CHAPTER-2

REVIEW OF LITERATURE
# Chapter-2: Review of Literature

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2.1 Introduction

The chemistry literature has practised exponential growth over the decades. Literature on heterocyclic chemistry and carbocyclic chemistry, like all other areas of chemistry, has experienced an enormous expansion, making it very difficult to keep up with the research reported in this field. Therefore, the review literature has become quite important to the researchers. Hence in this treatise an attempt is made to list the available and most common approaches of making common heterocyclic and carbocyclic compounds. Also listed are the various synthetic approaches of benzimidazoles, Benzothiazoles, polysubstituted pyrroles and functionalized cyclohexanones.

The present chapter contains the general sources and articles which provide an overview of the present work. Those articles containing topics restricted to specific ring systems are to be found in the relevant chapters of this reference work.

2.2 Synthetic approaches of various five-membered heterocyclic compounds

Five-membered heterocycles are good nucleophiles. Hence, reaction with bromine requires no Lewis acid and leads to substitution at all four free positions.

\[ \text{Scheme-2.2.1} \]
2.2.1 Synthetic approaches of Pyrrole, Furan and Thiophene:

**Paal-Knorr pyrrole synthesis:** The Paal-Knorr Pyrrole Synthesis involves the condensation of a 1,4-dicarbonyl compound with an excess of a primary amine or ammonia to get the corresponding pyrrole. The reaction can be conducted under neutral or weakly acidic conditions. Addition of a weak acid such as acetic acid accelerates the reaction, but the use of amine/ammonium hydrochloride salts or reactions at pH <3 lead to furans as main products.

Example: Synthesis of Atorvastatin (Lipitor)

![Scheme-2.2.2](image)

**Cyclization:**

![Scheme-2.2.3](image)

**Feist-Benary synthesis of furans:** The Feist–Benary synthesis is an organic reaction between α-halogen ketones and β-dicarbonyl compounds to get the corresponding substituted furan compounds.\(^{32,33}\) This condensation reaction is catalyzed by amines such as ammonia and pyridine. The first step in the ring synthesis is related to the Knoevenagel condensation. In the second step, the enolate displaces an alkyl halogen in a nucleophilic aliphatic substitution.
2,5-Disubstituted 3-iodofurans are readily prepared under very mild reaction conditions. Conjugated enyne acetates undergo iodo-cyclization in good yields. The resulting iodine-containing furans can be readily elaborated to 2,3,5-trisubstituted furans.\[^{[34]}\]

**Scheme-2.2.5**

**Gewald reaction for thiophene synthesis:** The Gewald reaction involves the condensation of a ketone (or aldehyde when $R^2 = H$) with a $\alpha$-cyanoester in the presence of elemental sulfur and base to give a poly-substituted 2-amino-thiophene.

**Scheme-2.2.6**

In the presence of CuI and TMEDA, a thiolation annulation reaction of 2-bromo alkynylbenzenes with sodium sulfide delivers various 2-substituted benzo[b] thiophenes in good yields. \[^{[35]}\]

**Scheme-2.2.7**
2.2.2 Synthetic approaches of 1,2-Azaoles: Pyrazoles can be synthesized from 1,3-dicarbonyls with hydrazine in presence of base.

\[
\text{R}_1 \quad \text{O} \quad \text{O} \quad \text{R}_2 + \text{NH}_2 \quad \xrightarrow{\text{base}} \quad \text{R}_1 \quad \text{N} \quad \text{R}_2
\]

Scheme-2.2.8

Example: Retrosynthesis of Sildenafil side chain

\[\text{Scheme-2.2.9}\]

2.2.3 Synthetic approaches of Isoxazoles: Isoxazoles can be made from 1,3-dicarbonyl compounds or β-ketoesters with hydroxylamine.

\[
\text{R}_1 \quad \text{O} \quad \text{O} \quad \text{R}_2 + \text{H}_2\text{N-OH} \quad \xrightarrow{\text{base}} \quad \text{R}_1 \quad \text{N} \quad \text{O} \quad \text{R}_2
\]

Scheme-2.2.10

The resacetophenone on nuclear prenylation with isoprene in presence of polyphosphoric acid at room temperature resulted the formation of 2,2-dimethyl-6-acetyl-7-hydroxy chroman in good yields. The chroman on condensation with different substituted benzaldehydes in the presence of 30% alcoholic alkali at room temperature results the formation of chalcone derivatives in good yields. The chalcones which were synthesized have been taken for the preparation of corresponding new isoxazole derivatives.\[^{36}\]
2.2.4 Synthetic approaches of 1,3-Azoles:

**Robinson-Gabriel synthesis:** Oxazoles and thiazoles can be obtained by the Robinson-Gabriel synthesis from 2-acylamino-ketones.

\[
\begin{align*}
\text{R}_1\text{NH} & \xrightarrow{H^+} \text{R}_1\text{N} = \text{R}_2 \xrightarrow{\text{NH}_2\text{OH},\text{HCl}} \text{N} = \text{R}_1 \xrightarrow{\text{EIOH},\text{KOH}} \text{R}_2
\end{align*}
\]

*Scheme-2.2.12*

2-acylamino-ketones react with phosphorus pentasulfide to form thiazoles.

\[
\begin{align*}
\text{R}_1\text{NH} & \xrightarrow{120^\circ C} \text{R}_1\text{N} & \text{S} & \xrightarrow{\text{R}_2}
\end{align*}
\]

*Scheme-2.2.13*

**Debus-Radziszewski imidazole synthesis:** The Debus-Radziszewski imidazole synthesis is an organic reaction describing the synthesis of an imidazole from a diketone, an aldehyde and ammonia. It is an example of a multicomponent reaction. In step one the diketone and ammonia form a diimine, which condenses with the aldehyde to produce imidazole.
2.2.5 Synthetic approaches of Indoles:

**Fisher Indole synthesis:** The conversion of aryl hydrazones to indoles requires elevated temperatures and the addition of Bronsted or Lewis acids.

![Scheme-2.2.15](image)

An operationally simple, atom-economic, palladium-catalyzed cyclization reaction of N-aryl imines, affords indoles via an oxidative linkage of two C-H bonds under mild conditions. The process allows quick assembly of indole rings from readily available anilines and ketones and tolerates a broad range of functional groups. [37]

![Scheme-2.2.16](image)
2.3 Synthetic approaches of various six-membered heterocyclic compounds

2.3.1 Synthetic approaches of Pyridines:

Pyridoxine, vitamin B6, has been synthesized by Guareschi ring synthesis. Condensation of cyanoacetic ester with acetoacetic ester in the presence of ammonia gives corresponding Pyridine derivatives. In a second type of synthesis a mixture of cyanoacetic ester and a ketone is treated with alcoholic ammonia.

![Scheme-2.3.1](image)

2.3.2 Synthetic approaches of Pyrimidines: Pyrimidines are obtained from 1,3-dicarbonyl compounds on reaction with amidines, guanidine, urea and thiourea.

![Scheme-2.3.2](image)
2.3.3 Synthetic approaches of Quinolines:

Doebner-Miller reaction: The Doebner–Miller reaction is the organic reaction of an aniline with α,β-unsaturated carbonyl compounds to get the corresponding quinolines.

Scheme-2.3.3

2.3.4 Synthetic approaches of Benzodiazepines:

Concise synthesis of benzodiazepines with Ugi Reaction: The Ugi four-component condensation between an aldehyde, an amine, a carboxylic acid and an isocyanide allows the hasty preparation of α-aminoacyl amide derivatives. The Ugi Reaction products can exemplify a wide variety of substitution patterns, and constitute peptidomimetics that have potential pharmaceutical applications. This reaction is thus quite important for generating compound libraries for screening purposes.

Scheme-2.3.4
2.4 Synthetic approaches of carbocyclic compounds

2.4.1 Synthetic approaches of Cyclopropane:

Activated cyclopropanes show versatile reactivity and are therefore influential building blocks in organic chemistry and natural product synthesis. Cyclopropanation refers any chemical process which generates cyclopropane rings. It is an important process in recent findings of chemistry as many useful compounds bare this motif; for example pyrethroids and a number of quinoline based antibiotics (Ciprofloxacin, Sparfloxacin, etc.). However the high ring strain present in cyclopropanes makes them challenging to produce and generally requires the use of highly reactive species, such as carbenes, ylids and carbanions.

**Simmons–Smith reaction:** Iodomethylzinc iodide is the reactive carbenoid in the Simmons–Smith reaction, which is usually formed by a reaction between diiodomethane and a zinc-copper couple.

\[
\begin{array}{c}
\text{R}_1\text{R}_2\text{R}_3\text{R}_4 + \text{ZnI} \\ \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{R}_4 + \text{ZnI}_2
\end{array}
\]

**Scheme-2.4.1**

Phenyliodonium ylides provide easy access to various 1,1-cyclopropane diesters using rhodium or copper catalysis. These are quite safer and convenient alternatives to the corresponding diazo compounds. [38]

\[
\begin{array}{c}
\text{R} + \text{PhI}\quad \xrightarrow{\text{Rh}_2(\text{esp})_2} \quad \text{R}\quad \text{esp}\quad \text{COO}^-
\end{array}
\]

**Scheme-2.4.2**
2.4.2 Synthetic approaches of Cyclobutane:

Cyclobutane is a cyloalkane and is a colourless gas and commercially available as a liquefied gas. Derivatives of cyclobutane are called cyclobutanes. Cyclobutane itself is of no commercial or biological significance, but more complex derivatives are important in biology and biotechnology. Its inherent ring strain makes formation of cyclobutanes difficult, yet it is this strain that makes cyclobutanes extremely useful in the organic synthesis.

\((E)\)- and \((Z)\)-silyl and aryl-substituted homoallylic methanesulfonates were converted to the corresponding cis- and trans-1-silyl-2-borylcyclobutanes as well as 1-phenyl-2-borylcyclobutanes in the presence of a Cul/dppp catalyst, bis(pinacolato) diboron, and KOtBu in THF. Stereospecific derivatizations of the cis- and trans-borylcyclobutanes were carried out to demonstrate the utility of borylcyclobutanes. \[^{39}\]

\[
\text{Scheme 2.4.3}
\]

2.4.3 Synthetic approaches of Cyclopentane:

Cyclopentane is used in the manufacture of synthetic resins and rubber adhesives and also as a blowing agent in the manufacture of polyurethane insulating foam, as found in many domestic appliances, more advanced technologies, such as computer hard drives and outerspace equipment employ multiply alkylated cyclopentane (MAC) lubricants because of their extremely low volatility.

Reduction of stilbenes with Na metal in dry THF allowed easy access to various 1,2-diaryl-1,2-disodiumethanes. These
diorganometallic intermediates gave 1,2-diarylethanes upon aqueous work up, or trans-1,2-diaryl-substituted cyclopentanes by cycloalkylation with 1,3-dichloropropanes. \[40\]

\[
\text{Scheme-2.4.4}
\]

**Hydroacetylation of Olefins:** \[41\]

\[
\text{Scheme-2.4.5}
\]

### 2.4.4 Synthetic approaches of Cyclohexane:

The specific array of functional groups in cyclohexane derivatives, and certainly in most cycloalkane molecules, is extremely important in chemical reactions, especially reactions involving nucleophiles. Substituents on the ring must be in the axial formation to react with other molecules.

**Conia-Ene Reaction:** The Conia-Ene reaction is Lewis acid-catalyzed, thermal or intramolecular reaction of unsaturated carbonyl compounds to yield cyclized products.

\[
\text{Scheme-2.4.6}
\]
2.5 Reviews for synthesis of 2-substitued 1,3-benzimidazoles

The broad survey of literature for the synthesis of 2-substitued 1,3-benzimidazoles revealed that many of these methods are quite effective and useful. However, most of them suffer from the use of acidic or similar reagents or hazardous organic solvents. These are not environmentally compatible and produce a large amount of waste. Moreover, the other drawbacks of these methodologies are the requirement of longer reaction time, higher temperature and expensive reagents/catalysts.

Various literature methods reported for the preparation of 1,2-disubstitued benzimidazoles are described here.

a. A.K. Tiwari et al. approach \[^{[43]}\]

Tiwari et al. developed a process to synthesize 2-substitued 1,3-benzimidazoles using Philips condensation, by condensing O-Phenylene diamine and carboxylic acid derivatives in 4N HCl.
b. Nagawade et al. approach \[44\]

Nagawade et al. demonstrated the synthesis of benzimidazoles in very good yields in solvent-free conditions from \(o\)-phenylenediamine and aldehydes in the presence of \(\text{BF}_3\cdot\text{OEt}_2\) as a catalyst.

\[
\begin{align*}
\text{R}^2\text{N} \quad \text{NH}_2 & + \text{OHC-}R' & \xrightarrow{\text{BF}_3\cdot\text{OEt}_2} & \text{R}^1\text{N} \quad \text{NH} \quad \text{R'}
\end{align*}
\]

Scheme-2.5.2

c. Wang Yulu et al. approach \[45\]

Wang Yulu et al. developed an efficient method for the synthesis of 2-substitued 1,3-benzimidazoles by employing an organocatalyst \(p\)-TsOH in DMF solvent at 80°C to get good yield.

\[
\begin{align*}
\text{R}^2\text{N} \quad \text{NH}_2 & + \text{OHC-}R' & \xrightarrow{\text{p-TsOH}} & \text{R}^1\text{N} \quad \text{NH} \quad \text{R'}
\end{align*}
\]

Scheme-2.5.3

d. A. Antom Smith et al. approach \[46\]

A. Antom Smith et al. was reported the synthesis of 2,3-dihydro-2-[1-(4-isobutyl phenyl) ethyl] ethyl]-1H benzo [d] Imidazole under harsh conditions.

\[
\begin{align*}
\text{R}^2\text{N} \quad \text{NH}_2 & + \text{OHC-}R' & \xrightarrow{\text{10\% KOH \ Reflux}} & \text{R}^1\text{N} \quad \text{NH} \quad \text{R'}
\end{align*}
\]

Scheme-2.5.4

e. Jat Rakesh Kumar et al. approach \[47\]

Jat Rakesh Kumar et al. developed a method for the synthesis of Benzimidazoles in which the reactants are condensed in the presence of an oxidant such as cupric acetate in ethanol and the reaction carried out at reflux temperature.
K. Niknam *et al.* have developed a novel approach for the synthesis of Benzimidazoles under microwave irradiation conditions. A mixture of 1,2-phenylenediamine, carboxylic acid, Methanesulfonic acid on alumina (AMA) were finely ground in a screw-capped teflon vessel. Microwave irradiation at 20% power was applied for 4-12hrs and he was reported excellent yields.

R. Haridas *et al.* developed under irradiation conditions, at high temperatures, efficient methods for the synthesis of Benzimidazoles by employing TMSCl as catalyst are described to get good yield.

A. John Blacker *et al.* Transition-metal-catalyzed hydrogen-transfer reactions have been used for the conversion of alcohols into benzimidazoles using Ru[PPh$_3$]$_3$(CO)H$_2$, Xantphos in toluene at reflux temperatures.
i. Hashem Sharghi et al. approach \[^{[51]}\]
Hashem Sharghi et al. described a highly selective synthesis of 2-substituted benzimidazole derivatives from the reaction of o-phenylenediamine derivatives and aromatic aldehydes in the presence of an organic salt, NH\(_4\)OAc, in absolute ethanol.

\[ \text{Scheme-2.5.8} \]

\[
\begin{align*}
\text{R}^1 \text{NH}_2 + \text{R}^2 \text{NH}_2 + \text{HO-C-R'} & \xrightarrow{\text{Ru(PPh}_3\text{)}_2\text{(CO)}\text{H}_2, \text{Xantphos}} \rightarrow \text{R}^1 \text{N} - \text{R}^2 \\
\text{C}_5\text{H}_1\text{NH}_2\text{HOAc, Toluene, Reflux} & \quad \xrightarrow{\text{CN}} \text{R}^1 \text{N} - \text{R}^2
\end{align*}
\]

\[ \text{Scheme-2.5.8} \]

j. Tomohiro Yamashita et al. approach \[^{[52]}\]
Tomohiro Yamashita et al. developed a method to synthesize 2-alkylbenzimidazoles by reacting o-phenylenediamine with an aldehyde in presence of a sulfur catalyst in DMA solvent at 100°C.

\[ \text{Scheme-2.5.9} \]

\[
\begin{align*}
\text{R}^1 \text{NH}_2 + \text{OHC-R'} & \xrightarrow{\text{NH}_4\text{(OAc)}_2, \text{EtOH, 80°C}} \rightarrow \text{R}^1 \text{N-R}^2 \\
\text{R}^1 \text{NH}_2 + \text{OHC-R'} & \xrightarrow{\text{NaHSO}_3, \text{DMA,100°C}} \rightarrow \text{R}^1 \text{N-R}^2
\end{align*}
\]

\[ \text{Scheme-2.5.9} \]

k. Zhengzhou Mao et al. approach \[^{[53]}\]
Zhengzhou Mao et al. developed under solvent-free and microwave irradiation conditions, efficient methods for the synthesis of 1,2-disubstitued benzimidazoles by employing oxidant potassium iodide as catalysts are described to get good yield.
Scheme 2.5.11

1. Shahnaz Rostamizadeh et al. approach[54]
Shahnaz Rostamizadeh et al. were developed a Solvent-Free Chemoselective Synthesis of Some Novel Substituted 2-Arylbenzimidazoles Using Amino Acid-Based Prolinium Nitrate Ionic Liquid as Catalyst.

Scheme 2.5.12

m. Songnian Lin et al. approach[55]
Songnian Lin et al. developed an efficient methodology for Benzimidazoles using Air as an oxidant in presence of Dioxane at reflux temperature. But heating dioxane in the presence of air is potentially explosive!

Scheme 2.5.13

n. Sunwoo Lee et al. approach[56]
Sunwoo Lee et al. have developed Copper-Catalyzed, One-Pot, Three-Component Synthesis of Benzimidazoles by Condensation and C-N Bond Formation and reported good to excellent yields.
2.6 Reviews on synthesis of 2-substitued 1,3-benzothiazoles

Benzothiazole is a versatile scaffold for investigational drug design. Among the all benzo heterocycles, benzothiazole has substantial place in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and noteworthy pharmacological activities. Since, a wide range of methods are available for synthesizing benzothiazole nucleus and its derivatives but a real need exists for novel approaches that support many kinds of structural diversity and various substitution. Recently, several new approaches have been reported, some of the most common methods for the synthesis of 2 substituted benzothiazole are as follows.

**a. Stephen O. et al. approach** [57]

Stephen O. synthesized (pyridinyl) benzothiazole using palladium complexes through 4-tert-butylpicolinic acid, 4-tert-butyl aniline, DCC, 4-PPA and CH$_2$Cl$_2$ to produce 2-tert-Butyl-pyridine-2-carboxylic acid (4-tert-butylphenyl)-amide which on reaction with Lawesson’s reagent produces carbothionic acid and finally cyclized to benzothiazole by potassium ferrocyanate.
Jacobson and Frankenbacher synthesized 2-substituted benzothiazole by heating of azobenzene with carbon disulfide in a sealed tube at 250°C for 5 hours.

Min Wang synthesized 4-fluorinated 2-phenylbenzothiazoles in a multi-step process which involves benzylation, oxidation, acid chloride formation etc.
Serdons. K. reported synthesis of benzothiazole in which o-anisidine was first reacted with p-nitrobenzoyl chloride to form N-2'-methoxyphenyl-4-nitrobenzamide. The amide was then converted to the thiobenzamide using Lawesson’s reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane- 2,4-disulphide) which is a useful thiation reagent to replace the carbonyl oxygen atoms of ketones, amides and esters by sulphur. In the presence of potassium ferricyanide, it cyclized to the 2-(4'-nitrophenyl)-benzothiazole.
**Scheme-2.6.4**

**e. Bakers et al. approach**[^61]

Umesh R. Pratap successfully employed bakers’ yeast to catalyze the condensation of 2-aminothiophenol and aldehydes in DCM to yield 2-substituted benzothiazoles in moderate to good yields under mild reaction condition.

**Scheme-2.6.5**

**f. Shivaraj et al. approach**[^62,^63]

Benzothiazole may be prepared by action of acid anhydrides (or) chlorides on O-amino phenols and formic acid in presence of acetic anhydride.

**Scheme-2.6.6**
g. Khokra Sukhbir L et al. approach \cite{64}

Treatment of o-aminothiophenols with substituted aldehydes affords the synthesis of 2-substituted benzothiazoles using different catalysts and reaction conditions.

Catalysts (a-f):

a. Montmorillonite, SiO$_2$/Graphite; Microwave, p-TsOH
b. Diethyl bromophosphonate/tert-Butyl hypochlorite, Acetonitrile
c. Cerium (IV) ammonium nitrate
d. H$_2$O$_2$ /HCl system in ethanol
e. AcOH /Air, Microwave/ Thermal Heating
f. Baker’s yeast, Dichloromethane

![Scheme-2.6.7]

Treatment of 2-aminothiophenol and substituted aromatic acids in presence of Polyphosphoric acid provides a good method to synthesize 2- substituted benzothiazoles and gives a good yield.

![Scheme-2.6.8]

h. Mu Xue-Jun et al. approach \cite{65}

Manganese (III) triacetate is an excellent one-electron oxidant, which has been widely employed to generate free radicals for cyclization reactions. Manganese triacetate is introduced as a new reagent to
replace potassium ferricyanide or bromine for radical cyclization of substituted thioformanilides. 2-Substituted benzothiazoles are generated in 6 min under microwave irradiation.

![Scheme 2.6.9](image)

**Scheme 2.6.9**

i. **Downer-Riley Nadale K et al. approach**[^66]

A new and general method has been developed for the intramolecular cyclization of thiobenzamides to benzothiazoles via aryl radical cations as reactive intermediates. The method utilizes phenyl iodine (III) bis(trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous Acetonitrile at room temperature to affect cyclization within 30 min in moderate yields.

![Scheme 2.6.10](image)

**Scheme 2.6.10**

j. **Haibo Wang et al. approach**[^67]

Haibo Wang et al. was described a novel approach for the synthesis of Benzothiazoles via Fe-catalyzed oxidative C-S bond formation.
A. John Blacker et al. Transition-metal-catalyzed hydrogen-transfer reactions have been used for the conversion of aldehydes into benzothiazoles in presence of Iridium complex (SCRAM catalyst).

**Scheme-2.6.11**

\[
\begin{align*}
\text{Oxidant} & : \underset{\text{FeCl}_3 \ 10 \text{ mol} \%}{\text{DMSO, 80°C}} \\
\text{R} & \underset{\text{S}}{\rightarrow} \underset{\text{R}}{\text{N}} \\
\text{R}_1 & \text{H} \\
\end{align*}
\]

**k. A. John Blacker et al. approach**[68]

A. John Blacker et al. Transition-metal-catalyzed hydrogen-transfer reactions have been used for the conversion of aldehydes into benzothiazoles in presence of Iridium complex (SCRAM catalyst).

**Scheme-2.6.12**

\[
\begin{align*}
\text{R} & \text{SH} \\
\text{NH}_2 & \rightarrow \underset{\text{R}}{\text{S}} \\
\text{R} & \end{align*}
\]

**2.7 Reviews for synthesis of 1,2-disubstitued benzimidazoles**

The broad survey of literature for the synthesis of 1,2-disubstitued benzimidazoles revealed that many of these methods are quite effective and useful most of them however, suffer from the use of acidic or similar reagents or hazardous organic solvents that are not environmentally compatible and produce a large amount of waste. Moreover, the requirement of longer reaction time, higher temperature and expensive reagents/catalysts are the other drawbacks of these methodologies.

Various literature methods reported for the preparation of 1,2-disubstitued benzimidazoles are described here.

**a. Zhang et al. approach**[69]

Zhang et al. developed under solvent-free and ultrasonic irradiation conditions, efficient methods for the synthesis of 1,2-disubstitued benzimidazoles by employing rare-earth metal chlorides as catalysts are described to get good yield.
b. Bahrami et al. approach [70]

Bahrami et al. developed a practical and convenient synthetic method for the facile synthesis of 1,2-disubstituted benzimidazoles, 2-substituted benzimidazoles in presence of Sodium dodecylsulfate and water to get good yield.

\[
\begin{align*}
\text{NH}_2 \quad \text{NH}_2 + \quad \text{ArCHO} & \quad \xrightarrow{\text{Sodium dodecylsulfate}} \quad \text{Ar} \quad \text{Ar} \\
\text{NH}_2 \quad \text{NH}_2 & \quad \xrightarrow{\text{H}_2\text{O, 25 °C}} \quad \text{Ar} \quad \text{Ar}
\end{align*}
\]

\textbf{Scheme-2.7.2}

c. Veisi et al. approach [71]

Veisi et al. synthesized one pot synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles by using with silica phenyl sulfonic acid as a solid acid heterogeneous catalyst in water to get good yield.

\[
\begin{align*}
\text{NH}_2 \quad \text{NH}_2 + \quad \text{RCHO} & \quad \xrightarrow{\text{Silica Phenyl Sulfonic Acid}} \quad \text{R} \\
\text{NH}_2 \quad \text{NH}_2 & \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{R}
\end{align*}
\]

\textbf{Scheme-2.7.3}

d. Kokare et al. approach [72]

Kokare et al. developed 2-aryl-1-arylmethyl-1H-benzimidazoles were efficiently synthesized from o-phenylenediamine and various substituted aldehydes using 10 mol% of oxalic acid to get good yield.
**e. Yadav et al. approach** [73]

Yadav et al. prepared 2-aryl-1-arylmethyl-1H-benzimidazoles under extremely mild conditions via the condensation of aryl-1,2-diamines with aromatic aldehydes using 10 mol% of bismuth triflate in water to get good yield.

\[
\text{R} \text{NH}_2 + \text{RCHO} \xrightarrow{10 \text{ mol}\% \text{ of bismuth triflate}} \text{N} \text{R} \text{N}_2
\]

**Scheme-2.7.4**

**f. Varala et al. approach** [74]

Varala et al. prepared 2-aryl-1-arylmethyl-1H-benzimidazoles under extremely mild conditions via the condensation of aryl-1,2-diamines with aromatic aldehydes using L-proline (10 mol%) to get moderate isolated yields (32–95%) under mild conditions using chloroform as a solvent at ambient temperature.

\[
\text{R} \text{NH}_2 + \text{RCHO} \xrightarrow{\text{L-Proline (10 mol\%)} \text{ Water}} \text{N} \text{R} \text{N}_2
\]

**Scheme-2.7.5**

**g. Salehi et al. approach** [75]

Salehi et al. developed the selective synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles from the reaction of o-phenylenediamines and aromatic aldehydes in the presence of silica sulfuric acid and ethanol or water to get good yield and the catalyst could be reused for several runs.

\[
\text{R} \text{NH}_2 + \text{RCHO} \xrightarrow{\text{L-Proline (10 mol\%)} \text{ Water}} \text{N} \text{R} \text{N}_2
\]
Jacob et al. synthesized 1,2-disubstituted benzimidazoles using SiO$_2$/ZnCl$_2$ and a solvent-free condition is described. This method furnishes selectively and in good yields the corresponding 1,2-bis(organyl)benzimidazoles starting from o-phenylenediamine and aromatic or aliphatic aldehydes.

Sharma et al. are developed a simple, efficient, and environmentally benign method has been developed for the exclusive formation of biologically significant 2-aryl-1-arylmethyl-1H-benzimidazoles under the heterogeneous catalysis of Amberlite IR-120 in aqueous media in good yields. The catalyst is recyclable without loss of activity.

Huiqiang et al. used ionic liquid to promote the condensation of o-phenylenediamine with aldehydes and afford corresponding 2-aryl-1-
aryl methyl-1H-1,3-benzimidazoles efficiently. The absence of a catalyst and recyclability on the non-volatile it makes this an environment friendly methodology for selective synthesis of 2-aryl-1-aryl methyl-1H-1,3-benzimidazoles.

Scheme 2.7.10

**k. Ravi et al. approach** [79]

Ravi et al. used Zn-proline (5mol %) performs as a novel water-soluble and recyclable Lewis acid catalyst for the selective synthesis of 1,2-disubstituted benzimidazoles from wide range of substituted o-phenylenediamines and aldehydes in moderate to get good isolated yields using water as solvent at ambient temperature.

Scheme 2.7.11

**l. Niknam et al. approach** [80]

Niknam et al. developed a highly selective synthesis of 2-aryl-1-aryl methyl-1H-1,3-benzimidazoles from the reaction of o-phenylenediamines and aromatic aldehydes in the presence of metal hydrogen sulfates \([M(HSO_4)_n]\) in water and also under solvent-free conditions in good yields.

Scheme 2.7.12
m. Beheshtiha et al. approach \[^{[81]}\]

Beheshtiha et al. developed efficient and green synthesis of 1,2-disubstituted benzimidazoles using brønsted acid ionic liquid \([\text{[(CH}_2)_4\text{SO}_3\text{HMIM}][\text{HSO}_4]]\) in water at room temperature to get good yields.

\[
\text{NH}_2 \text{NH}_2 + 2\text{RCHO} \xrightleftharpoons{\text{[(CH}_2)_4\text{SO}_3\text{HMIM}][\text{HSO}_4]}^{\text{Water, 25 °C}} \text{R-N} + \text{not formed}
\]

![Scheme-2.7.13](image)

n. Radatz et al. approach \[^{[82]}\]

Radatz et al. used of glycerol as solvent in the catalyst-free synthesis of benzodiazepines and benzimidazoles in good yields by the condensation of o-phenylenediamine with several ketones and aldehydes respectively.

![Scheme-2.7.14](image)

o. Bandyopadhyay et al. approach \[^{[83]}\]

Bandyopadhyay et al. used mesoporous mixed metal oxide nanocrystals of Al\(_2\)O\(_3–\)Fe\(_2\)O\(_3\), Al\(_2\)O\(_3–\)V\(_2\)O\(_5\) and Al\(_2\)O\(_3–\)CuO as heterogeneous catalysts for the preparation of series of medicinally significant 1,2-disubstituted benzimidazoles. This protocol provided greater selectivity, cost-efficiency, clean reaction profiles, simple work-up procedure and good yields.
Sun et al. developed a process in the presence of catalytic amount of iodine, in THF–H₂O, the condensation of aldehydes with 1,2-phenylenediamine gave the benzimidazole derivatives under mild conditions in good yields. The method can be used for the synthesis of 2-substituted benzimidazoles or 1, 2-disubstituted benzimidazoles.

Dabiri et al. developed an environmentally benign method for the rapid and selective synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles by the reaction of o-phenylenediamines and aromatic aldehydes in the presence of 1-methylimidazolium trifluoroacetate ([Hmim]TFA) at room temperature under aqueous conditions is described. The ionic liquid is reusable and could be recycled for several runs without any decrease in its efficiency.
r. Saha et al. approach \cite{86}

Saha et al. developed a simple and efficient procedure for the synthesis of 2-substituted benzimidazoles has been developed by a one-pot reaction of \( o \)-phenylenediamine with aromatic aldehydes in the presence of an ionic liquid, \([\text{pmim}]\text{BF}_4\) at room temperature in open air without any organic solvent. The ionic liquid is recycled. A remarkable influence of the substituent on the imidazolium unit of the ionic liquid on the outcome of the reaction is observed.

![Scheme-2.7.18](image)

s. Wan et al. approach \cite{87}

Wan et al. developed the one-pot synthesis of 1,2-disubstituted benzimidazoles has been achieved in excellent efficiency and selectivity at room temperature via trimethylsilyl chloride promoted reaction of \( o \)-phenylenediamine with aldehyde. This green catalyst system has also been successfully extended to the synthesis of quinoxalines via the reaction of \( o \)-phenylenediamine with \( \alpha \)-bromoketone. Water displayed a specific functionality in mediating the selectivity, and remarkable advantages over organic solvents in terms of yields as well as in the work up procedure of the reactions.

![Scheme-2.7.19](image)
t. Bandyopadhyay et al. approach[88]
Bandyopadhyay et al. synthesized 1,2-disubstituted benzimidazoles under mild reaction conditions using Al$_2$O$_3$–Fe$_2$O$_3$ nanocrystals as heterogeneous catalyst.

![Scheme-2.7.20](image)

u. Mohammadizadeh et al. approach[89]
Mohammadizadeh et al. introduced trifluoroacetic acid (TFA) is a commercially available, inexpensive and effective catalyst for the selective and eco-compatible synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles via condensation reaction of o-phenylenediamine derivatives and aromatic aldehydes in ethanol/water at room temperature.

![Scheme-2.7.21](image)

v. Lei et al. approach[90]
Lei et al. developed a simple and efficient one-pot synthesis of 1H-benzimidazole derivatives using thiamine hydrochloride (VB$_1$) as the organocatalyst from o-phenylenediamine and aldehyde in dimethylformamide is described. Compared to classical reaction conditions, this new method consistently has the advantages of excellent yields, metal-ion-free procedure, good recovery and reusability of catalyst.
Ma et al. developed a simple method for the synthesis of several 1,2-disubstituted benzimidazoles catalyzed by strongly acidic SBA-15-supported poly(4-styrenesulfonyl-(perfluorobutylsulfonyl)imide) (PSFSI) is described. The protocol furnished the products in moderate yield and good selectivity in the condensation of o-phenylenediamine with structurally diverse aldehydes under mild conditions.

Sharghi et al. synthesized benzimidazole derivatives for condensation of o-phenylenediamine with different aldehydes in presence of PTSA/graphite and N,N-dimethylaniline/graphite were found to good yield.
Based on above literature, 1,2-disubstituted benzimidazoles are also be accessed by direct one-step condensation of o-phenylenediamines with aldehydes by involving the influence of different acid catalysts under various reaction conditions or by using polymer-supported hypervalent iodine (PDIAS) as a reagent.

\section*{2.8 Reviews for synthesis of substituted pyrrole compounds}

\textbf{a. Ekkati AR \textit{et al.} approach} \cite{93}

The synthesis of N-acylpyrroles from primary aromatic amides and excess 2,5-dimethoxytetrahydrofuran in presence of one equivalent of thiocarbonyl chloride offers short reaction times and mild reaction conditions.
b. Tejedor D et al. approach \[94\]
A new microwave-assisted rearrangement of 1,3-oxazolidines scaffolds is the basis for a new, metal-free, direct and modular construction of tetra substituted pyrroles from terminal-conjugated alkynes, aldehydes and primary amines.

\begin{equation}
\text{Scheme-2.8.2}
\end{equation}

c. Rao HSP et al. approach \[95\]
Several aryl-substituted pyrrole derivates were prepared conveniently in a microwave-assisted one pot-reaction from but-2-ene-1,4-diones and but-2-yne-1,4-diones via Pd/C-catalyzed hydrogenation of the C-C double bond / triple bond followed by amination-cyclization.

\begin{equation}
\text{Scheme-2.8.3}
\end{equation}

d. Suzuki D et al. approach \[96\]
Coupling of acetylene, nitrile and a titanium reagent generated new azatitanacyclo pentadienes in a highly regioselective manner. The subsequent reaction with sulfonyl acetylene and electrophiles gave substituted pyridines virtually as a single isomer. Alternatively, the reaction of azatitanacyclopentadienes with an aldehyde or another nitrile gave pyrroles having four different substitutents again in a regioselective manner.
Various 2,3,4-trisubstituted pyrroles are easily accessible in one step from readily available acetylenes and acceptor-substituted methyl isocyanides by base mediated or copper-catalyzed cycloadditions.

A mild, gold(I)-catalyzed acetylenic Schmidt reaction of homopropargyl azides gave regiospecific substituted pyrroles. A mechanism in which azides serve as nucleophiles toward gold(I)-activated alkynes with subsequent gold(I)-aided expulsion of dinitrogen is proposed.

An efficient and regioselective palladium-catalyzed cyclization of internal alkynes and 2-amino-3-iodoacrylates gave good yields of highly functionalized pyrroles.
h. Martin R et al. approach\cite{100}

A general, highly flexible Cu-catalyzed domino C-N coupling / hydroamination reaction constitutes a straightforward alternative to existing methodology for the preparation of pyrroles.

\begin{center}
\textbf{Scheme-2.8.7}
\end{center}

i. Binder JT et al. approach\cite{101}

Propargyl vinyl ethers and aromatic amines are effectively converted into tetra- and penta- substituted 5-methylpyrroles through a silver (I)-catalyzed propargyl-Claisen rearrangement, an amine condensation, and a gold (I)-catalyzed 5-exo-dig heterocyclization in a convenient one-pot process.

\begin{center}
\textbf{Scheme-2.8.8}
\end{center}

j. Lu G et al. approach\cite{102}

An efficient synthesis of 2, 3, 4-trisubstituted pyrroles via intermolecular cyclization of alkylidenecyclopropyl ketones with amines were observed. A mechanism involves a distal cleavage of the C-C bond of the cyclopropane ring.

\begin{center}
\textbf{Scheme-2.8.9}
\end{center}
A range of 2, 5-disubstituted and 2, 4, 5-trisubstituted pyrroles can be synthesized from dienyl azides at room temperature using ZnI$_2$ or Rh$_2$(O$_2$CC$_3$F$_7$)$_4$ as catalysts.

The CuI / N,N-dimethylglycine-catalyzed reaction of amines with γ-bromo-substituted γ, δ-unsaturated ketones in the presence of K$_3$PO$_4$ and NH$_4$OAc gave the corresponding polysubstituted pyrroles in very good yields.

A new use of Wittig-Type reagents as 1,3-dipolar cycloaddition precursors and in pyrrole synthesis.
n. Alizadeh A et al. approach [106]

The reaction of an enaminone, which can be derived from two primary amines and diketene, in the presence of nitrostyrene gives functionalized pyrrole derivatives in very good yields.

2.9 Reviews for synthesis of functionalized cyclohexanones

The broad survey of literature for the synthesis of functionalized cyclohexanones revealed that many of these methods are fairly effective and useful. However, most of them suffer from the use of hazardous reagents and solvents that are environmentally incompatible and generate a large amount of waste. Moreover, the obligation of longer reaction time, higher temperature and expensive reagents/catalysts are the other drawbacks of these methodologies.

Various literature methods reported for the preparation of functionalized cyclohexanones are described here.
a. Knoevenagel et al. approach

Knoevenagel described the synthesis of functionalized cyclohexanones with Ammonia.

![Scheme-2.9.1]

b. Subbu Perumal et al. approach

The five-component tandem reaction of ethyl acetoacetate with aromatic aldehydes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in ethanol affords t(3),t(5)-diaryl-t(4)-[(E)-3-aryl-2-propenonyl]-r(2)-ethoxycarbonylcyclohexanones stereo selectively in good yields presumably via Knoevenagel condensation.

![Scheme-2.9.2]

c. Pandiarajan et al. approach

Pandiarajan et al. developed an efficient method for the synthesis of functionalized cyclohexanones by employing methylamine in ethanol solvent.

![Scheme-2.9.3]
d. R. P. Tripathi et al. approach \textsuperscript{[110]}

R. P. Tripathi et al. reported Knoevenagel/Michael/Aldol reactions of aromatic aldehydes and b-keto esters/ketones in a sequential manner yielded functionalized cyclohexanones in good yields.

\begin{center}
\textbf{Scheme-2.9.4}
\end{center}

\begin{center}
\begin{align*}
\text{O} & \text{O} \quad \text{+} \\
\text{O} & \text{O} \\
\text{Piperidine} & \text{EtOH, RT} \\
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{C}_2\text{H}_5\text{OOC} & \text{COOC}_2\text{H}_5 \\
\end{align*}
\end{center}

\begin{center}
\text{e. Rajanarendar et al. approach \textsuperscript{[111]}}
\end{center}

Rajanarendar et al. developed a method for the synthesis of functionalized cyclohexanones via Knoevenagel condensation in the presence of piperidine in ethanol under microwave irradiation.

\begin{center}
\textbf{Scheme-2.9.5}
\end{center}

\begin{center}
\begin{align*}
\text{O} & \text{O} \quad \text{+} \\
\text{C} & \\
\text{Piperidine} & \text{Ethanol} \\
\text{Microwave} & \\
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{C}_2\text{H}_5\text{OOC} & \text{COOC}_2\text{H}_5 \\
\end{align*}
\end{center}

\begin{center}
\text{f. Gein V. L. et al. approach \textsuperscript{[112]}}
\end{center}

Gein V. L. et al. have developed a novel approach for the synthesis of functionalized cyclohexanones via Knoevenagel condensation in the presence piperidine in t-butanol at 50-60°C.

\begin{center}
\textbf{Scheme-2.9.6}
\end{center}

\begin{center}
\begin{align*}
\text{O} & \text{O} \quad \text{+} \\
\text{A} & \\
\text{Piperidine} & \text{t-Butanol} \\
50-60°C & \\
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{C}_2\text{H}_5\text{OOC} & \text{COOC}_2\text{H}_5 \\
\end{align*}
\end{center}
g. Titova, Yu. A. et al. approach \cite{113,114}

Titova, Yu. A. et al. developed efficient methods for the synthesis of functionalized cyclohexanones with ethylacetoacetates and aromatic aldehydes by employing aluminium oxide as catalyst in presence of base morpholine in Acetonitrile at 40°C.

\begin{equation}
\text{Scheme-2.9.7}
\end{equation}

h. Walker approach \cite{115}

Walker had developed a new route of synthesis for functionalized cyclohexanones with N-benzyl-trimethylammonium hydroxide.

\begin{equation}
\text{Scheme-2.9.8}
\end{equation}

i. Knoevenagel et al. approach \cite{116}

Knoevenagel et al. developed a robust process for the synthesis of functionalized cyclohexanones employing with diethylamine.

\begin{equation}
\text{Scheme-2.9.9}
\end{equation}
j. Harjit Singh et al. approach \[117\]
Harjit Singh et al. Michael additions have been advantageously performed by using surface mediated solid phase reactions employing anhydrous zinc chloride impregnated alumina at ambient temperature.

\[ \text{Scheme-2.9.10} \]

k. Morrell et al. approach \[118-120\]
Morrell et al. developed efficient methods for the synthesis of highly functionalized cyclohexanones by employing with sodium ethanolate and benzylidenanilin-acetoacetic acid ester.

\[ \text{Scheme-2.9.11} \]

l. Haensel W. et al. approach \[121\]
Haensel W. et al. were developed an efficient route for the synthesis novel functionalized cyclohexanones With 1,4-diaza-bicyclo[2.2.2]octane in ethanol.

\[ \text{Scheme-2.9.12} \]