

## **CHAPTER-I**

### **General introduction**

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#### I.1. A brief introduction of C-hetero bond

The backbone of many organic compounds is composed of C–C bonds, but the function of these molecules is often derived from the presence of heteroatoms, such as nitrogen, oxygen and sulphur, which are held in these molecules by C–heteroatom bonds. Although, C-heteroatom bond forming reactions is thermodynamically much more favourable than C-C cross coupling reactions, C-heteroatom bond formation has occupied unique site in organic chemistry. For example, most of the pharmaceuticals often contain C–N bonds and almost all natural products contain C–O bonds.

Heterocyclic compounds in which C–N, C–O or C–S bonds are present in the ring structure are found in all applications of chemistry. In spite of these, C-heteroatoms containing compounds has ability to stabilize the metals ions through ligation or complexation in both biological and non-biological system, for example, magnesium and iron in chlorophyll and haemoglobin are stabilized by nitrogen ligands. There are various organic compounds having carbon-hetero bond which shows important catalytic activities for the various organic transformations. The well known organocatalyst composed of carbon-heteroatom bonds are crown-ethers, quaternary ammonium salt (eg. tert-butyl ammonium bromide) called phase transfer catalyst which promotes the complicated organic transformation in a easier way by stabilizing the metal ions through ligation.

#### I.2. Objectives and scope of the thesis

The area of C-heteroatom bond forming reactions has experience an enormous application due to their wide range of application in designing the compound with chemical or biological interest. Numerous works have been done and substantial amount of methodologies have been developed for their synthesis. Most of the reported methodological works are not straight-forward, easy or environmentally benign. The development of new methodologies is still going on to reach the mild and green approach for the sustainable development. As there are numerous varieties of compound having carbon-heteroatom, the methodological based work on some of them is

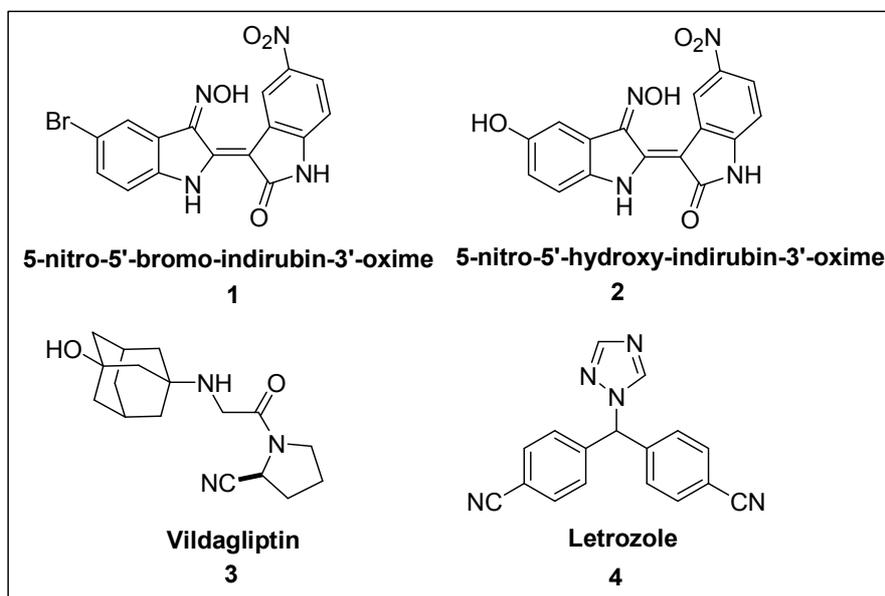
embodied in this thesis. The thesis covered the synthesis of epoxy-derivatives of few steroids by *m*CPBA on silica or CHCl<sub>3</sub>, selective synthesis of mono and dioximes on silica, FeCl<sub>3</sub> mediated organo nitrile synthesis, MgCl<sub>2</sub>.6H<sub>2</sub>O catalyzed synthesis of 2-substituted benzimidazoles and synthesis of highly substituted imidazole on titanium-silica solid support. The unique structural or biological features of these selected carbon-heteroatom compounds prompted author to carry out the present methodological work.

The major aim of this thesis is to provide new methodological work for the synthesis these useful compounds by carbon-hetero bond forming reaction. The new methodologies described in this thesis are mild, cost-effective, environment friendly which definitely meet the present demand under the aspect of green and sustainable development.

### **I.3. Brief review of the compounds described in this thesis**

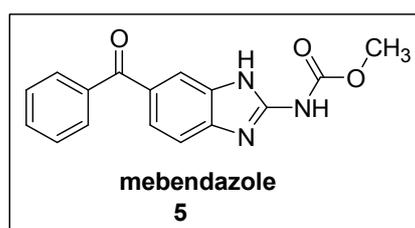
#### **I.3.1. Biological profile of compounds having carbon-hetero bond**

Carbon-heteroatom functionality is an important structural feature in most of the biologically active compounds. For example, 5, 5'-substituted indirubin-3'-oxime derivatives (**1,2**) found potent cyclin-dependent kinase inhibitors with anticancer activity.<sup>1</sup> Vildagliptin (**3**) is amino-nitrile containing antidiabetic drug in which the nitrile bearing carbon is not fully substituted, letrozole (**4**) is the aromatase inhibitor for the treatment of breast cancer (**fig. I.1**).<sup>2</sup>



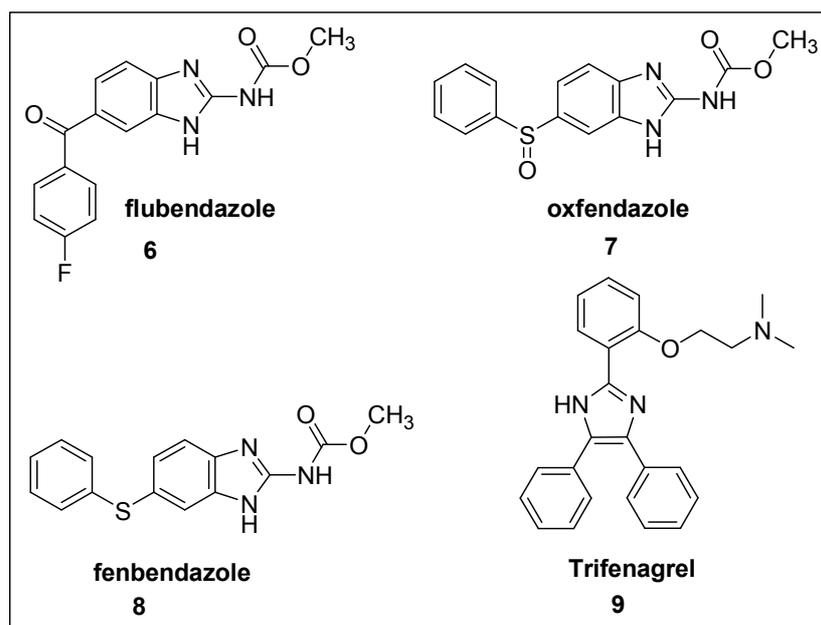
**Fig.I.1.** Biologically potent drugs having carbon-heteroatom bonds

Carbon-nitrogen bond containing heterocycle has also remarkable medicinal value with respect to their inhibitory activity and their favourable selectivity ratio. Extensive biochemical and pharmacological studies have confirmed that these classes of moiety are effective against various strains of microorganisms. One of the carbon-nitrogen containing heterocycle called benzimidazole and its derivatives are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin-B<sub>12</sub>. This ring system is present in numerous bioactive compounds having antiprotozoal,<sup>3</sup> antihelmintics,<sup>4</sup> anti-HIV,<sup>5</sup> anticonvulsant,<sup>6</sup> antiinflammatory,<sup>7</sup> antihepatic,<sup>8</sup> and antineoplastic,<sup>9</sup> antiulcer,<sup>10</sup> activities. Many of these derivatives are widely used for the treatment of parasitic diseases. One of the first drugs representing these compounds, now widely used in helminthology, was mebendazole (**fig. I.2.**)



**Fig.I.2.** Mebendazole

At present, more than twenty of these derivatives are used as antihelminth preparations in the world veterinary and medical practice, including flubendazole (6), oxfendazole (7), fenbendazole (8), trifenagrel (9) (fig.I.3.). Another heterocycle containing carbon-nitrogen bond is imidazole which is strongly associated with many important biologically active molecules. The most important is the amino acid histidine which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of haemoglobin. The suitable substitutions of these derivatives are valuable in treatment of many systemic fungal infections. Imidazoles belong to the class ofazole antifungals or treatment for the parasitic deceases.



**Fig.I.3.** Examples of benzimidazole and imidazole drugs

#### **I.4. Application of carbon-hetero bond containing intermediate in organic synthesis**

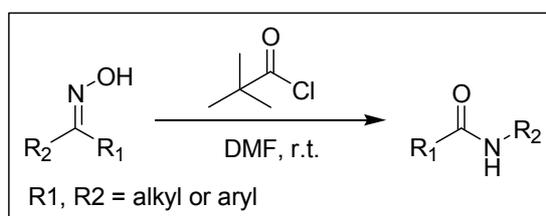
##### **I.4.1. Application of epoxide in organic transformations**

Epoxides are considered as versatile intermediates in organic synthesis, which are susceptible to nucleophilic attack to form the substituted hydroxyl products.<sup>11</sup> Ring

opening of epoxides with nucleophilic reagents is an useful tool for the preparation of several 1, 2-disubstituted products.<sup>12</sup> Literature review revealed that substantial amount of organic transformation have been carried out with epoxides for the preparation of wide range of organic compounds.<sup>13-17</sup>

#### I.4.2. Application of oximes in organic transformations

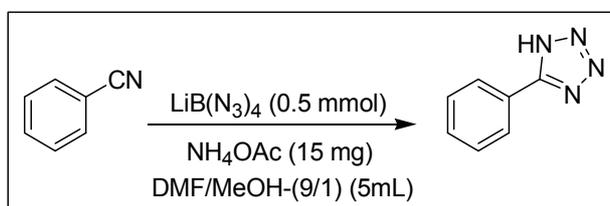
Oximes are used extensively for the protection of carbonyl function. This compounds not only represents the series of derivatives of carbonyl compounds but also used as useful intermediate for the important organic synthesis and functional group transformations. Particularly, the manufacture of cyclohexanone oxime represents a key step in the sequence of the nylon 6 production. In spite of having a huge industrial and medicinal uses, the other important and interesting application of oximes is functional group transformations and synthesis of nitrogen containing heterocycles such as Beckmann rearrangement for the synthesis of amide from ketoxime. Recently reported advance methodologies for the preparation of amide from ketoximes includes, cyanuric chloride catalyzed Beckmann rearrangement of ketoximes into amides under mild condition with HCl and ZnCl<sub>2</sub> as effective cocatalyst,<sup>18</sup> perfluoroalkylsulfonyl fluoride-mediated abnormal Beckmann rearrangement for the transformation of steroid 17-oximes to the corresponding alkene nitriles regioselectively,<sup>19</sup> pivaloyl chloride/DMF a mild inexpensive and non-toxic system for the conversion of oximes to corresponding amides<sup>20</sup> (**scheme. I.1**), triphosphazene catalyzed Beckmann rearrangement of ketoximes to lactams,<sup>21</sup> mercury-catalyzed rearrangement of ketoximes into amides and lactams,<sup>22</sup> ruthenium-catalyzed oxime to amide rearrangement.<sup>23</sup>



**Scheme.I.1.**Beckmann rearrangement of oximes using pivaloyl chloride

### I.4.3. Application of nitriles in organic transformations

Nitriles are useful precursor for the synthesis of wide range of nitrogen containing heterocyclic compounds. The nitriles are widely used for the preparation of nitrogen containing heterocyclic compounds such as synthesis of pyridine derivatives<sup>24</sup> single-step synthesis of pyrimidine derivatives,<sup>25</sup> synthesis of 3, 5-diaryl-1, 2, 4-thiadiazoles in 1-butyl-3-methylimidazolium bromide promoted by (NH<sub>4</sub>)<sub>2</sub>S and (2, 4, 6-trichloro-1, 3, 5-triazine) TCT–DMSO,<sup>26</sup> synthesis of highly functionalized pyridines by cyclotrimerization of one nitrile with two alkynes in the presence of water-soluble cobalt(I) catalyst in the aqueous media,<sup>27</sup> synthesis of 5-substituted 1*H*-tetrazoles through 1, 3-dipolar cycloaddition of boron-azides and nitriles<sup>28</sup> (**scheme I.2.**), preparation of 2-substituted pyrrolidines from commercially available nitriles,<sup>29</sup> the Ni(0)-catalyzed the synthesis of variety of pyridines by intermolecular dehydrogenative [4 + 2] cycloaddition reaction of 1, 3-butadienes with nitriles,<sup>30</sup> AgNO<sub>3</sub> catalyzed synthesis of 5-substituted-1*H*-tetrazole via [3+2] cycloaddition of nitriles and sodium azide in refluxing DMF.<sup>31</sup>



**Scheme.I.2.** Synthesis of 5-substituted 1*H*-tetrazoles

### I.4.4. Application of benzimidazole in organic transformations

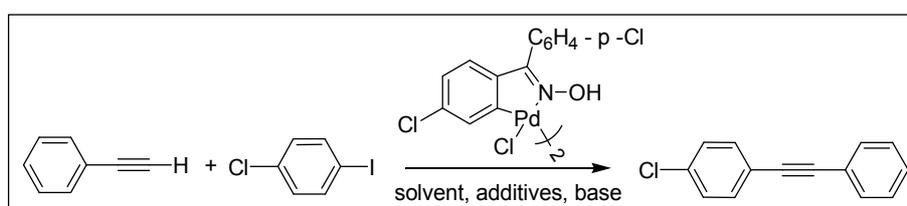
Benzimidazoles are one of versatile compounds having wide application in numerous research areas such as synthesis of tripodal fluorescent receptor bearing benzimidazole motifs as recognition sites in the pods of the receptor which is highly selective fluorescent chemosensor for iodide in aqueous solution,<sup>32</sup> benzimidazole and related ligands for Cu-catalyzed azide-alkyne cycloaddition,<sup>33</sup> hybrid NH<sub>2</sub>-benzimidazole ligands for efficient Ru-catalyzed asymmetric hydrogenation of aryl ketones.<sup>34</sup>

#### I.4.5. Application of imidazoles in organic transformations

As imidazole moiety is associated with many bioactive useful organic compounds, it plays a useful starting material for the synthesis of wide range of nitrogen containing physiologically active natural and synthetic compounds.<sup>35</sup> Due to the presence of two nitrogen atom, the suitable derivatives of the imidazole act as important ligand to many transition metals. Imidazole serves as a useful organic counterpart for the preparation of ionic liquids. Now days, imidazoles is also used as organo-catalyst for considerable organic transformation.

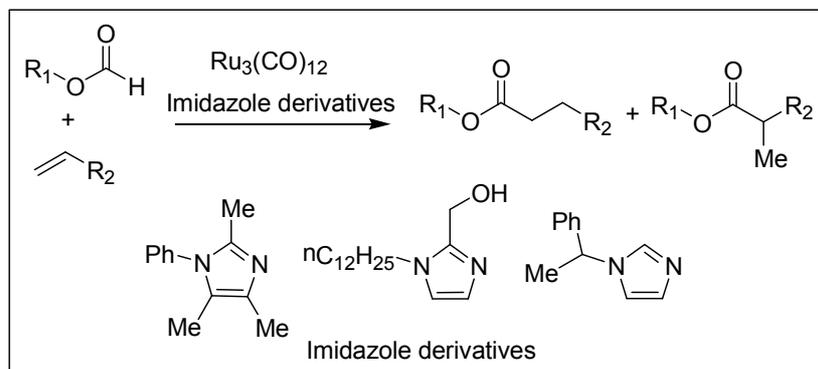
#### I.5. Role of oximes, benzimidazoles and imidazoles derivatives in organic ligands

Carbon-heteroatom containing organic compounds plays an important role in the development of transition metal coordination chemistry due to their versatile bonding modes. Oximes and their metal complexes are of current interest for their various physicochemical properties, reactivity patterns and potential applications in many important chemical processes in medicine and catalysis. The aryl palladium complexes especially ortho functionalized aryl complexes have the numerous interesting applications in organic synthesis. Catalytic C–C or C–heteroatom coupling reactions are usually carried out in the presence of aryl palladium complexes with nucleophiles. Oxime based palladacycles have gained a special attention in modern organic synthesis due their ubiquitous use in variety of catalytic transformations (**Scheme.I.3.**)<sup>36-40</sup> Literature review reveals that benzimidazole and related ligands are also used for the effective ligands in various transformation such as Cu-catalyzed azide-alkyne cycloaddition,<sup>41</sup> hybrid NH<sub>2</sub>-benzimidazole ligands for efficient Ru-catalyzed asymmetric hydrogenation of aryl ketones.<sup>42</sup>



**Scheme.I.3.** Oxime palladacycles catalyzed Sonogashira cross-coupling

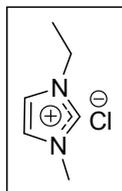
Various derivatives of imidazole are used as a useful ligand for considerable number of transition metals. Kei Manabe et al.<sup>43</sup> reported the Ru-catalyzed hydroesterification of alkenes using formates, affording one-carbon elongated esters in high yields using imidazole derivatives as a effective ligand (**scheme.I.4.**). Aaron Aponick et al.<sup>44</sup> reported the design, preparation and implementation of an imidazole-based chiral biaryl P, N-ligand for asymmetric catalysis where the ligand found to perform exceptionally well in the enantioselective coupling. Roman Sívek, Filip Bureš et al.<sup>45</sup> reported the synthesis and application in asymmetric synthesis of imidazole based potential bi-and tridentates ligand.



**Scheme.I.4.** Ru-catalyzed hydroesterification of alkenes

### I.6. Use of imidazole for the preparation of ionic liquid

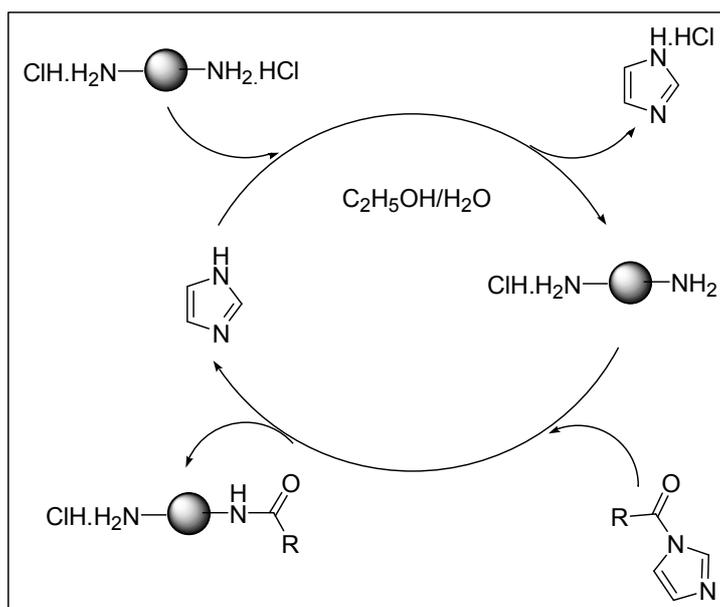
Imidazole-based ionic liquids have found uses in several applications including potential water treatment agents due to their ability to coordinate with metal atoms, and they are also recognized for their potential as green organic solvents due to their lack of volatility.<sup>46</sup> Furthermore, a unique combination of various alkyl substituents and counteranions enables tuning of the properties of the liquid to meet the demands of the application. The first imidazole based ionic liquid was 1-ethyl-3-methylimidazolium chloride (**fig.I.4.**). Later on anion exchange with more hydrolytically stable anions such as  $\text{BF}_4^-$ ,  $\text{PF}_6^-$ ,  $\text{NO}_3^-$ ,  $\text{SO}_4^-$ , or acetate that the resulting ionic liquids were quite stable.<sup>47</sup> This development led to the birth of the imidazole-based modern day ionic liquid.



**Fig.I.4.1**-Ethyl-3-methylimidazolium chloride

### I.7. Role of imidazoles and its derivatives in catalysis

Imidazole and imidazole tuned with transition metal shows highly effective catalytic properties for numerous organic transformations. Yasuhiro Uozumi et al.<sup>48</sup> reported self-assembled poly(imidazole-palladium) as highly active reusable catalyst for the allylic arylation/alkenylation of allylic acetates and carbonates with tetraarylborates, arylboronic acid, and alkenyl boron reagents in alcohol and/or water. Later on, the same group again reported the self-assembled copper sulfate and a poly-(imidazole-acrylamide) amphiphile as highly efficient solid phase catalyst for the Huisgen 1, 3-dipolar cycloaddition of a variety of alkynes and organic azides, including the threecomponent cyclization of a variety of alkynes, organic halides, and sodium azide.<sup>49</sup> M. P. Kaushik et al.<sup>50</sup> reported an simple imidazole catalyzed selective monoacylation of symmetrical aliphatic primary and secondary diamine (**scheme.I.5.**).



**Scheme.I.5.** Imidazole catalyzed selective monoacylation of symmetrical diamine

Marc L. Snapper et al.<sup>51</sup> reported use of an amino acid based imidazole catalyst for the enantioselective catalytic silylation of racemic diols which offers access to enantiomerically enriched monosilylated regioisomers.

### **I.8. Conclusion**

Compounds having carbon-hetero bonds have a broad scope in the area of designing the molecules with a chemical, biological or pharmaceutical interest. Most of the pharmaceuticals are covered by the compounds having carbon-hetero bonds. The bioactive natural products include carbon-heteroatom bond in their functional site. Therefore, molecules having carbon-hetero bond would be the suitable intermediates for natural product synthesis. Chemically interesting suitable molecules having bi or multifunctional system would perform efficient ligands for the complicated organic transformations. Carbon-hetero bond can be more easily functionalize than carbon-carbon non polar olefin bond. Functional groups inter-conversion, preparation of bi-or multifunctional compounds can be easily carry out by applying suitable reagents to carbon-hetero bond. With these huge importance and broad scope of carbon-hetero bond, author felt necessary to find a mild and easiest route for the synthesis of such type of important organic intermediate under mild, easy and straightforward approach.

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