CHAPTER – 7
SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES CATALYZED BY NIOBIUM (V) CHLORIDE
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Section 7.1: Synthesis of benzimidazoles from orthophenylenediamine and aldehydes:

Similarly same procedure was adopted to ortho-phenylenediamine with benzaldehyde in presence of the catalyst niobium pentachloride in acetonitrile at room temperature to obtain, 2-phenyl-1H-benzo[d] imidazole (3a). The reaction was completed within 3 hours, which was followed by TLC. Then the solvent was removed from the reaction mixture under reduced pressure and residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to get the crude products, which were purified by column chromatography using silica gel (60-120 mesh), while eluting with ethyl acetate-hexane mixture (2:8). Pure product, 2-phenyl-1H-benzo[d] imidazole (3a) was obtained as a white solid, in 89% yield as shown in the table-7.1.1.

The product (3a) was identified by their spectroscopy data. The $^1$H NMR spectra for this compound shows a multiplet at δ 7.25-7.35 integrating for 3 protons belongs to para position of phenyl ring and C-5 and C-6 positions of imidazole ring, a multiplet at δ 7.50-7.60 integrating for 2 protons of meta positions of phenyl ring, a multiplet at δ 7.68-7.75 integrating for 2 protons of ortho positions of phenyl ring and a multiplet at δ 8.20-8.30 integrating for 2 protons of C-4 and C-7 of imidazole ring. In a similar manner, 3b, 3c, 3d and 3e were confirmed by their spectral data as mentioned below.
Table 7.1.1: Niobium chloride catalyzed synthesis of benzimidazoles:

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2-Phenyl-1*H*-benzo[d]imidazole (3a): White solid. Mp. 294-295°C. IR (KBr): ν 3406, 3047, 1589, 1540, 1443, 1409, 1483, 1275, 1118, 736, 704 cm⁻¹; ¹H NMR (DMSO-d₆): δ 7.25-7.35 (m, 3H), 7.50-7.60 (m, 2H), 7.68-7.75 (m, 2H), 8.20-8.30 (m, 2H); EIMS: m/z (%): 195 (m⁺ 10), 175 (5), 160 (5). The NMR and mass spectra are presented in fig.7.1.1 respectively.

2-Benzyl-1*H*-benzo[d]imidazole (3b): Solid, Mp. 179-180°C. IR (KBr): ν 1665, 1597, 1535, 745 cm⁻¹; ¹H NMR (CDCl₃): δ 4.60 (s, 2H), 7.58-7.20 (m, 9H); EIMS: m/z (%): 208 (m⁺ 100).
7.1.1. H NMR and mass spectrum of 2-Phenyl-1H-benzo[g]imidazole (3a)
2-(4-Methylphenyl)-1H-benzimidazole (3c): Solid, Mp. 223-225°C. IR (KBr): \( \nu \) 3397, 3026, 2989, 2828, 1613, 1514, 1481, 1453, 1412, 1383, 1346, 1282, 1250, 1184, 1158, 1156, 1114, 1021, 988 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)):\( \delta \) 2.35 (s, 3H), 5.50 (brs, 1H), 7.50-7.60 (m, 4H), 7.80-7.95 (m, 2H), 8.05 (d, 2H), 8.50 (d, 2H); EIMS \( m/z \) (%): 208 (m\(^+\) 100), 195 (20), 179 (30), 161 (20), 153 (30), 149 (20), 140 (30), 136 (20), 128 (20). The IR, NMR and mass spectra are presented in fig. 7.1.2 and fig. 7.1.3 respectively.

2-(3-Chlorophenyl)-1H-benzimidazole (3d): White powder. Mp. 231-233°C. IR (KBr): \( \nu \) 3059, 1619, 1593, 1440, 1421, 1269, 836, 750 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 4.20 (brs, 1H, NH) 7.45-7.60 (m, 2H), 7.62-7.72 (m, 2H), 7.82-7.95 (d, 2H), 8.45-8.50 (m, 2H); EIMS: \( m/z \) (%): 228 (m\(^+\) 100), 194 (05). The NMR and mass spectra are presented in fig. 7.1.4 respectively.

2-(Naphthalene-2yl)-1H-benzimidazole (3e): White powder. Mp. 218-219°C. IR (KBr): \( \nu \) 3425, 3047, 2924, 2853, 1624, 1605, 1447, 1385, 748 cm\(^{-1}\); \(^1\)H NMR (DMSO-d6): \( \delta \) 6.70-6.90 (m, 2H), 7.20-735 (m, 2H), 7.55-7.80 (m, 4H), 7.90-8.10 (m 2H), 8.30 (d, 1H); EIMS: \( m/z \) (%): 245 (m\(^+\) 100), 243 (5), 141 (10). The NMR and mass spectra are presented in fig. 7.1.5 respectively.
7.1.2. IR spectrum 2-(4-methylphenyl)-1H-benzimidazole (3c)
7.1.3. $^1$H NMR and mass spectrum of 2-(4-methylphenyl)-1H-benzo[d]imidazole (3c)
7.1.4. $^1$H NMR and mass spectrum of 2-(3-chlorophenyl)-1H-benzo[d]imidazole (3d)
7.1.5 H NMR and mass spectrum of 2-(naphthalene-2-yl)-1-h-benz[d]imidazole (3e)
Section 7.2: Synthesis of benzimidazoles from OPD & aldehydes:

The another experiment was carried out with α-phenylenediamine and 4-hydroxy benzaldehyde were reacted in presence of the catalyst niobium chloride in acetonitrile at reflux condition the reaction was completed with 3.5 hours to get the corresponding product, 2-(4-hydroxyphenyl)-1H-benzo[d]iazole (3f) in 81% yield, as shown in the table-7.2.1.

The obtained pure product was identified by their spectroscopy data. The ¹HNMR spectra for these compound shows a doublet at δ 6.90 integrating for 2 proton belongs to aromatic protons, a multiplet at δ 7.05-7.15 integrating for 4 protons belong to aromatic protons, a doublet at δ 7.75 integrating for 2 protons belongs to aromatic protons.

Table-7.2.1: Niobium chloride catalyzed synthesis of benzimidazoles:

<table>
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<tr>
<th>Entry</th>
<th>Diamine</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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</tbody>
</table>
4-(1H-Benzodimidazole-2yl) phenol (3f): White powder. Mp. 229-230°C. IR (KBr): ν 3376, 3290, 3027, 2807, 1697, 1611, 1591, 1515, 1443, 1394, 1268, 1246, 839, 745 cm⁻¹. ¹H NMR (DMSO-d₆): δ 6.90 (d, 2H), 7.05-7.15 (m, 4H), 7.75 (d, 2H); EIMS: m/z (%). 210 (m⁺100), 193 (5), 191 (20), 183 (10), 181 (5), 139 (40), 154 (5), 137 (5). The NMR and mass spectra are presented in fig.7.2.1 respectively.

2-(3,4,5-Trimethoxyphenyl)-1H-benzodimidazole (3g): White solid. Mp. 258-259°C; IR (KBr): ν 2924, 2851, 1601, 1495, 1463, 1416, 1282, 1096, 1020, 899, 801, 749, 693 cm⁻¹.; ¹H NMR (CDCl₃): δ 3.90 (s, 3H), 4.00 (s, 6H), 7.43-7.60 (m, 2H), 7.62-7.70 (d, 2H), 7.85-7.95 (m, 2H); EIMS: m/z (%). 284 (m⁺100), 269 (10), 255 (10), 224 (5), 195 (5). The IR, NMR and mass spectra are presented in fig.7.2.2 and fig.7.2.3 respectively.

2-(Furan-2-yl)-1H-benzodimidazole (3h): Solid. Mp. 295-296°C. IR (KBr): ν 2927, 2857, 1741, 1609, 1545, 1462, 1379, 1189, 1069, 751, 597 cm⁻¹.; ¹H NMR (DMSO-d₆): δ 6.30 (d, 1H), 6.65 (s, 1H), 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). The NMR and mass spectra are presented in fig.7.2.4 respectively.
7.2.1. $^1$H NMR and mass spectrum of 4-(1'H-benzo[d]imidazole-2-yl)phenol (3f)
7.2.2. FTIR spectrum of 2-(3, 4, 5-trimethoxyphenyl)-1H-benzo[d]imidazole (3b)
7.2.4. $^1$H NMR spectrum of 2-{furan-2-yl}-1-/- benzo[d]imidazole (3h)
2-(4-Nitrophenyl)-1H-benzo [d] imidazole (3i): Yellow powder. Mp. 312-314 °C. IR. (KBr): \( \nu \) 3042, 1604, 1515, 1434, 1353, 854, 745, 710 cm\(^{-1}\); \(^1\)H NMR (DMSO-d6): \( \delta \) 7.10-7.15 (m, 2H), 7.30 (d, 2H), 7.35 (d, 1H), 7.40 (t, 1H), 7.45 (t, 1H), 8.0 (dd, 2H); EIMS: \( m/z \) (%): 240 (m+100), 226 (5), 211 (10), 194 (20), 182 (5). The NMR and mass spectra are presented in fig. 7.2.5 respectively.

2-(Pyridine-2-yl)-1H-benzo[d]imidazole (3j): Solid. Mp. 245-248 °C. IR (KBr): \( \nu \) 3068, 1449, 1402, 1280, 746, cm\(^{-1}\); \(^1\)H NMR (DMSO-d6, 200 MHz): \( \delta \) 6.30 (brs, 1H, NH), 6.90-7.10 (m, 1H), 7.45-7.70 (m, 2H), 7.80-7.90 (m, 2H), 8.10 (t, 1H), 8.55 (d, 1H), 7.50-7.60 (m, 1H), 7.60-7.70 (m, 1H), 7.80-7.90 (d, 2H) 8.55 (d, 1H); EIMS: \( m/z \) (%): 196 (m+15) The NMR and mass spectra are presented in fig. 7.2.6 respectively.
7.2.6. 1H NMR and mass spectrum of 2-(pyridine-2-yl)-1H-benz[d]imidazole (3)
Section 7.3: Synthesis of benzimidazoles from OPD & cinnmaldehyde:

The next experiment was carried out with ortho-phenylenediamine and cinnamaldehyde, were reacted in presence of the catalyst lanthanum chloride in acetonitrile at reflux condition the reaction was completed with 4 hours to obtain the corresponding product, \((E)-2\text{-styryl-1H-benzo[d]}\text{imidazole (3k)}\) in 81% yield as shown in the table -7.3.1.

The obtained pure product was identified by their spectroscopy data. The \(^1\text{H}\) NMR spectra for these compound shows a multiplet at \(\delta 6.33-6.55\) integrating for 2 protons belongs to ethylene, a multiplet at \(\delta 7.15-7.55\) integrating for 7 protons belongs to aromatic protons, a doublet at \(\delta 7.70\) integrating for 2 protons belongs to aromatic protons.

Table 7.3.1: NbCl\(_5\) catalyzed synthesis of benzimidazoles:

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<th>Entry</th>
<th>Diamine</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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</table>
(E)-2-Styryl-1H-benzo[d]imidazole (3k): Solid. Mp. 201-203°C. IR. (KBr): ν 3377, 3027, 2924, 2853, 1948, 1805, 1633, 1598, 1495, 1449, 1402, 1355, 1326, 1284, 1194, 1153, 1070, 1018, 963, 918, 841, 737, 691, 558 cm⁻¹; ¹H NMR (DMSO-d₆): δ 6.33-6.55 (m, 2H), 7.15-7.55 (m, 7H), 7.70 (d, 2H); EIMS: m/z (%). 220 (m⁺15), 195 (5), 174 (5), 155 (5), 144 (5), 134 (5). The IR and NMR spectra are presented in fig.7.3.1 and 7.3.2 respectively.

4-(1H-Benzol[d]imidazole-2yl) benzonitrile (3l): White crystal solid. Mp. 261-262°C. IR (KBr): ν 3417, 3047, 2912, 2222, 1605, 1454, 1408, 748 cm⁻¹; ¹H NMR (CDCl₃): δ 7.45-7.60 (m, 2H), 7.82-8.90 (m, 2H), 8.05 (d, 2H), 8.50 (d, 2H); EIMS m/z (%): 220 (m⁺100), 211(10), 196 (5), 186 (5).

2-(4-Fluorophenyl)-1H-Benzol[d]diazole (3m): White solid. Mp. 247-248°C. IR. (KBr): ν 3053, 2930, 1663, 1624, 1545, 1486, 1440, 1315, 1277, 1229, 1094, 1034, 1004, 972, 833, 795, 746, 690 cm⁻¹; ¹H NMR (DMSO-d₆): δ 7.15-7.20 (m, 2H), 7.20-7.40 (d, 2H), 7.45-7.52 (m, 2H), 7.60-7.70 (m, 2H); EIMS: m/z (%). 212 (m⁺100), 193 (5). The IR and NMR and mass spectra are presented in fig.7.3.3 and fig. 7.3.4 respectively.
7.3.1. IR spectrum of (E)-2-styryl-1H-benzo[d]imidazole (3k)
7.3.3. IR spectrum of 2(4-fluorophenyl)-1H-benzo[d]imidazole (3m)
4-(1H-Benz[d]imidazol-2-yl)-N,N-dimethyl benzenamine (3n): White solid. Mp, 288-290°C. IR. (KBr): υ 2853, 2800, 1740, 1611, 1561, 15276, 1446, 1389, 1362, 1324, 1278, 1230, 1200, 1167, 1106, 1064, 948, 819, 800, 744, 769 cm⁻¹.; ¹H NMR (DMSO-d₆): δ 2.90 (s, 3H), δ 3.05 (s, 3H), 6.60 (d, 2H), 6.95 (d, 2H), 7.10 (d, 2H) 7.60 (d, 2H); EIMS: m/z (%). 237 (m⁺100), 157 (30), 134 (80), 109 (10). The IR and NMR and mass spectra are presented in fig.7.3.5 and fig. 7.3.6 respectively.
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7.3.5. IR spectrum of 4(1-benzoyl)imidazo[2,1-b]-1,2,5-thiadiazole (3h)
7.3.6. $^1$H NMR and mass spectrum of 4-(1H-benzo[d]imidazol-2-yl)-N, N-dimethylbenzenamine (3n)
Section 7.4: Mechanism for NbCl$_5$-catalyzed synthesis of substituted imidazoles

The mechanism for this reaction is discussed in the scheme-13 and it comprised in to two major steps. The first step involves nucleophilic attack of the primary amine ($\text{NH}_2$) of ortho-phenylenediamine on the partially positive carbonyl carbon of aldehyde. This ultimately results in the formation of a Schiff base. The second step then involves intermolecular ring closure, as a result of the nucleophilic attack of the second NH$_2$ on the slightly positive imine carbon. The subsequent loss of a hydrogen atom results into the formation of the required product. In both the cases, the catalyst played role for the activation of carbonyl carbon and in the cyclization step.

Scheme-13: Plausible mechanism