1/1), ethanol/water (1/1) and toluene (shown in Table 1) were chosen as the medium for a comparison. It was found that compound 1 (1 mmol), 2 (1 mmol) and NH$_4$OAc were mixed together with ZnO (5 mol%) and solvent (5 mL) stirred at room temperature. It was found that acetonitrile (entry 1, Table 1) gave the highest yield of the desired product. When other mentioned solvents (Table 1) were used, the reaction suffered many disadvantages such as more reaction time and lower yields.

**Table 1.** Optimization of reaction condition for synthesis of 2, 4, 5-triphenyl 1H-imidazole derivatives using 5 mol% ZnO catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time, h</th>
<th>Yields\textsuperscript{a}, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>6</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>THF/Water</td>
<td>5</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>Acetonitrile/Water</td>
<td>4</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol/Water</td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>9</td>
<td>39</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yields

The progress of reaction by using solvents revealed that when the reaction was performed in acetonitrile, it proceeded much faster than in other solvents; to afford entry 3 in 93% yield (Table 2). A similar reaction was also carried out in solvents toluene in (Table 1), in this case, the reaction took longer reaction time with less yields.

**Table 2.** Synthesis of 2,4,5-triphenyl-1H-imidazole derivatives in the presences of ZnO catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time, min</th>
<th>Yield\textsuperscript{b}, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>3a</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>4-Me</td>
<td>3b</td>
<td>75</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>4-Br</td>
<td>3c</td>
<td>60</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>2-Cl</td>
<td>3d</td>
<td>62</td>
<td>84</td>
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<td>3e</td>
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<td>89</td>
</tr>
<tr>
<td>6</td>
<td>3-NO2</td>
<td>3f</td>
<td>70</td>
<td>85</td>
</tr>
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<td>7</td>
<td>2-OH</td>
<td>3g</td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>3-OMe</td>
<td>3h</td>
<td>90</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>4-OH</td>
<td>3i</td>
<td>85</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>3,4-(OMe)2</td>
<td>3j</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>2-NO2</td>
<td>3k</td>
<td>62</td>
<td>74</td>
</tr>
<tr>
<td>12</td>
<td>4-NO2</td>
<td>3l</td>
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<td>3o</td>
<td>93</td>
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</table>

\textsuperscript{b}All yields refer to isolated products

The synthetic strategy is based on the condensation of 1, 2-diphenylethanenedienones with variety of aldehydes and amines in the presence of an excess of NH$_4$OAc, resulting in 2, 4, 5-triphenyl 1H - imidazole derivatives 3a-o by using 5 mol% of ZnO catalyst. Initially, benzil 1 in acetonitrile was treated with an equimolar quantity of variety of aromatic benzaldehyde, excess of NH$_4$OAc stirred at room temperature for 60 - 90 min to furnish 2, 4, 5 - triphenyl 1H - imidazole derivatives, 3a-o (Table 2) in 63 - 93% yields.
To examine the scope and limitations of this reaction, we carried out the reaction of various aromatic aldehydes including both electron donating and electron withdrawing substituents in ortho, meta and para positions of benzaldehyde (Table 2). We found that the reaction proceeded very efficiently in all cases and the reaction time decreased for aldehydes containing electron withdrawing substituents. The best result was obtained with 4-bromobenzaldehyde (93% yield, entry 3, Table 2) and the least yield (63%) was obtained from 4-methyl benzaldehyde after stirring for 75 min (Table 2, entry 2).

**Conclusion**

We have reported an efficient procedure for the synthesis of 2,4,5-triphenyl-1H-imidazole 3a-o derivatives using ZnO as a reusable, non-toxic, non-corrosive, inexpensive and commercially available heterogeneous catalyst. The method also offers some other advantages such as clean reaction, low loading of catalyst, high yields of products, short reaction times and use of various substrates, which make it a useful and attractive strategy for the synthesis of 2,4,5-triphenyl-1H-imidazole derivatives.

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**References**

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