CHAPTER-I

1.1 Introduction

Heterocyclic compounds are cyclic organic compounds with one or more heteroatom such as oxygen, sulfur or nitrogen in ring structure in addition to carbon atom. Owing to immense biological, pharmaceutical, and industrial applications, heterocyclic compounds among many organic molecules, have gained lot of interest in past few decades[1]. Amongst the various heterocyclic compounds available, N-containing heterocyclic compounds finds an extensive range of applications in numerous fields like pharmacology, drug industry, and analytical chemistry[2–4]. N-containing heterocyclic compounds serves as a fundamental subunit in many natural products such as hormones, vitamins and antibiotics[5]. Interestingly, the core structure of several natural products such as serotonin (1)[6] , thiamine (2)[7], morphine (3)[8], codeine (4)[9], coniine (5)[10], caffeine (6)[11], nicotine (7)[12] etc. contains N-containing heterocyclic compounds (Fig 1.1).

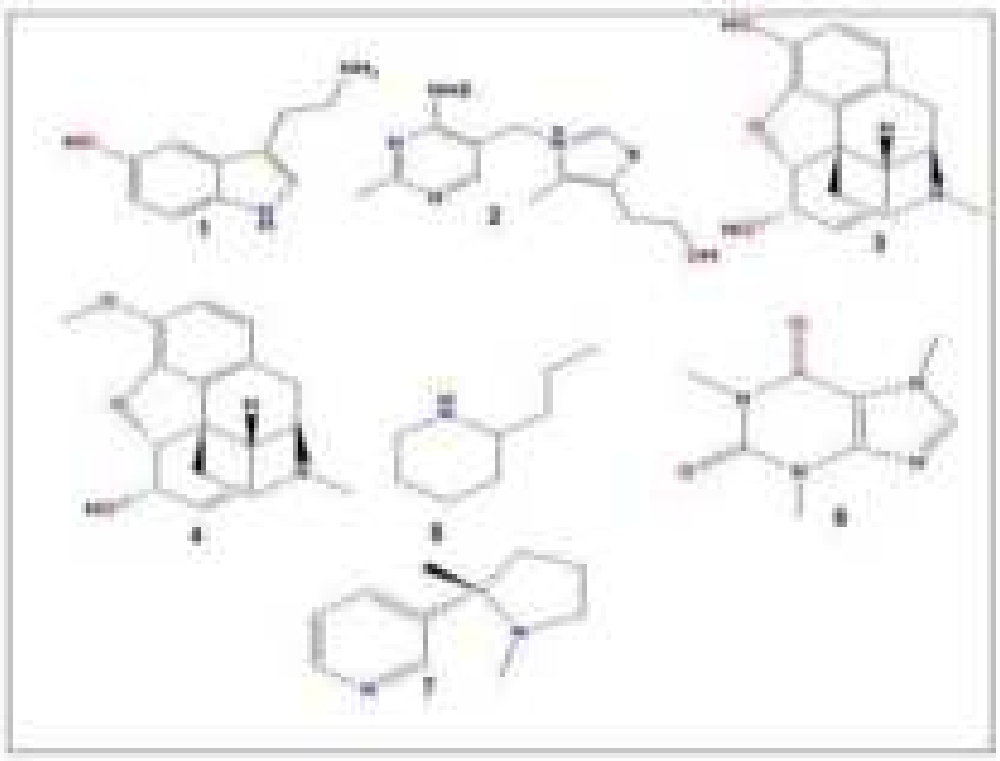


Fig. 1.1. Examples of naturally occurring N-containing heterocyclic compounds.

During the past few decades, N-containing heterocyclic compounds have been an active field of research due to their diverse and numerous biological activities and therefore, they have become an active target to the synthetic chemist in the field of total synthesis of natural products[13-14]. Moreover, several prescribed drugs like Risperidone (8) (Schizophrenia)[15], Timolol (9) (Anti-glaucoma agent)[16],

Sunitinib (10) (Renal cell carcinoma and gastrointestinal stromal tumors)[17], Anastrozole (11) (Migraine)[18] and Rufinamide (12) (Anticonvulsant)[19] etc. contains N-containing heterocyclic scaffold (Fig. 1.2).

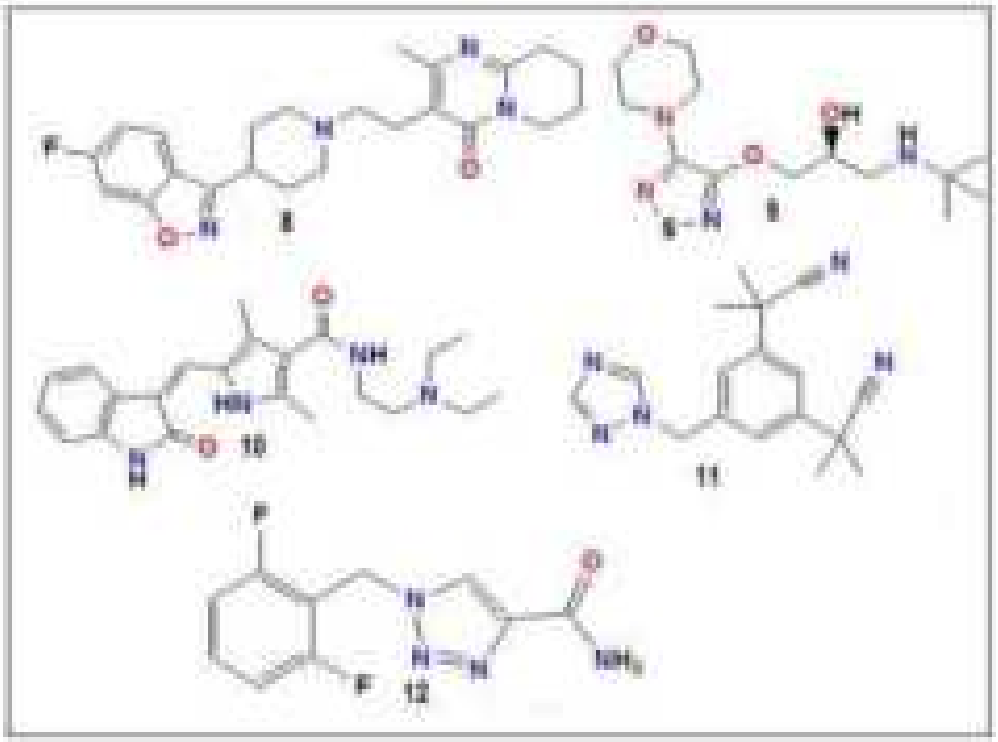


Fig. 1.2. Molecular structure of some of the prescribed drugs containing N-heterocyclic scaffold.

The worth of the heterocyclic compounds in medicinal field and biological systems can be understood from their presence in amino acids like histidine and tryptophan to DNA and RNA[20]. Purine and Pyrimidine skeleton of thymine (13), cytosine (14), uracil (15), guanine (16) and adenine (17) contain N-heterocyclic scaffold (Fig.1.3) and they are essential building blocks of nucleic acids, DNA and RNA[21]. According to FDA database nearly 75% unique small-molecule drugs contain a nitrogen heterocycle[22].

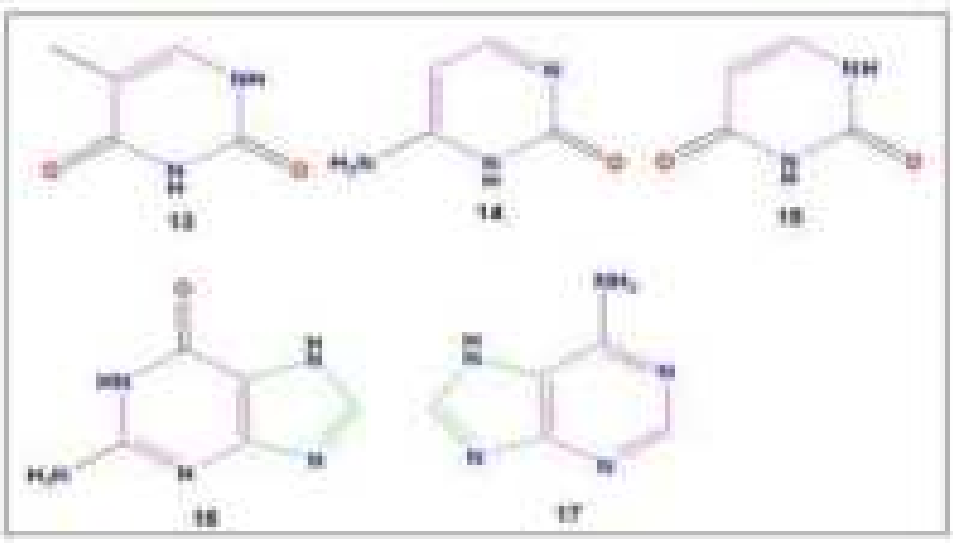


Fig. 1.3. Molecular structures of nitrogenous Bases of DNA and RNA.

Interesting structural features of the N-containing heterocyclic compounds allows them to establish a diverse type of weak interactions such as hydrogen bonding, dipole-dipole interaction, hydrophobic effect and π-π stacking etc., with the enzymes and receptors of the biological targets with high affinity which in turn is essential in the field of medicinal chemistry for the discovery of new therapeutic agents/drug molecules[23–25]. Looking at the diverse applications of heterocyclic compounds in the pharmaceutical industries, many think tanks are engaged in synthesising biologically active heterocyclic compounds for the betterment of humans and the society as a whole[26–30]. Structures of some of the N-containing heterocyclic scaffolds such as imidazole (18), indole (19), pyrazole (20), pyrimidine (21), pyrazine (22), morpholine (23), triazole (24), quinoline (25) and isoquinoline (26) are depicted in Fig. 1.4.

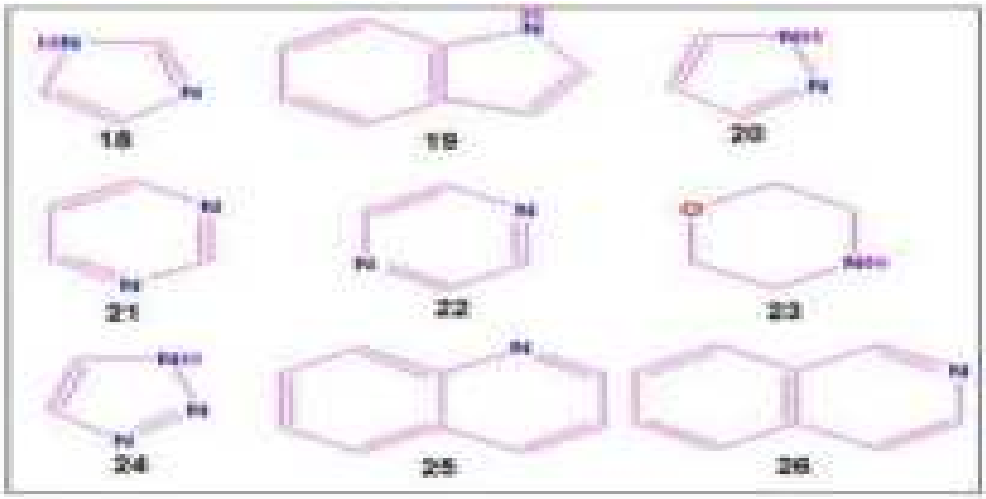


Fig. 1.4. Molecular structure of some of the N-Heterocyclic scaffolds.

Also, biologically important amino acid, namely histidine (27), tryptophan (28) and proline (29) contain N-heterocyclic motifs in their main structure (Fig. 1.5).

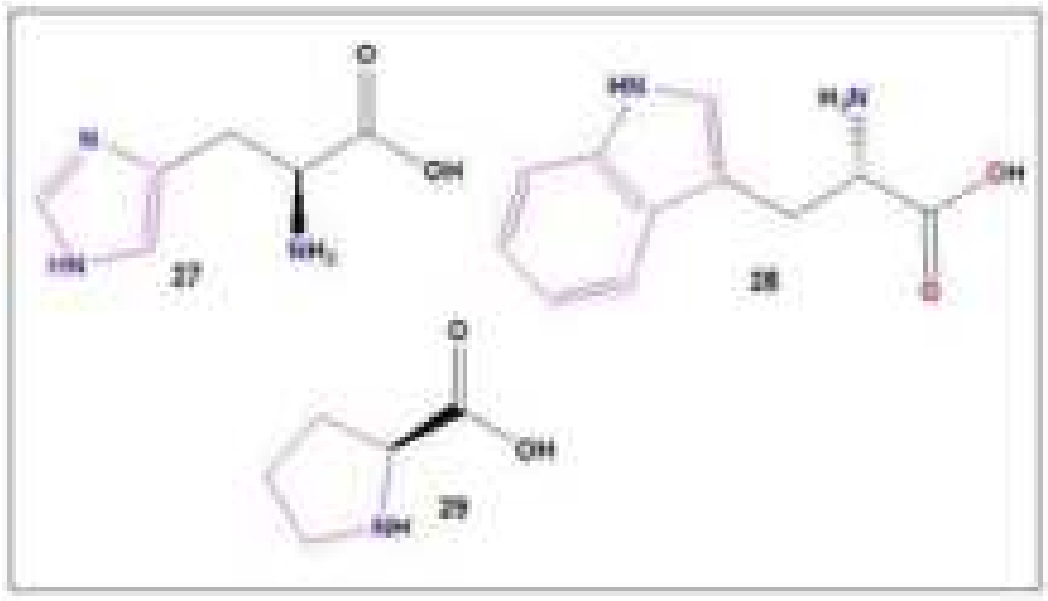


Fig. 1.5. Molecular structures of amino acids containing N-heterocyclic motifs.

Hemoglobin and Chlorophyll are the best examples of Metal Porphyrins which contains N- heterocycle and they are responsible for transport of Oxygen in animals and photosynthesis in plants respectively. The ability of N atom in N-heterocyclic compounds to form hydrogen bonds with potential biological targets has been fully exploited by the medicinal chemists to develop pharmaceutically important therapeutic agents/ drugs for the treatment of various diseases[31-32]. Penicillin (30)[33], Cephalosporins (31)[34], Puromycins (32)[35] are important classes of Antibiotics which contain N-heterocyclic scaffold in their skeleton structure (Fig. 1.6). N-heterocyclic compounds having 5 or 6 membered rings play a key role in metabolism of all living cells[36]. Nitrogen containing heterocyclic scaffold are present in a wide variety of drug such as antidiabetic[37], anti-inflammatory[38], antidepressant[39], antitumor[40], antimalarial[41], anti-HIV[42], antibacterial[43], antifungal[44], antiviral[45], herbicidal[46] and insecticidal[47] etc. Structures of some of the biologically active compounds having N-heterocyclic motif are Clotrimazole (33), Fluconazole (34), Flucytosine (35), Piroxicam (36), Celecoxib (37), Sparfloxacin (38), Furalazine (39), Nitrofurantoin (40), Levetiracetam (41), Phenytoin (42) and Phenobarbital (43)) are shown in Fig. 1.7.

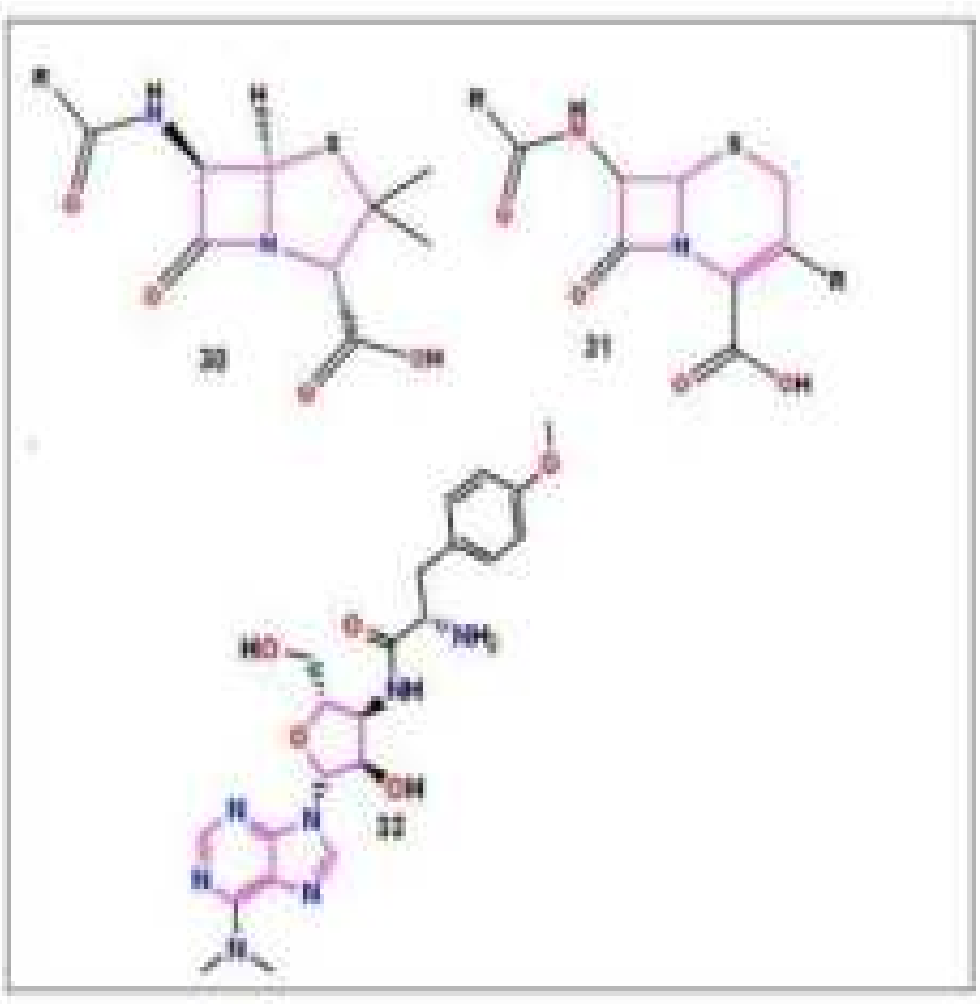


Fig. 1.6. Molecular structure of Penicillin, Cephalosporin and Puromycin.

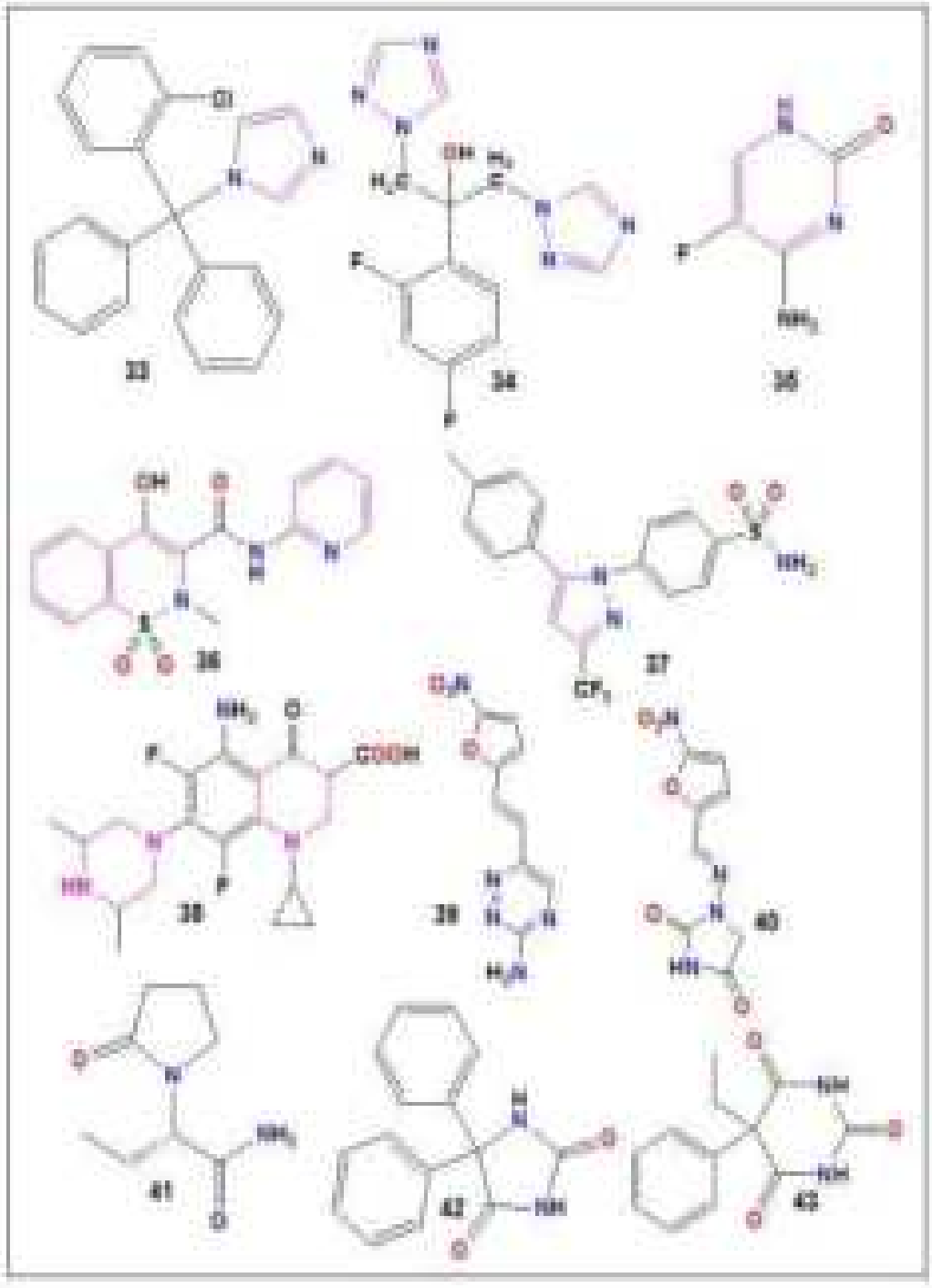


Fig. 1.7. Structures of some of the biologically active N-heterocyclic motifs

Though the N-heterocyclic compounds are ubiquitous in nature, but their expense is not sufficient to meet the necessities of the increasing demand every day. Therefore, chemists are always looking for a novel and cost-effective synthetic procedure for the synthesis of these naturally occurring valuable heterocyclic

scaffolds in the laboratories as well as in industries to fulfill the ever-increasing demand of these heterocyclic compounds[48].

Thus, the synthesis of N-heterocyclic compounds is one of the most attractive areas of research due to their unique structures with the extensive applications in the fields of organic, pharmaceutical and material chemistry[49]. During the last few decades, much of the work is focused on the development of new reaction methodology for the synthesis of N-heterocyclic compounds in the laboratory and in industrial scale and current literature survey revealed that a vast number of works are documented in this field[50–55]. However, these documented methodologies/ procedures have associated with some drawbacks such as use of expensive and toxic solvents, non-ecofriendly processes, expensive/incompetent catalysts, poor yields, incompatibility with other functional groups, difficult product purification and isolation techniques etc[56,57].

1.2 Green chemistry

The concept of green chemistry was coined by Prof. Paul. T. Anastas in early 1990s in a special program launched by the US Environmental Protection Agency (EPA) to implement sustainable development in chemistry and chemical technology by industry, academia and government[58]. Green chemistry is a new philosophical approach which exclusively utilizes a set of principles to develop process and products to reduce or eliminate hazardous substances and this new approach may also be known as ***"Environmentally benign"*** chemistry, ***"Clean chemistry"*** and ***"benign-by-design chemistry***"[59].

The term Green chemistry may be defined as ***"design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances''***[60].

Alternatively, green chemistry may also be defined as the ***"utilization of a set of principles that eliminates or reduces the use or the generation of hazardous substances in the design, manufacture and application of chemical products or materials"*** [58].

Prof. Anastas highlighted that the green chemistry is all about redesigning of chemical processes i.e., making industrial chemistry safer, cleaner and more energy efficient staring from synthesis to clean-up to disposal[58]. The main aim of green chemistry is to develop products and processes in energy efficient way, less waste generation, use of less organic solvents or no use of solvents, have no environmental or health problems, recycling of the products or environmental degradation to harmless materials[61]. One of the key goals of green chemistry is to prevent pollution at its source than dealing with pollution after it has occurred. The Green chemistry also known as sustainable chemistry encourages the design of the products and processes that minimize the use and generation of hazardous chemicals[62].

Green chemistry, being a philosophy of sustainable chemistry applies to different branches of chemistry such as organic chemistry, inorganic chemistry, analytical chemistry, biochemistry and physical chemistry[63]. Since in industrial scale, huge

quantities and numerous varieties of small starting molecules, reagents, solvents, acid, base etc., are involved for production of different products and these chemical processes produces a large quantity of hazardous and undesired by-products in addition to the desired products which in turn pollute the environment and public health[64]. Therefore, the pressing need of the chemist is to minimize the chemical waste and in order to address the current environmental pollution due to hazardous chemicals, Prof. Anastas and Warner[58] coined a set of twelve principles of green chemistry. These principles are: -

1. **Waste Prevention**: It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom Economy or Efficiency**: Synthetic Methods should be designed in such a way so as to maximize the incorporation of all materials used in the process into the final product. The concept of atom economy was introduced by Trost[65] and it represents how much of the reactant end up in the final product. The percentage atom economy was introduced by Sheldon[66] as follows:

   $$\text{Atom economy} = \frac{Molecular\ weight\ of\ the\ desired\ products}{Molecular\ weight\ of\ all\ products} \times 100\%$$

   Among synthetic chemists, the concept of atom economy is most widely used measure of the green chemistry.
3. **Less Hazardous Chemical Synthesis**: Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**: Chemical products should be designed to preserve efficacy of function while minimizing their toxicity.
5. **Safer Solvents and Auxiliaries:** The use of auxiliary substances should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency**: Energy requirements of chemical processes should be recognized for their environmental and economic impacts should be minimized.
7. **Use of Renewable Feed stocks**: A raw material or feed stock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives**: Unnecessary derivatization should be minimized or avoided, if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis:** Catalytic reagents are superior to stoichiometric reagents.
10. **Design for Degradation of Chemical Products**: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time Analysis for Pollution Prevention**: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently safer Chemistry for Accident Prevention**: Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

After the introduction of the new philosophical concept of Green chemistry or Sustainable chemistry, a vast number of literature is available with many interesting examples where the principles of green chemistry has been implemented for the development and designing of the different chemical reactions/processes in industrial as well as in laboratory scale[67]. Still, greater effort is being undertaken to develop and design an ideal chemical processes/reaction that begins from non-polluting starting materials, leads to no secondary by-products and requires no harmful solvents to carry out the chemical conversion or to isolate and purify the final product[68]. Many new analytical techniques which utilize the green chemistry principles have also been documented[69]. There are numerous approaches of green chemistry such as Microwave technology[70], Ultrasonication[71], Solvent-free synthesis or use of Green Solvents[72], Photo catalysis[73], Hydrothermal Synthesis[74], Magnetic-field assisted synthesis[75], Grinding technique[76], Ball milling technique[77] to carry out organic synthesis. In this research work, we focused on the synthesis of some N-containing heterocyclic compounds under solvent free condition as solvent free reactions are gaining more importance now a days due to its efficiency, economic, short reaction time and high product yield.

1.2.1 Solvent free synthesis

"No Coopora nisi Fluida", a famous statement given by the ancient Greek philosopher Aristotle, meaning "No reaction occurs in the absence of solvent" had a paramount influence on the advancement of the modern sciences and has provided one of the prominent reasons why organic reactions are carried out in solvents[72]. This statement is no longer valid as a large number of chemical reactions occur in solid state without solvent. Such solvent free or solid-state reactions have many advantages such as simple to handle, reduced pollution, comparatively cheaper to operate than the reactions carried out in solvents[78]. Interestingly, organic reaction in solid state is more efficient and more selective than those carried out in a solvent medium and they are largely green and therefore industrially useful[79]. Among the various proposed green procedure for the organic reaction, solvent-free or solid-state synthesis holds a leading position and therefore, a generalized concept is that ***"the best solvent is no solvent"***[80].

Solvent free synthesis or solid-state reactions have many advantages over the reaction carried out in solvent medium. Since, solvent is omitted from the reaction, therefore, from the prospect of economy one saves money on the solvent and it is environmentally friendly[81]. Solid state reaction or solvent free reaction is not a new

concept, in fact, Wohler's synthesis of urea (44) in 1882 is a historically significant organic reaction[82] (Fig.1.8)

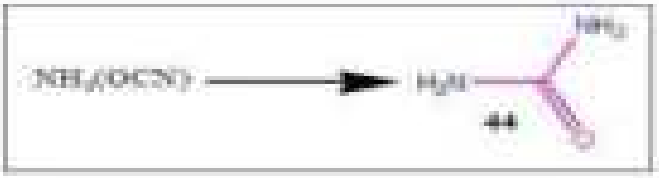


Fig. 1.8. Wohler's Synthesis of ammonia.

Examples of organic reactions carried out under solvent free conditions are numerous in the literature. For example, Baeyer-Villiger oxidations of ketones with *m*-chloroperbenzoic acid and it was found that this reaction proceeds much faster in the solid state than in solution at room temperature[83] (Fig.1.9).

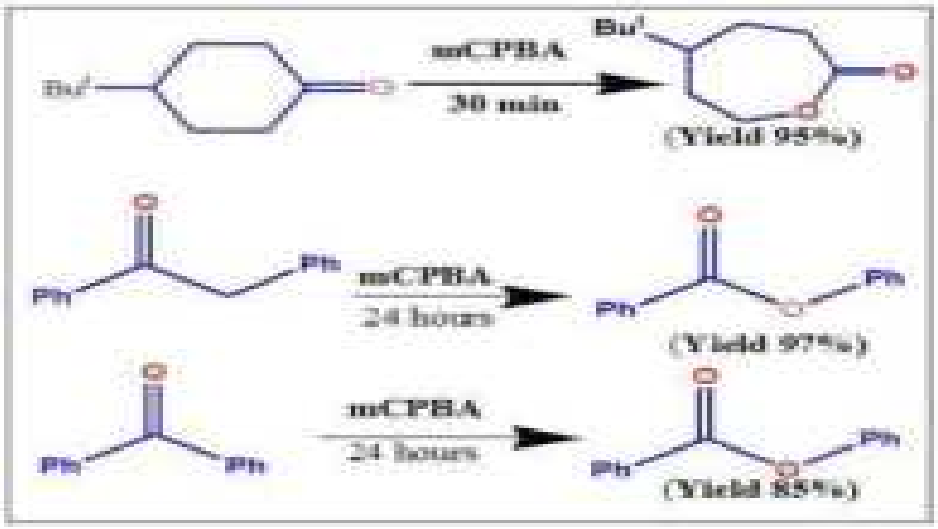


Fig. 1.9. Bayer-Villiger oxidation of ketones with mCPBA

Claisen rearrangement of allyl phenol to o-allylphenol (45) is another early record of organic synthesis carried out in solvent free condition[84] (Fig. 1.10).

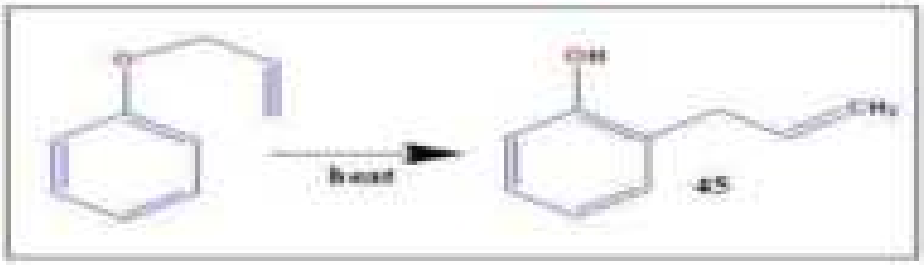


Fig. 1.10. Claisen rearrangement

Many other important organic reactions such as Michael addition[85](46), Aldol condenation[86](47), Stobbe condensation[87](48), Thorpe reaction[88](49), Tischenko reaction[89](50) and Heck reaction[90](51) etc., are also found to proceed efficiently in solvent free reaction conditions in contrast to the reaction carried out in solvent medium (Fig. 1.11). Furthermore, these reactions under solvent free conditions are highly atom and energy efficient and are highly chemo selective[91].

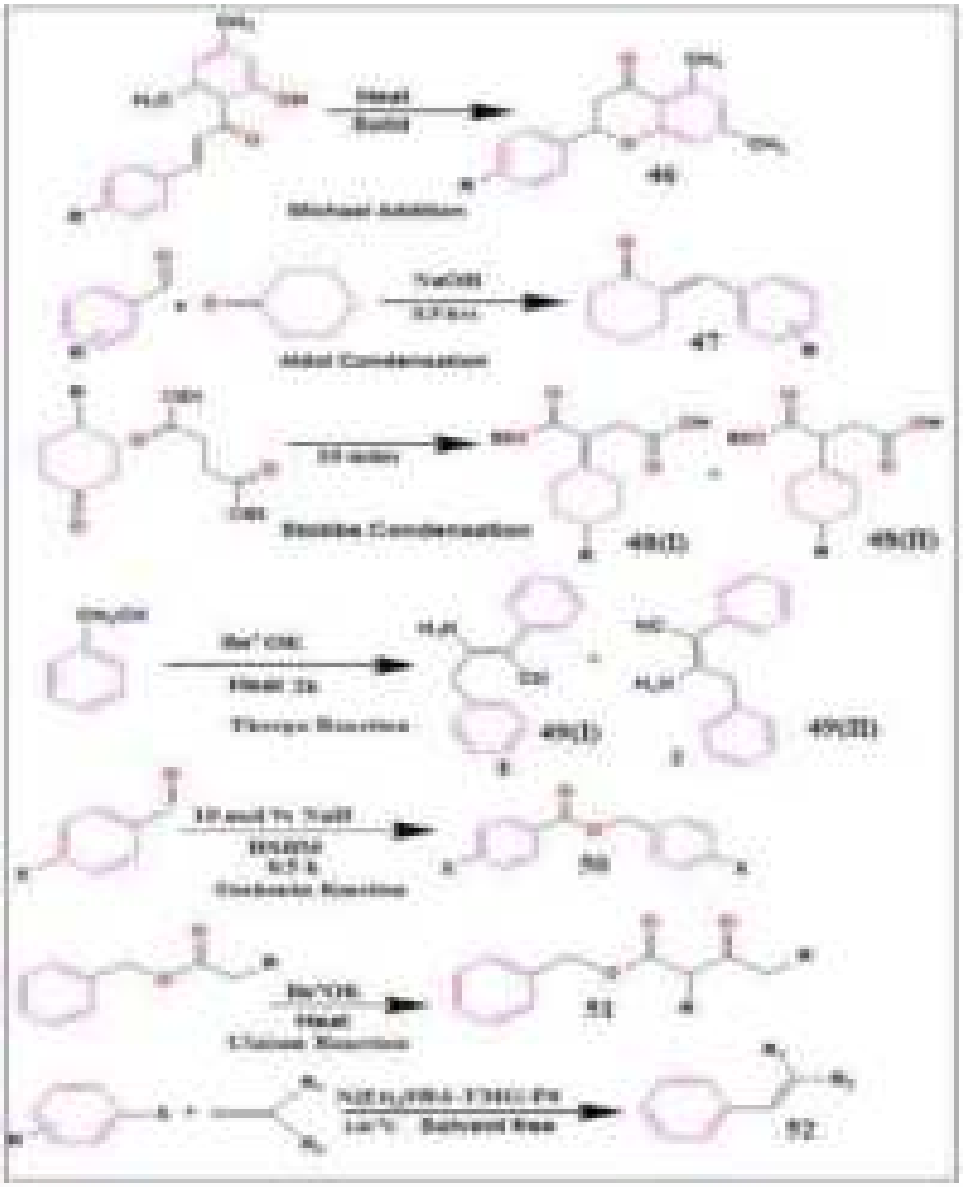


Fig. 1.11. Important organic reactions in solvent free condition.

Solvent free reactions are operationally simple; reduce pollution, comparatively economical and especially important in industries and therefore, various new methodologies and techniques have been developed to make the solvent free reaction more economical, more efficient and with less pollution[92,93]. Microwave[70], Ultrasonication[71], Grinding[76] and Ball milling[77] techniques are highly developed methodologies for the solvent free synthesis of industrially and clinically important organic molecules. Unfortunately, it has been observed that solid state reactions do not completely meet the meaning of no solvent since significant amount of solvent is still essential for adsorption of reactants and elution of products at the pre and post reaction stages respectively[94]. Since, our research work is focused on the synthesis of N-containing heterocyclic compounds under green reaction condition and therefore we are restricting our discussion with the solvent free synthesis of N-containing heterocyclic compounds only. During the past few decades, a vast number of works are documented towards the solvent free synthesis of different N-containing heterocyclic compounds under green reaction conditions[95–98]. The N-containing heterocyclic compound possesses distinct characteristics and therefore has gained immense importance in the rapidly growing fields of organic, medicinal chemistry and the pharmaceutical industry[99]. A number of solventless reaction protocols for the synthesis of different N-heterocyclic compounds such as pyrrole[100](53), substituted imidazole[101](54), dihydropyrimidinones[102](55), substituted pyridines[103](56), substituted quinolones[104](57), imidazo[1,2-a]pyridines[105](58), imidazo[1,2-a]pyrazines[106](59) and imidazo[1,2-a]pyrimidines[107](60) etc., have been developed during the past decades (Fig. 1.12). Since, green chemistry being a terminal goal for synthetic organic chemists, which requires chemical processes with high chemoselectivities and facile reaction systems and apparently, solvent free reaction condition meet the most of the criteria of the green chemistry. Therefore, solvent free synthesis is gaining a lot of interest in view of designing and development of new materials, processes, systems, and products that are benign to human health and the sustainable environment[108]. Though, we may not be able to avoid organic solvents during the synthesis of fine chemicals, nevertheless, continuous attempts have been made to devise and explore synthetic methods in the area of green chemistry. Thus, one way to achieve this goal is to adopt solvent free reaction condition as it will save environment and cuts cost of production by elimination of the use of expensive and hazardous solvents[72].

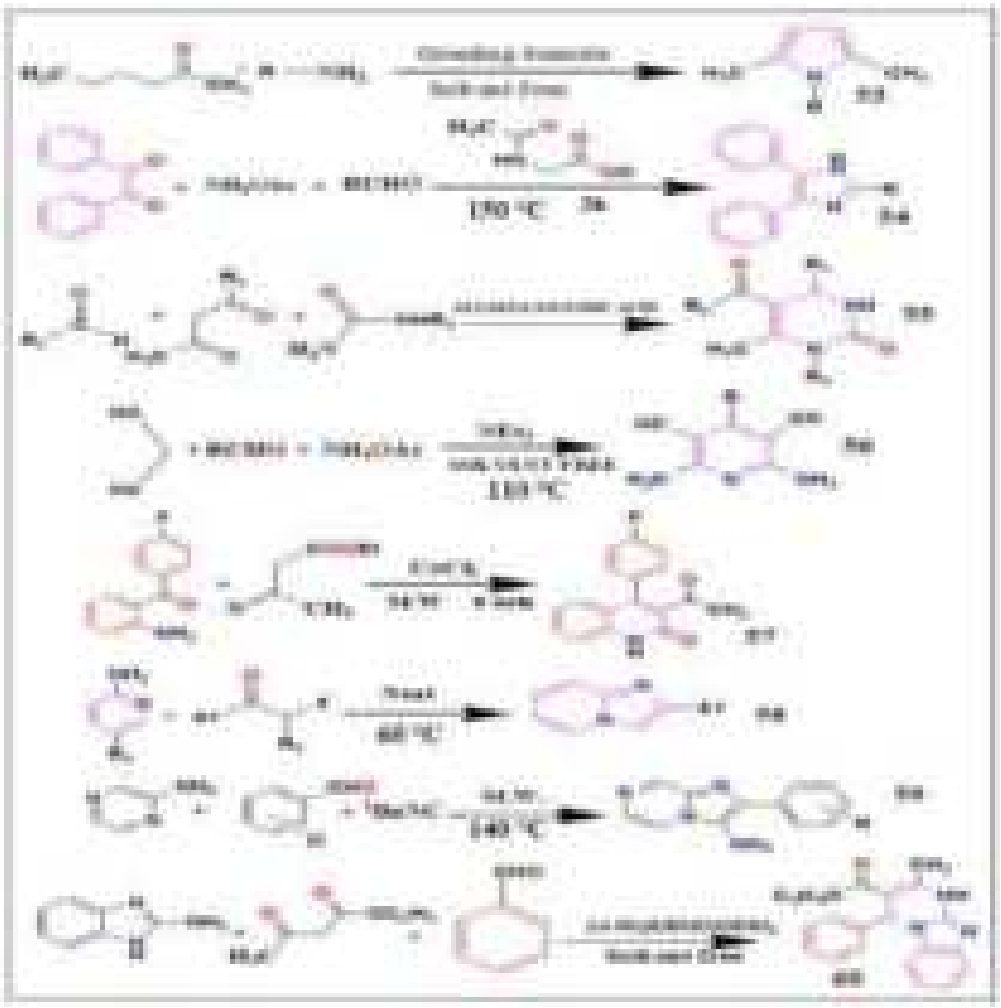


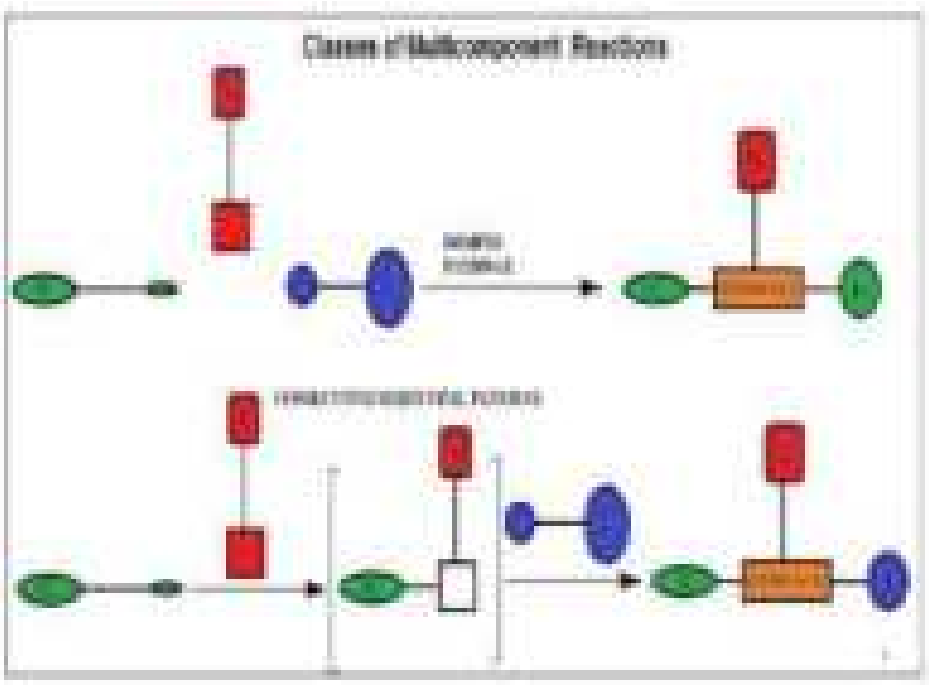
Fig. 1.12. Solventless reaction protocols for synthesis of some N-containing Heterocyclic compounds.

1.2.2 Multicomponent Reactions

In earlier days, the efficiency of the reaction for synthetic chemist was in terms of yield of the product, selectivity and number of steps involved in the synthesis. However, after the introduction of the concept of green chemistry and its underlying 12 principles, a broader concept for the design of chemical reactions evolved which includes criteria for waste generation, use of reagents and solvents, use of hazardous chemicals, energy intensity and general safety[109]. The main objective of green chemistry is to redesign the process in an economical and efficient protocol for the synthesis of valuable chemicals and it does not necessarily focus on the development of novel methods, but rather provides alternative sustainable variant to existing ones and most importantly, different synthetic strategies to include environmental considerations as early as in the process design stage[110]. In this context, Multicomponent Reactions (MCRs), where more than two reactants combine in a

sequential manner to give highly selective products that retain majority of the atoms of the starting material serves as a good example to meet the most of the requirements of the green chemistry[111]. Thus, Multicomponent Reactions (MCRs) are gaining lot of interest during these days for the synthetic chemist in view of the fact that this reaction condition is highly efficient and economical[112–114]. Multicomponent reactions (MCRs) find a prominent position in the organic synthesis as this method provides an option to bring together three or more reagents in one-pot, incorporating most of the atoms from the reagents in the final structure and decreases the time of the reaction[115]. A Multicomponent Reaction is in general a domino process, where a sequence of elementary steps of the chemical transformation is collaged to a single step. The domino reaction is also sometimes referred to as tandem reaction as this type of reaction has many advantages over conventional methods such as high atom economy, shorter reaction time, environmentally friendly, low cost and easy work up procedure[116]. Since, MCRs are one pot reactions; therefore, one can rapidly access large libraries of organic compounds with varied substitution in a single step by eliminating rigorous multistep syntheses[117].

According to J. Zhu, MCRs may be appropriately defined as "*process involving sequential reactions among three or more reactant components that co-exist in same reaction mixture*". Most interestingly, MCRs rely on the reactant components that are compatible with each other and do not undergo alternative reaction to form other products or by-products apart from the desired product[118]. Moreover, MCRs have many advantages such as simple experimental setup, high yield, atom economy, short reaction time, eco-friendly etc. over the classical approach for the synthesis of important organic motifs[119]. Thus, due to above underlying advantages, multi-component reactions (MCRs) are considered to be pertinent methodological arsenal in synthetic and medicinal chemistry and these reactions have been advantageously employed in diverse synthetic transformations over classical methods which usually involve many steps with tedious procedures[120]. The MCRs can be divided into three distinct categories; i) the domino pathway in which the solvent, catalyst and the reagents are present in same reaction vessel at the start of the reaction, ii) sequential pathway is the second class of MCRs in which the reaction condition remains the same during the whole sequence but reactant components are added in well-defined sequential order from step to step and iii) The consecutive MCRs is the last class in which the components are added stepwise (as in sequential MCRs), but the reaction conditions may be altered with each reaction step[121](Scheme 1.1).

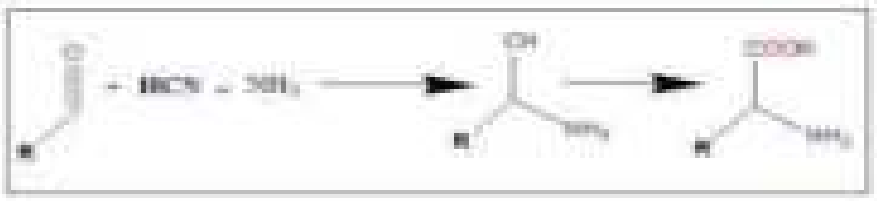


Scheme. 1.1. Graphical illustration of the classes of MCRs

Thus, designing and development of Multicomponent Reaction strategies incorporating the principle of green chemistry and using renewable and recyclable materials, using solvent-free conditions, green solvents, and green or reusable catalyst, using nonclassical conditions such as microwave technologies, ultrasonic irradiations is becoming a hotspot in the synthetic research field[122].

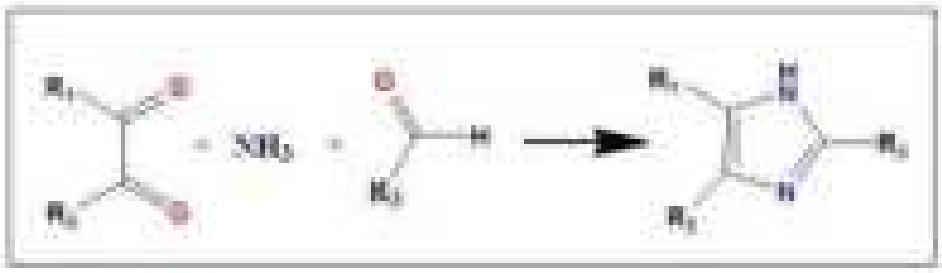
1.2.2.1 Historical development of Multicomponent Reactions

The historical development of Multicomponent Reactions can be traced back to the year 1850 where Adolf Strecker synthesized α-amino acid through one pot multicomponent condensation of aldehydes, HCN and NH_3. The three-component condensation of the above reagents leads to the formation of α-amino nitriles which is the main intermediate of the Strecker's synthesis. Subsequent hydrolysis of the α-aminonitrile results in to the formation of α-amino acid. Thus, historically Strecker's reaction may be regarded as a first multicomponent reaction and this reaction represents one of the most straightforward and economically viable multicomponent reaction[123](Scheme 1.2).



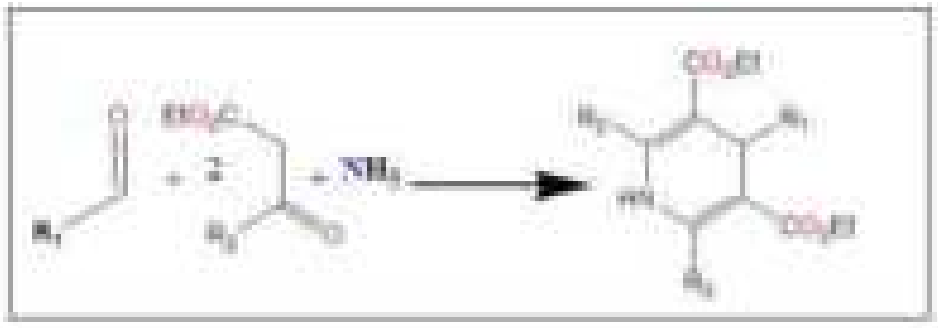
Scheme. 1.2. Strecker's Reaction

The Debus-Radziszewski imidazole synthesis was another step in the field of multicomponent reaction which was coined by Heinrich Debus in 1858[124] and later developed by Bronislaw Leonard Radziszewski in 1882[125,126]. In this multicomponent reaction, an imidazole scaffold was prepared by cyclocondensation of diketone, aldehyde and ammonia (Scheme 1.3).



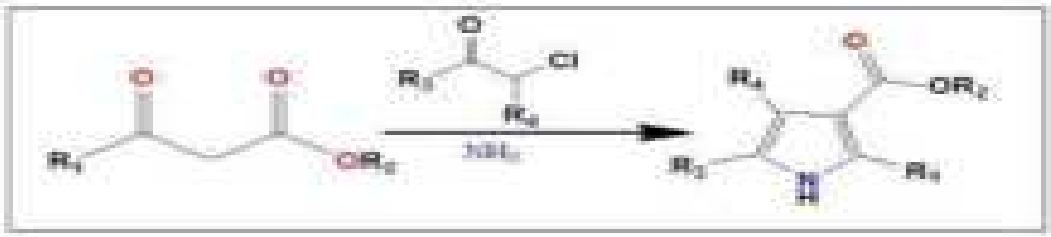
Scheme. 1.3. Debus-Raziszewski Synthesis.

Further progress in multicomponent synthetic chemistry was realized when Hantzsch (1881) synthesized symmetrically substituted dihydropyridines from one pot cyclocondensation of NH_3, aldehydes and two equivalent of β-ketoesters[127](Scheme 1.4).



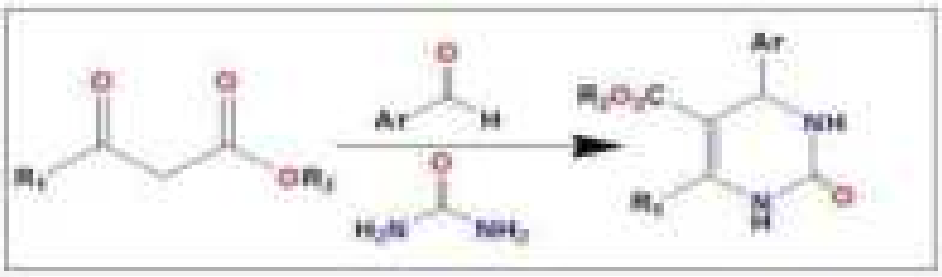
Scheme. 1.4. Hantzch Synthesis of substituted dihydropyridines

The Hantzsch synthesis of pyrrole involving ammonia (or primary amine), β-ketoester and α-haloketones is another contribution towards the development of multicomponent reaction[128] (Scheme 1.5).



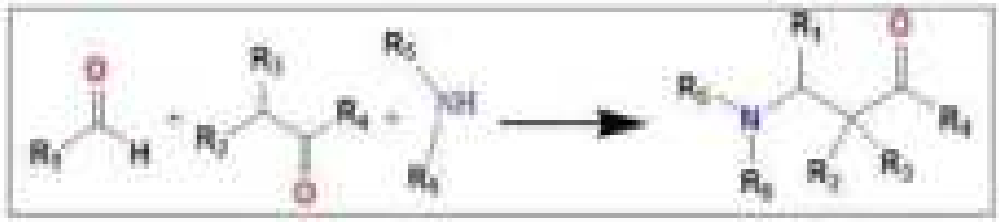
Scheme. 1.5: Hantzch Synthesis of pyrrole.

Another development in the field of Multicomponent Reaction can be visualized through the work of an Italian Chemist Pietro Bigenelli in the year 1891 wherein he adopted a three-component acid catalyzed cyclocondensation of β-ketoester, aromatic aldehydes and Urea to synthesized substituted Dihydropyrimidinones[129] (Scheme 1.6).



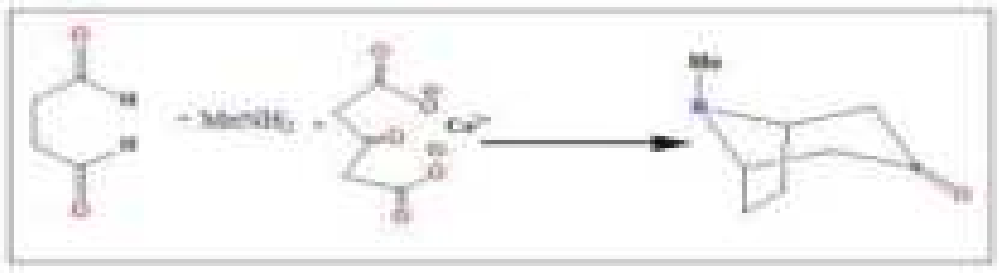
Scheme. 1.6. Bigenelli synthesis of dihydropyrimidinones

In the year 1912, Carl Mannich discovered a one-pot Multicomponent Reaction for the synthesis of optically active β-aminocarbonyl compounds through the condensation of amine derivatives, enolizable carbonyl compounds and non-enolizable aldehyde. This reaction is known as the famous Mannich reaction and the optically active compound serves as a valuable building block for the asymmetric synthesis of various pharmaceutical scaffolds and natural products[130] (Scheme 1.7).



Scheme. 1.7. Mannich Reaction

Moreover, Robinson synthesis of bioactive alkaloid Tropinone in 1917 can be taken as the first important application of MCRs in natural product synthesis[131]. The one-pot cyclocondensation of succinic di-aldehyde, methylamine and calcium salt of acetonedicarboxylic acid yielded biologically active Tropinone (Scheme 1.8).

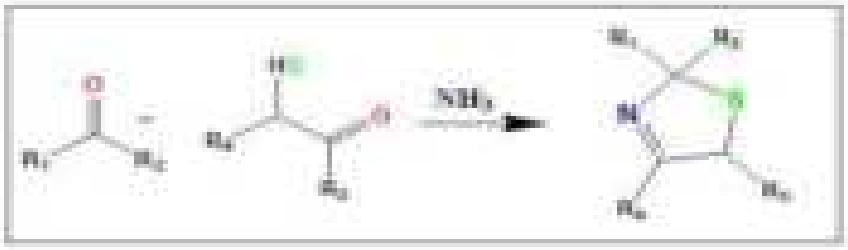


Scheme. 1.8. Robinson's synthesis of bioactive alkaloid

Bucherer and Bergs, in 1934 successfully synthesized hydantoins utilizing four component one pot condensation of HCN, aldehydes, ammonia and CO_2[132]. This reaction is very important as the hydantoins on hydrolysis transformed into α-amino acid (Scheme 1.9)

Scheme. 1.9. Bucherer and Bergs synthesis.

A-4CR reaction i.e., Asinger-4 component reaction was reported by Friedrich Asinger (1956) is an important four component reaction where α-halogenated carbonyl compounds, Thiols and ammonia undergo cyclocondensation to afford thiazolines. An interesting feature of Asinger reaction is that the sodium hydrogen sulphide is generated in-situ from the thiols and subsequently the sodium hydrogen sulphide reacts with carbonyl compounds and ammonia to give thiazolines[133] (Scheme 1.10).

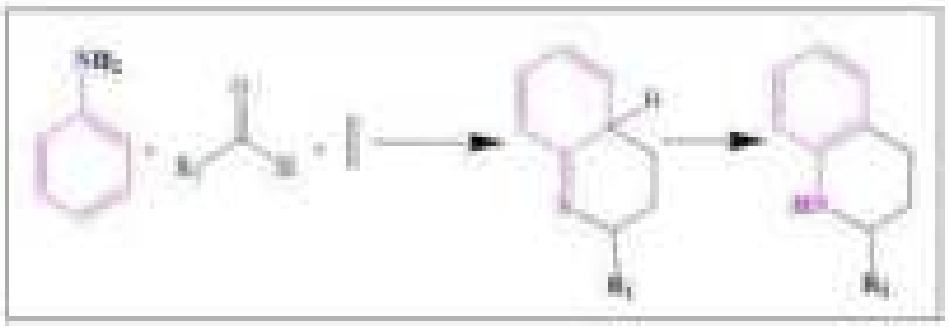


Scheme. 1.10. Asinger Reaction

Ugi reaction, a four-component reaction for the synthesis of α-acylaminoamides by reacting aldehydes, primary amines, carboxylic acid and isocyanides discovered by Ivar Ugi (1959) is one of the most important and highly utilized multicomponent reaction in organic synthesis[134] (Scheme 1.11).

Scheme. 1.11. Ugi Reaction

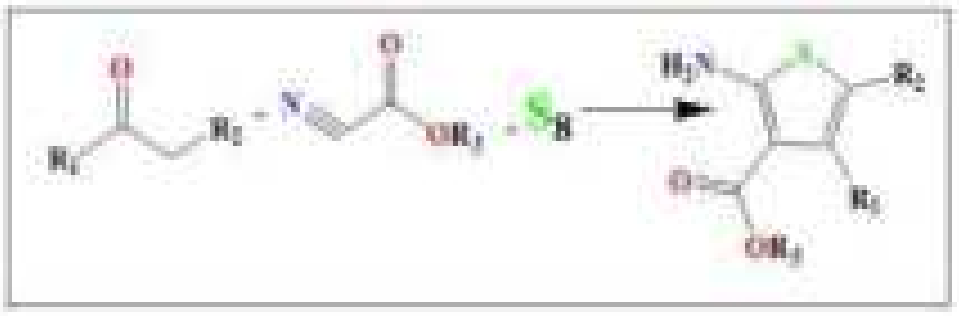
Similarly, Povarov's (1965) acid catalysed three component cyclocondensation reaction where N-aryl imine produced in situ by the reaction between aromatic amine and aromatic aldehyde undergo cyclocondensation with alkene to afford substituted quinolines is an excellent example of Multicomponent reaction[135] (Scheme 1.12)



Scheme. 1.12. Povarov's reaction

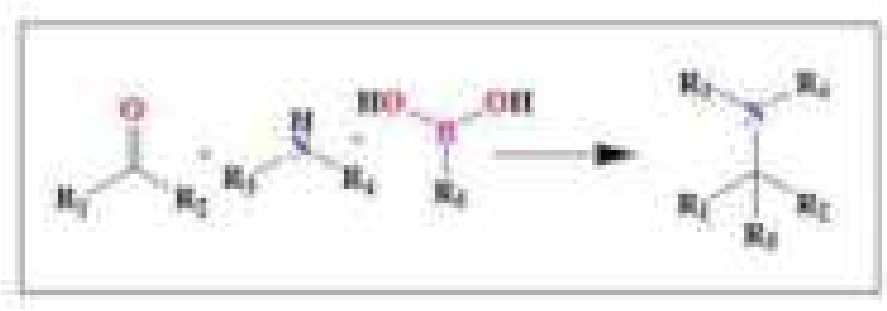
.

The Gewald's synthesis (1966) of substituted thiophene at room temperature via one-pot multicomponent condensation between aldehydes, ketones or 1, 3-dicarbonyl compounds with activated nitriles and sulfur in presence of amine is another milestone in the development of Multicomponent Reactions[136] (Scheme 1.13).



Scheme. 1.13. Gewald's Synthesis

Though the Multicomponent Reactions (MCRs) have been known for over 100 years; however, MCRs gained importance in the early 1990s after the introduction of combinatorial chemistry and related library-synthesis strategies[137]. Petasis Multicomponent Reaction, coined by N. A. Petasis in 1993 may be viewed as a powerful synthetic strategy developed in the last decade for the preparation of amine derivatives from the condensation of amines, carbonyl derivatives and aryl- or vinyl boronic acid[138] (Scheme 1.14).



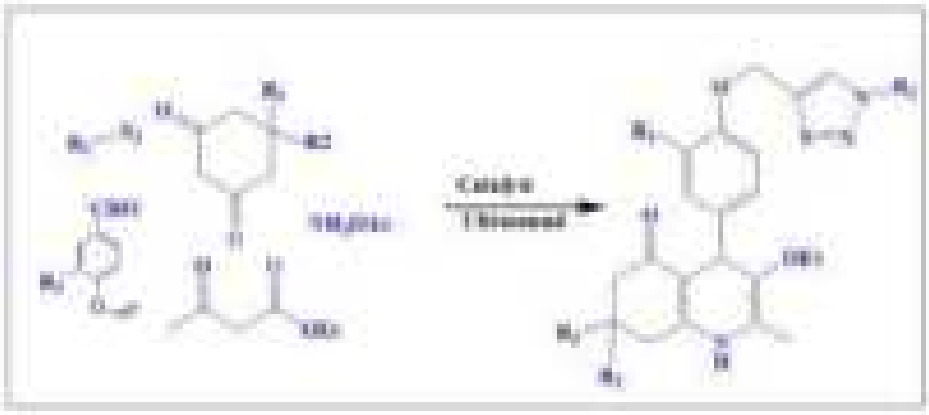
Scheme. 1.14. Petasis Multicomponent Reaction

Many new MCRs have been documented during the past few decades and many new variants of synthetic strategies have been developed for the synthesis of libraries of different fine chemicals[139]. Over the years, the advancement of multicomponent reaction has taken a rapid pace and now a days, MCRs of different types involving 3, 4, 5, 6, 7 and even 8 reactant components in a single reaction mixture have been developed.

For example, Z. Li *et.al.,* have developed a four component one-pot synthesis of isoxazole skeleton and they have successfully developed the procedure for the synthesis of perfluoroalkyl isoxazoles by using simple perfluoroalkyl reagents[140] (Scheme 1.15).

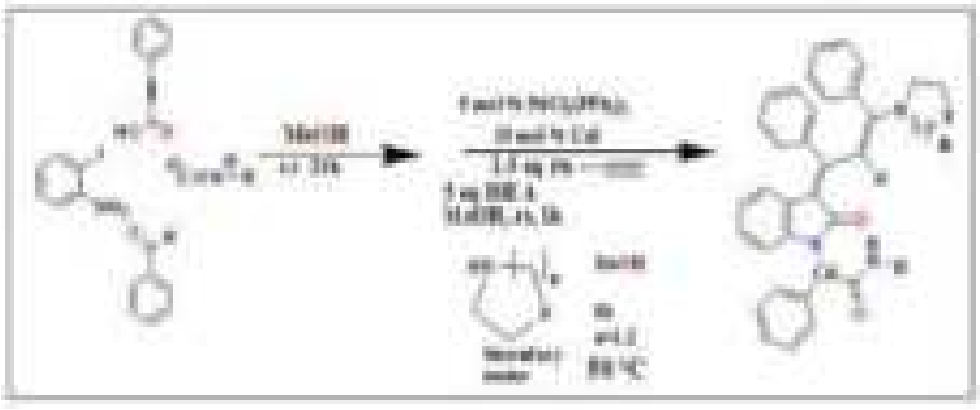
Scheme. 1.15. Synthesis of perfluoroalkyl isoxazoles by using perfluoroalkyl reagents.

Khurana *et.al*. have developed a simple and efficient one-pot five component reaction for the synthesis of 1,2,3 –triazole linked 1,4-dihydropyridines under green condition using PEG-400 as a solvent medium[141] (Scheme 1.16).



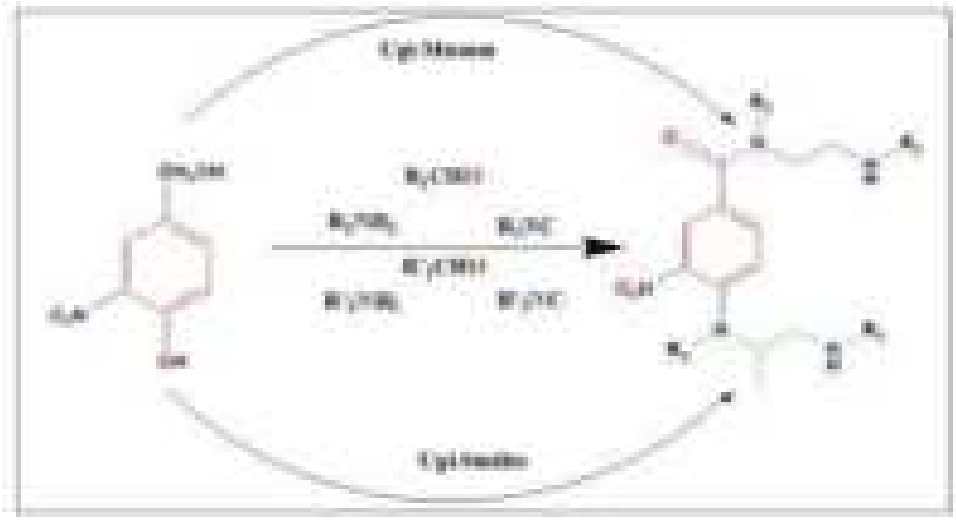
Scheme. 1.16. Synthesis of 1,4-dihydropyridines under green condition using PEG-400

S. Balalaie *et.al*. successfully utilized a Sequential One-Pot Ugi/Heck Carbocyclization/Sonogashira/Nucleophilic Addition reaction for the synthesis of 3-Arylidene-2-oxindoles and it serves as a good example of a six-component condensation reaction[142] (Scheme 1.17).



Scheme. 1.17. Sequential One-Pot Ugi/Heck Carbocyclization/Sonogashira/Nucleophilic Addition reaction.

As a seven-component reaction, Bernhard Westermann *et.al.* have utilized different chemoselectivities of the Ugi–Mumm and the Ugi–Smiles reaction in a sequential multicomponent reaction to afford highly diverse peptide and glycopeptides motifs[143](Scheme1.18)



Scheme. 1.18. Ugi-Mumm and Ugi Smiles Reaction.

Romano V. A. Orru *et.al.,* have developed a one-pot eight component reaction by utilizing union of Multicomponent Reactions to achieve a one-pot 8CR that involves nine new bond formations and eleven points of diversity[144].

By virtue of considerable economic and ecological interest, Multicomponent Reactions have emerged as important tools for the rapid generation of molecular complexity and diversity with predefined functionality in the field of drug discovery[145]. Thus, the overall historical development of Multicomponent Reactions is shown in Fig 1.13

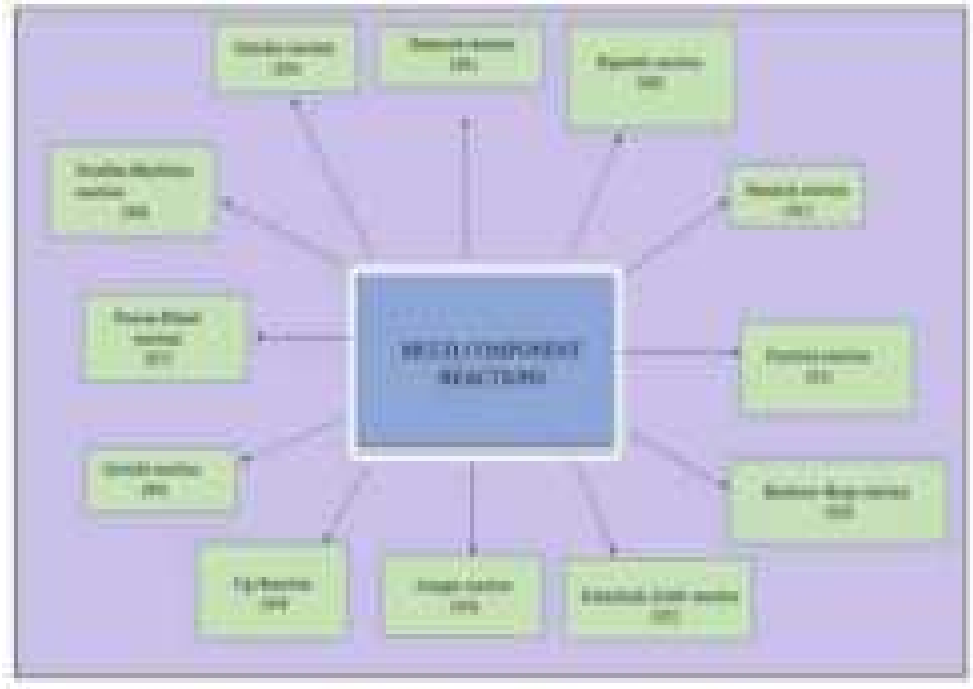


Fig. 1.13. Historical Development of Multi Component Reactions

Moreover, the present-day organic synthesis demands the designing of an operationally simple, useful and practical strategy which is cost effective and has less detrimental impact on the environment. A rational design strategy in Multicomponent Reactions (MCRs) are playing a chief role in current scenario because of the convergent nature, higher atom economy, and easy experimental procedures in the production of target compounds by the introduction of several diversity elements in a single operation, minimization of waste, labor, time, and cost, and thus, much work has been done to extend the scope of the well known classical Multicomponent Reactions to newer systems[146].

Interestingly, Multicomponent Reactions carried under solvent free conditions are gaining much attention during last decades as because these reactions are finding much application in diversity Oriented Synthesis (DOS) [147]. Since, the demand for both clean and efficient chemical syntheses is becoming more urgent, the MCRs carried out under solvent free conditions compensate this demand as because solvent-free methods open up many possibilities to modernize classical procedures by making them cleaner, safer, and easier to perform[148]. Several solvent free reaction protocols have been developed for almost all the classical Multicomponent Reactions namely, Strecker[149], Bigenelli[150], Passerini[151], Mannich[152], Hantzsch[153], Ugi[154], Gewald[155], Petasis[156], Radziwenski[157] etc. Moreover, the solvent free organic reactions have aroused the attention of organic as well as medicinal chemists during the last few decades and will add more modern techniques and procedure for chemo-, regio-. Stereoselective synthesis of high-value chemicals and synthesis of libraries of small molecules under solvent free condition in near future[146].

Therefore, all these factors prompted us to undertake the research work in the field of development of eco-friendly synthetic methodology for the synthesis of some important N-containing heterocyclic compounds using inexpensive transition metal borates as a catalyst under solvent free condition. In this research work, we focused our study on the Multicomponent green synthesis of some selected N-heterocyclic compounds such as 2,4,5-triarylimidazole, 3,4-dihydropyrimidin-2(1*H*)-one, 1-hydroxyimidazole-3-oxide and 1,2-disubstituted benzimidazole derivatives using inexpensive transition metal borate catalysts under solvent free conditions. Furthermore, we extended our research work towards the detailed theoretical (DFT), ADME and molecular docking study of the synthesized products in order to gain an insight into the potential application of the synthesized products in different scientific fields. The molecular structures of the studied N-heterocyclic scaffolds (as 2, 4, 5-triarylimidazole (61), 3, 4-dihydropyrimidin-2(1*H*)-one (62), 1-hydroxyimidazole 3-oxide (63) and 1,2-disubstituted benzimidazoles (64)) are given in Fig. 1.4.

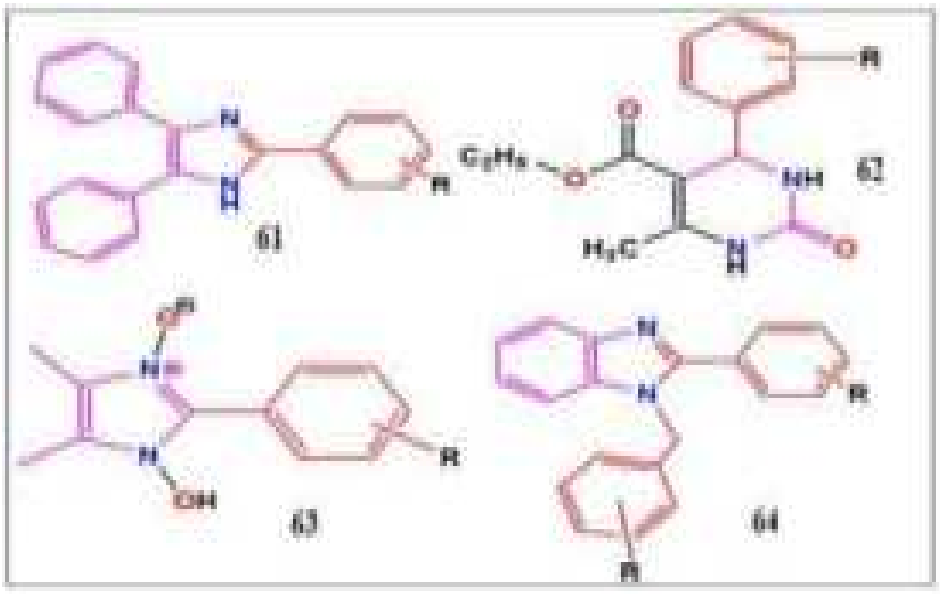


Fig. 1.4. Molecular structure of 2,4,5-triarylimidazole, 3,4-dihydropyrimidin-2(1*H*)-one, 1-hydroxyimidazole 3-oxide and 1,2-disubstituted benzimidazoles.

1.3 Brief information about the studied N-heterocyclic scaffolds

1.3.1 2,4,5-triarylimidazole

Among many N-containing heterocyclic compounds, imidazole, a five-membered nitrogenous scaffold occupies a unique position due to its wide range of pharmacological and biological properties[158]. Imidazole and its derivatives, has the unique ability to form strong hydrogen bonds with biological targets as well as it has high affinity for the metals present in active site of many proteins[159]. Furthermore, by virtue of the ability of forming hydrogen bonds with important biological targets, imidazole possesses diverse biological properties such as antimicrobial[160], anticancer[161], antihistamatic[162], anti-inflammatory[163] and antiviral[164] etc. Interestingly, imidazole scaffold is found to present in many drugs such as clotrimazole[165](33), ketoconazole[166] (65), omeprazole[167](66), Losarton[168](67), Eprosartan[169](68), and Trifenagrel[170](69) etc. (Fig. 1.15).

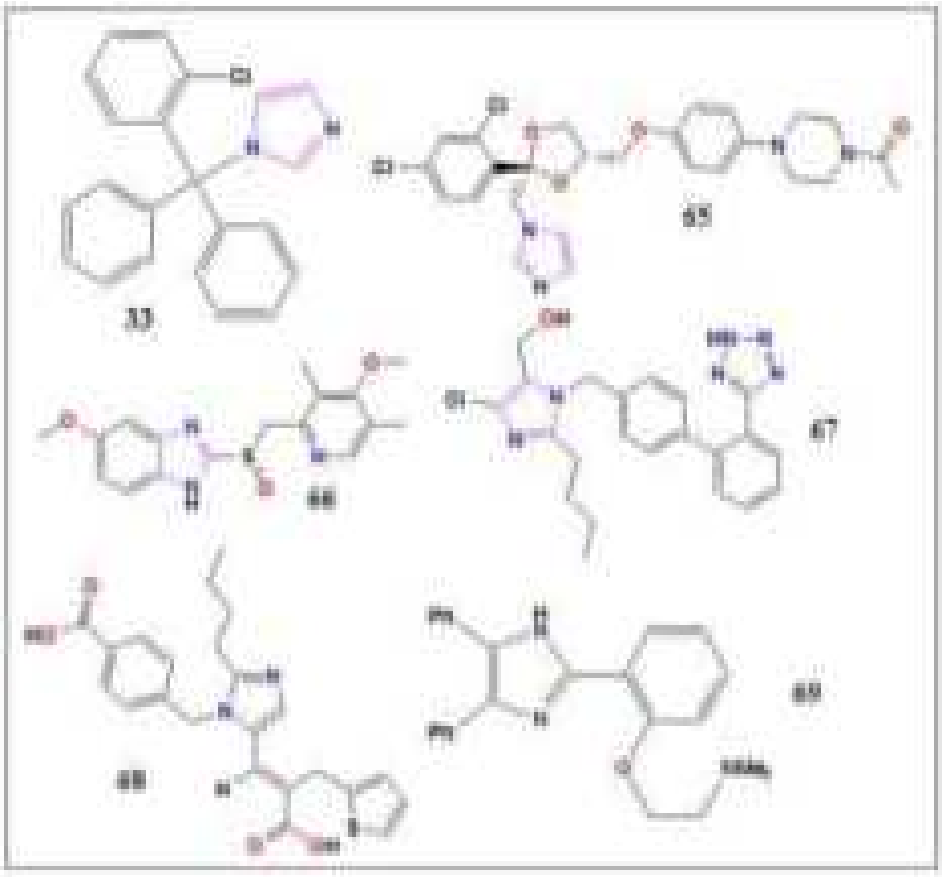


Fig. 1.15. Structures of few drugs containing imidazole scaffold.

It is also found in many naturally occurring biomolecules like histidine[171](27), histamine[172] (70) and biotin[173](71) (Fig. 1.16).

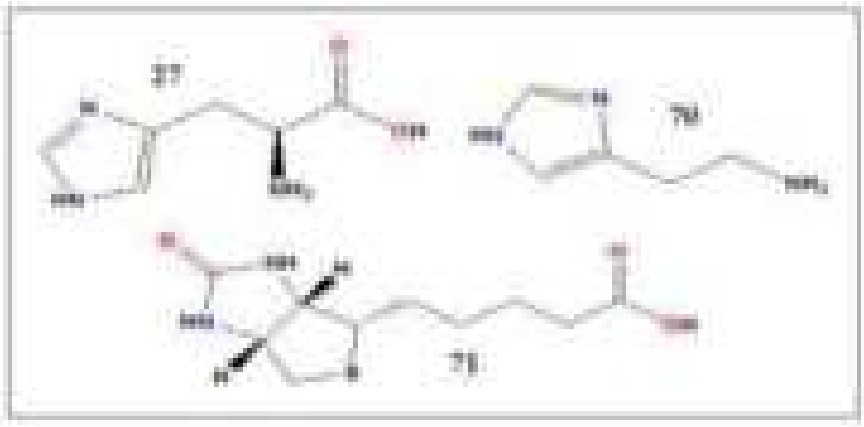


Fig. 1.16. Structures of few naturally occurring biomolecules

Substituted imidazole derivatives fall on the category of important class of N-heterocycles due to their wide range of pharmacological and biological properties and that are a subject of intensive current research[58]. Among several imidazole-based

scaffolds that have been known so far, 2,4,5-trisubstituted imidazoles occupy a special place in the area of natural, pharmaceutical and synthetic organic chemistry owing to their numerous biological and pharmacological properties[174–176]. Some substituted triarylimidazole derivatives have been found to exhibit selective antagonists of glucagon receptor[177](72), inhibitors of Interleukin 1 (IL-1) (73) biosynthesis[178] and P38MAP kinase inhibitor[179](74) (Fig. 1.17). In recent years, much attention has been focused to the substituted imidazole derivatives due to their diversified therapeutic activities such as antibacterial[180], antifungal[181,182], antiviral[183–185], antitubecular[186], antidepressant[187], antitumor[188], herbicide[189] and plant growth regulators[190]. Apart from the biological activities, substituted imidazole derivatives finds extensive applications in various fields such as fluorescence labeling agents[191], biological imaging agents[192], non-linear optics[193], cosmetics[194], polymer chemistry[195], agro chemicals[196], material science (OLEDS, optical electronics, dye sensitized solar cells)[197], photosensitive compounds in photography[198] and corrosion inhibitors[199]. Highly substituted imidazoles such as clemizole (antihistaminic agent)[200](75), nocodazole (antinematodal)[201](76), azathioprine (anti-rheumatoid arthritis)[202](77), dacarbazine (anticancer)[203,204](78) are commercially available drugs for the treatment of different diseases (Fig.1.18).

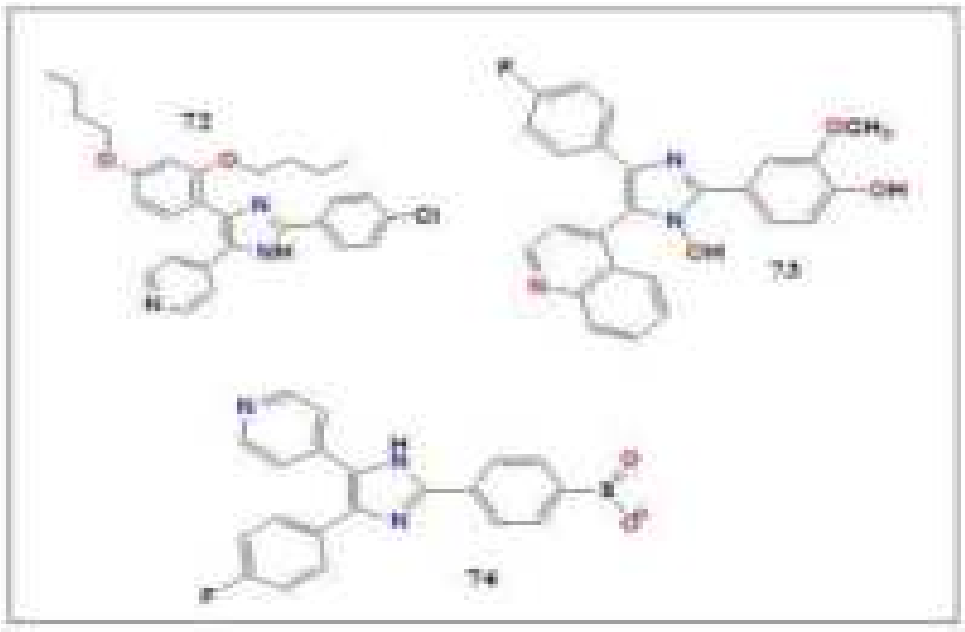


Fig. 1.17. Structures of some biologically important substituted imidazoles.

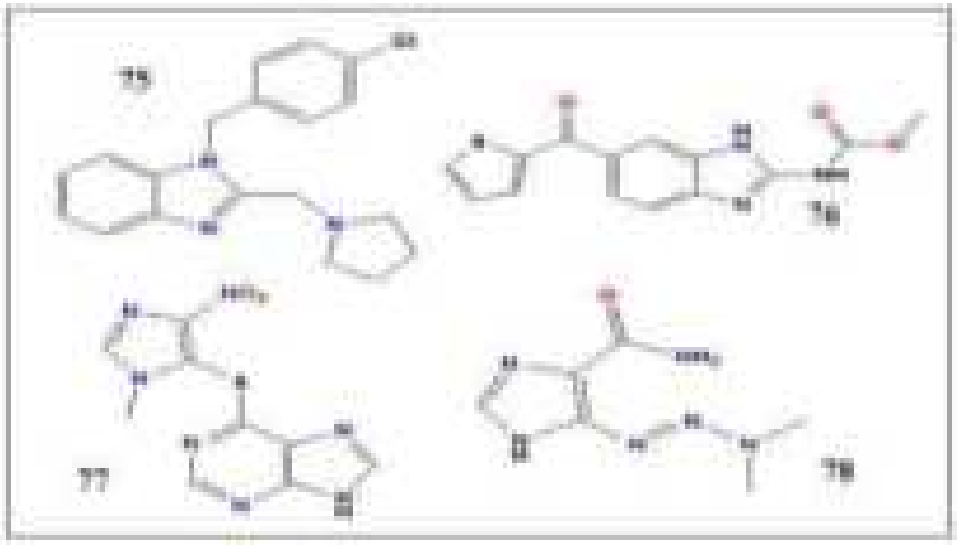


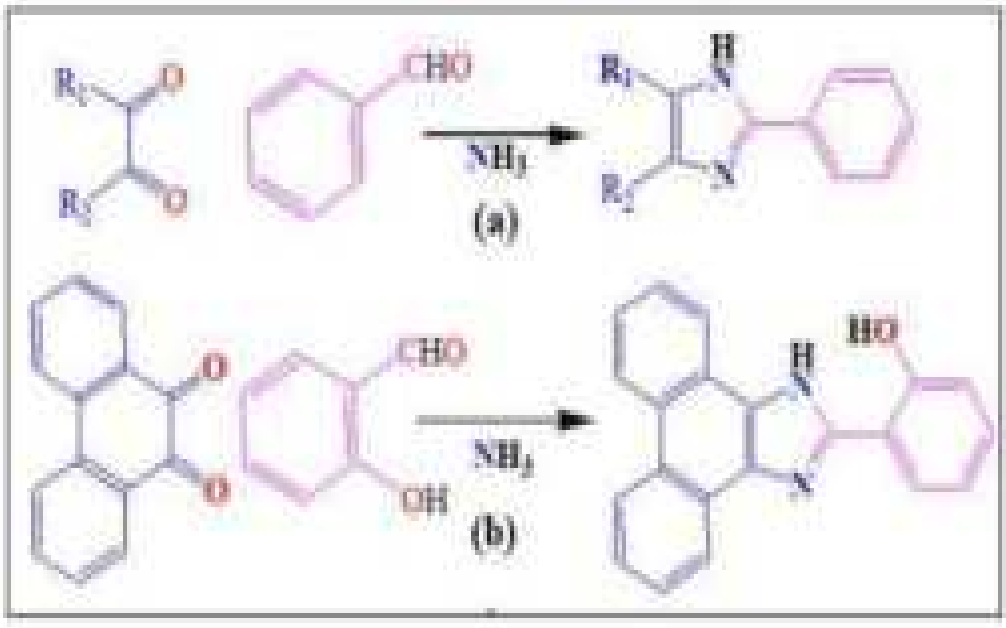
Fig. 1.18. Structures of few drugs having Imidazole Scaffold.

Thus, looking at the importance of the imidazole scaffold in different fields, various synthetic methodologies have been developed during the last few decades and numerous new synthetic methods are developing on daily basis[205].

1.3.1.1 Various synthetic routes for the synthesis of 2, 4, 5-triarylimidazole

1.3.1.2 Classical method

In 1882, Radziszewski and Japp independently reported the first synthesis of 2,4,5-triarlimidazole by cyclo-condensation of 1, 2-dicarbonyl compound with an aldehyde in presence of ammonia as a nitrogen source in acidic medium[125,206] (Scheme 1.19 a-b).



Scheme. 1.19. a) Radziszewski and **b)** Japp imidazole synthesis

After the successful synthesis of triaryl imidazoles by Radiziszewski and Japp, various synthetic modifications have been made in this approach. The most common modification that has been made is the use of ammonium acetate in place of ammonia as a nitrogen source. Till date, even after more than 150 years of discovery, the imidazole scaffold is attracting many researchers due to their potential applications in different fields. Therefore, recent developments in the area of synthesis of 2,4,5-triarylimidazole are discussed herein and a general scheme is shown in Scheme 1.20.

Scheme. 1.20. Modern synthetic route for the synthesis of 2, 4, 5-triarylimidazole derivatives.

Current literature review revealed that numerous synthetic procedures have been documented using various catalysts under the classical conditions.

Li-Min Wang *et.al.* developed an operationally simple method for the synthesis of 2,4,5-triaryimidazole (3) by condensation of 1,2-diketone (1) and aldehyde (2) in presence of Ammonium acetate using Yb $(OTf)_3$ catalyst. The Key feature of this method was the reusability of the catalyst and high yield of the products[207].

Mazaahir Kidwai *et.al.* used molecular iodine as a catalyst for an efficient synthesis of (3) using in ethanol solvent. The key features of this reaction were: i. reaction was easy to carry out, ii. Inexpensive and non-toxic reagents were used, iii. High yield of products[208].

Majid M. Heravi *et.al.* used $NiCl_2.6H_2O$- a lewis acid supported on acidic alumina as a catalyst for the synthesis of (3) in ethanol medium. The reaction proceeded in short time under milder conditions using cheap $NiCl_2.6H_2O$ catalyst[209].

A.F. Mohammed *et.al.* developed a facile method for the synthesis of tri substituted imidazoles under ethanol-water mixture using sulphanilic acid as an organo catalyst[210].

In another development, Jaiprakash Sangshetti *et.al.* used cheaply available Cerric Ammonium Nitrate as an efficient catalyst for the preparation of (3) in ethanol-water solvent[211].

Lakshman. S. Gadekar *et.al.* used solecite as a heterogenous catalyst for the synthesis of (3) via a three-component reaction in ethanol solvent[212].

A. Yasodha *et.al.* reported the synthesis and biological activities of various substituted triphenyl imidazoles in acetic acid medium[213].

Babasaheb. P. Bandgar *et.al.* developed an efficient one pot synthesis of (3) using zinc oxide (ZnO) as a catalyst in acetonitrile at room temperature to form the desired 2,4,5-triaryimidazole in excellent yield[214].

J-T. Li. *et.al*. and Swati D. Burungale *et.al.* independently reported the synthesis of (3) in acetic acid medium[215,216].

Paul.D. Sanasi *et.al.* have used nano copper and cobalt ferrite catalysts for the synthesis of (3) in ethanol solvent[217].

J. Madhavi *et.al.* developed an efficient and environmentally benign method for the synthesis of (3) using ZrO_2 catalyst for the first time in methanol and chloroform medium[218].

Nora Chouha *et.al.* used citric acid as an organo catalyst for a three-component reaction for the synthesis of (3) in refluxing ethanol[219].

Vishvanath. D. Patil *et.al.* reported $PbCl_2$ and Pb $(OAc)_2$ as an efficient catalyst for the synthesis of (3) in ethanol solvent[220-221].

1.3.1.3 Green method

Apart from the above cited conventional classical methods for the synthesis of 2,4,5-triarlimidazole derivatives (3), during the past, numerous methodologies such as solvent free, ultrasound mediated and microwave irradiation under green reaction conditions have been reported.

1.3.1.3.1 Solvent free synthesis

It has been an interesting observation that the reactions carried out in conventional organic solvents has many disadvantages and therefore synthetic chemists are paying more attention to the development of new methodologies based on solvent-free conditions[146]. Current literature review revealed that there are numerous reports on the solvent free synthesis of 2,4,5-triarylimidazole derivatives (Scheme 1.21).

Scheme. 1.21. Synthesis of 2,4,5-triarylimidazole derivatives under solvent free conditions.

Arshia Parveen *et.al.* reported an efficient method for the synthesis of triaryl imidaozles (3) using molecular I_2 as a catalyst under solvent free conditions and the reaction was processed by grinding the contents in a mortar and pestle with excellent yield of products[222].

In another solvent free synthesis of triarylimidazole, Runxia Wang *et.al.* reported Yttrium (III) trifluoroacetate as an excellent catalyst for the synthesis of tri aryl imidaozles (3) under solvent free and neat conditions. It was observed that for aldehydes having electron donating or electron withdrawing groups at ortho and para positions the reaction was gave very good results[223].

Bahador Karami *et.al.* reported Fe_3O_4 nanoparticles as an efficient catalyst for the synthesis of triaryl imidazoles under heating conditions without any solvent[224].

Bibi Fatemeh Mirjalilli *et al.* used trichloromelamine as an efficient catalyst for the synthesis of triaryl imidazoles under solvent free conditions in a short reaction time and with high yield of products[225].

Behrooz Maleki *et.al.* reported the use of sulfuric acid immobilized on silica gel as a catalyst for the synthesis of triaryl imidazoles (3) under solvent free conditions[226].

B.F. Mirjalili *et.al.* used nano $SnCl_4$ for the one pot synthesis of triaryl imidazoles (3) under solvent free conditions[227].

Janardhan Banothu *et.al.* reported a one pot three component synthesis of triaryl imidazoles (3) using an ionic liquid (4-sulfobutyl) tris(4-sulfophenyl) phosphonium hydrogen sulfate(4-SB) T(4-SPh) $PHSO_4$ as a catalyst[228].

Goutam Brahmachari *et.al*. utilized titanium dioxide as an effective and clean catalyst for the synthesis of Triaryl imidazoles (3) under solvent free conditions and the main advantage of this reaction was the easy recyclability of the catalyst and high yield of the products[229].

Adel A. Marzouk *et.al.* reported the use of diethyl hydrogen phosphate as a catalyst for the synthesis of triarylimidazole (3)[230].

P.V. Maske *et.al*. used papain as a catalyst with water as a solvent for the preparation of triaryl imidazoles (3)[231].

K. Nikoofar *et.al.* used ZnO nanorods as catalysts for their efficiency, reusability, and their mild reaction conditions for the synthesis of triaryl imdazoles (3) with water as a solvent[232].

M. Vosoughi *et.al.* used ZSM-5-SO_3H as an efficient catalyst for the synthesis of triaryl imidazoles (3) under solvent free conditions[233].

Ghodsi Mohammadi Ziarani *et.al.* used sulfonic acid functionalized SBA-15 nanoporous material as a solid catalyst for the synthesis of tri aryl imidazoles under solvent free conditions[234].

Mohammad Alikarami *et.al*. used benzyltriphenylphosphonium chloride (BTPPC) as an inexpensive and an efficient catalyst catalyst for the synthesis of tri aryl imidazoles (3) under solvent free conditions[235].

1.3.1.3.2 Microwave irradiation

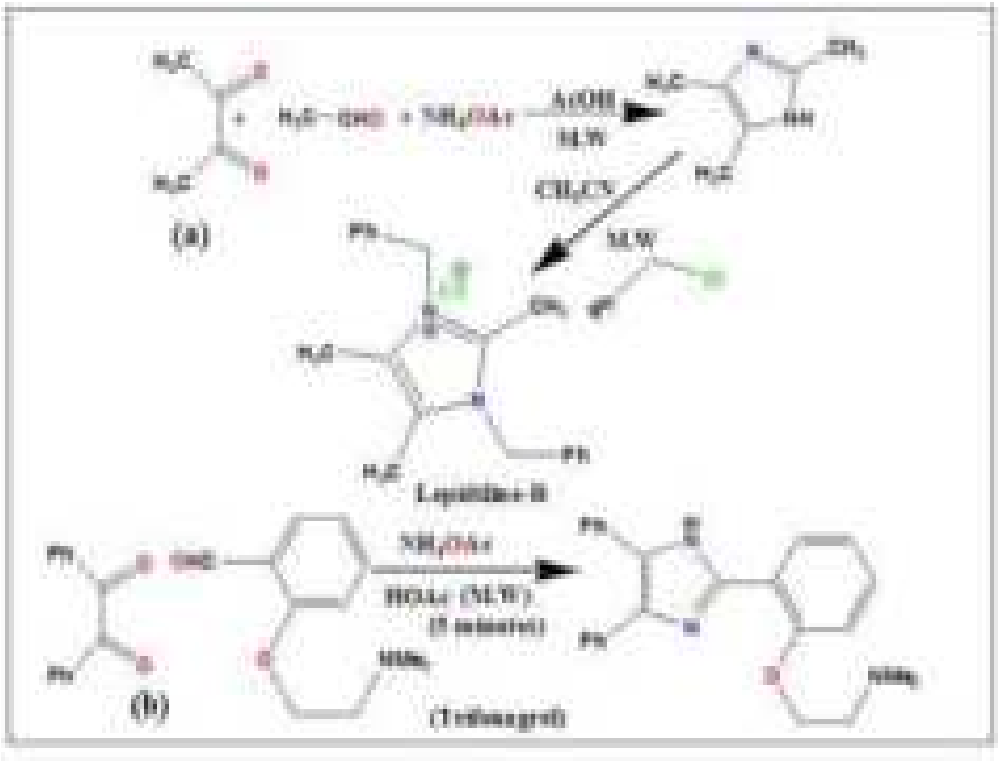
In early 1990's various chemical transformations were achieved by adopting microwave irradiation as a heating source by various laboratories to synthesize the desired products in short reaction time since it was realized that microwave irradiation could be used as an alternate energy source to carry out chemical transformation in minutes instead of hours or even days[236]. In Microwave assisted organic synthesis, the rate of the reaction can be accelerated and the product can be synthesized selectively[237]. Therefore, solvent free microwave assisted organic synthesis provides an added advantage such as short reaction time, rapid heating, high temperature and selective heating for chemical transformation as compared to conventional heating method[238]. Thus, Microwave Assisted Organic Synthesis (MAOS) has become an important tool for the rapid and efficient synthesis of

biologically active heterocyclic scaffolds[239]. Current literature review revealed that numerous synthetic protocols for the synthesis of triaryl imidazoles under microwave irradiation have been reported by various research groups (Scheme 1.22).

Scheme. 1.22. Synthesis of 2,4,5-triaryl imidazoles under microwave irradiation.

Saeed Balalaie *et.al.* used Zeolite HY and silica gel for the synthesis of (3) using (1) and (2) under microwave irradiation and under solvent free condition[240].

In another report Scott E. Wolkenberg *et.al.* utilized microwave technique for the synthesis of triaryl imidazoles from (1) and (2) in presence of ammonium acetate and Acetic acid and they extended this protocol further to synthesize Lepidiline-B and Trifinagrel as shown in (Scheme 1.23a and 1.23b)[241].



Scheme. 1.23. (**a)** Synthesis of Lepidiline, **(b)** Synthesis of Trifenagrel

K. Shelke *et.al.* reported a microwave induced one pot synthesis of triaryl imidazoles (3) with glyoxylic acid as a catalyst. The reaction was done in solvent free condition. The main advantages of this reaction were faster reaction time, cheaper and available catalyst and higher yield of the products[242].

In another development for the Microwave induced synthesis of triarylimidazole derivatives (3), Santosh V. Nalage *et.al.* reported polyethylene glycol as an efficient catalyst and claimed to be a cleaner approach towards imidazole synthesis[243].

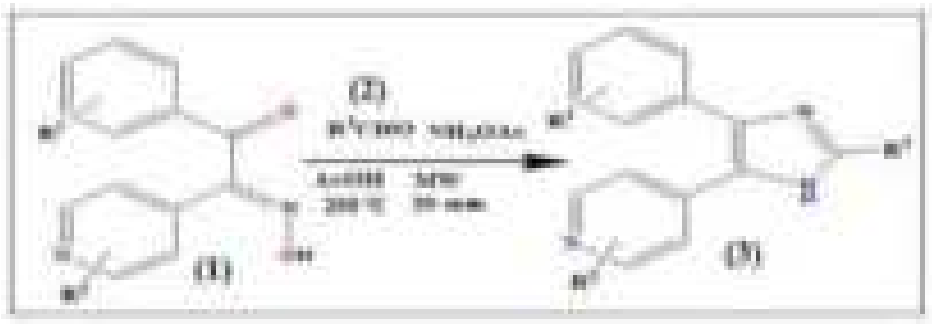
In a similar instance, Javad Safari *et.al.* utilized $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ as an efficient catalyst for the synthesis of triaryl imidazoles (3) by a one component, three pot condensation reaction under solvent free conditions and microwave irradiation[244].

Kiran F. Shelke *et.al.* reported cellulose sulfuric acid as a solid-state catalyst under microwave irradiation for the synthesis of triaryl imidazoles (3) under solvent free conditions and the key feature of this reaction was easy preparation of the catalyst, recyclability of the catalyst and high yield of the products[245].

Edouard Chauveau *et.al.,* reported a highly efficient catalyst free method for the synthesis of triaryl imidazoles (3) in water under microwave irradiation[246].

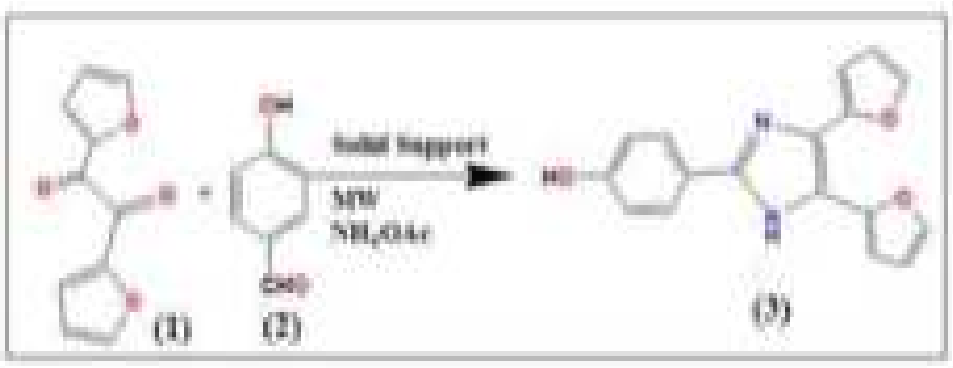
Zinat Gordi *et.al.,* utilized Zeolite as an efficient catalyst under Microwave irradiation for the synthesis of triaryl imidazoles in solvent free condition[247].

Alternatively, Andrew P. Combs *et.al.* reported an efficient procedure for the synthesis of 2,4,5-Triaryl-imidazoles (3) directly from the keto-oxime (1) and an aldehyde (2) in moderate to good yields via cyclization to the N-hydroxyimidazole and they have reported an unprecedented in situ thermal reduction of the N−O bond upon microwave irradiation at 200 °C for 20 min (Scheme 1.24)[248].



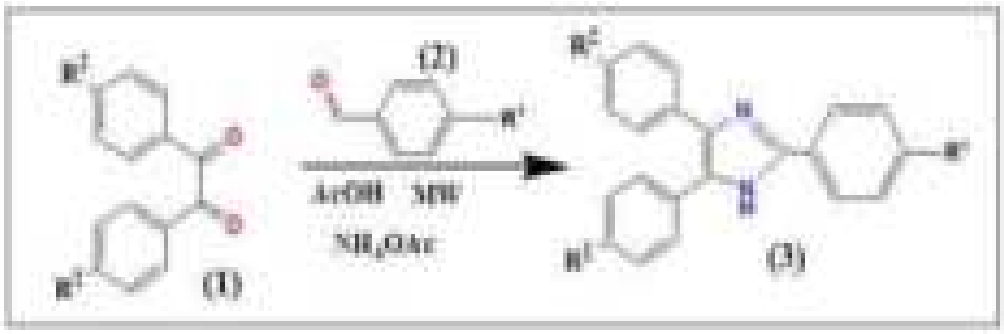
Scheme. 1.24: Synthesis of substituted tri-aryl imidazole from keto-oxime

Similarly, S.C. Hu, reported a solvent-free microwave-assisted method for the synthesis of 2-substituted-4,5-di(2-furyl)-1H-imidazole (3) in moderate to good yield by condensation of furil (2) with aldehydes over acidic alumina impregnated with ammonium acetate[249] (Scheme 1.25).



Scheme. 1.25. Microwave assisted synthesis of 2-substituted-4,5-di(2-furyl)-1H-imidazole.

In another study, Zhou *et.al*. have reported the synthesis of 2,4,5-triarylimidazoles (3) by the cyclocondensation of substituted benzil (1) with the differently substituted aromatic aldehydes (2) and NH_4OAc under catalyst-free, solvent-free and microwave irradiation conditions[250](Scheme 1.26).



Scheme. 1.26. Microwave assisted, solvent and catalyst free synthesis of tri-aryl imidazoles.

K. M. E. Shaieb alternatively synthesized tri-substitutedimidazole derivatives (3) containing carboxamido and cyano groups at position 4 and 5 respectively by condensing diaminomaleonitrile (1) with acid chloride (2) in the presence of catalytic amount of NEt_3 under microwave conditions[251] (Scheme 1.27).

Scheme. 1.27. Synthesis of tri-substituted imidazoles containing carboxamido and cyano groups.

1.3.1.3.3 Ultrasonic method

During the past few decades, many chemical transformations have been performed with the aid of ultrasonic irradiation. The ultrasonic irradiation has been used to accelerate various catalytic reaction including both homogenous and heterogeneous reaction systems. The use of ultrasonic irradiation to accelerate chemical reactions has been termed as sonochemistry[252]. In 1917, Langevin made the first commercial application of ultrasonics and Richards and Loomis first utilized the effect of ultrasonic energy in chemical reaction in 1927[252]. There are numerous reports on the synthesis of triarylimidazole using ultrasonic irradiation as an energy source and we are discussing some of the reported procedure of synthesis of triarylimidazoles (3) under ultrasonic irradiation (Scheme 1.28).

Scheme1.28. Synthesis of 2,4,5-triaryl imidazoles under Ultrasound irradiation

Kiran F. Shelke *et.al.* synthesized triaryl imidazole (3) under Ultrasonic irradiation using boric acid as a catalyst in aqueous media[253].

In another report, Kiran F. Shelke *et.al.* reported the Ultrasound assisted synthesis of triaryl imidazoles (3) in aqueous media using Cerric Ammonium Nitrate as a catalyst and the key feature of this reaction was the non-toxic nature of Cerric Ammonium Nitrate[254].

Similarly, Hongjun Zang *et.al.* synthesized the triaryl imidazole derivatives (3) using an efficient ionic liquid caytalyst 1-ethyl-3-methylimidazole acetate ([EMIM]OAc under Ultrasonic irradiation[255].

Deepak Nagargoje *et.al.* used diethyl bromophosphate as an oxidant for the one pot synthesis of triaryl imidazoles (3) in acetonitrile as a solvent and ultrasound irradiation[256].

J. Safari *et.al*. utilized sulfamic acid functionalized Fe_3O_4 nano particles as an effective catalyst for the synthesis of triaryl imidazoles (3) under Ultrasound radiation in ethanol medium[257].

Paul D. Sanasi *et.al.* reported an ultrasound assisted one-pot synthesis of triaryl imidazoles (3) using spinel nano copper ferrite as a heterogeneous catalyst in ethanol medium[258].

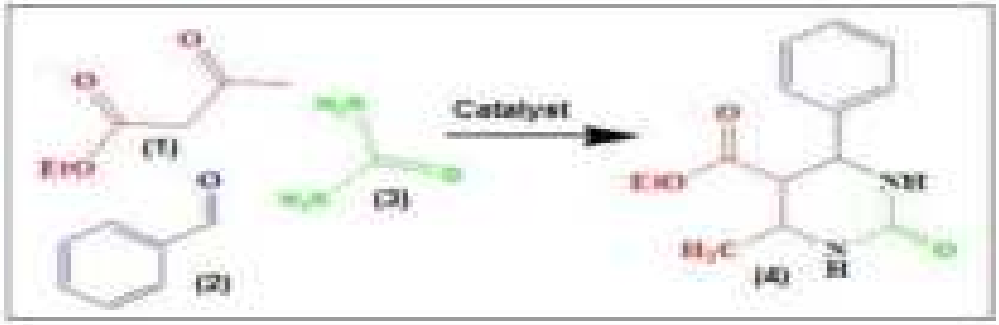
In another report, Mohsen Esmaelipour *et.al.* utilized a green protocol for the synthesis of triarylimidazole (3) under Ultrasound irradiation by using Dendrimer-PWA^n nanoparticles as a catalyst under solvent free conditions[259].

Esmaiel Eidi *et.al.* developed a one pot sonochemical reaction for the synthesis of triaryl imidazoles (3) using $CoFe_2O_4$ nanoparticles as an efficient catalyst in ethanol medium[260].

Balaji S. Londhe *et.al.* devised a green reaction for the synthesis of triarylimidazoles (3) under Ultrasound radiation in methanol using Baker's yeast as a catalyst[261].

1.3.2 Various synthetic routes for the preparation of 3,4-dihydropyrimidine-2-(1H)-ones

The Bigenelli reaction is a one pot three-component reaction in which 3,4-dihydropyrimidin-2(1*H*)-ones (4) are produced by the cyclocondensation of β-dicarbonyl compounds (1), aryl aldehyde (2), Urea (3) and and this reaction was coined by Pietro Bigenelli in 1891[129] (Scheme 1.29).



Scheme. 1.29. Synthesis of 3,4-dihydropyrimidine-2-(1H)-ones

The Bigenelli compounds, 3,4-dihydropyrimidin-2(1*H*)-ones (79) are somewhat similar to dihydropyridines also known as Hantzsch pyridines as the preparation of these compounds also require the same reactants as required for

preparation of Bigenelli compounds. The reaction can also be carried out by replacing urea by thio-urea to yield 3,4-dihydropyrimidine-2-(1H)-thiones (80) (Fig. 1.19)

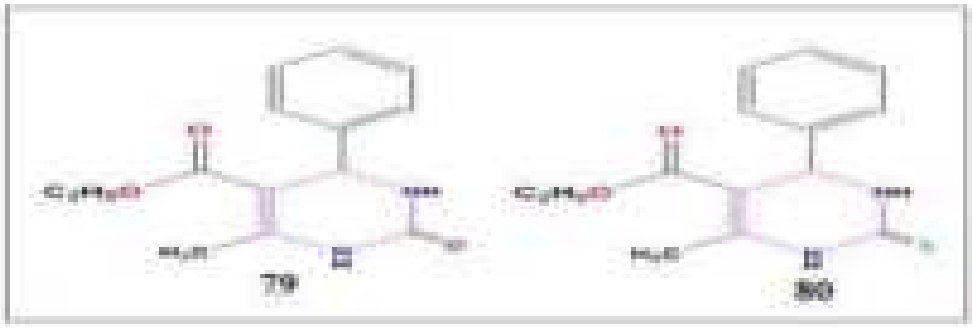


Fig. 1.19. Structures of 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidine-2-(1H)-thiones

In recent years, Dihydropyrimidinones (DHPMs) have attracted a lot of interest of chemists owing to their biological and therapeutic uses[262]. This compound serves as one among the five classes of Calcium Channel blocking drugs[263]. They also have anti-viral[264], anti-inflammatory[265], anti-bacterial[266], α-1a-adrenergic antagonist[267], anti-cancer[268] and anti-hypersensitive properties[269]. In fact, Monastrol was the first Bigenelli compound that exhibited anti-cancer activity[270]. Due to the diverse biological activities of the Bigenelli products, the Bigenelli reactions have been considered as one of the most important Multi-component Reactions (MCRs)[271]. Some representative Bigenelli Compounds having Calcium Channel Blocking (81 a, b), Anti-tumor (82 a, b) and Anti-inflammatory (83 a, b) properties are depicted in Fig. 1.20.

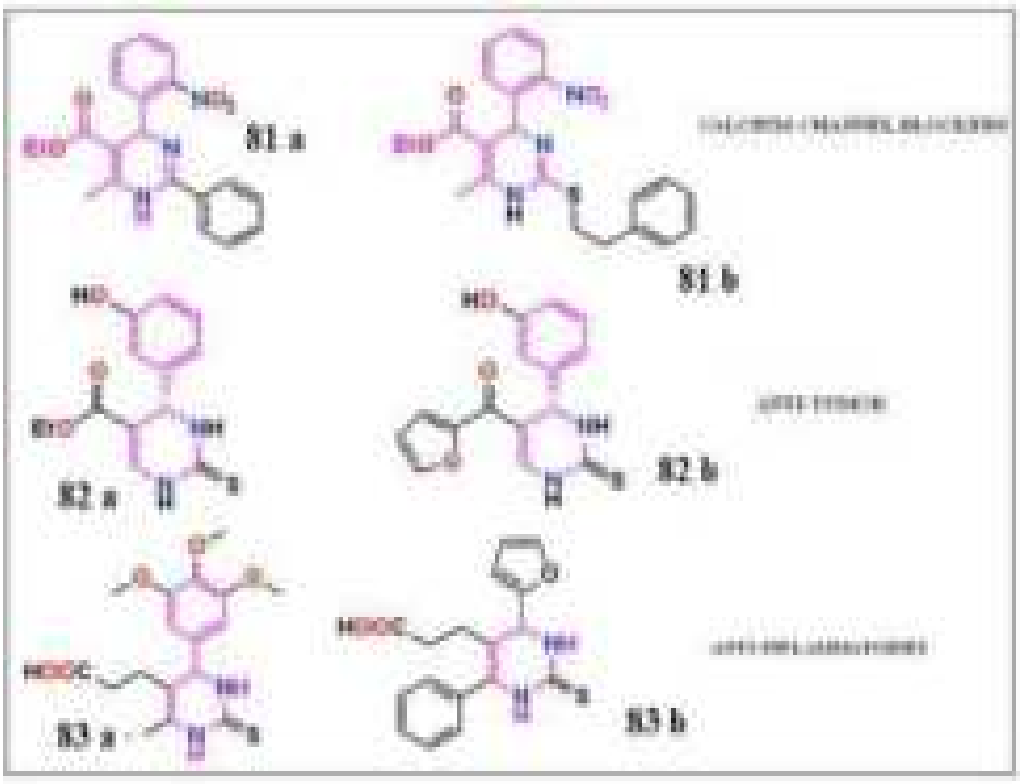
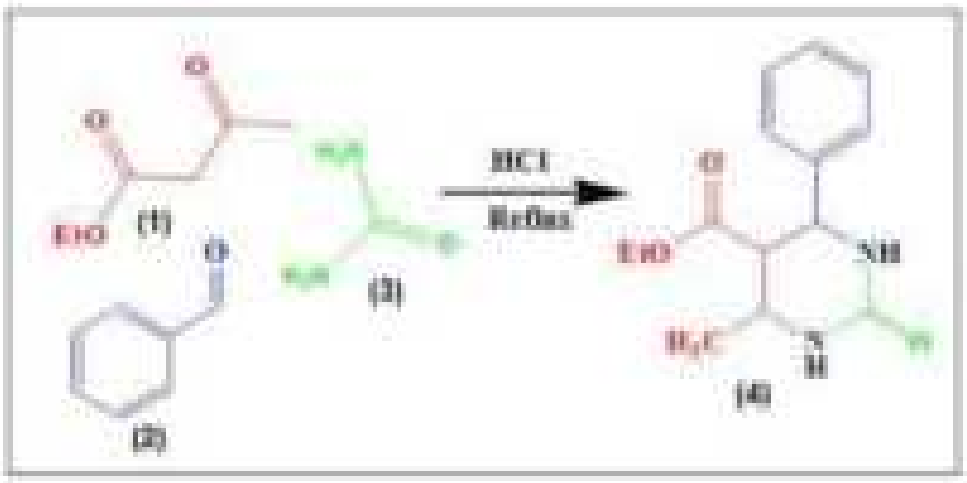


Fig. 1.20. Some biologically important Bigenelli Compounds

During the last few decades, Dihydropyrimidinones (DHPMs or Bigenelli compounds) have gained a lot of interest to organic as well as medicinal chemist as this class of compounds exhibit wide verities of interesting therapeutic and pharmacological activities[272]. Thus, looking at the importance of the dihydropyrimidones scaffold in different fields, various synthetic procedures have been developed during the last few decades and numerous new synthetic methods are developing on daily basis for the synthesis of simple dihydropyrimidones to multi-functionalized dihydropyrimidones[273].

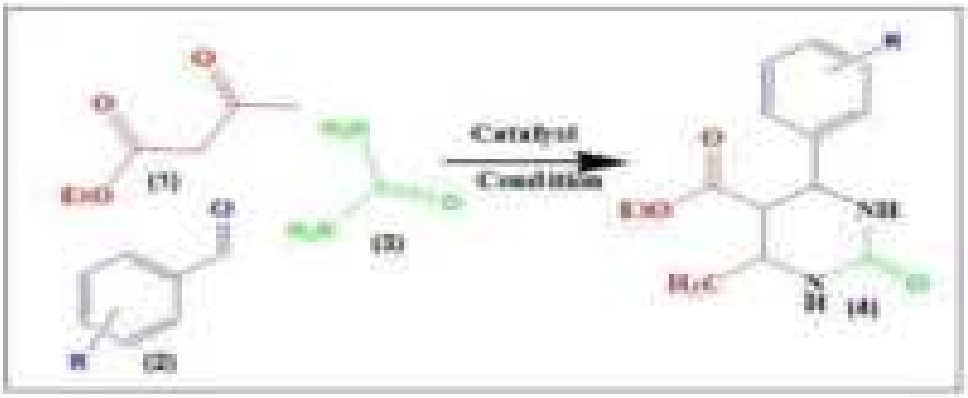
1.3.2.1 Classical method

It was the Italian chemist Pietro Bigenelli for the first time who synthesized 3, 4-dihydropyrimidin-2(1*H*)-one (4) by an acid catalysed condensation of ethyl acetoacetate (1), benzaldehyde (2) and urea (3) in ethanol solvent[129] (Scheme 1.29).



Scheme 1.29. Classical method for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one

The conventional Bigenelli reaction suffers from a lot of drawbacks but the most important and worth mentioning drawback is the low yield of the products. Hence various modifications were employed to overcome the drawbacks of the conventional procedure[274] (Scheme 1.31).



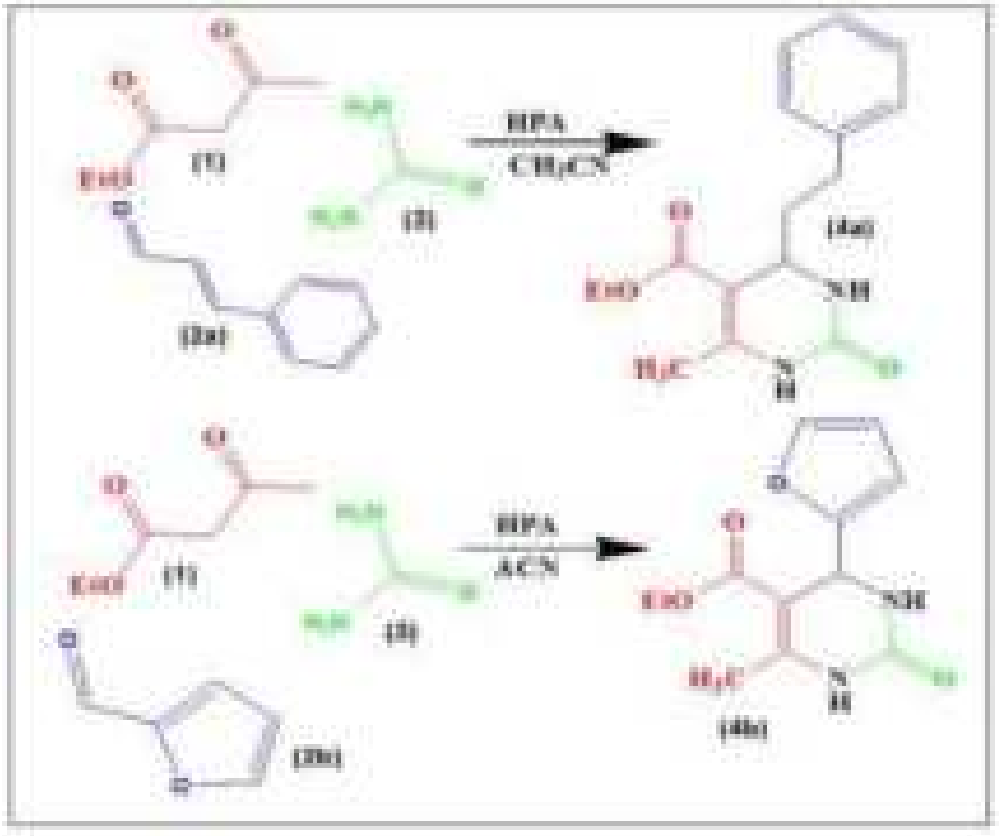
Scheme. 1.31. Synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one

B. C. Ranu *et.al*. used Indium (III)chloride as a lewis catalyst for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-one (4) using β- dicarbonyl compounds (1), aryl aldehyde (2), urea (3) in THF solvent[275].

R. S. Bhosale *et.al.* reported a simple procedure for the synthesis of (4) using iodine as a catalyst in toluene [276].

In another development, E. Rafiee *et. al*. reported a multi component synthesis of (4) using Keggin-type hetero poly acids (HPA) such as $H_3PW_{12}O_{40}$ (PW), $H_3PMo_{12}O_{40}$ (PMo) and $H_4SiW_{12}O_{40}$ (SiW) as catalysts in acetonitrile solvent and they reported that even acid sensitive aldehydes like cinnamaldehyde

(2a) and furfural (2b) gave excellent yield of the products (4a and 4b) respectively[277] (Scheme 1.32).



Scheme. 1.32. Synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one from Cinnamaldehyde and Furfural.

R. Gupta *et.al.* used covalently anchored sulfonic acid onto silica as an efficient catalyst for the synthesis of (4) in acetonitrile solvent[278].

Similarly, Suresh *et.al*. reported Lactic acid as an organo catalyst for the synthesis of (4) in Ethanol solvent medium[279].

Hossein Eshghi *et.al.* used Preyssler heteropolyacid supported on silica coated $NiFe_2O_4$ nanoparticles (NFS-PRS) as a catalyst for the synthesis of (4) in ethanol medium[280].

Zakaria Benzekri *et.al.* reported a method for the synthesis of (4) employing dicalcium phosphate dihydrate (DCPD) as an efficient and reusable catalyst in ethanol medium[281].

Shanmugam Prakash *et.al.* used CuO nano particles as a catalyst for the synthesis of (4) in ethanol Solvent[282].

S. Kaul *et.al.* used Montmorillonite-KSF as an efficient catalyst for one-pot green synthesis using dihydropyrimidinones (4) and they evaluate their cytotoxic activity[283].

Chen-Jiang Liu *et.al*. used Copper (II) Sulfamate as an efficient catalyst for the synthesis of (4) in acetic acid solvent[284].

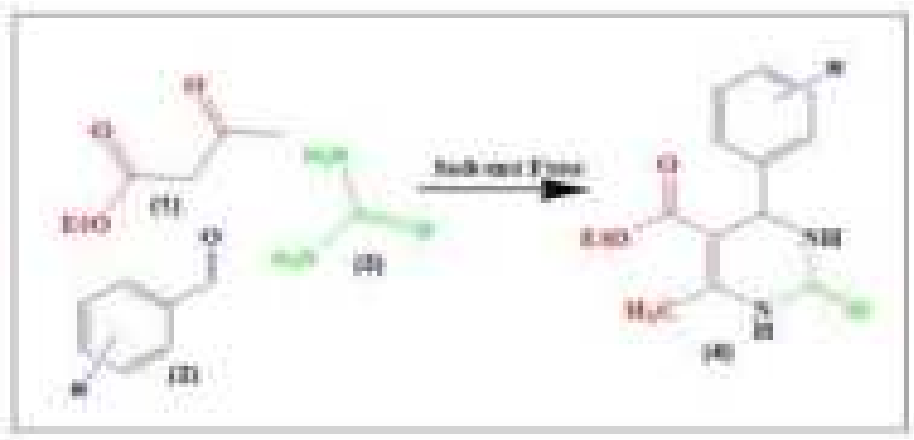
S. K. Prajapati *et.al.* reported tris(pentafluorophenyl)borane as an efficient catalyst for the synthesis of (4) in ethanol medium[285].

1.3.2.2 Green method

Among the various Multi-Component Reactions, Bigenelli reaction being a three-component reaction is usually employed for the direct synthesis of 3, 4-dihydropyrimidinone derivatives and finds a significant importance in organic synthesis[286]. The 3, 4-dihydropyrimidinone and its derivatives generally show diverse pharmacological and biological properties[287]. The current literature review revealed that there are numerous reports on the synthesis of Bigenelli products by classical methods but these documented procedures suffer from many drawbacks such as use of toxic reagent, low yield of the product, environmental hazards, cost, use of expensive catalyst, use of acid, high reaction temperature etc[288–290]. Thus, the development of highly efficient methods for the synthesis of these valuable products in economical and eco-friendly way is highly demanding and presents a great challenge for the scientific community[291–293]. During the past few decades, several improvements were made towards the synthesis of Bigenelli products such as good reaction conditions, use of catalysts/reagents, transition metal–based reagents, ionic liquids, polymer-immobilized reagents etc, but above all, the green chemical approach such as solvent free synthesis[293], microwave assisted[294], and ultrasound irradiation[295] are the best suited methods for the green synthesis of Bigenelli products. Many new improvements have been recently reported for the synthesis of the Bigenelli compounds.

1.3.2.2.1 Solvent free synthesis

Owing to important pharmacological and medicinal properties exhibited by Bigenelli products, there has been a growing interest in the improvement of the synthesis of DHPMs by Bigenelli reaction[296]. In recent years, solvent free synthesis is gaining a lot of interest by virtue of the fact that it is operationally simple, efficient, green, and cost-effective[297]. There are lots of works on the solvent free synthesis of 3, 4-dihydropyrimidinone (4) and its derivatives that has been documented during the past few years[298] (Scheme 1.33).



Scheme. 1.33. Solvent free synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one derivatives

Hadi Adibi *et.al.* employed Iron (III) trifluoroacetate [Fe $(CF_3CO_2)_3$] and trifluoromethanesulfonate [Fe $(CF_3SO_3)_3$] as an efficient catalyst for the synthesis of (4) under solvent free condition[299].

In another development, B. C. Ranu *et.al.* reported a catalyst free synthesis of (4) in solvent free condition[300].

Fang Dong *et.al.* reported a one pot synthesis of (4) using SO_3H-functional Brønsted-acidic halogen-free task-specific room-temperature ionic liquids (TSILs) under solvent free conditions[301].

S. L. Jain *et.al.* reported a catalyst free and polyethylene glycol assisted synthesis of (4) under green condition[302].

Sanny Verma *et.al*. employed PEG-embedded thiourea dioxide (PEG.TUD) as an efficient catalyst for the synthesis of (4) under solvent free condition[303].

Suresh Patil *et.al*. developed a clean and green procedure for the synthesis of (4) by using lemon juice at room temperature under solvent free condition[304].

In another work, Suresh Patil *et. al.* reported the synthesized (4) utilizing pineapple juice at room temperature under solvent free condition[305].

Jaggi Lal *et.al*. reported a green method for the synthesis of (4) using Mg–Al–CO_3 hydrotalcite as a reusable catalyst under solvent free conditions[306].

Najmadin Azizi *et.al*. used a simple deep eutectic solvent based on tin (II) chloride (tin (II) chloride-choline chloride) as a catalyst as well as a solvent for the synthesis of (4)[307].

H. Sachdeva *et al.* used lithium-acetate and phosphoric acid as a catalyst for the synthesis of (4) under solvent free conditions[308].

A. Borse *et.al*. synthesized (4) using a mixture of phosphorus pentoxide(P_2O_5) and methane sulfonic Acid ($MeSO_3H$) as a catalyst under solvent free conditions[309].

M. Dewan *et.al.* used copper nanoparticles (Cu-NPS) as an efficient catalyst for the synthesis of (4) under solvent free condition[310].

Z. Karimi-Jaberi used trichloroacetic acid as a catalyst for the synthesis of (4) under solvent free conditions[311].

B. B. Fatemeh Mirjalili *et al.* used nano-$TiCl_4.SiO_2$ as an efficient catalyst for the synthesis of (4) in solvent free conditions[312].

Y. Zhang *et. al.* reported the use of brønsted acidic ionic liquid [Btto][*p*-TSA] as an efficient catalyst for the synthesis of (4) under solvent free conditions[313].

Vijay V. Dabholkar *et.al.* reported an efficient and green synthesis of (4) using calcined Mg/Fe hydrotalcite catalyst under solvent free conditions[314].

Mahbube Taei *et. al.* reported an efficient procedure for the synthesis of (4) using aluminate sulfonic acid nano particles (ASA-NPS) under solvent free conditions[315].

Fe^{+3} montmorillonite-K10 was used a catalyst for the synthesis of (4) by Leila Zare Fekri *et.al.* under solvent free conditions and they adopted a grinding method for the synthesis of 3, 4-dihydropyrimidinone derivatives[316].

H. Yuan *et.al.* used gallium (III) chloride as an efficient and reusable catalyst for the synthesis of (4) under solvent free conditions[317].

T. S. Choudhare *et.al.* used dioxane-HCl complex as a catalyst for the synthesis of (7) under solvent free conditions[318].

1.3.2.2.2 Microwave irradiation

Microwave assisted synthesis of 3, 4-dihydropyrimidinone are gaining lot of interest these days since microwave energy is an unconventional energy source and they have uniform heating rate for all the reactant molecules[319]. A vast number of literatures are available for the synthesis of 3, 4-dihydropyrimidinone derivatives utilizing microwave irradiation techniques.

Misra *et.al.* employed calcium chloride ($CaCl_2$) as an inexpensive catalyst for the synthesis of 3, 4-dihydropyrimidinone derivatives (4) under microwave irradiation and solvent free condition[320].

Polystyrenesulfonic acid (PSSA) has been used as a catalyst for the synthesis of (4) by R. S. Varma *et. al.* under microwave irradiation[321].

H. R. Shaterian *et.al.* employed alumina sulfuric acid (Al_2O_3-SO_3H) as an efficient and recyclable catalyst for the microwave assisted synthesis of (4) under solvent free conditions[322].

In another work, H. W. Zhan *et.al.* documented a procedure for the synthesis of (4) under microwave irradiation without any solvent and catalyst[323].

D. Kumar *et.al.* employed aluminium chloride ($AlCl_3.H_2O$) as a green and efficient catalyst for the synthesis of (3) under microwave irradiation in solvent free conditions[324].

K. K. Pasunooti *et.al.* utilized an inexpensive and efficient Cu $(OTf)_2$ salt as a novel catalyst for the synthesis of (4) under microwave assisted synthesis in ethanolic medium[325].

A. Kuraitheerthakumaran *et.al*. reported an efficient method for the synthesis of (4) using lanthanum oxide (La_2O_3) as a catalyst under solvent free conditions[326].

R.K. Sharma and co-workers used silica immobilized nickel complex as an efficient, inexpensive and highly recyclable catalyst for the synthesis of (4) under solvent free and microwave irradiation[327]**.**

Interestingly, V. Srivastava reported an efficient and green synthetic method for the preparation of (4) using ionic liquid [Hmim][Tfa] as a catalyst under microwave irradiation[328].

Similarly, M. Shingare reported the synthesis of (4) using ionic liquid N-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulphate [TEBSA][HSO_4] as an efficient catalyst for under microwave condition[329].

S. K. Padan *et. al.* reported the use of fruit juice (Apple, Pomegranate and grape) as a catalyst for the synthesis of (4) under microwave irradiation[330].

Moradi *et. al.* reported Fe_3O_4@meglumine sulfonic acid (Fe_3O_4@MSA) as an efficient and green catalyst for the synthesis of (4) under microwave irradiation[331].

1.3.2.2.3 Ultrasonic irradiation

Nowadays, chemical reactions are accelerated using ultrasound irradiation and form an interesting strategy in organic synthesis[332]. Ultrasonication not only speeds up the chemical reactions but also decreases the number of steps for chemical reaction and the cruder reagents can be used and reactions can be initiated without any additives. The phenomenon of acoustic cavitations of ultrasound is responsible for chemical effects and the primary chemical reactions result from a transient state of higher temperatures and pressures[333]. Current literature review revealed that numerous ultrasound-mediated Bigenelli synthesis of 3,4-dihydropyrimidinones has been reported in the presence various catalyst under green reaction condition (Schemes 1.34).

Scheme. 1.34. Ultrasound assisted synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one derivatives

Zhidovinova *et. al.* reported that the classical Bigenelli reaction for the synthesis of 3,4-dihydropyrimidinone (thione) (4) derivatives when carried out in

(EtOH and HCl) under microwave irradiation is accelerated by a factor of more than 40 times[334].

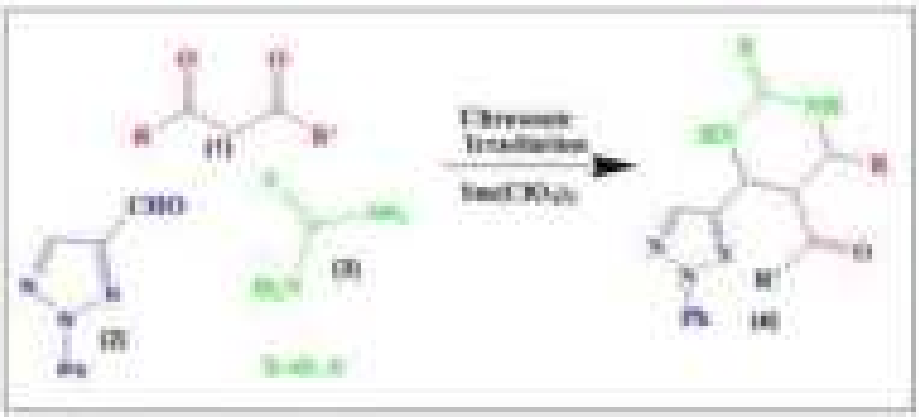
In another development, Li *et. al.* reported the synthesis of 3, 4-dihydropyrimidinones (4) under ultrasonic condition using aminosulfonic acid as a catalyst[335].

In another report, Yadav *et al*. employed ceric ammonium nitrate (CAN) as a catalyst in ultrasound promoted Bigenelli reaction in methanolic medium[336] (Scheme 1.35). They varied the substrate scope such as Heteroaryl, aromatic (electron-poor or electron-rich), aliphatic, and α, β-unsaturated aldehydes and, in all cases, they obtained the desired 3, 4-dihydropyrimidinones (4) compounds in good yields and with high purity.

Scheme. 1.35. Ultrasound assisted synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one derivatives using CAN catalyst.

Similarly, C. W. Nogueira, reported the synthesis of 3, 4-dihydropyrimidinone (4) derivatives under ultrasonic irradiation using inexpensive ammonium chloride as a catalyst in methanol solvent[337].

Wang *et. al.* reported an efficient synthesis of novel 4-(2-phenyl-1,2,3-triazol-4-yl)-3,4-dihydropyrimidin-2(1H) -(thio) ones (4) from 1,3-dicarbonyl compounds (1) 2-phenyl-1,2,3- triazole-4-carbaldehyde (2), and urea (3) or thiourea (3) under US irradiation using Samarium perchlorate as an efficient catalyst and the main advantages of this methodology are milder reaction conditions, shorter reaction times, and excellent yield[338] (Scheme 1.36).



Scheme. 1.36. Synthesis of novel 4-(2-phenyl-1,2,3-triazol-4-yl)-3,4-dihydropyrimidin-2(1H)-(thio)ones

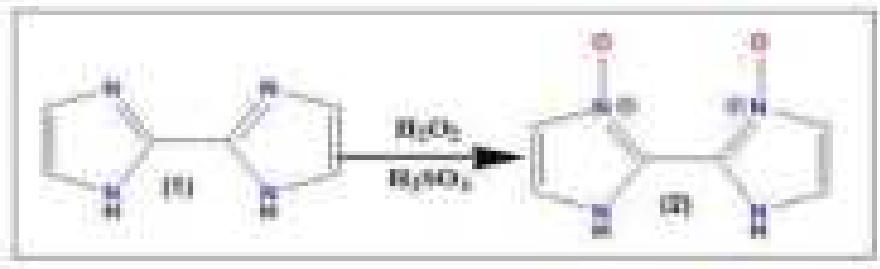
L. Zhi-Ping *et al.* reported iodine catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Under Ultrasound Irradiation[339].

M. A. Pasha *et al*. reported silica iodide as an efficient catalyst for the one pot three component synthesis of 3,4-dihydropyrimidine-2-(1H) ones/thiones under ultrasound irradiation[340].

1.3.3 Various synthetic routes for the preparation of Imidazole N-oxide

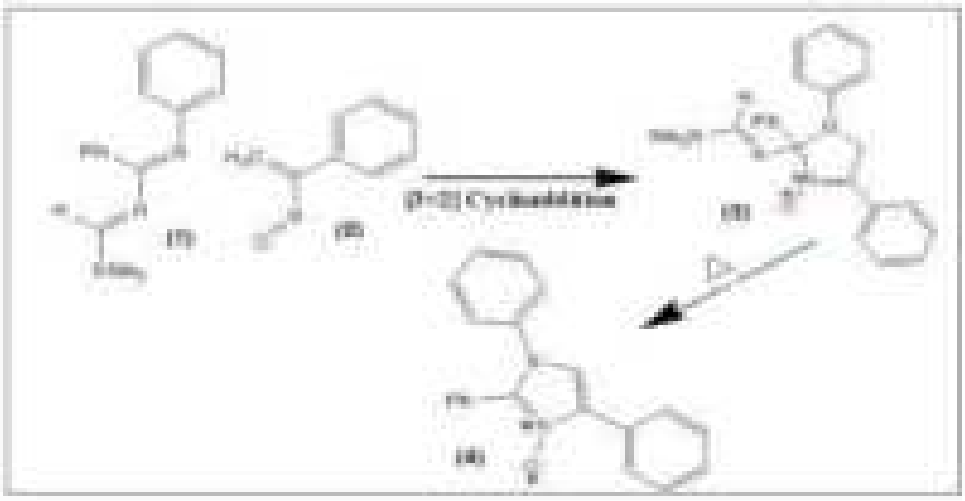
Imidazole derivatives play a crucial role in different biological processes and they exhibit wide range of biological activities[341]. Among many known imidazole derivatives, Imidazole N-oxide are interesting compounds and they are the key building blocks in advance heterocyclic chemistry[342], natural product synthesis[343], co-ordination chemistry[344] and catalysis[345]. Thus, among many heterocyclic N-oxide compounds, imidazole N-oxides constitute a practically valuable class of five-membered aromatic N-heterocycles[346]. Because of the diverse application of the imidazole N-oxide, various synthetic methods have been reported during the past few decades.

R. Kuhn *et. al*. in 1958 prepared imidazole-N-oxide (2) by using 2,2'-diimidazolyl (1) with dilute hydrogen peroxide in acidic medium[347] (Scheme 1.37).



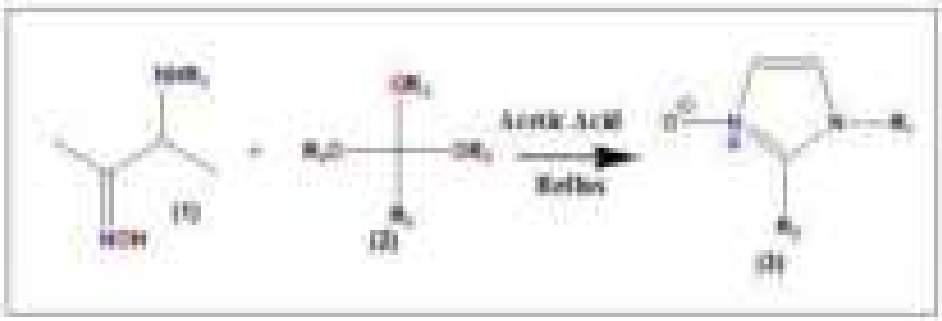
Scheme. 1.37. Synthesis of Imidazole-N-oxide by using 2,2'-diimidazolyl

Arun.K. Sharma *et. al.* reported (3+2) Cycloaddition 1-aryl-4-dimethylamino-1,3-diaza-1, 3-butadienes (1) with α-nitrososty renes (2) to give corresponding nitrone (3) derivatives which on subsequent heating resulted in corresponding N-oxide derivative (4)[348] (Scheme 1.38).



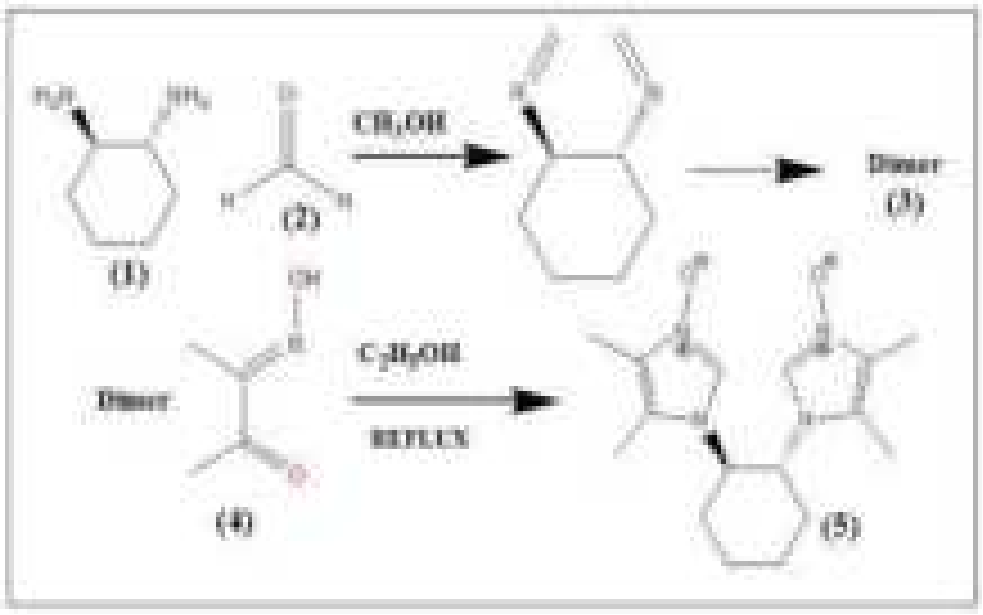
Scheme. 1.38. Synthesis of Imidazole-N-oxide from 1-aryl-4-dimethylamino-1,3-diaza-1, 3-butadienes

Hugo Cercetto *et.al.* successfully synthesized imidazole-N-oxides (3) by cyclocondensation of α-amino oximes (1) with triethyl orthoformate (2) in refluxing acetic acid medium[349] (Scheme1.39).



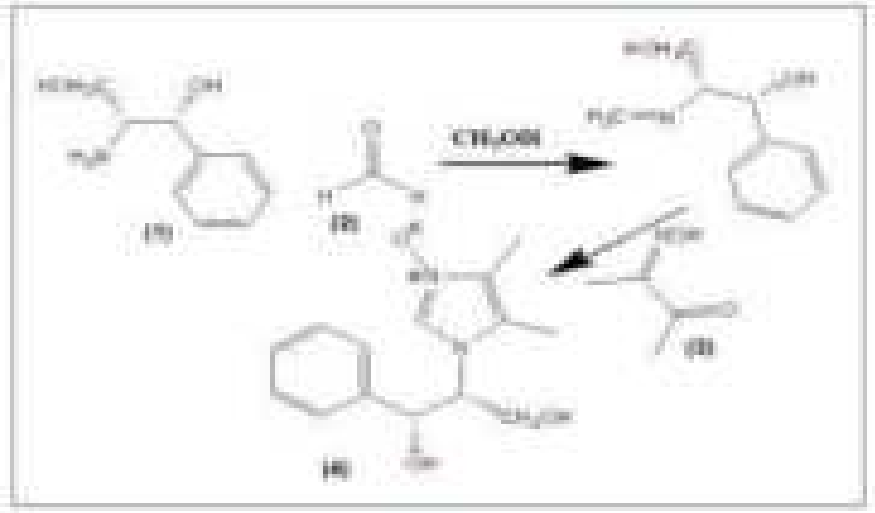
Scheme. 1.39. Synthesis of imidazole-N-oxides from α-amino oximes and triethyl orthoformate

Paulina Mucha *et.al.* synthesized enentiomerically pure imidazole-N-Oxide (5) from trans-1,2-diaminocyclohexane (1) by using diacetyl monoxime (4) under reflux conditions[350] (Scheme 1.40). They first prepared the dimer of imine of the diaminocyclohexane (1) and formaldehyde (2) and subsequent reaction of dimer (3) with diacetylmonoxime yielded the product (5).



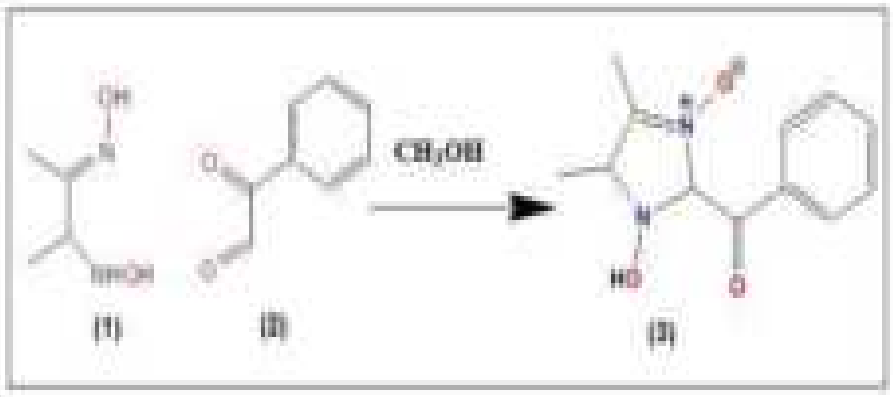
Scheme. 1.40. Synthesis of enantiomerically pure imidazole-N-oxide

Paulina Mucha *et.al.* also devised another method for the synthesis of enantiomerically pure imidazole-N-oxide (4) using 1-phenylethylamine (1) with formaldehyde (2) and diacetyl monoxime (3)[351] (Scheme 1.41).



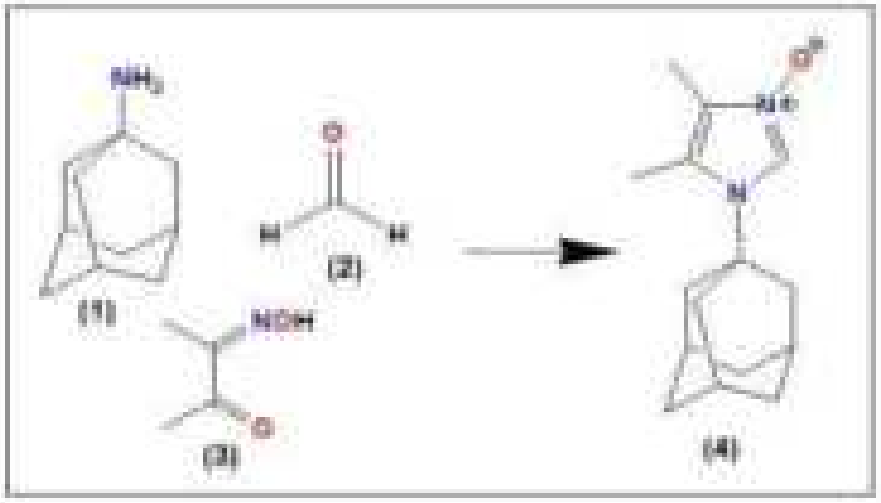
Scheme. 1.41. Synthesis of enantiomerically pure imidazole-N-oxide

S. A. Amitina *et.al.* successfully synthesized imidazole-N-oxide (3) derivative by condensing 3-hydroxyamino-2-butanone oxime (1) with phenyl glyoxal (2) at room temperature in methanol solvent medium[352](Scheme 1.42)



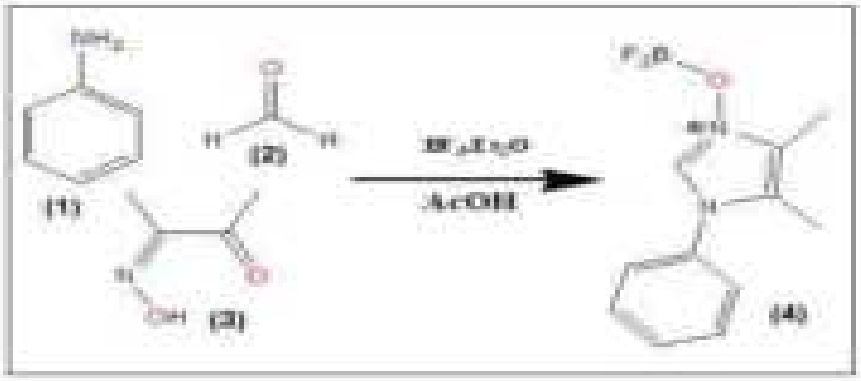
Scheme. 1.42. Synthesis of imidazole-N-oxide from 3-hydroxyamino-2-butanone oxime.

M Jasinski *et. al.* reported a synthetic method for the preparation of a bulky imidazole-N-oxide (4) using 1-amino admantane (1) with formaldehyde (2) and diacetyl monoxime (3) in Acetic acid medium[353] (Scheme 1.43).



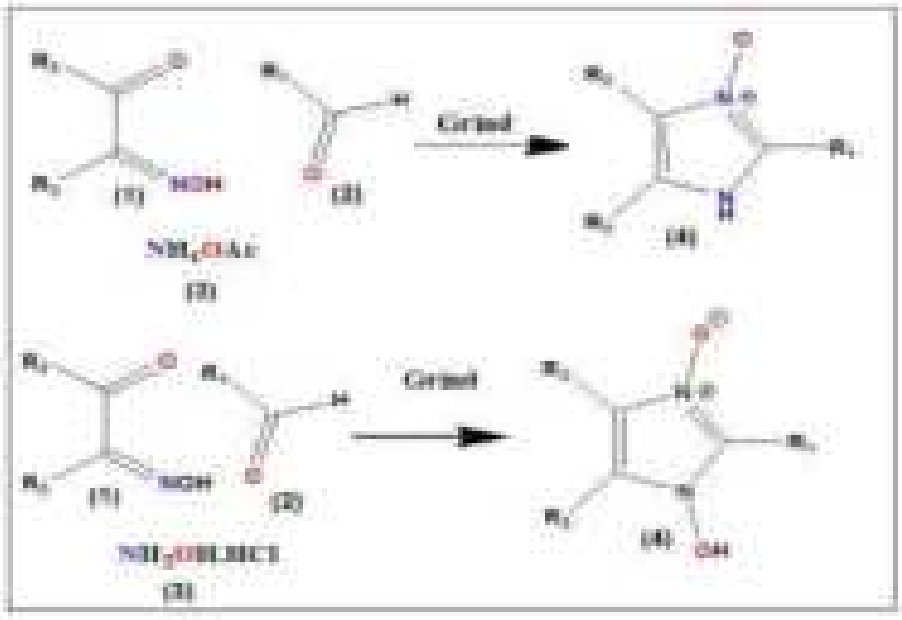
Scheme. 1.43. Synthesis of bulky bulky imidazole-N-oxide using 1-amino admantane

V. S. Mityanov *et.al.* devised a method for the synthesis of aryl imidazole-N-oxides (4) which was stabilized as a Boron trifluoride derivative using Boron trifluoride etherate in acetic acid[354](Scheme 1.44)



Scheme. 1.44. Synthesis of aryl imidazole-N-oxides

K. Pradhan *et.al.* have reported a solvent free, self catalysed reaction for the synthesis of N-substituted imidazole-3-oxides (4) using an aldehyde (1), diacetylmonoxime (2) and ammonium acetate (3). The same group also reported the synthesis of 1-hydroxy-imidazole-3-oxides (4) using hydroxyl amine hydrochloride (3) instead of ammonium acetate (3)[355] (Scheme 1.45).



Scheme. 1.45. Solvent free, self catalysed reaction for the synthesis of N-substituted imidazole-3-oxides

Imidazole derivatives finds an extensive application in many fields and current literature review revealed that there are limited reports on the synthesis of imidazole N-oxide under green condition and therefore, these factors prompted us to carry out the solvent free synthesis of imidazole N-oxide derivatives.

1.3.4 Various synthetic routes for the preparation of 1,2-substituted benzimidazole

Benzimidazole (84) is a bicyclic aromatic heterocyclic compound having a benzene ring fused to the imidazole ring[356]. Owing to the numerous significant properties such as therapeutics, benzimidazole scaffold have occupied a prominent place in medicinal chemistry[357]. Benzimidazole scaffold, a small nitrogen containing heterocycle is a versatile pharmacophore having a diverse range of biological activities such as antiulcer[358], antifungal[359], antimicrobial[360], antiasthamatic[361], anti-inflammatory and analgesic[362], antidiabetic[363], antitubeculor[364], antiviral and antiprotozoal[365] and anticancer[366] etc. Among many N-containing heterocyclic scaffolds, benzimidazole nucleus serves as a fundamental building block that is incorporated in many natural and synthetic molecules displaying wide range of biological activities[367,368] (Fig 1.21).

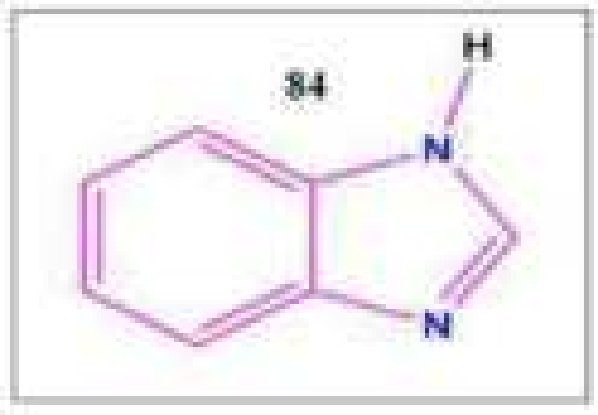


Fig. 1.21. Structure of Benzimidazole

Among the various type of benzimidazole derivatives, 1, 2-substituted benzimidazoles have gained a lot of interest because this class of compounds exhibit diverse type of biological activities such as antitumor activity[369](85), AT1 receptor antagonists[370] (86), antileukemia agent[371](87), ischemia-reperfusion injury[372](88), hypertension[373](89) and obesity[374](90) (Fig.1.22).

In recent years, 1, 2-disubstituted benzimidazole scaffold have attracted great attention due to their wide applications in new drugs such as antihypertensive drugs[375](91), $GABA_A$ receptor agonists[376](92) and the hepatitis C virus (HCV) NS5B polymerase inhibitors[377](93) (Fig.1.23).

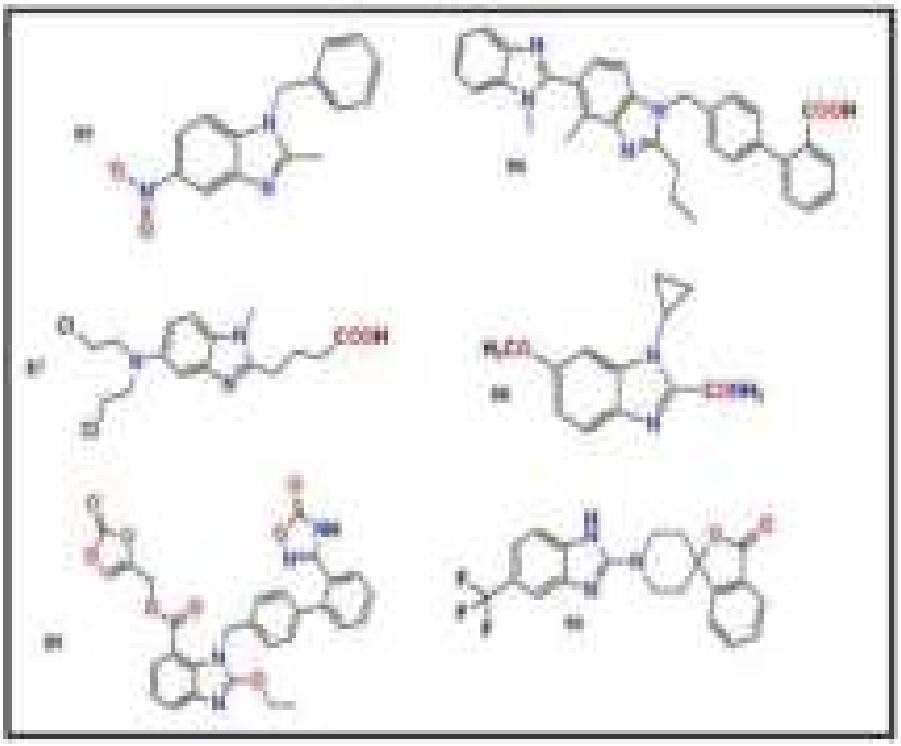


Fig. 1.22. Some of the biologically important Benzimidazole derivatives

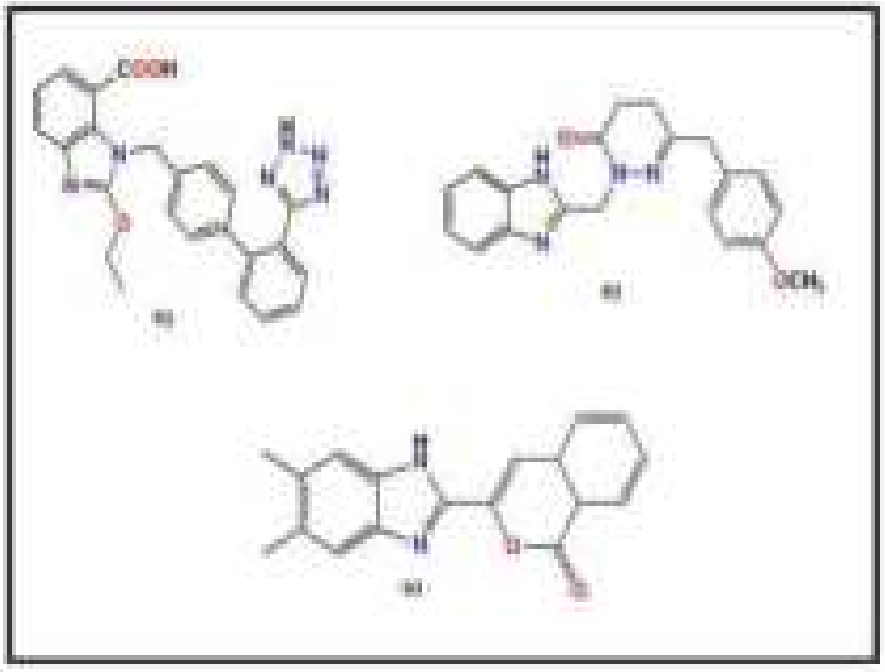
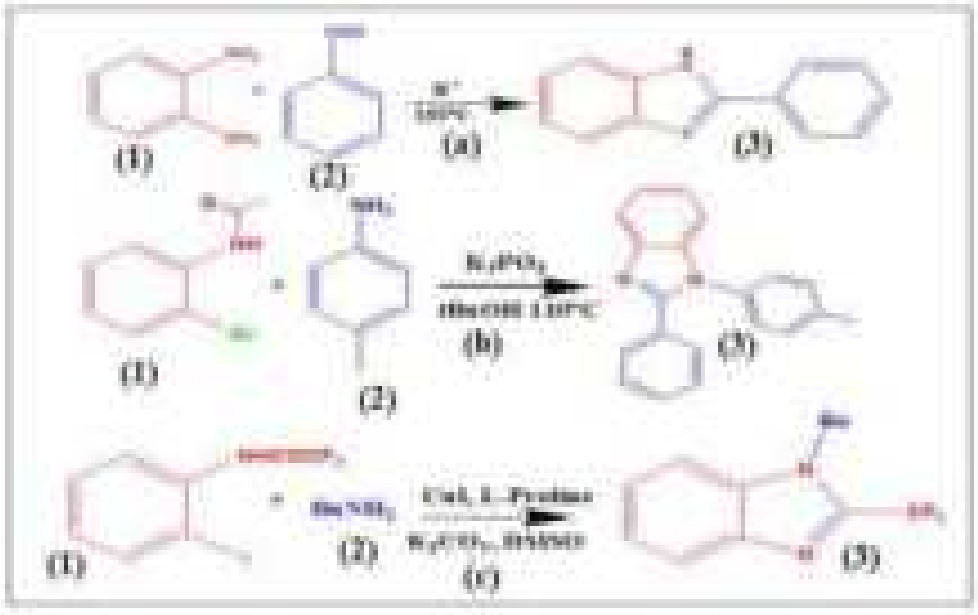


Fig. 1.23. Some of the important drugs containing benzimidazole nucleus

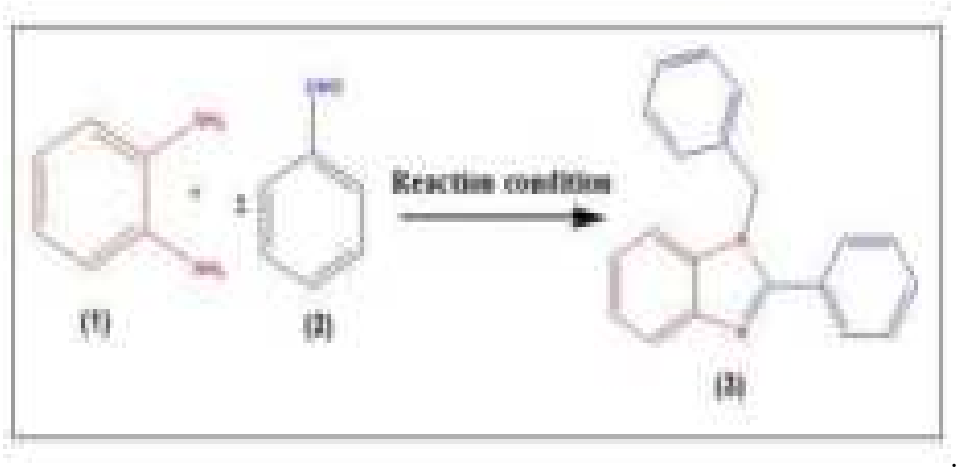
The synthesis of benzimidazoles involves the construction of C–N bond, which is an important category of transformation in organic synthesis[378]. A numerous method for the synthesis of 1,2-disubstituted benzimidazoles (3) such as condensation of anilines (1) with aldehydes (2) under relatively harsh conditions, direct oxidative coupling of amines to imines, and transition metal-catalyzed intramolecular cyclization have been reported during the past[379–381](scheme 1.46).



Scheme. 1.46. Numerous methods for the synthesis of disubstituted benzimidazoles

However, the above cited methods have some serious drawbacks such as harsh and strict reaction conditions, expensive catalysts, longer reaction time and environmental hazards and considering such harsh conditions there could be a possibility of decomposition of substrates or products thus, it is noteworthy to find and explore milder conditions for the synthesis of 1,2-disubstituted benzimidazoles[382].

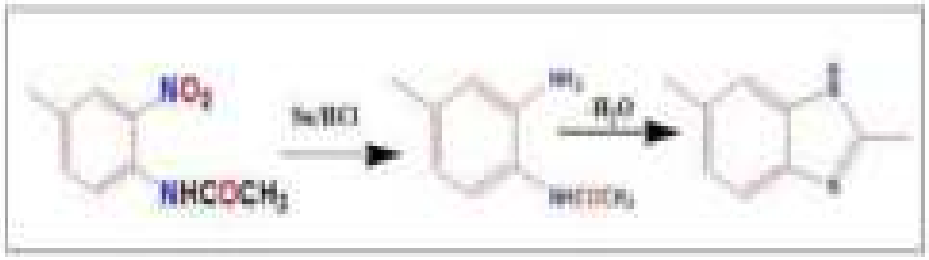
A considerable number of literature report is available for the synthesis of 1,2-disubstituted benzimidazole derivatives under different reaction conditions. A simple method for the synthesis of 1, 2-disubstituted benzimidazole (3) involves the cyclocondensation of o-phenylenediamine (1) with aldehyde (2) in 1:2 molar ratio[383] (Scheme 1.47).



Scheme. 1.47. Synthesis of 1,2-disubstituted Benzimidazole

1.3.4.1 Classical and non-classical approach

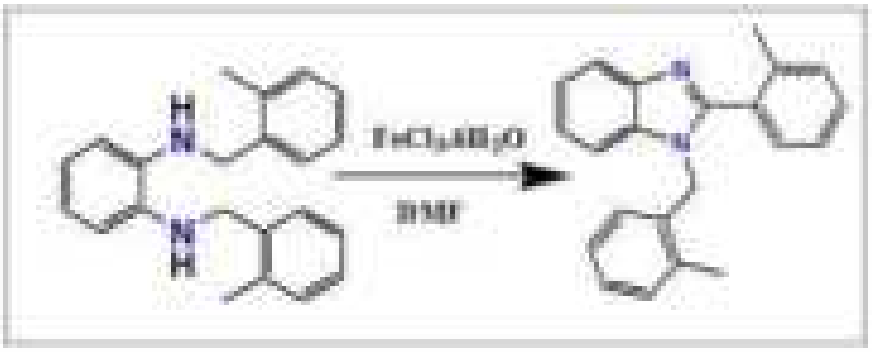
The first benzimidazole, 2,5-dimethylbenzimidazole (2) was synthesized by Hoebrecker [11], by reduction and dehydration of 2-nitro-4-methylacetanilide (1) in 1872.[384] (Scheme 1.48)



Scheme. 1.48. Hoebrecker's synthesis of Benzimidazole

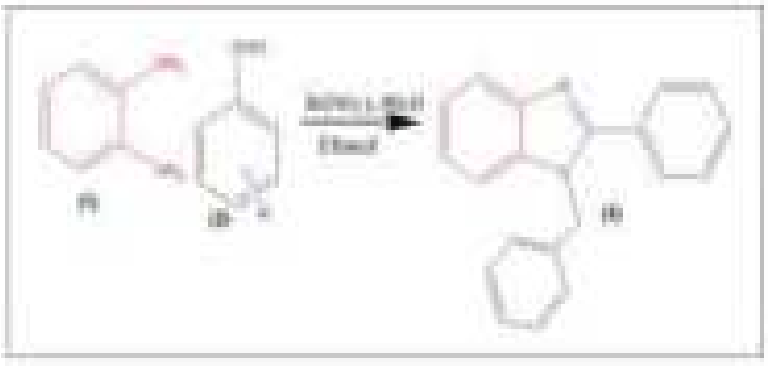
Various methods for the synthesis of benzimidazole have been developed by the condensation of o-phenylenediamine with aldehydes, carboxylic acids, or their derivatives (nitriles, amidates, orthoesters etc).[385]

Pawan Thapa *et.al.* employed $FeCl_3.6H_2O$ as an efficient catalyst for the synthesis of 1,2 disubstituted imidazoles (2) using *N, N'*-disubstituted-*o*-phenylenediamine (1) in DMF[386](Scheme 1.49).



Scheme. 1.49. Synthesis of 1,2 disubstituted imidazoles using *N, N'*-disubstituted-*o*-phenylenediamine.

P. P. Mahulikar *et.al*. used bismuth nitrate as a catalyst for the synthesis of (3) using (1) and (2) in ethanolic medium[387] (Scheme 1.50).

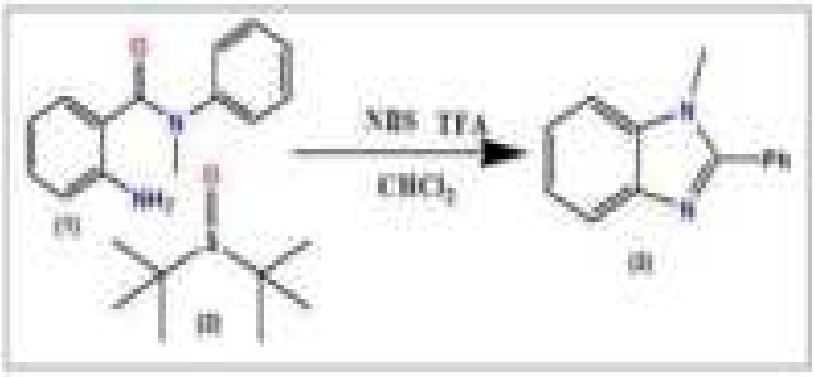


Scheme. 1.50. Synthesis of 1,2 disubstituted benzimidazole using Bismuth nitrate as catalyst

Praneetha V developed a method for the synthesis of (3) using 2-substituted benzimidazole derivatives (1), NaOH and chloroacetyl chloride (2)[388] (Scheme 1.51).

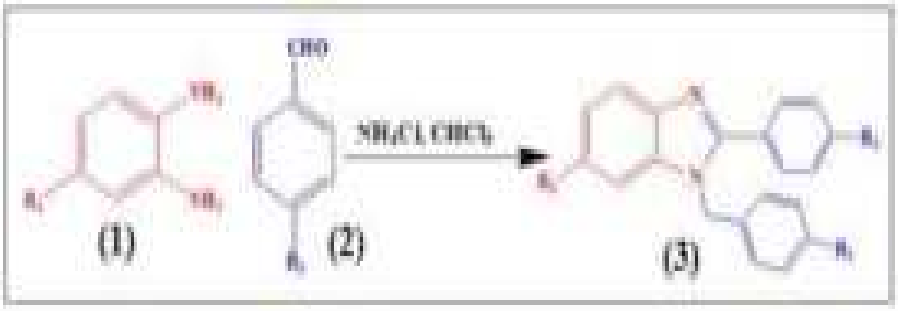
Scheme. 1.51. Synthesis of benzimidazole derivatives from chloroacetyl chloride

Z. Sun *et. al.* reported a method for the synthesis of (3) utilizing an aza-wittig equivalent process from a derivative of o-phenylene diamine (1), tertiary butane sulfoxide (2) and NBS under acidic conditions[382](Scheme 1.52).



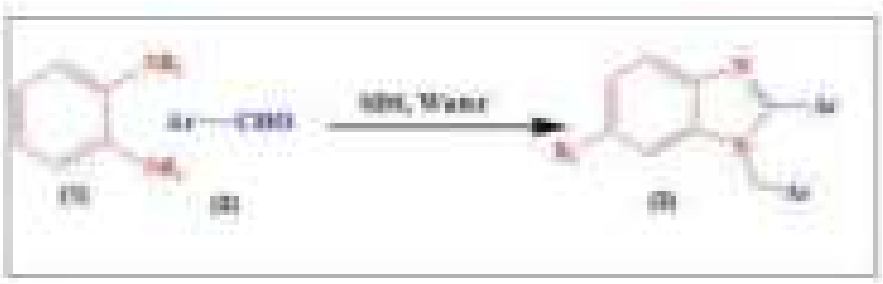
Scheme. 1.52. Synthesis of benzimidazole derivatives from tertiary butane sulfoxide

S. M. Abdur Rahman *et. al*. have reported the synthesis of 1, 2-disubstituted benzimidazoles (3) by cyclocondensation ortho-phenylene derivatives (1) and aromatic aldehyde (2) utilizing ammonium chloride as an inexpensive catalyst in chloroform solvent[389](Scheme 1.53).



Scheme. 1.53. Synthesis of benzimidazole derivatives using Ammonium chloride catalyst

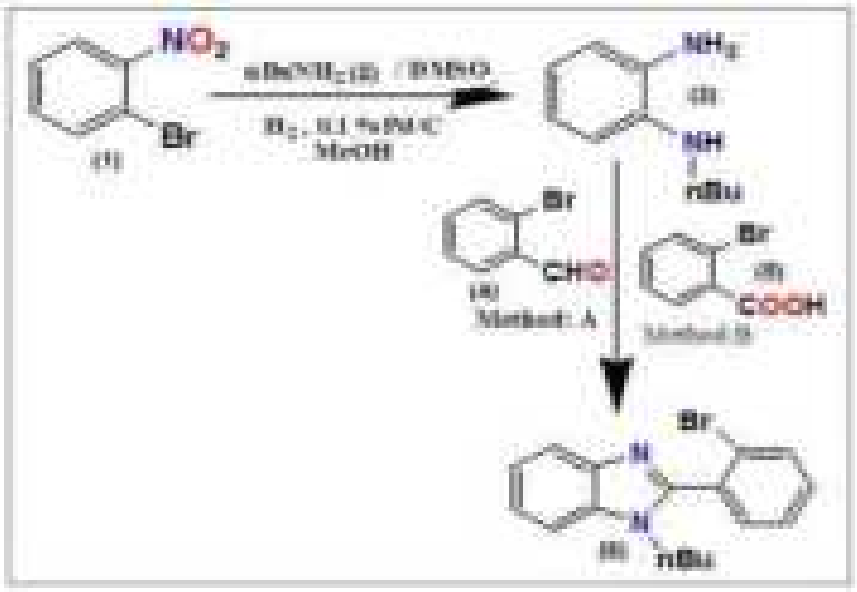
In another report, A. Nejati *et.al*. synthesized 1,2-disubstituted benzimidazoles (3) by the cyclocondensation of 1,2-phenylenediamine (1) and aryl aldehydes (2) in aqueous micellar media, using sodium dodecylsulfate (SDS) as a catalyst and surfactant to stabilize organic substrate[390] (Scheme 1.54).



Scheme 1.54. Synthesis of benzimidazole derivatives using SDS catalyst

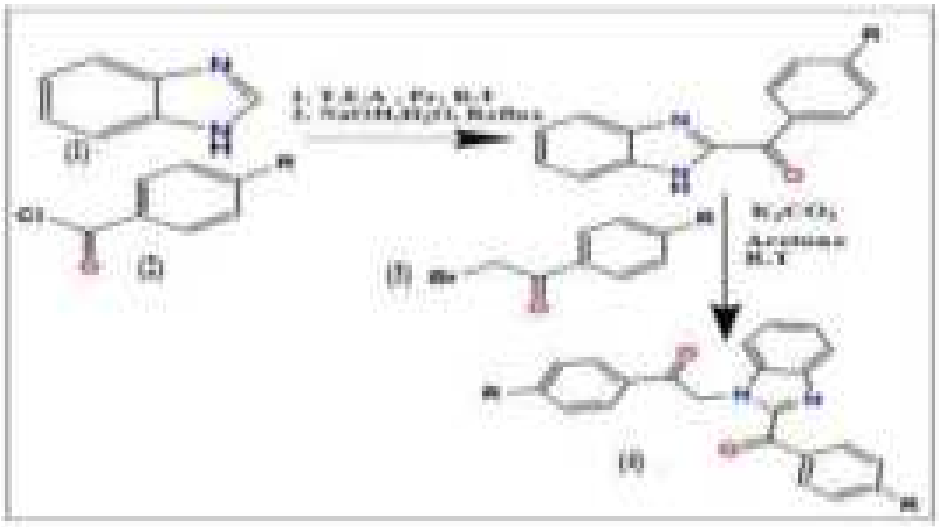
Z.B. Song *et.al.* have reported the synthesis of 1, 2-disubstituted benzimidazole derivatives (3) by cyclocondensation reaction of 1, 2-phenylenediamine (1) and aryl aldehydes (2) in lactic acid medium without adding any additives[391].

A.J. Blatch *et. al.* reported the synthesis of 1, 2-disubstituted benzimidazole (6) by subsequent reduction of Ortho-bromo nitrobenzene (1) with t-Bu-NH_2 (2) in DMSO solvent and cyclization of reduced product (3) with ortho bromo benzaldehyde (4) and ortho bromo benzoic acid (5) in two separate synthetic procedures[392] (Scheme 1.55).



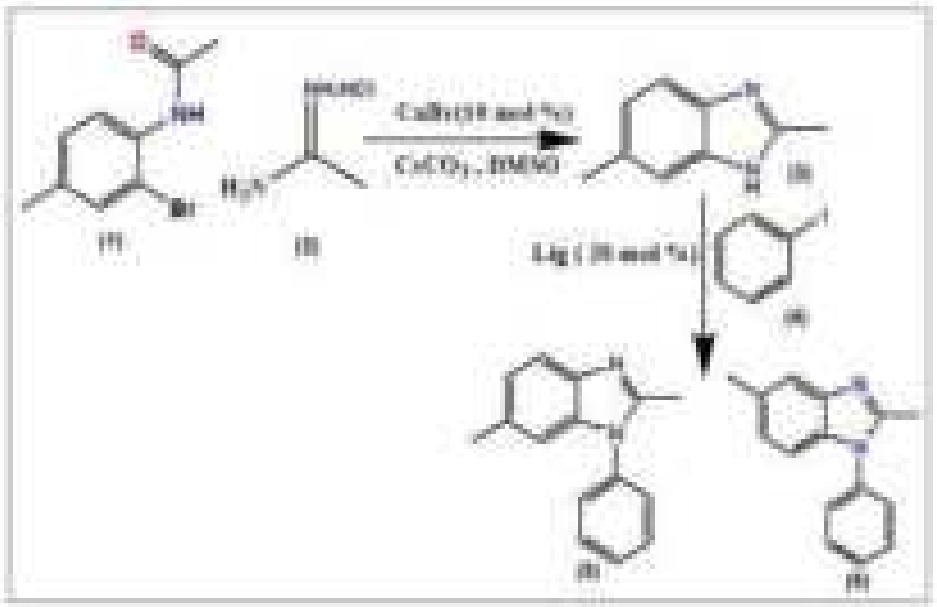
Scheme 1.55. Two separate procedures for synthesis of benzimidaole derivatives

S. Demirayak *et.al.* developed a method for the synthesis of 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles (4) using benzimiadazoles (1), acyl chlorides (2), and 2-bromoacetophenones (3) under various solvents[393] (Scheme 1.56)



Scheme. 1.56. Synthesis of 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles

Zhao *et.al.* reported a one pot method for the synthesis of two regioisomers of 1,2 disubstituted benzimidazoles (5 and 6). They first prepared 2- substituted-1H-benzimidazole (3) from N-(2-bromo-4-methylphenyl) acetamide (1) and amidine hydrochloride (2) in the presence of CuBr and $CsCO_3$ and then by using a combination 3,4,7,8-tetramethyl-1,10-phenonthraline ligand with aryl iodide (4) they converted 2- substituted-1H-benzimidazole to two regio isomers of 1,2-Disubstituted benzimidazoles (5 and 6)[394] (Scheme 1.57).

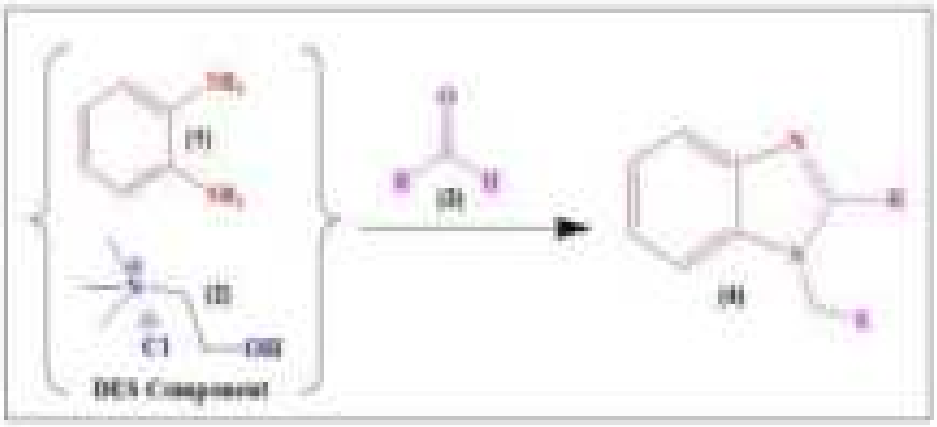


Scheme. 1.57. Synthesis of two regio isomers of 1,2-Disubstituted benzimidazoles

C.T. Brain *et.al.* employed Palladium based catalyst for the synthesis of 1,2-Disubstituted benzimidazoles (2) using amidines (1), NaO^tBu, K_2CO_3 in toluene solvent and under refluxing conditions[395] (Scheme 1.58).

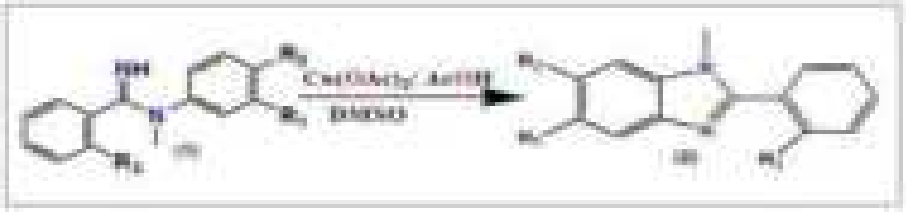
Scheme. 1.58. Synthesis of Benzimidazoles using Palladium based catalyst

M. Loredana *et. al.* reported the synthesis of privileged benzimidazole (4) scaffolds by condensing aldehyde (3) and (1:1) mixture of orthophenelynediamine (1) and choline chloride (2) as an active deep eutectic solvent[396] (Scheme 1.59).



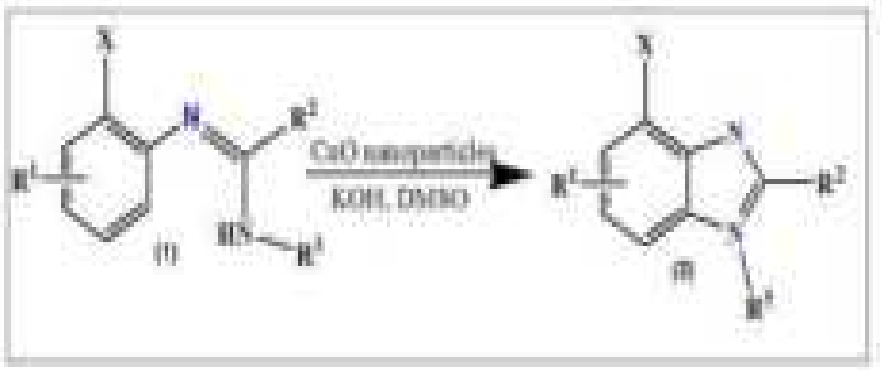
Scheme. 1.59. Synthesis of benzimidazole scaffold by using an active deep eutectic solvent.

Buchwald *et.al.* employed copper acetate as an efficient catalyst for the preparation of N-methylated benzimidazoles (2) from amidines (1) in DMSO solvent[397] (Scheme 1.60).



Scheme. 1.60. Synthesis of Benzimidazoles from amidine.

T. Punniyamurthy *et.al.* devised an efficient method for the synthesis of substituted benzimidazoles (2) by using CuO nanoparticles as a catalyst by using ortho-halo-aryl amidines (1) in DMSO solvent[398] (Scheme 1.61).

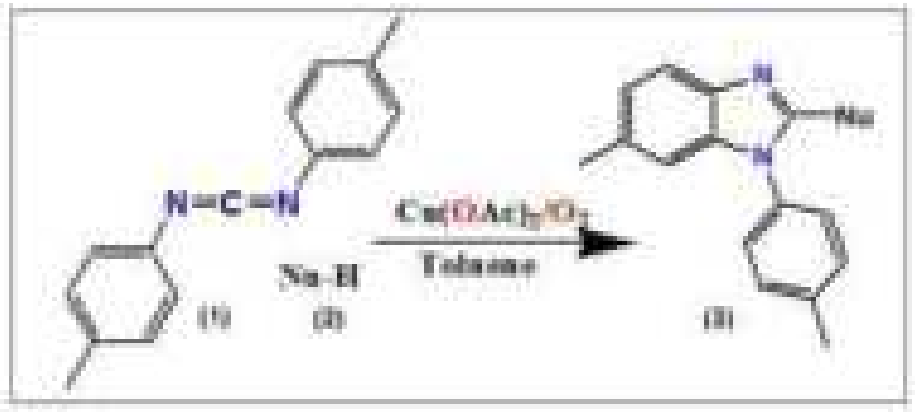


Scheme. 1.61. Synthesis of benzimidazoles by using CuO nanoparticle as catalyst.

The same group once again reported a method for the synthesis of benzimidazoles (2) using ortho-bromo-amidines (1) using a combination of $Co(acac)_2.2H_2O$ and 1,10 phenanthroline as a catalyst in presence of K_2CO_3in Toluene solvent[399] (Scheme 1.62).

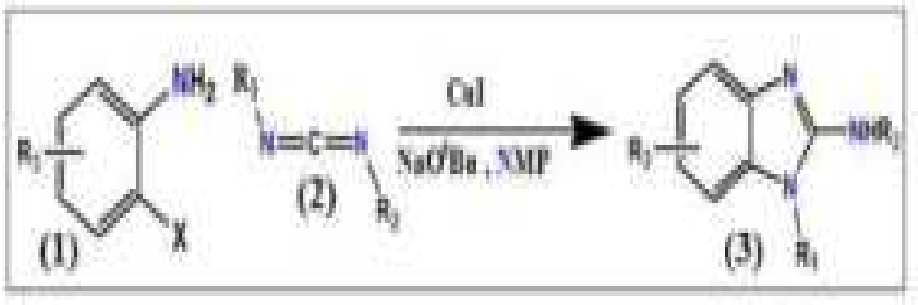
Scheme. 1.62. Synthesis of benzimidazoles using ortho-bromo-amidines.

Bao *et.al.* employed Cu $(OAc)_2$ as a catalyst for the synthesis of substituted benzimidazole (3) derivatives using diarylcarbodiimides (1) and various nucleophiles (2) in toluene solvent[400](Scheme 1.63).



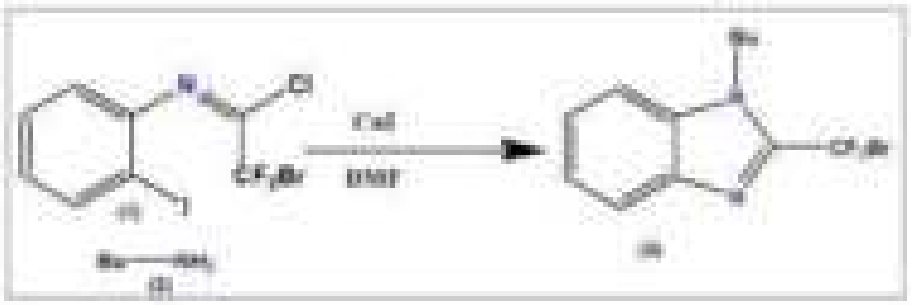
Scheme. 1.63. Synthesis of benzimidazole derivatives using diarylcarbodiimides

S. Cai *et.al.* used copper iodide as an efficient catalyst for the synthesis of a variety of substituted benzimidazoles (3) from ortho-halo anilenes (1) and carbodiimides (2) in presence of NaO^{t}Bu and N-methyl-2-pyrrolidine (NMP) as a solvent[401] (Scheme 1.64).



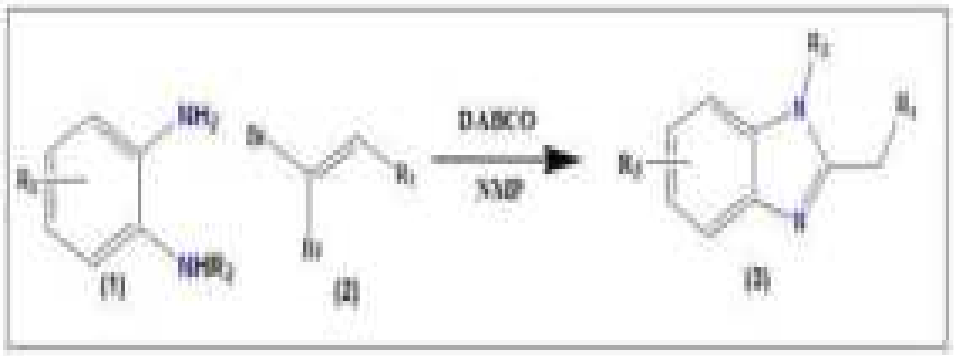
Scheme. 1.64. Synthesis of benzimidazole from ortho-halo anilines

Y. Wu *et.al.* reported the synthesis of 2-fluoroalkylbenzimidazoles (3) from N-aryl bromodifluoroacetimidoylchlorides (1) and primary amines (2) using copper iodide as a catalyst in DMF solvent[402] (Scheme 1.65)



Scheme. 1.65. Synthesis of 2 fluoroalkylbenzimidazoles

Schmidt *et.al*. employed 1,4-diazabicyclo [2.2.2]octane (DABCO) as an efficient catalyst for the synthesis of substituted benzimidazoles (3) from 1,1 dibromoethene (2) and ortho-diamino benzene (1) using NMP as a solvent[403] (Scheme 1.66)



Scheme. 1.66. Synthesis of substituted benzimidazoles using DABCO as a catalyst.

Siddapa *et.al.* employed benzoyl peroxide as a catalyst for the synthesis of substituted benzimidazoles (2) from substituted orthophenylene diamine (1) and dibromomethylarenes (2) in presence of KO^{t}Bu and molecular iodine under reflux conditions and DMF as a solvent[404] (Scheme 1.67).

Scheme. 1.67. Synthesis of substituted benzimidazoles from dibromomethylarenes.

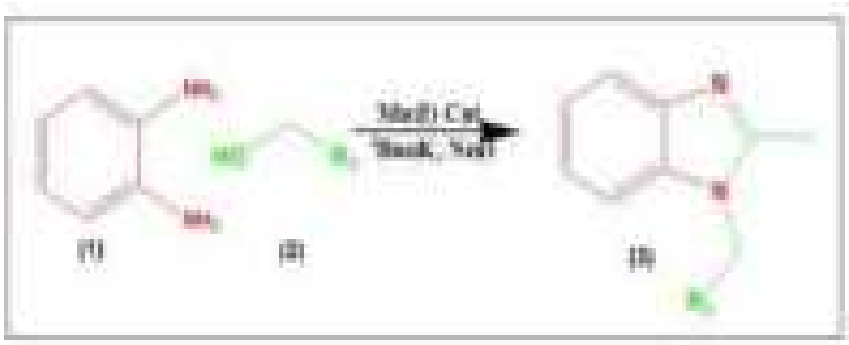
1.3.4.2 Green Method

There are numerous classical and nonclassical methods reported during the past for the synthesis of 1, 2-disubstituted benzimidazole derivatives. However, the reported procedure suffers from some serious drawbacks such as use of hazardous solvents, harsh reaction condition, expensive catalyst, environmental hazards, and long reaction time etc[405]. Therefore, by looking at the importance of this heterocyclic scaffolds, numberous green reaction methodologies for the synthesis of 1, 2-disubstituted benzimidazole derivatves have been developed for the past few decades[406]. A number of modifications in the synthetic approach such as the use of environmentally friendly solvents[378], solvent free reaction conditions[407], Microwave assisted synthesis[408], Ultrasound irradiation[409] etc has been reported. These modifications largely contribute to the sustainability of the entire production system by greatly reducing industrial waste[410].

1.3.4.2.1 Solvent free synthesis

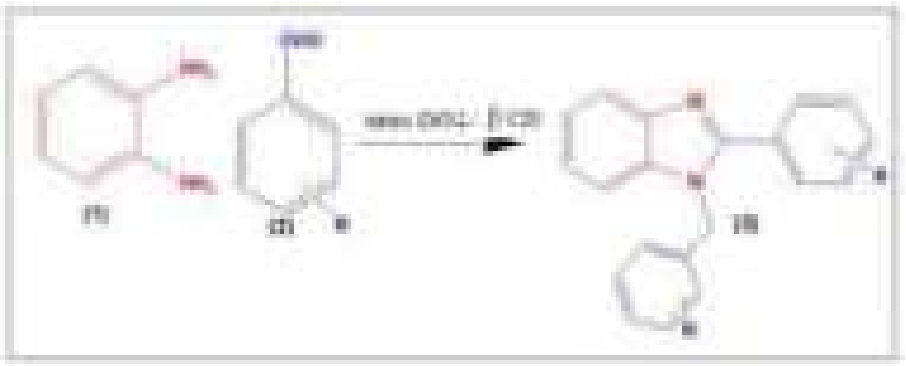
Solvent free synthesis is gaining a lot of interest these days as this technique has numerous advantages such as reduced pollution, low costs, and simplicity in process and handling and these factors have significance important in chemical industry[91]. Current literature review revealed that a variety of literatures are available for the solvent free synthesis of 1,2-disubstituted benzimidazole derivatives.

D. Srimani *et. al.* have reported an efficient protocol for the solvent free synthesis of 1, 2-disubstituted benzimidazole (3) derivatives by acceptor less dehydrogenative coupling of aromatic diamine (1) with primary alcohols (2) using phosphine free tridentate Mn(I) complex as a catalyst[411] (Scheme 1.68).



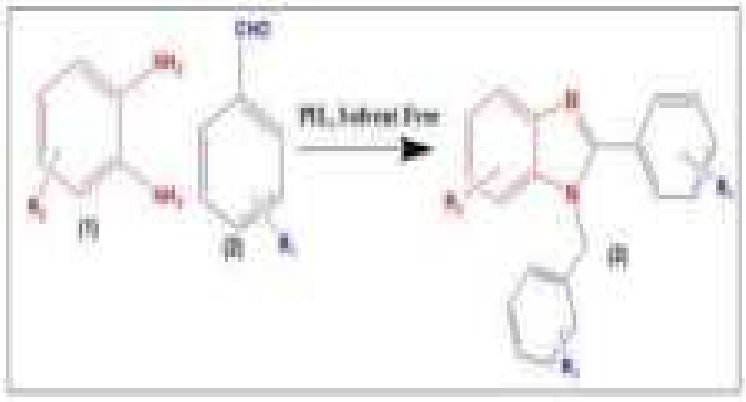
Scheme. 1.68. Synthesis of 1,2 disubstituted benzimidazole by dehydrogenative coupling.

S. Shashikanth *et.al.* have utilized ZrO_2-supported-β-cyclodextrin (ZrO_2-β-CD) as an efficient catalyst for the solvent free synthesis of 1, 2-disubstituted benzimidazole derivatives (3) by condensation of orthophenylene diamine (1) and aromatic aldehydes (2)[412] (Scheme 1.69)



Scheme. 1.69. Synthesis of bezimidazole derivatives using (ZrO_2-β-CD) catalyst

D. K. Maiti *et. al.* have repoted the green synthesis of 1,2-disubstituted and 2- substituted benzimidazoles with outstanding selectivity using protic ionic liquid (PIL)-substrate as a catalyst utilizing grind stone chemistry under solvent free condition[413] (Scheme 1.70).



Scheme. 1.70. Synthesis of 1,2-disubstituted benzimidazole using PIL.

R. Nongkhlaw *et. al.* utilized the grind stone technique to synthesize 1, 2-disubstituted benzimidazole derivatives (3) by condensation of ortho phenylenediamine (1) and various substituted aldehydes (2) using p-toluenesulfonic acid as a catalyst under solvent free condition[414].

M. Barcellos *et. al.* have reported the use of $Nb_2O_5.5H_2O$ as an efficient catalyst for the solvent free synthesis of 1, 2-disubstituted benzimidazole derivatives (3) by condensation of ortho phenylenediamine (1) and various substituted aliphatic and aromatic aldehydes[415].

Similarly, D. O. Jang *et. al.* reported the synergetic catalytic effect of ionic liquid and ZnO nanoparticle for the selective synthesis of 1, 2-disubstituted benzimidazoles (3) under solvent free condition utilizing ball-milling techniques[383].

1.3.4.2.2 Microwave assisted synthesis

Microwave heating now a days has been used as an alternative power source for the chemical transformation reaction. Since the microwave assisted organic synthesis has many advantages such as instantaneous heating, high temperature, selectivity etc. over the conventional techniuques[416]. A number of literature reports are available for the microwave assisted synthesis of 1, 2-disubstituted benzimidazole derivatives.

M. Nardi *et. al.* reported a highly efficient protocol for the synthesis of 1,2-disubstituted benzimidazoles (3) by the cyclization of N-phenyl-o-phenylenediamine (1) and aromatic aldehyde (2) using microwave irradiation employing $Er(OTf)_3$ as a catalyst [417] (Scheme 1.71).

Scheme. 1.71. Synthesis of 1,2-disubstituted benzimidazole using microwave irradiation

D. Azarifar *et. al*. reported acetic acid-promoted condensation of orthophenylendiamine (1) and aldehyde (2) under microwave irradiation to produce 1, 2-disubstituted benzimidazole (3)[418] (Scheme 1.72).

Scheme. 1.72. Synthesis of 1, 2-disubstituted benzimidazole derivatives from orthophenylene diammine

P. Aniket *et. al.* reported microwave assisted synthesis of 1, 2-disubstituted benzimidazole (3) by condensation of *o*-phenylenediamine (1) and aldehydes (2) catalysed by molecular Iodine in aqueous media[419] (Scheme 1.73).

Scheme. 1.73. Synthesis of 1, 2-disubstituted benzimidazole by using molecular I_2 as catalyst

R. G. Jacob *et. al.* reported an easy and versatile method for the synthesis of 1,2-disubstituted benzimidazoles (3) using $SiO_2/ZnCl_2$ and solvent-free conditions and Microwave irradiation[420].

P. Bandyopadhyay *et. al.* developed an efficient catalytic method for the synthesis of 1, 2-disubstituted benzimidazole (3) using mesoporous mixed metal oxide nanocrystals of Al_2O_3-Fe_2O_3, Al_2O_3-V_2O_5 and Al_2O_3-CuO as a catalyst under microwave irradiation[421].

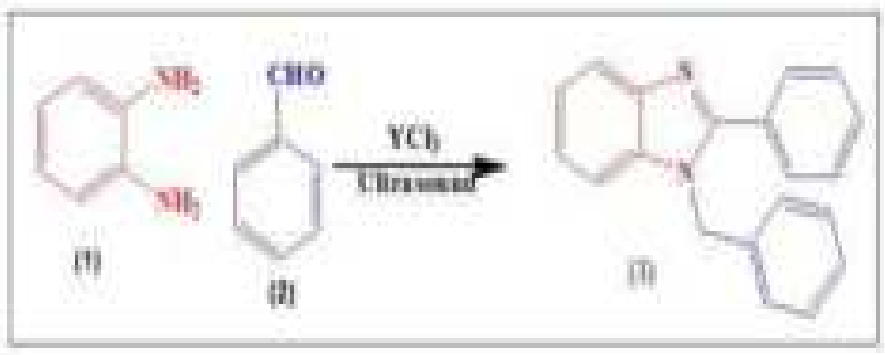
1.3.4.2.3 Ultrasound irradiation

During the past few decades, several synthetic protocols have been developed for the synthesis of 1,2-disubstituted benzimidazole derivatives. However, the classical approach for the synthesis of above said compound has some serious drawbacks such as harsh reaction condition, expensive catalyst, environmental hazard, use of toxic solvents and long reaction time. Again, a major limitation of the classical method for the synthesis of 1,2-disubstituted imidazole is the poor selectivity in terms of N-1 substitution, which results in the formation of two compounds, i.e., 2-substituted benzimidazole along with 1, 2-disubstituted benzimidazole as a mixture. Several modifications in the synthesis of 1, 2-disubstituted benzimidazole derivatives have been documented during the past. Ultrasonic assisted synthesis is one of the most important and significant modification towards the goal for making the synthetic pathway environmentally friendly. Ultrasound-promoted synthesis of 1, 2-disubstituted benzimidazole of suitably functionalized substrates, allows the regioselective as well as provides milder and selective reaction conditions. A number of literatures are available for the ultrasonic assisted synthesis of 1, 2-disubstituted benzimidazole derivatives.

B. Kumar *et. al.* reported the synthesis of 1, 2-disubstituted benzimidazole derivatives (3) under ultrasound irradiation by condensing o-phenylenediamine (1) with aldehydes (2) using SiO_2/CCl_3COOH catalyst[422] (Scheme 1.74).

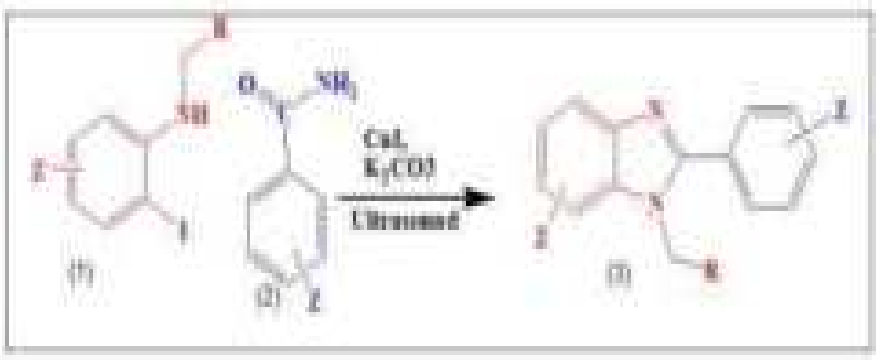
Scheme. 1.74. Synthesis of 1, 2-disubstituted benzimidazole derivatives under Ultrasound irradiation.

S.W. Wang *et. al.* devised a method for the synthesis of 1, 2-disubstituted benzimidazole (3) derivatives using rare-earth metal chlorides as efficient Catalysts under Ultrasound irradiation[423] (Scheme 1.75).



Scheme. 1.75. Synthesis of 1, 2-disubstituted benzimidazoles using YCl_3

M. Pal *et.al.* have reported the ultrasound assisted synthesis of 1, 2-disubstituted benzimidazole (3) derivatives utilizing CuI as an efficient catalyst under ultrasound irradiation by cyclocondensation of N-substituted 2-iodoanilines (1) and Benzamide derivatives (2)[424](Scheme 1.76)



Scheme. 1.76. Synthesis of 1, 2-disubstituted benzimidazole derivatives using CuI as an efficient catalyst.

R. S. Salunkhe *et. al.* reported Ultrasound promoted synthesis of 1, 2-disubstituted benzimidazoles (3) using aqueous hydrotropic solution by condensing o-phenylenediamine (1) with aldehydes (2)[425] (Scheme 1.77).

Scheme. 1.77. Synthesis of 1, 2-disubstituted benzimidazoles using aqueous hydrotropic solution.

Similarly, S. W. Park *et. al.* developed a method for the synthesis of 1, 2-disubstituted benzimidazole (3) utilizing Amberlite IR-120 as a catalyst under Ultrasound irradiation[426].

C. Wang *et. al.* reported the synthesis of 2-Aryl-1-arylmethyl-1*H*-benzimidazoles (3) catalyzed by bronsted acidic ionic liquid under ultrasonic irradiation[427].

In another report, C. G. R. Nallagondu *et. al.* documented natural dolomitic limestone-catalyzed synthesis of 1, 2 disubstituted benzimidazoles (3), dihydropyrimidinones, and highly substituted pyridines under ultrasound irradiation[428-429].

1.4 Brief information about the Transition Metal Borates

The chemistry of Transition metal borates is one of the vast and interesting fields of chemistry. The pioneers of borate chemistry were scientists like Hawthorne, Grimes and Braunschweig who have done tremendous work in this field[429–432].The chemistry of borates is very similar to the chemistry of phosphates and silicates. Transition metal borates finds tremendous applications in the glass industries due to their channel like structure morphology[433-434] and "Boron Anamoly" in which these borates have been found to alter their structures with changing conditions[435-436]. Borates containing transition metals have interesting properties like humidity resistant and are luminescent[437], bright visible colours give rise to different optical transitions[438], use in glass electrodes[439], nonlinear optical device materials[433], lithium-ion batteries[440,441]. As a matter of fact, it is the transition metal which plays an important role in developing the properties of these borates[442]. These borates are also used in laser luminescent solar energy concentrators (LSCS) and optical communication devices[443]. In the past few decades, the research on borate materials has been rapidly expanding mainly because of their rich structural chemistry and potential applications in mineralogy and industry[444-445]. Current literature revealed that only a few reports are documented for the catalytic activity of borate salts during past few years.

J. Liu *et. al*. utilized Transition Metal Borides and Borates as an electrocatalyst for oxygen evolution reaction[446].

S. Ghosh *et. al.* reported the Hydroboration reactions using transition metal borane and borate complexes[447].

In another report, Y. Liu *et. al.* employed Ni-Fe-Boride as a catalyst for oxygen evolution reaction[448].

Thus, it was thought worthwhile to explore the catalytic efficiency of few transition metal borates for the one-pot multicomponent synthesis of some N-containing heterocyclic compounds under green reaction conditions.

1.5 Objectives of the research work

The main aim of this work is to explore the catalytic activity of transition metal borates and to` develop the novel, efficient, convenient, selective and environmentally benign synthetic methods for the synthesis of Nitrogen containing heterocyclic compounds. However the objective of the current research focuses on the following:

- To explore the catalytic efficiency of some transition metal borates in the green synthesis of Nitrogen containing heterocyclic compounds in order to search for a novel mild and efficient procedure.
- To develop an efficient, operationally simple, environmentally benign, and straight forward general method for the synthesis of Nitrogen containing heterocyclic compounds.
- To carry out detailed analytical and spectroscopic characterization of synthesized heterocyclic compounds.
- Theoretical Studies involving DFT, analysis of Non-Linear Optical properties (NLO), Pharmacokinetic analysis and molecular docking study of some selected synthesized derivatives.

1.6 References

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