LITERATURE REVIEW:

SYNTHESIS OF BENZIMIDAZOLES:

Wright J. B.\textsuperscript{1} Detailed reviews covering the synthesis & chemistry of both imidazoles and benzimidazole have been published. Generally, benzimidazoles can be synthesized from a variety of starting materials and a few of them are listed below in detail.

1. \textit{o}-Phenylenediamines
2. \textit{o}-(N-acylamino and –arylamino)aryl amines and nitroarenes
3. \textit{o}-Nitroarylamines and \textit{o}-dinitroarenes
4. \textit{o}-substituted-N-benzylideneanilines
5. Amidines and
6. Other heterocyclic compounds.

FROM \textit{o}-PHENYLENEDIAMINE:

\textit{o}-Phenylenediamine (1) reacts with

(a) Carboxylic acids and their derivatives,

(b) Imino-ethers,

(c) Carbonyl compounds and

(d) Nitriles to yield differently substituted benzimidazoles.

By reaction with carboxylic acids and their derivatives:

2-Substituted benzimidazoles may be synthesized in good yields by condensing \textit{o}-phenylenediamine (1) with carboxylic acids under a wide variety of conditions.

Ladenburg A.\textsuperscript{2} first prepared 2, 5 (or 2, 6)-dimethylbenzimidazole by refluxing 4-methyl-\textit{o}-phenylenediamine in glacial acetic acid. The parent benzimidazole (2) was prepared in 1878 by heating (1) with formic acid\textsuperscript{3} (Scheme-1).
Since then, a large number of benzimidazoles have been synthesized from 1 and aliphatic acids.

**Wagner E. C.** reported improved yields of 2-methyl-benzimidazole from 1 and acetic anhydrides by using dilute hydrochloric acid. Similarly, it was also observed that treatment of the free base of 5 i.e., 4-methyl-\(o\)-phenylenediamine with acetyl chloride in refluxing benzene yielded 2, 5 (2, 6)-dimethylbenzimidazole whereas the corresponding 4-methyl -N, N’-diacetyl-\(o\)-phenylenediamine was the sole product when the reaction was carried out at room temperature.  

**Phillips M. A.** describes the most satisfactory method for the synthesis of 2-alkylbenzimidazoles (3, \(R = \text{alkyl}\)) was developed by Phillips, which involves refluxing equimolar quantities of the diamine and the aliphatic carboxylic acid in 4N hydrochloric acid for 3 -4 hr (Scheme-2).

**Ramanathan V.** For aromatic carboxylic acids, however, Phillips procedure fails to give any respectable yields of 2-arylbenzimidazoles. Aromatic carboxylic acids were reported to give good yields of 2-arylbenzimidazoles (4, \(R = \text{Ar}\)) when heated with 1 in a sealed tube at 180-190°C.
Green H.\textsuperscript{10} The mechanistic pathway for the formation of benzimidazoles by the reaction of 1 with organic acids has already been studied. Further, the role of hydrochloric acid in the reaction has also been investigated. The catalytic action of hydrochloric acid is explained on the basis of activation of the carboxyl group by the protonation of oxygen. The intermediate in the reaction is the addition product formed by the attack of the unshared electron pair of one nitrogen onto the carbonyl group of the protonated acid. However, Phillips\textsuperscript{9} concluded that the monoacyl derivative\textsuperscript{11} was the necessary key intermediate for formation of benzimidazole ring (\textbf{Scheme-3}).

\begin{align*}
\text{\textbf{Scheme - 3}}
\end{align*}

\textbf{Chaudhari R. B.}\textsuperscript{12} A better procedure for the preparation of 2-arylbenzimidazoles (4), from 1 and aromatic carboxylic acid involves the use of polyphosphoric acid\textsuperscript{13} (PPA) or polyphosphate ester\textsuperscript{14} (PPE) as dehydrating agent.
Raut C. N.\textsuperscript{15} Alternatively, phosphoruspentoxide has also been reported as a dehydrating agent for the preparation of 2-arylbendimidazole derivatives. (Scheme-4).

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{H} & \quad \text{R-COOH} \\
\text{H} & \quad \text{PPA or PPE} \\
\text{H} & \quad \text{or P}_2\text{O}_5 \\
\text{H} & \quad \text{R} \quad \text{R (Aryl)} \\
\text{H} & \quad \text{NH} \\
\text{H} & \quad \text{R (Aryl)} \\
\end{align*}
\]

\textbf{Scheme - 4}

The methods described above have been utilized in recent years for the synthesis of a variety of benzimidazoles carrying thiazolyl, thiadiazolyl and isothiazolyl substituents at 2-position\textsuperscript{16,17}.

Kanaoka Y.\textsuperscript{18} Similarly, the other benzimidazoles synthesized include 1-aryl-5-amino; 2-trifluoromethyl; 2, 6-bis (trifluromethyl)-4-nitro; 2-β-mercaptoethyl; 2-(1-amo-no-alkyl) and 2-(p-iodostyryl) benzimidazole etc. The reaction between 4-methyl-o-phenylenediamine dihydrochloride (5) and esters was first investigated by, who prepared 5(6)-methylbenzimidazole (6, X = 5(6)-methyl) by condensation of equimolar amounts of (5) and ethyl formate at 225ºC in a sealed tube for 3 hr (Scheme-5).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{NH}_2 \\
\text{H} & \quad \text{NH}_2 \\
\text{H} & \quad \text{2HCl} \\
\text{H} & \quad \text{O} \quad \text{C}_2\text{H}_5 \\
\text{H} & \quad \text{225ºC} \\
\text{Sealed tube, 3 hrs} \\
\end{align*}
\]

\textbf{Scheme - 5}

2-Methylbenzimidazole (3, R = CH\textsubscript{3}) was obtained by prolonged treatment of OPDA (1) with acetic anhydride, whereas treatment for a shorter period yielded only N, N’-diacetyl o-phenylenediamine (7) (Scheme-6).
Nair M. D.\textsuperscript{19} reported improved yields of 2-methyl- benzimidazole from 1 and acetic anhydrides by using dilute hydrochloric acid. Similarly, it was also observed that treatment of the free base of 5 i.e., 4-methyl-\(\alpha\)-phenylenediamine with acetyl chloride in refluxing benzene yielded 2, 5 (2, 6)-dimethylbenzimidazole whereas the corresponding 4-methyl \(-N, N'\)-diacetyl-\(\alpha\)-phenylenediamine was the sole product when the reaction was carried out at room temperature.

\[
\text{NH}_2 \quad \text{NH}_2 \\
\text{(1)}
\]

![Scheme - 6](image)

Niementowski V. S.\textsuperscript{20} obtained 2-substituted 5(6)-methylbenzimidazoles (8, \(X=5(6)\)-methyl, \(R=H, \text{CH}_3\) or Ph) by heating free base (5) with the corresponding amides (\textbf{Scheme-7}).

\[
\text{H}_3\text{C} \quad \text{NH}_2 \\
\text{NH}_2 \quad \text{NH}_2 \\
\text{(5)}
\]

![Scheme - 7](image)