CHAPTER I

A Brief review on Carbon-hetero bond transformation reactions and carbon-hetero bond formation reactions

I.A. Introduction to carbon-hetero bond

Although C-C bond forms the backbone of organic compounds, their functions often depend upon the presence of hetero atoms such as nitrogen, oxygen, sulphur, phosphorus, halogens etc within their moiety. These molecules have been known to have a vast array of versatile synthetic applications. Carbon-hetero functional group has been extensively used in the designing of various pharmaceutically significant compounds. These molecules also have their significant influence in the field of agrochemical industries as well. Apart from this, they are considered to be powerful starting materials for the construction of naturally occurring biological active compounds like amino acids, glycosides, naturally occurring heterocyclic compounds etc. Some of the carbon-hetero compounds are also utilized in synthesis of polymers. They also have been extensively used as ligands in synthesis of a number of transition metal catalysts which in turn is applied in the synthesis of a large number of organic compounds.

Carbon-hetero bond transformation reactions and carbon-hetero bond formation reactions have been extensively used as important tool in skeleton construction for synthesis of numerous drugs in pharmaceutical industries (Figure I.1).

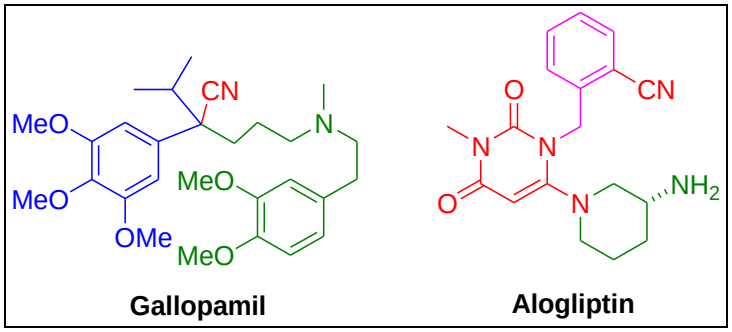


Figure I.1. Biologically active molecules containing carbon-hetero moiety

These reactions also promise an alternative way in designing molecules that are being used as surrogates for synthesis of biologically active compounds (Figure I.2). Beside, carbon-hetero bond formation reaction shares its impact on human health and modern everyday life technologies like antibiotics, food, perfumes, polymers, etc and in research field also.

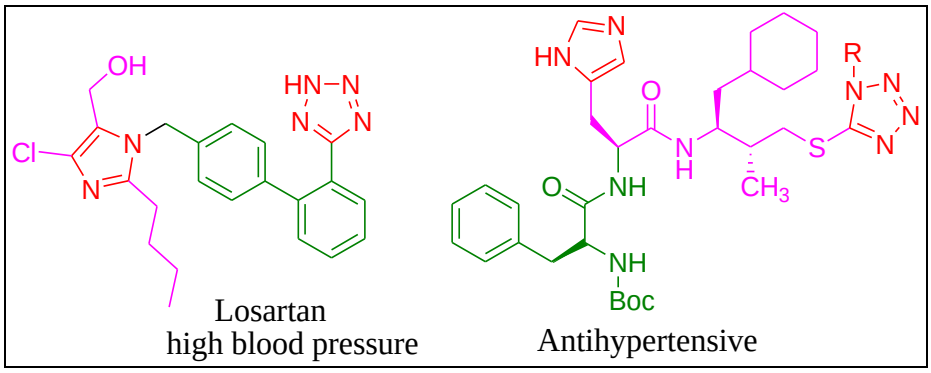


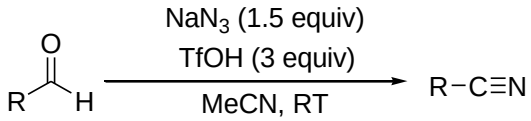
Figure I.2. Molecules with carbon-hetero bonds used as drugs

I.B. Carbon-hetero bond transformation reactions

A number of methodologies have been reported in literature for reactions involving carbon-hetero bond formation. A brief review has been discussed in this section.

I.B.1 Synthesis of nitriles from aldehydes

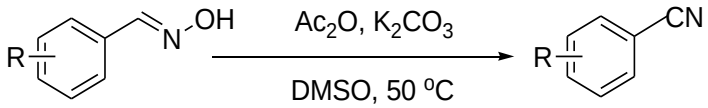
Aldehydes can be readily converted into nitriles using Schmidt reaction using sodium azide. K. R. Prabhu *et al.*[1] have reported method for synthesis of nitriles from aldehydes using TfOH as catalyst. The reaction was supposed to proceed via the in situ formation of hydrazoic acid (Scheme I.1).



Scheme I.1. Synthesis of nitriles from aldehydes

I.B.2. Synthesis of nitriles from oximes

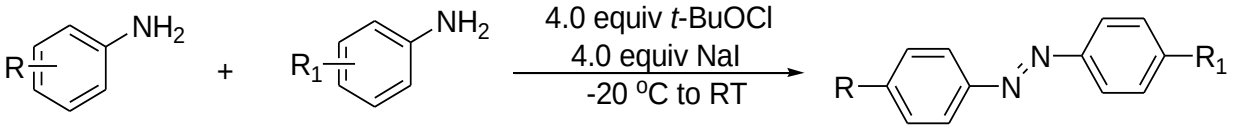
Y. Song *et al.*[2] reported synthesis of oxime from nitrile using acetic anhydride as the dehydrating agent. Wide range of aromatic aldoximes, aliphatic aldoximes and hetercyclic oximes has been successfully transformed into nitriles with good yield using this protocol (Scheme I.2).



Scheme I.2. Synthesis of nitriles from oximes using acetic anhydride

I.B.3. Synthesis of azobenzenes from anilines

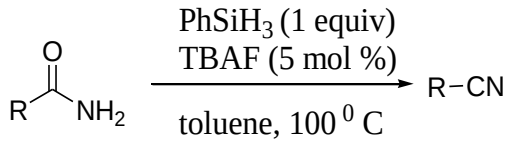
Y. Takeda *et al.*[3] have reported development of cost-efficient procedure for oxidative dimerization of aromatic amines to azobenzenes using *tert*-butyl hypochlorite (*t*-BuOCl) and NaI. The advantage of this protocol as stated by them was the synthesis of unsymmetrical azobenzenes along with symmetrical ones (Scheme I.3).



Scheme I.3. Oxidation of anilines for synthesis of azobenzenes

I.B.4. Synthesis of nitriles from amides

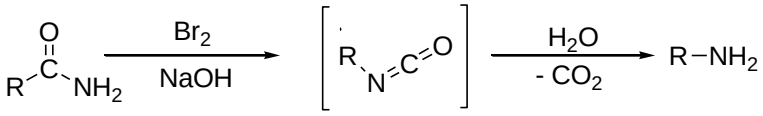
With catalytic amount of tetra-butyl ammonium fluoride (TBAF) and using silanes, M. Beller *et al.*[4] were able to convert aliphatic/aromatic amides into nitriles. The synthetic method showed high degree of selectivity under mild condition (Scheme I.4).



Scheme I.4. Synthesis of nitriles from amides

I.B.5. Hofmann degradation reaction for conversion of amides to amines

An important reaction for conversion of conversion of primary amides into primary amines was reported by Hofmann as early as 1881 and is known as Hofmann degradation reaction[5]. The reaction is carried out in presence of bromine and sodium hydroxide. Sodium hypobromite is formed first by the reaction between bromine and base, which again transfers the amine into isocyanate. Primary amines are formed by hydrolysis of the isocyanate in presence of heat (Scheme.I.5).

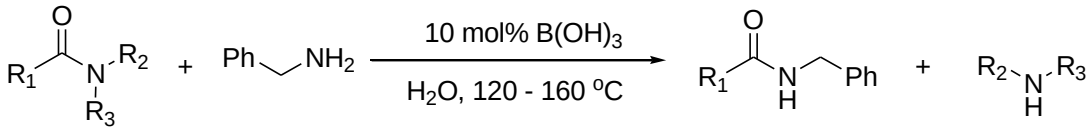


Scheme I.5. Hofmann degradation reaction

I.B.6. Transamidation reaction

Interconversion of amides commonly known to be transamidation reaction has received much importance because it offers a methodology of alternative strategy for synthesis of amides without using any carboxylic acid. Amides although are poor electrophiles, but in presence of appropriate catalyst and activating agents, they reacts with amines resulting in interconversion of amide derivatives.

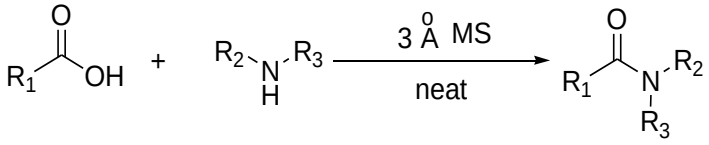
Recently boric acids have been used by T. B. Nguyen *et al.*[6] as catalyst for transamidation of primary, secondary and tertiary amides. The reaction was carried out neat at high temperature in presence of water. Good yield of the products obtained was reported by them (Scheme I.6).



Scheme I.6. Transamidation reaction

I.B.7. Conversion of acids to amides

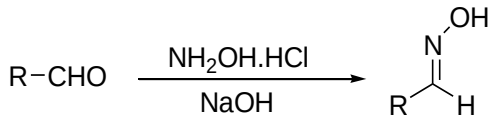
An environmentally friendly method was reported recently for efficient conversion of carboxylic acids to amides under thermal condition using molecular sieves. Various aliphatic, aromatic and heterocyclic acids were converted into corresponding amides by reacting with primary, secondary and also aromatic amines with good yield of the products as reported by L. J. Gooben and his co-workers[7] (Scheme I.7).



Scheme I.7. Conversion of carboxylic acids to amides

I.B.8. Conversion of aldehydes into oximes

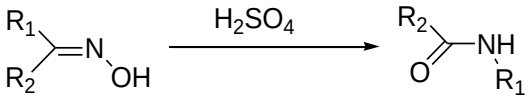
An efficient, environmental friendly protocol for the synthesis of oximes from aldehydes was reported by C. B. Aakeroy and co workers[8] using hydroxyl amine and sodium hydroxide. Various aldehydes including aliphatic, aromatic, heterocyclic aldehydes were converted into corresponding oximes with excellent yield without the use of any toxic solvents (Scheme I.8).



Scheme I.8. Conversion of aldehydes into oximes

I.B.9. Beckmann rearrangement

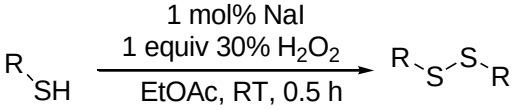
Conversion of oximes to respective amide takes place in presence of an acid during Beckmann rearrangement[9]. Apart from acid a number of reagents have been reported to catalyze Beckmann rearrangement (Scheme I.9). Few of them are thionyl chloride, tosyl chloride, triethylamine, trimethylsilyl iodide[10] etc.



Scheme 1.9. Beckmann rearrangement

I.B.10 Synthesis of disulphides from thiols

Iodine or Iodide ion have been successfully used as a catalyst in the oxidation of thiols to disulphides in presence of hydrogen peroxide by M. Kirihara *et al.*[11] Good yield of disulphides were reported under environment friendly conditions (Scheme I.10).



Scheme I.10. Synthesis of disulphides from thiols

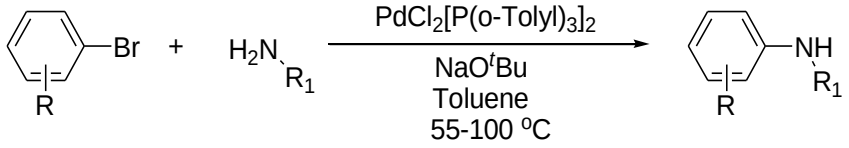
I.C. Carbon-hetero bond formation reactions

Similarly a number of methodologies have been reported for the synthesis involving carbon-hetero bond transformation reactions. Here also we place forward a brief review in these reactions.

I.C.1. C-N bond formation reaction

Buchwald–Hartwig[12] amination is an important reaction where C-N bond formation takes place. It is a palladium-catalyzed reaction where coupling of amines and aryl halides takes place with

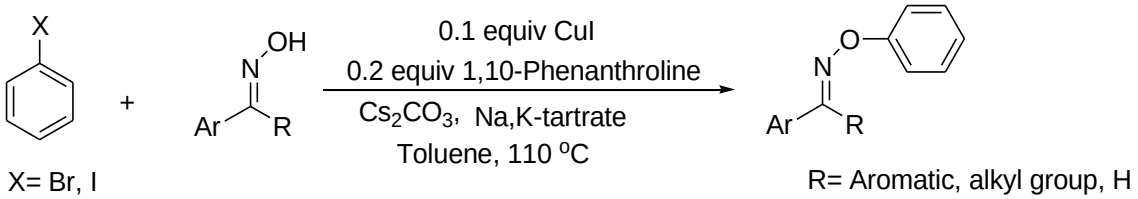
the formation of C-N bond (Scheme I.11). As C-N bond is present in abundant natural products and phermaceuticals, this reaction have a huge implication in industrial preparation of pharmaceuticals.



Scheme I.11. Buchwald–Hartwig amination reaction

I.C.2. C-O bond formation reaction

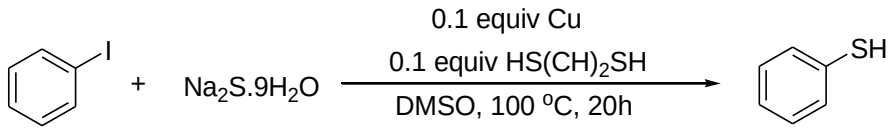
P. De *et al.*[13] reported the synthesis of o-aryloximes by the coupling of aryl halides and oximes. The reaction was catalyzed by CuI in toluene or DMSO and Cs_2CO_3 was used as a base. The reaction was reported to furnish good yield of the products (Scheme I.12).



Scheme I.12. CuI-mediated cross-coupling of aryl halides and oximes

I.C.3. C-S bond formation reaction

Using copper-catalyst, direct synthesis of aryl thiols was reported by H. Xue *et al.*[14] recently in 2017. Aryl iodides were converted into aryl thiols in good yield by using sodium sulfide .The reaction was reported to be aided by 1,2-ethanedithiol and sodium sulfide was used as ultimate sulphur source (Scheme 1.13) .

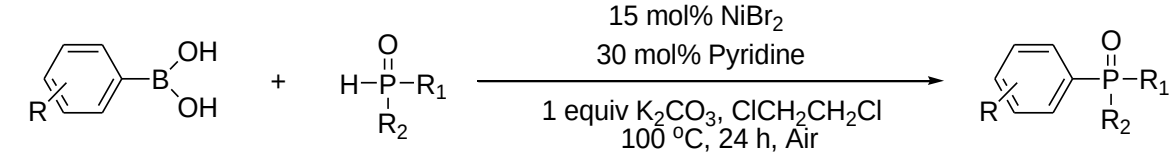


Scheme I.13. Copper catalyzed synthesis of aryl thiols

I.C.4. C-P bond formation reaction

G. Hu and his co-workers[14] recently reported Ni-catalyzed cross coupling reaction where aryl boronic acids were coupled with H-phosphinate esters, H-phosphites and H-phosphine oxides furnishing various aryl-phosphorus compounds. The reaction was performed in absence of

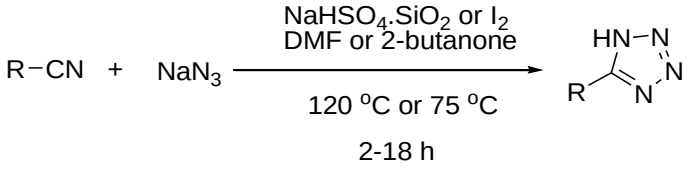
oxidant in most cases. Commercially available cheap $NiBr_2$ was used as a catalyst in mild reaction condition which was the main feature of the reaction along with good yield of the product (Scheme I.14).



Scheme I.14. Ni- catalyzed C-P formation reactions

I.C.5. Synthesis of 5-Substituted 1*H*-tetrazoles from nitriles

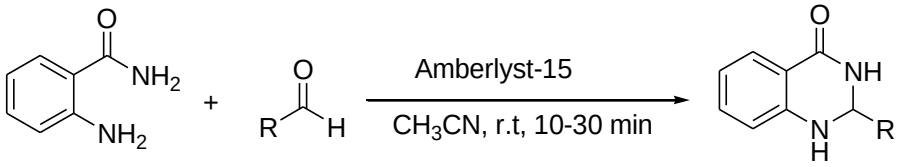
Recently, in the year 2009, B. Das *et al*.[6] have synthesized 5-Substituted 1*H*-tetrazoles using silica-supported sodium hydrogen sulfate or iodine. Here vast array of nitriles including aliphatic, aromatic, hetero nitriles as well as chloroalkyl nitriles are converted to 5-substituted 1*H*-tetrazoles with excellent yield (Scheme I.15).



Scheme I.15. Synthesis of 5-substituted 1*H*-tetrazoles using iodine or silica-supported sodium hydrogen sulfate

I.C.6. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

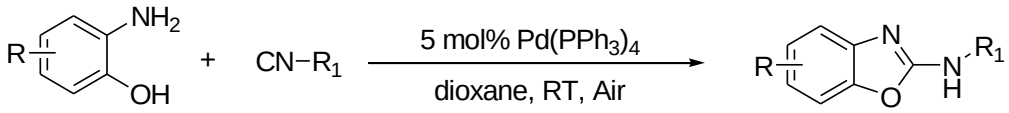
P. V. N. S. Murthy *et al.*[17] have reported a clean method for the synthesis of 2,3-dihydro quinazolin-4(1*H*)-ones using Amberlyst-15 as a catalyst where a number of dihydro quinazolinone derivatives were synthesized from aldehydes and 2-aminobenzamide (Scheme I.15).



Scheme I.16. Amberlyst-15 catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

I.C.7. Synthesis of 2-aminobenzoxazoles

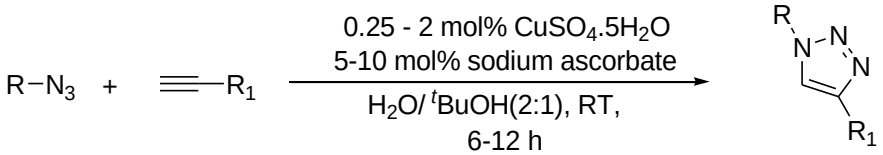
B. Liu *et al.*[18] recently reported palladium-catalyzed synthesis of 2-aminobenzoxazoles under mild conditions. The method was performed by aerobic oxidation of o-aminophenols using isocyanides (Scheme I.17). They further reported the utility of this reaction in the synthesis of other important N-hetero systems.



Scheme I.17. Synthesis of 2-aminobenzoxazoles from o-aminophenols

I.C.8. Synthesis of 1,4-disubstituted 1,2,3-triazoles

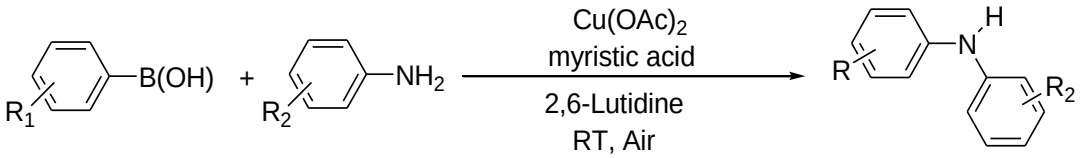
By coupling acetylides and azides, F. Himo *et al.*[19] reported synthesis of 1,4-disubstituted 1,2,3-triazoles (Scheme I.18). The method was reported to be highly reliable and provided high scope with respect to the reactants.



Scheme I.18. Synthesis of 1,4-disubstituted 1,2,3-triazoles by coupling acetylides and azides

I.C.9. Chan−Evans−Lam coupling reaction

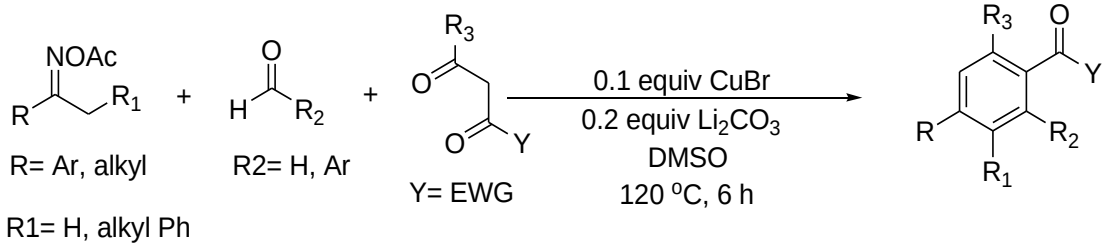
J. C. Antilla *et al.*[20] have reported the coupling of amines with arylboronic acids using copper(II) acetate as catalyst. The reaction was performed at room temperature using myristic acid and 2,6-lutidine as a base. Coupling using functionalized anilines were obtained in good yield using this reaction (Scheme I.19).



Scheme I.19. Chan−Evans−Lam coupling reaction

I.C.10. Cu-catalyzed three-component synthesis of functionalized pyridines

H. Jiang *et al.*[21] reported copper catalyzed synthesis of multi substituted pyridines with C-C/C-N bond formation (Scheme I.20). Use of inexpensive catalyst, high-step economy and redundant of extra oxidant is the main features of the protocol.



Scheme I.20. Cu-catalyzed three-component synthesis of functionalized pyridines

I.D. Conclusion

Thus we see that various synthetic methods are developed for carbon-hetero bond transformation reactions and carbon-hetero bond formation reactions. But most of them lack their significance due to use of expensive and toxic metal catalysts and reactants, harsh reaction conditions, abnormally longer reaction time, low yields, use of toxic solvents, workup difficulties etc. It is clear that there still lies an ample opportunity for improvement in development of carbon-hetero bond transformation reactions and carbon-hetero bond formation reactions.

I.E. References

References are given in BIBLIOGRAPHY under Chapter I.