Synthesis and Characterization of Some 2-Substituted Benzimidazoles

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Abstract
The synthesis of substituted benzimidazoles through a one-pot condensation of o-phenylenediamines (or derivatives) with aryl aldehydes in the presence of HCl/H₂O₂ system in acetonitrile at room temperature is described. Short reaction time, large-scale synthesis, easy and quick isolation of the products, and excellent yields are the main advantages of this procedure.

Keywords: Benzimidazoles, aryl aldehyde, o-phenylenediamine

INTRODUCTION
The imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar, five membered heteroaromatic molecule with 3C and 2N atom in 1 and 3 positions. It was first named as guanoxine (first synthesis with glyoxal and ammonia) scheme 1.

Imidazole is a class of very important heterocyclic compounds, which can be found in many natural products. They are recognized to exhibit a large variety of important biological and pharmacological activities. Medicinal chemistry is the discipline concerned with determining the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compounds based largely on the modification of structure and then identifying their biological activity. Many of these reaction conditions require the use of strong base or high temperature or produce acids as byproducts. In view of recent demands for development of environmentally benign processes, amidil, catalytic, and atom economical methodology must be developed. To the best of our knowledge, only few catalytic reactions which produce imidazoles have been reported. The azoles class of antifungal agent is chemically either an imidazole or a triazole group joined to an asymmetric carbon atom as their functional pharmacophore. They all work by blocking the active site of an enzyme variously known as lanosterol 14α-demethylase or cytochrome P450DM. The affinity for P450 and the activity of the azole antifungals is not only determined by the affinity of the nitrogen for the heme iron, but also by that of the N-1 substituent for the apoprotein moiety of P450. This affinity for the apoprotein not only determines the activity of theazole antifungal, but also its selectivity. The remaining part of theazole antifungal fits in the simila way like lanosterol in hydrophobic groove by interacting with Met-313 and the P-methyl group of Thr-318. More than any other antifungal class, the azoles have been steadily refined and improved upon over the course of almost 50 years. The original synthesis of imidazole utilized glyoxal, formaldehyde, and ammonia and established that the formation of four N-C bonds was a viable route. Although classical methods were derived from this early success, the reaction suffered low yields, mixtures of products (including reversed aldol condensations and oxazole formation), and lack of generality. Synthetic methodology alternatives are many and varied and have resorted to harsh conditions (e.g., the formamide synthesis, which requires excess reagents, H₂SO₄ as a condensing agent, 150-200 °C, 4-6 h, 40-90%).

Benzimidazoles: General Procedure
In a round-bottomed flask (100 mL) equipped with a magnetic stirrer, a solution of o-phenylenediamine (or derivatives) (1.0 mmol), and aryl aldehyde (1.0 mmol) in MeCN (50 mL) was prepared. Aq 30% H₂O₂ (7.0 mmol) and aq 37% HCl (3.5 mmol) were added and the mixture was stirred at room temperature for the time indicated in Table 1. The progress of the reaction was monitored by TLC (eluent: n-hexane–EtOAc, 7:3). When the starting materials had completely disappeared, the mixture was quenched by adding H₂O (10 mL), extracted with EtOAc (4 *10 mL), and the combined extracts were dried (MgSO₄). The filtrate was evaporated and the corresponding benzimidazole was obtained as only product (Table 1). An identical procedure was employed using o-phenylenediamine (2.0 mmol) and terephthalaldehyde (134.1 mg, 1.0 mmol in the presence of aq 30% H₂O₂ (7.0 mmol) and aq 37% HCl (3.5 mmol) for the synthesis of bis-benzimidazoles 15 (Table 1).

Table 1 Physical Properties of Chemical compounds

<table>
<thead>
<tr>
<th>NO</th>
<th>MF</th>
<th>m.p.(°C)</th>
<th>Time (min)</th>
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<tr>
<td>a</td>
<td>C₆H₄cinO₂</td>
<td>178-180</td>
<td>75</td>
</tr>
<tr>
<td>b</td>
<td>C₆H₄N₂O₂</td>
<td>185-188</td>
<td>60</td>
</tr>
<tr>
<td>c</td>
<td>C₆H₄N₂</td>
<td>193-195</td>
<td>25</td>
</tr>
<tr>
<td>d</td>
<td>C₆H₄N₂O₂</td>
<td>200-201</td>
<td>80</td>
</tr>
<tr>
<td>e</td>
<td>C₆H₄N₂O₂</td>
<td>185-187</td>
<td>60</td>
</tr>
<tr>
<td>f</td>
<td>C₆H₄N₂</td>
<td>178-180</td>
<td>45</td>
</tr>
<tr>
<td>g</td>
<td>C₆H₄N₂O₂</td>
<td>210-212</td>
<td>95</td>
</tr>
<tr>
<td>h</td>
<td>C₆H₄N₂O₂</td>
<td>198-200</td>
<td>45</td>
</tr>
</tbody>
</table>

1: 1 (2-(4-chlorophenyl)-IH-benz[cd]imidazol-5-yl)(phenyl)methane. (a)

It was prepared by reacting (3,4-diaminophenyl)(phenyl)methane (1 mmol, 0.212 g) with 4-hydroxybenzaldehyde (1 mmol, 0.14 g). Yield 95%, m.p. = 178-180°C. IR (cm⁻¹, KBr disk): 1647 (C= N).

1: 2 (2-(4-hydroxyphenyl)-IH-benz[cd]imidazol-5-yl)(phenyl)methane (b)

It was prepared by reacting (3,4-diaminophenyl)(phenyl)methane (1 mmol, 0.212 g) with...
4-chlorobenzaldehyde (1 mmol, 0.12 g). Yield = 92%, m.p. = 185-188°C.
IR (6 cm⁻¹, KBr disk): 1668 cm⁻¹ (C=N).

1: 3 3,4-di(1H-benzo[d]imidazol-2-yl)benzene. (c)
It was prepared by reacting benzene-1,2-diamine (2 mmol, 0.216 g) with terephthalaldehyde (1 mmol, 0.134 g). Yield = 90%, m.p. = 193-195°C. IR (6 cm⁻¹, KBr disk): 1620 cm⁻¹ (C=N).

1: 4 (2-(4-(dimethylamino)phenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone. (d)
It was prepared by reacting (3,4-diaminophenyl)(phenyl)methanone (1 mmol, 0.212 g) with 4-(dimethylamino)benzaldehyde (1 mmol, 0.149 g). Yield = 98%, m.p. = 189-201°C. IR (6 cm⁻¹, KBr disk): 1674 cm⁻¹ (C=N).

1: 5 (2-(2-hydroxy-3-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone. (e)
It was prepared by reacting (3,4-diaminophenyl)(phenyl)methanone (1 mmol, 0.212 g) with 2-hydroxy-3-methoxybenzaldehyde (1 mmol, 0.152 g). Yield = 97%, m.p. = 185-187°C. IR (6 cm⁻¹, KBr disk): 1647 cm⁻¹ (C=N).

1: 6 4-(1H-benzo[d]imidazol-2-yl)phenol. (f)
It was prepared by reacting benzene-1,2-diamine (1 mmol, 0.108 g) with 4-hydroxybenzaldehyde (1 mmol, 0.122 g). Yield = 95%, m.p. = 178-180°C. IR (6 cm⁻¹, KBr disk): 1662 cm⁻¹ (C=N).

1: 7 7-methyl-2-(4-(4-methyl-1H-benzo[d]imidazol-2-yl)phenyl)benzo[d]imidazole(g)
It was prepared by reacting 3-methylbenzene-1,2-diamine (2 mmol, 0.244 g) with terephthalaldehyde (1 mmol, 0.134 g). Yield = 95%, m.p. = 210-212°C. IR (6 cm⁻¹, KBr disk): 1662 cm⁻¹ (C=N).

1: 8 2-(1H-benzo[d]imidazol-2-yl)-6-methoxyphenol. (h)
It was prepared by reacting (benzene-1,2-diamine (1 mmol, 0.108 g) with 2-hydroxy-3-methoxybenzaldehyde (1 mmol, 0.152 g). Yield = 97%, m.p. = 198-200°C. IR (6 cm⁻¹, KBr disk): 1604 cm⁻¹ (C=N).

RESULTS AND DISCUSSION

Imidazol are an important class of compounds because of their utility as antibiotics and antifungal agents. On the use of a combination of hydrogen peroxide and the respective hydrohalic acid as a green halogenating agent for arenes inspired us to explore the potential of this system for the synthesis of 2-substituted benzimidazoles by the condensation of o-phenylenediamine (or derivatives) with aryl aldehydes. In there paper, I wish to report a new and efficient method for the synthesis of 2-substituted benzimidazoles by the condensation of o-phenylenediamine (or derivatives) with aldehydes using aqueous HCl and H₂O₂ as efficient oxidant system in acetonitrile at room temperature. The route for the synthesis of 2-substituted benzimidazoles is shown in Scheme 2.

\[
\begin{align*}
R_1\text{NH}_2 + R_2\text{H} & \xrightarrow{\text{H}_2\text{O}, \text{MeCN}, \text{rt}} R_1\text{N} \quad \text{IR} (\text{cm}^{-1}, \text{KBr disk}) = 3136, 1600, 1365, 1647, 1610, 1570 \text{ cm}^{-1} \\
\end{align*}
\]

The IR spectra of 2-(4-chlorophenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone. (a) shows a vibration at 3016 cm⁻¹ (aromatic C-H), 1647 cm⁻¹ (C=O), 1365 cm⁻¹ (C-N), 1600 cm⁻¹ (aromatic C=C) and 3136 cm⁻¹ (H-N).
The IR spectra of (2-(4-hydroxyphenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone (b) shows a vibration at 3157 cm\(^{-1}\) (aromatic C-H), 1707 cm\(^{-1}\) (C=O), 1357 cm\(^{-1}\) (C-N), 1668 cm\(^{-1}\) (aromatic C=C), 3280 cm\(^{-1}\) (O-H) and 3464 cm\(^{-1}\) (H-N).

The IR spectra of 1,4-di(1H-benzo[d]imidazol-2-yl)benzene (c) shows a vibration at 3043 cm\(^{-1}\) (aromatic C-H), 1400 cm\(^{-1}\) (C-N), 1620 cm\(^{-1}\) (aromatic C=C), and 3340 cm\(^{-1}\) (H-N).

The IR spectra of (2-(4-(dimethylamino)phenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone (d) shows a vibration at 3105 cm\(^{-1}\) (aromatic C-H), 2950 cm\(^{-1}\) (aliphatic C-H), 1674 cm\(^{-1}\) (-C=O), 1342 cm\(^{-1}\) (C-N), 1593 cm\(^{-1}\) (aromatic C=C) and 3325 cm\(^{-1}\) (H-N).

The IR spectra of 2-(2-hydroxy-3-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone (e) shows a vibration at 3059 cm\(^{-1}\) (aromatic C-H), 2978 cm\(^{-1}\) (aliphatic C-H), 1604 cm\(^{-1}\) (-C=O), 1365 cm\(^{-1}\) (C-N), 1566 cm\(^{-1}\) (aromatic C=C) and 3059 cm\(^{-1}\) (H-N).

The IR spectra of 4-(1H-benzo[d]imidazol-2-yl)phenol (f) shows a vibration at 3009 cm\(^{-1}\) (aromatic C-H), 1357 cm\(^{-1}\) (C-N), 1577 cm\(^{-1}\) (aromatic C=C), 1662 cm\(^{-1}\) (-C=N) and 3305 cm\(^{-1}\) (H-N).

The IR spectra of 7-methyl-2-(4-(4-methyl-1H-benzo[d]imidazol-2-yl)phenyl)-1H-benzo[d]imidazole (g) shows a vibration at 3128 cm\(^{-1}\) (aromatic C-H), 2914 cm\(^{-1}\) (aliphatic C-H), 1662 cm\(^{-1}\) (-C=N), 1596 cm\(^{-1}\) (C-N), 1541 cm\(^{-1}\) (aromatic C=C) and 3294 cm\(^{-1}\) (H-N).

The IR spectra of 2-(1H-benzo[d]imidazol-2-yl)-6-methoxyphenol (h) shows a vibration at 3008 cm\(^{-1}\) (aromatic C-H), 2904 cm\(^{-1}\) (aliphatic C-H), 1604 cm\(^{-1}\) (-C=N), 1516 cm\(^{-1}\) (aromatic C=C) and 3059 cm\(^{-1}\) (H-N).

1H-NMR spectral analysis of imidazol:
The 1H-NMR spectra of the imidazol (a-h) are included in table(3) and their spectra. The 1H-NMR spectra of 2-(2-hydroxy-3-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone (a) showed singlet N-H δ(10.35) ppm and can be seen in figure.
The 1H-NMR spectra of the aromatic region of a shows multiplet signal at 6.82-8.44 ppm for 12 protons.

2- The 1H-NMR spectra (2-(4-hydroxyphenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone (b) showed singlet N-H δ(9.67) ppm and multiplet signal at 6.74-7. 89 ppm for 12 protons and singlet -CH3 δ(2.55) ppm 6 protons

3- The 1H-NMR spectra 1,4-di(1H-benzo[d]imidazol-2-yl)benzene. (c) showed singlet N-H δ(5.71) ppm and multiplet signal at 6.67-8.07 ppm for 12 protons

4- The 1H-NMR spectra (2-(4-(dimethylamino)phenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone. (d) showed singlet N-H δ(8.76) ppm and multiplet signal at 7.56-8.34 ppm for 12 protons and singlet -CH3 δ(2.55) ppm 6 protons

5- The 1H-NMR spectra (2-(2-hydroxy-3-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone. (e) showed singlet N-H δ(10.19) ppm and multiplet signal at 6.86-7.88 ppm for 11 protons and singlet -CH3 δ(2.67) ppm 3 protons and singlet O-H δ(8.61) ppm.

6- The 1H-NMR spectra 4-(1H-benzo[d]imidazol-2-yl)phenol. (f) showed singlet N-H δ(10.20) ppm and multiplet signal at 6.86- 8.38 ppm for 8 protons singlet O-H δ(8.40) ppm.
7- The 1H-NMR spectra 7-methyl-2-(4-(4-methyl-1H-benzo[d]imidazol-2-yl)phenyl)-1H-benzo[d]imidazole (g) showed singlet N-H δ(8.59) ppm and multiplet signal at 6.81-8.36 ppm for 10 protons and singlet -CH3 δ(2.44) ppm 6 protons

8- The 1H-NMR spectra 2-(1H-benzo[d]imidazol-2-yl)-6-methoxyphenol . (h) showed singlet N-H δ(9.45) ppm and multiplet signal at 6.77-7.84 ppm for 6 protons and singlet -CH3 δ(3.38) ppm 3 protons and singlet O-H δ(8.50) ppm

13C-NMR spectra of imidazole:

The 13C-NMR spectral of the imidazoles (a-h) are included in table (3) and its spectra are shown in figures 9,10,11,12,13,14,15,16. The 13C-NMR spectra of (2-(4-chlorophenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone. (a) shows two peaks, appeared at δ 169 ppm for Carbonyl group and δ 157 ppm for (C=N) .

<table>
<thead>
<tr>
<th>NO</th>
<th>Chemical Shift</th>
<th>Aliphatic</th>
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<th>Carboxyl group</th>
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<tr>
<td>a</td>
<td>-</td>
<td>157</td>
<td>153-114</td>
<td>169.5</td>
</tr>
<tr>
<td>b</td>
<td>-</td>
<td>156</td>
<td>152-115</td>
<td>169</td>
</tr>
<tr>
<td>c</td>
<td>-</td>
<td>144</td>
<td>134-107</td>
<td>-</td>
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<td>d</td>
<td>45</td>
<td>157</td>
<td>135-115</td>
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<td>f</td>
<td>-</td>
<td>159</td>
<td>148-115</td>
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<tr>
<td>g</td>
<td>37</td>
<td>153</td>
<td>151-108</td>
<td>-</td>
</tr>
<tr>
<td>h</td>
<td>55</td>
<td>161</td>
<td>156-114</td>
<td>-</td>
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Mass spectral analysis.
The Mass spectral data of the prepared imidazoles a,b,c,d,e,f,g,h are showed in the Figures 17,18,19,20,21,22,23,24.

The Mass spectra of (2-(4-chlorophenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone. (a) showed the molecular ion peak m/z = 332, showed the important fragmentation peaks in m/z = 227 (R%100), m/z = 118 (R%2), m/z = 226 (R%69).

The Mass spectra of (2-(4-hydroxyphenyl)-1H-benzo[d]imidazol-5-yl)(phenyl)methanone (b) showed the molecular ion peak m/z =314, and showed the important fragmentation peaks in m/z = 119 (R%60), m/z = 258 (R%6), m/z = 99 (R%5)

REFERENCES
10- Earlier reports described microwave assisted conditions for the tion with equal or greater potency (5-21-fold) than synthesisoff imidazoles on solid support (AZO3, SiO2, and zelite HY), and these procedures were limited to triarylimidazoles. See: Balalaie, S.; Arabanian, A.; Hashtroudi, M. S. Monatsh. Chem. 2000, 131, 945.Usyatsinsky, A. Y.; Khmelinskyy, V. L. Tetrahedron Lett. 2000, 41, 5031.In general, although solvent-free conditions were commonly used with multimode commercial microwaves (“kitchen” microwave ovens), they are incompatible with currently employed, temperature- and pressure-controlled, single-mode scientific reactors.