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Research Article

### Facile and Efficient Synthesis of Benzimidazoles Using Zinc Acetate

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#### ABSTRACT

Benzimidazoles have been efficiently synthesized in high yields by treatment of 1,2-phenylenediamine with aldehydes using Zinc acetate in acetonitrile. An absolute testing was carried out with ortho-phenylenediamine and 3,4,5-trimethoxy benzaldehyde in the absence of the catalyst zinc acetate and the essential 3,4,5-trimethoxy benzimidazole product was not establish even after stirring for 15 hours. Aromatic aldehydes responded very well to afford the consistent products of benzimidazole derivatives in very good to outstanding yields. In overall, the aromatic aldehydes having electron donating groups and electron withdrawing groups are reacting very healthy.

#### 1. Introduction

The Benzimidazole moiety is found in various bioactive compounds having antiviral, antiulcer, antihypertension and anti-cancer properties. Benzimidazoles are precise impotent intermediates in synthetic ways and helps as ligands for irregular catalysts [1-8]. The great contour of biological presentations of the benzimidazole compounds has provoked widespread studies of their synthesis. Therefore, various efforts have remained completed to synthesize benzimidazole derivatives. The most common methods for the preparation of benzimidazole derivatives contains the reduction of an ortho-phenylenediamines and carbonyl compounds. The reduction of ortho-phenylenediamine with carboxylic acid often needs strong acidic settings and high temperatures. [9,10] The other method includes the oxidative cyclo-dehydrogenation of Schiff bases, which is generated from ortho-phenylenediamine and aldehyde in occurrence of numerous catalysts.

This is the most prevalent methods in common for the synthesis of benzimidazole derivatives. The catalysts compounds are ceric ammonium nitrate,  $K_3PO_4$ , oxone, sulfamic acid, DDQ, PhI (OAc)<sub>2</sub>, Iodine and  $KHSO_4$ , [11-17] In addition, numerous catalysts such as metal halides & metaloxy chlorides, [18-22] metal oxides, PTSA, metal triflates, Air, [23-30] ionic liquid, hetero polyacid, BDSB, [31-33] proline, solid supported, polymer supported catalysts, [34 & 35] microwave promoted, [36-39] and clay zic [40] reactions have been described in the literature. Unfortunately, several of these approaches suffer from disadvantages such as extreme reaction conditions, low yields, tedious workup measures and co-occurrence of several side reactions. As a consequence, the overview of a competent and mild scheme is still required to overcome these restrictions.

As part of our research program in developing various synthetic practices we report, the synthesis of benzimidazoles using zinc acetate as a competent catalyst. The catalyst is identified as an efficient catalyst in the literature for numerous organic transformations [41].

#### 2. Material and Methods

##### 2.1 Experimental Section

Melting points were noted on Buchi R-535 apparatus and are uncorrected. IR spectra were verified on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr discs. <sup>1</sup>H NMR spectra were noted on Gemini-200 spectrometer in  $CDCl_3$  using TMS as internal standard. Mass spectra were documented on a FinniganMAT 1020 mass spectrometer operating at 70 eV.

##### 2.2 General Procedure:

A combination of ortho-phenylenediamine (1.0 mmol) and aldehyde (1.2 mmol) in presence of zinc acetate (10 mol %) was stirred in acetonitrile (5 ml) at room temperature. The improvement of the reaction was observed by thin layer chromatography (TLC). After completion of the reaction as indicated by TLC, the solvent was detached under reduced pressure. The residue was liquified in ethyl acetate and washed with water and brine. The organic layer was dehydrated over  $Na_2SO_4$  and concentrated under reduced pressure. The crude yields were purified by column chromatography.

Figure-1. Example of benzimidazole based drugs

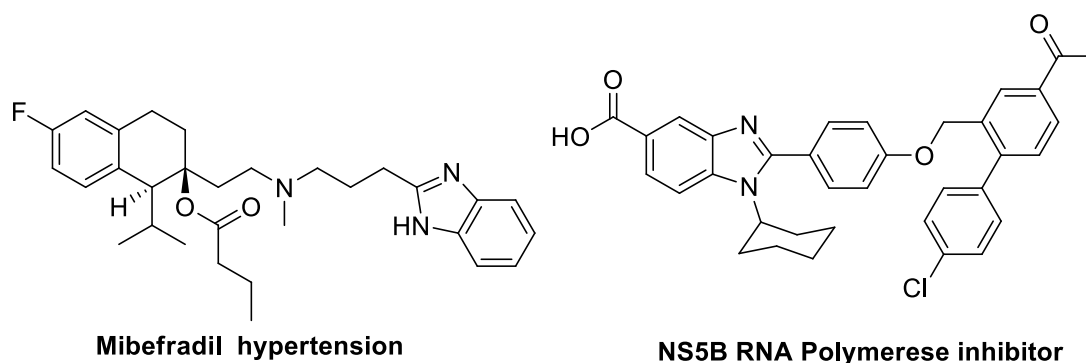
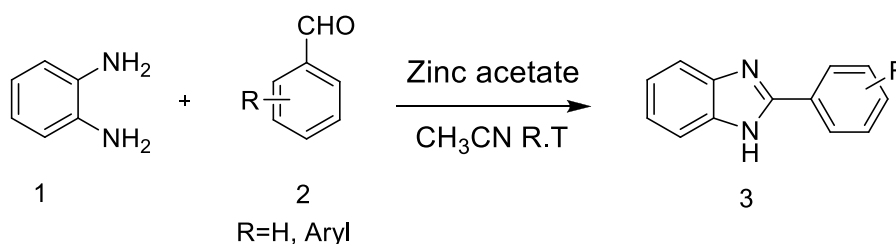


Figure-2. Yield of 2-(3,4,5-trimethoxyphenyl)-1H-benzo[d]imidazole (3) from the Reaction between 1,2-phenylenediamine (1) and 3,4,5-trimethoxybenzaldehyde (2)



All the yields were recognized by their  $^1\text{H}$  NMR, IR and mass spectroscopy data.

### 2.3 Spectral data for selected compounds:

#### 2.3.1. 2-(3,4,5-Trimethoxyphenyl)-1H-benzo[d]imidazole (3a):

White solid. Melting rang. 259 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  2924, 2851, 1601, 1495, 1463, 1416, 1282, 1096, 1020, 899, 801, 749, 693  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.90 (s, 3H), 4.00 (s, 6H), 7.43-7.60 (m, 2H), 7.65 (s, 2H), 7.85-7.95 (m, 2H); EIMS  $m/z$  (%): 285 ( $m^+100$ ), 269 (10), 255 (10), 224 (5).

#### 2.3.2 4-(1H-Benzo[d]imidazol-2-yl)-N,N-dimethyl benzenamine (3b):

White solid. Melting rang. 288-290 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  2853, 2800, 1740, 1611, 1561, 15276, 1446, 1389, 1362, 1324, 1278, 1230, 1200, 1167, 1106, 1064, 948, 819, 800, 744, 769, 583  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.90 (s, 6H), 6.70 (dd, 2H), 6.95 (d, 2H), 7.10-7.25 (m, 2H), 7.60 (dd, 2H); EIMS  $m/z$  (%): 238 ( $m^+100$ ), 157 (30), 134 (80), 109 (10).

#### 2.3.4 2-(Furan-2-yl)-1H-benzo[d]imidazole (3c):

Solid. Melting rang 296 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  2927, 2857, 1741, 1609, 1545, 1462, 1379, 1189, 1069, 751, 597  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.30 (d, 2H), 7.15-7.35 (m, 2H), 7.40 (d, 1H), 7.65 (d, 2H); EIMS  $m/z$  (%): 184 ( $m^+100$ ), 158 (20), 137 (5), 133 (5).

#### 2.3.5. (E)-2-Styryl-1H-benzo[d]imidazole (3d):

Solid. Melting rang 201-203 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  3377, 3027, 2924, 2853, 1948, 1805, 1633, 1598, 1495, 1449, 1402, 1355, 1326, 1284, 1194, 1153, 1070, 1018, 963, 918, 841, 737, 691, 558  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.40 (dd, 1H), 6.55 (d, 1H), 7.15-7.55 (m, 7H), 7.70 (d, 2H); EIMS  $m/z$  (%): 220 ( $m^+115$ ), 195 (5), 174 (5), 155 (5), 144 (5), 134 (5).

#### 2.3.6 2-(4-Fluorophenyl)-1H-benzo[d]imidazole (3e):

White solid. Melting rang 248 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  3053, 2930, 1663, 1624, 1545, 1486, 1440, 1315, 1277, 1229, 1094, 1034, 1004, 972, 833, 795, 746, 690, 618, 568  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.15-7.20 (m, 2H), 7.20-7.40 (m, 2H), 7.45-7.52 (m, 2H), 7.60-7.70 (m, 2H), 8.00 (brs, 1H); EIMS  $m/z$  (%): 212 ( $m^+100$ ), 193 (5), 215 (15), 168 (5), 155 (5), 136 (5), 129 (5), 95 (5).

#### 2.3.7 2-p-Tolyl-1H-benzo[d]imidazole (3f):

White solid. Melting rang 275 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  3397, 3027, 2922, 2858, 1813, 1514, 1481, 1452, 1412, 1383, 1348, 1282, 1250, 1183, 1157, 1114, 1021, 987, 823, 746, 612  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.35 (s, 3H), 4.42 (brs, 1 NH), 6.95 (d, 2H), 7.10 (d, 2H), 7.28 (d, 2H), 7.55 (d, 2H); EIMS  $m/z$  (%): 208 ( $m^+100$ ), 195 (15), 179 (20), 161 (10), 153 (10), 149 (5), 140 (20), 136 (5), 126 (10), 122 (5).

#### 2.3.8 2-Phenyl-1H-benzo[d]imidazole (3g):

White power. Melting rang 295 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  3406, 3047, 1589, 1540, 1443, 1409, 1483, 1275, 1118, 736, 704  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.50 (brs, 1H), 7.20-7.40 (m, 2H), 7.50-7.75 (m, 5H), 7.70 (d, 2H), 8.25 (d, 2H); EIMS  $m/z$  (%): 195 ( $m^+10$ ), 175 (5), 160 (5).

#### 2.3.9. 4-(1H-Benzo[d]imidazole-2yl) phenol (3h):

White power. Melting range 229-230 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  3376, 3290, 3027, 2807, 1697, 1611, 1591, 1515, 1443, 1394, 1268, 1246, 839, 745  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  6.90 (d, 1H), 7.05-7.15 (m, 4H), 7.75 (d, 2H), EIMS  $m/z$  (%): 210 ( $m^+100$ ), 193 (5), 191 (20), 183 (10), 181 (5), 169 (40), 154 (5), 137 (5).

#### 2.3.10 2-(3-Chlorophenyl)-1H-benzo[d]imidazole (3i):

White powder. Melting rang 232-234 $^{\circ}\text{C}$ ; IR (KBr):  $\nu$  3059, 1619, 1593, 1440, 1421, 1269, 836, 750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$  MHz):  $\delta$  7.45-7.60 (m, 4H), 7.62-7.72 (m, 2H), 8.30-8.45 (m, 2H); EIMS  $m/z$  (%): 229 ( $m^+100$ ).

#### 2.3.11 2-(Naphthalene-2yl)-1H-benzo [d] imidazole (3j):

White powder. Melting rang 218-219°C. IR (KBr):  $\nu$  3425, 3047, 2924, 2853, 1624, 1605, 1447, 1385, 748  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  6.70-6.90 (m, 2H), 7.20-7.35 (m, 2H), 7.55-7.80 (m, 4H), 7.90-8.10 (m, 2H).; EIMS  $m/z$  (%): 245 ( $m^+$  100), 243 (5), 141 (10).

### 2.3.12 2-(4-Nitrophenyl)-1H-benzo [d] imidazole (3l):

Yellow powder. Melting rang 314°C. IR (KBr):  $\nu$  3042, 1604, 1515, 1434, 1353, 854, 745, 710.  $\text{Cm}^{-1}$ .:  $^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  7.10-7.15 (m, 2H), 7.30 (d, 1H), 7.35 (d, 1H), 7.40 (t, 1H), 7.45 (t, 1H), 8.0 (dd, 2H), 13.0 (brs, 1H); EIMS  $m/z$  (%): 240 ( $m^+$  100), 226 (5), 211 (10), 194 (20), 182 (5).

### 2.3.13 2-(Pyridine-2-yl)-1H-benzo[d]imidazole (3l):

Solid. Melting rang 245-248°C.; IR (KBr):  $\nu$  3068, 1449, 1402, 1280, 746,  $\text{cm}^{-1}$ .:  $^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  6.85 (m, 2H), 7.00-7.10 (m, 1H), 7.45-7.55 (m, 1H), 7.80-7.90 (m, 2H), 8.10 (t, 1H), 8.65 (d, 1H).; EIMS  $m/z$  (%): 196 ( $m^+$  15).


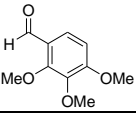
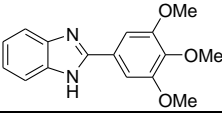

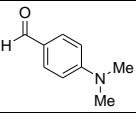
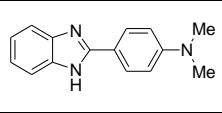

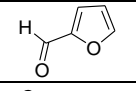
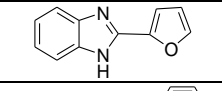

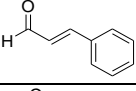
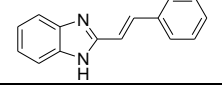

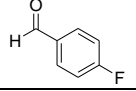
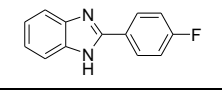

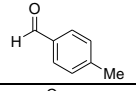
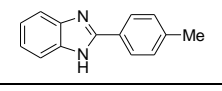

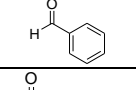
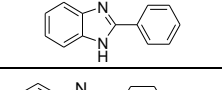

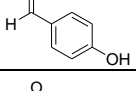
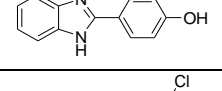

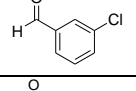
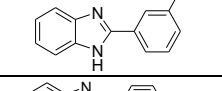

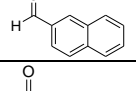
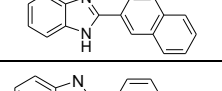

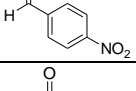
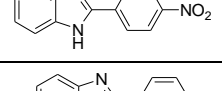

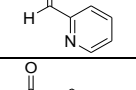
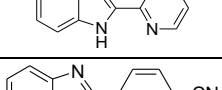

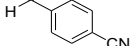
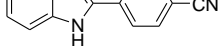
White crystalsolid. Melting rang 262°C. IR (KBr):  $\nu$  3417, 3047, 2912, 2222, 1605, 1454, 1408, 748  $\text{cm}^{-1}$ .:  $^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  5.50 (brs, 1H), 7.45-7.60 (m, 2H), 7.82-7.90 (m, 2H), 8.05 (d, 2H), 8.50 (d, 2H), EIMS  $m/z$  (%): 220 ( $m^+$  100), 211(10), 196 (5), 186 (5).

## 3. Results and Discussion

In a distinctive experiment, 1,2-phenylenediamine (OPD) 1 and 3,4,5-trimethoxy benzaldehyde were reacted in attendance of zinc acetate in acetonitrile at room temperature to give the corresponding product, (3,4,5-trimethoxyphenyl)-1H-benzo[d]imidazole (3) in outstanding yield. The reaction was finished within 2 hours.

An absolute testing was carried out with *ortho*-phenylenediamine and 3,4,5-trimethoxy benzaldehyde in the absence of the catalyst zinc acetate and the essential 3,4,5-trimethoxy benzimidazole product was not establish even after stirring for 15 hours. Lastly, it was decided that the appropriate

Table 1. Zinc acetate catalyzed synthesis of benzimidazoles

Entry	Diamine	Aldehyde	Product (3a-3m)	Time (h)	Yields (%)
a				2.0	94
b				2.5	87
c				2.0	89
d				3.0	85
e				2.0	84
f				2.5	91
g				3.0	87
h				2.5	85
i				2.5	90
j				3.0	86
k				3.0	87
l				2.5	85
m				2.5	88

### 2.3.14 4-(1H-Benzo[d]imidazole-2-yl) benzonitrile (3m):

conditions for the reduction is in a solvent and in the attendance

of an activator or promoter. Aromatic aldehydes responded very well to afford the consistent products of benzimidazole derivatives in very good to outstanding yields. In overall, the aromatic aldehydes having electron donating groups and electron withdrawing groups are reacting very healthy. All the reactions were completed within 2.0 to 4.0 hours of reaction period and the gained produces also 84 to 94%.

#### 4. Conclusions

In conclusion, the zinc acetate has been working as a novel and effectual catalyst for the synthesis of benzimidazoles in noble yields from ortho-phenylenediamine and a wide diversity of aldehydes. All the reactions were approved at room temperature, though using the catalyst zinc acetate in 10 mol%. The reaction situations were precise mild and the isolation of yields also very informal.

#### Competing Interests

The authors have declared that no competing interests exist.

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