CHAPTER I

A brief review on approaches towards the synthesis of biologically active carbocyclic and heterocyclic systems

I.1. Introduction

A group of compounds in which all the constituent atoms of the ring is made up of carbon atoms are called carbocyclic compounds. If any of these carbon atoms is being replaced by at least one hetero atom (nitrogen, oxygen, sulfur etc) or non-carbon atom that is known as heterocyclic compound. Carbon can form a wide variety of compounds as because it is tetravalent and it has catenation property (Figure I.1). Carbocyclic compounds are mainly produced by joining of two or more carbocycles together in different ways. These carbocycles are most common in all kinds of natural products. Carbocyclic skeletons hold great importance in various types of organic compounds, pharmaceuticals, natural products, agrichemicals and bioactive molecules etc. Whereas heterocyclic compounds got significant importance as because they are useful in making building blocks of biologically active compounds. Ursane, a carbocyclic compound, has anti-inflammatory property. Betulin, a carbocyclic compound, derived from birch tree, has anti-HIV, anti-cancer, anti-inflammatory property. It is selectively used for HIV-1 to inhibit the growth of the virus. Lupeol, another carbocyclic compound, which is normally found in green peeper, cabbage etc, has anti-cancer, anti-inflammatory property (Figure I.2). On the other hand, some heterocyclic systems like Phenylbutazone is used as anti-inflammatory drug, Losartan is used to control high blood pressure etc. Therefore, carbocyclic and heterocyclic systems have significant importance in our day-to-day life (Figure I.3).

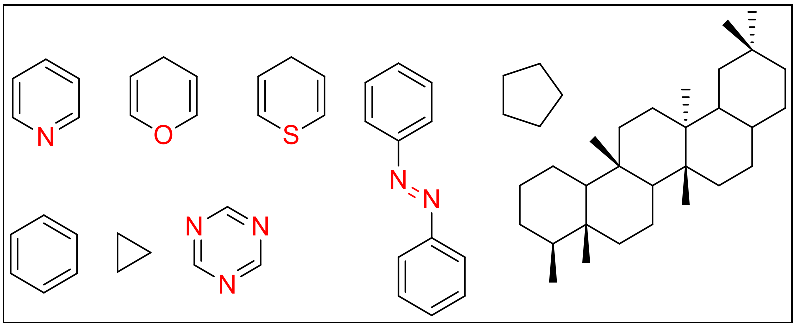


Figure I.1. Some known carbocyclic and heterocyclic skeleton

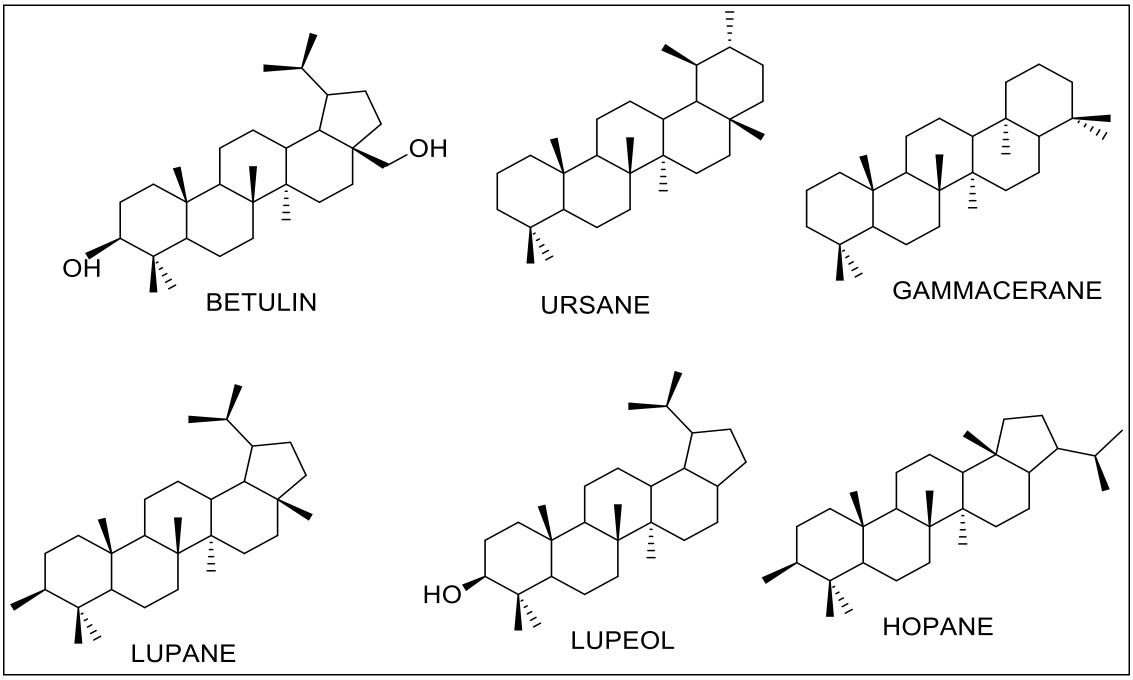


Figure I.2. Some biologically active carbocyclic compounds

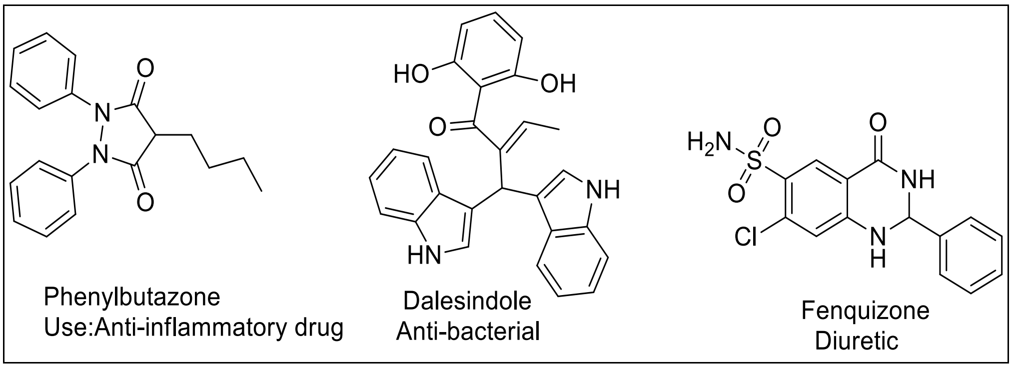


Figure I.3. Some biologically active heterocyclic compounds

Now a day, there is raising demand for more eco-benign protocols in the field of organic synthesis. Simultaneously carbocyclic and heterocyclic compounds contain wide range of application. So strategies to synthesize these compounds are always of great priority.

I.2. Synthesis of carbocyclic compounds

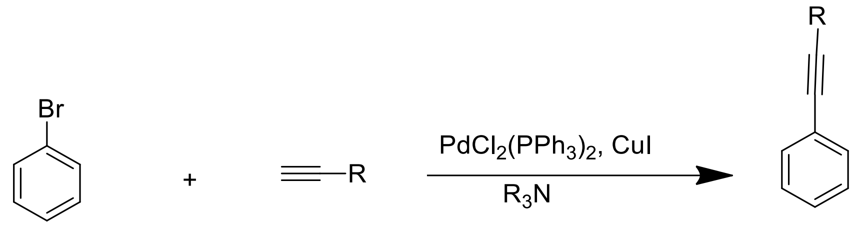
A number of strategies have been reported in literature towards the transformation reactions of carbocyclic compounds. A brief review has been discussed in this section.

I.2.1. Carbon-carbon bond formation reactions

Carbon-carbon bond formation reaction plays a vital role in the organic synthesis for the construction of variety structurally diverse organic molecules. A number of methodologies have been reported in literature for reactions involving carbon-carbon bond formation. A brief review has been discussed in this section.

I.2.1.1. Sonogashira coupling reaction

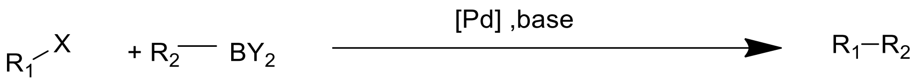
In the year 1975, Sonogashira introduced a powerful protocol towards C-C bond forming reaction. The reaction was carried out between the terminal alkynes with aryl or vinyl halides by using a palladium catalyst, a copper (I) co-catalyst, and an amine base.[1-2] This reaction has been widely applied to diverse areas such as natural products synthesis, heterocyclic synthesis and material science.[3] Copper salts were found to be the most common co-catalyst (Scheme I.1).



Scheme I.1. Sonogashira Coupling reaction

I.2.1.2. Suzuki coupling reaction

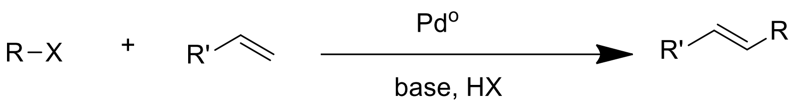
The cross-coupling reaction of organic halides, with organoboron compounds by using phosphine-based palladium catalysts, was introduced by A. Suzuki *et al.*[4] It is diverse in nature and an important method for the generation of unsymmetrical biaryls from arylboronic acids and aryl halides by using a single step. It is very important for the synthesis of natural products as well as pharmaceuticals, herbicides, conducting polymers (Scheme I.2).[5]



Scheme I.2. Suzuki Coupling reaction

I.2.1.3. Heck coupling reaction

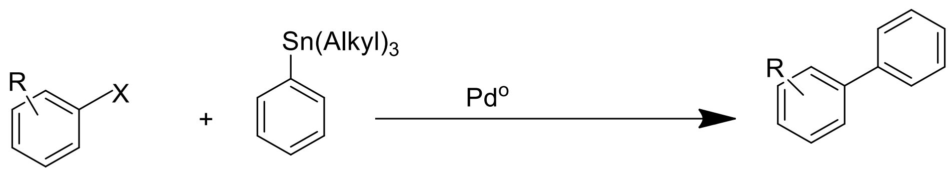
C-C coupling reaction between the alkene and unsaturated halide (or triflate) by using the palladium catalyst (or palladium nano-material based catalyst) in the presence of a base to form a substituted alkene is known as Heck Coupling reaction (Scheme I.3).[6]



Scheme I.3. Heck coupling reaction

I.2.1.4. Stille coupling reaction

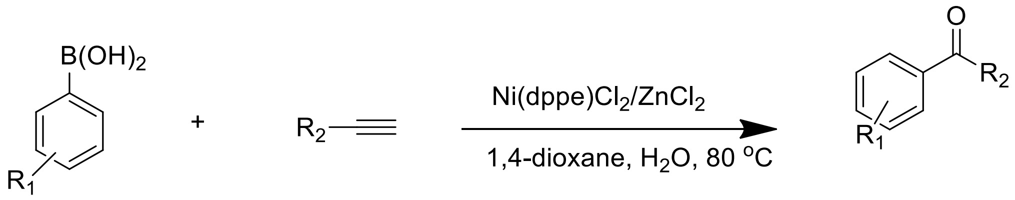
In Stille coupling reaction, a method was provided by which the C-C bond formation happened through the coupling of alkenyl and aryl halides with the help of organostannanes and associated with of palladium catalyst (Scheme I.4).[7]



Scheme I.4. Stille coupling reaction

I.2.1.5. Direct synthesis of arylketones

C. Chien-Hong *et al.* has recently been introduced an efficient and convenient nickel-catalyzed addition reaction of the arylboronic acids and nitriles towards the synthesis of aryl ketones. By this reaction different types of aryl ketone derivatives have been synthesized so far (Scheme I.5).[8]



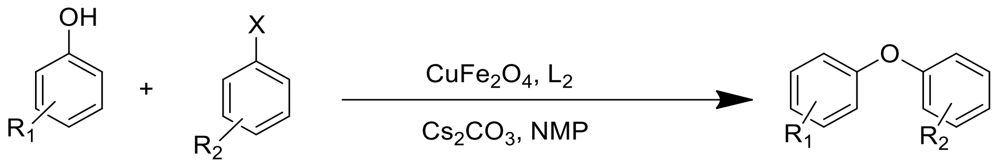
Scheme I.5. Direct synthesis of aryl ketones

I.2.2. Carbon-hetero bond formation reactions

A wide number of methodologies have been reported for the transformation reaction of carbocyclic compounds which involved the formation of carbon–hetero bond formation. A very short review has been discussed below.

I.2.2.1. C-O bond formation reaction

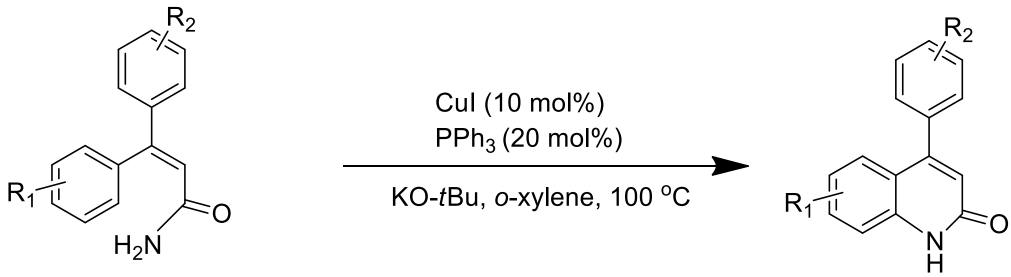
The Ullmann C-O coupling by the reaction of phenols and aryl halides was repoted by W. Yang *et al.* in the presence of the air stable copper ferrite ($CuFeO_4$) nano-particle catalyst.[9] This reaction yielded good amount of the products and the catalyst was easily recovered by using the external magnetic field (Scheme I.6).



Scheme I.6. Copper ferrite ($CuFeO_4$) nanoparticle catalyzed Ullmann C-O coupling reaction

I.2.2.2. C-N bond formation reaction

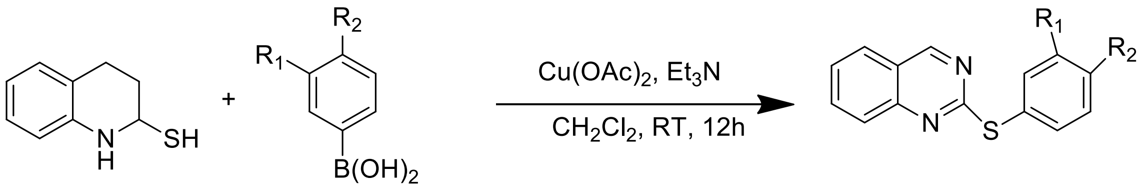
Cacchi *et al.* developed new method by utilizing Cu as a catalyst for the construction of 2-quinolones. The process was developed on the basis of intra-molecular C–H functionalization/C–N bond formation. The reaction was carried out by the use of CuI (10 mol%) as catalyst with PPh_3 (20 mol%) and KO-*t*Bu in *ortho*-xylene solvent at 100 ^oC for 5 to 24 h in aerobic conditions (Scheme I.7).[10]



Scheme I.7. Copper iodide (CuI) catalyzed reaction for the construction of 2-quinolones

I.2.2.3. C-S bond formation reaction

N. K. Katari *et al.* developed a Chan-Lam coupling reaction for the synthesis of S-aryl aryl/heteroaryl-quinazoline and in this reaction, 1,4-dihydroquinazoline was treated with huge variety of aryl and hetero-arylboronic acids by using $Cu(OAc)_2$ as a catalyst in CH_2Cl_2 solvent (Scheme I.8).[11]



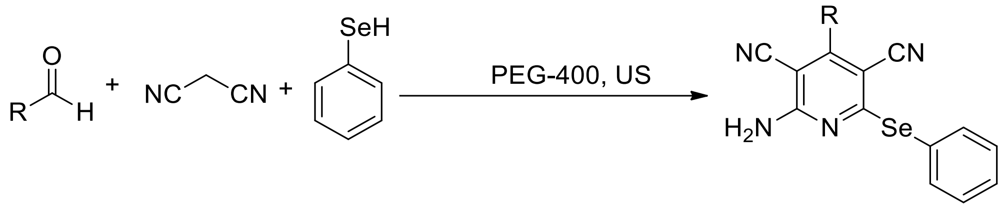
Scheme I.8. [$Cu(OAc)_2$] catalyzed C-S bond formation reaction

I.3. Approachs towards the synthesis of heterocyclic compounds

A number of methodologies have been reported so far in literature for synthesis towards heterocyclic compounds having nitrogen, oxygen, sulphur, selenium in their skeleton. A brief review has been discussed in this section.

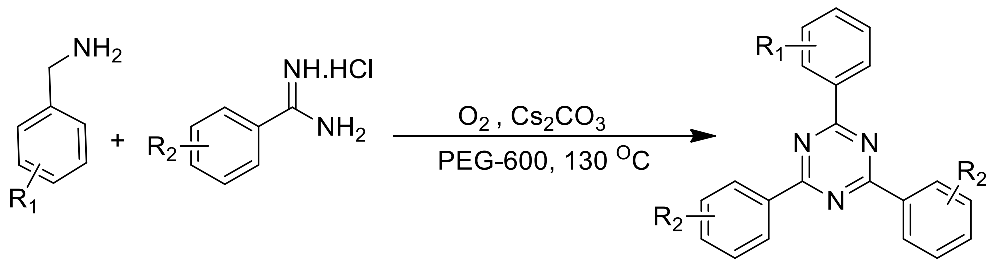
I.3.1. Synthesis of *N*-containing heterocyclic compound

In the year 2015, Md. N. Khan *et al.* had carried out one-pot three-component strategy for the synthesis of series 2-aminoselenopyridine derivatives from aldehydes, malononitrile and benzeneselenol in PEG-400 by using ultrasound (Scheme I.9).[12] In this methodology, a number of four new bonds such as one C–N, one C–Se and two C–C is formed. Molecules having pyridine moiety with selenium may be regarded as biologically potent.



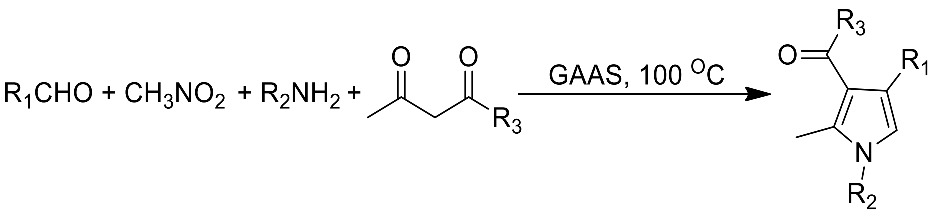
Scheme I.9. PEG-400 mediated synthesis of 2-aminoselenopyridine

In the year 2016, the synthesis of 1,3,5-triazines from substituted benzylamines and amidines in PEG-600 was carried out by A. R. Tiwari *et al.* in 2016. This protocol was found to be free from transition-metal, phosphine ligand and in this method molecular oxygen as an oxidant (Scheme I.10).[13] A series of 1,3,5-triazines derivatives were synthesized in moderate to good yields.



Scheme I.10. PEG-600 mediated synthesis of 1,3,5-triazines

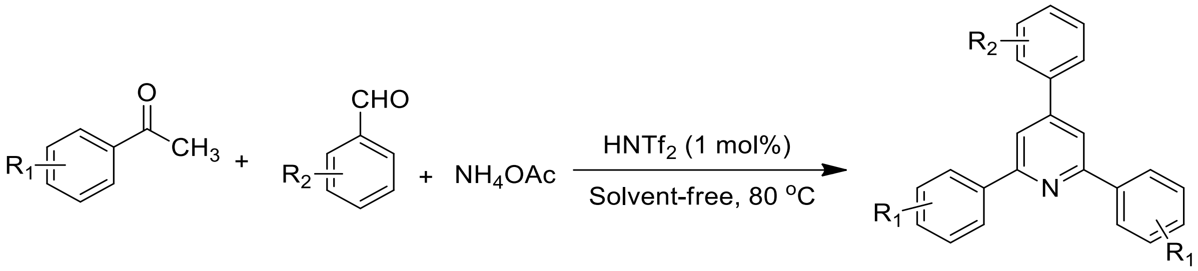
B. -L. Li *et al.* carried out the synthesis of functionalized polysubstituted pyrroles by using four-component reaction of amines, aldehydes, 1,3-dicarbonyl compounds and nitromethane in 50% GAAS (Scheme I.11).[14] In this reaction, there was no added catalyst and could be recycled and reused several times without loss of its efficiency. The structures of the derived products were identified from their IR, ^{1}H NMR, ^{13}C NMR spectra, MS and elemental data analysis.



Scheme I.11. Synthesis of pyrroles in gluconic acid aqueous solution

Under metal and solvent-free conditions and by using triflimide as an effective catalyst in the year 2019, H. Wang *et al.* introduced one-pot three-component synthesis for of 2,4,6-

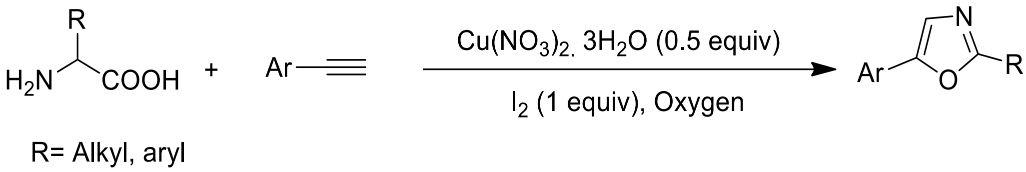
triarylpyridines from aromatic aldehydes, substituted acetophenones and ammonium acetate (Scheme I.12).[15]



Scheme I.12. One-pot three-component synthesis of 2,4,6-triarylpyridines using triflimide

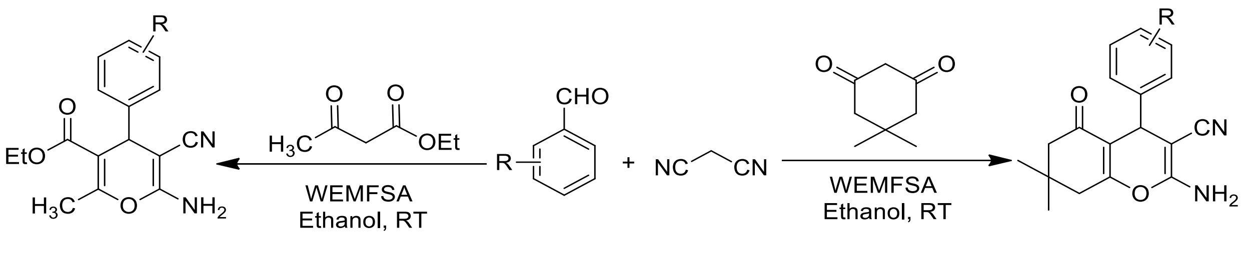
I.3.2. Synthesis of *O*-containing heterocyclic compound

The synthesis of 2,5-disubstituted oxazoles from easily available precursors namely, arylacetylenes and α-amino acids in the presence of $Cu(NO_3)_2.3H_2O$ and iodine was carried out by J. Wanga *et al.* in the year 2019 (Scheme I.13).[16] This reaction process includes the $I_2/Cu(NO_3)_2.3H_2O$-supported transformation of arylacetylene to α-iodo acetophenone.



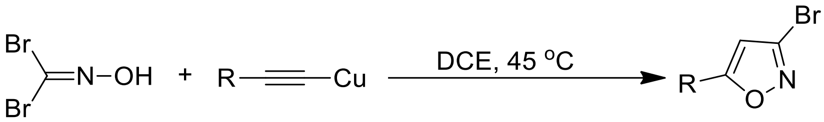
Scheme I.13. Synthesis of 2,5-Disubstituted Oxazoles

Muskmelon fruit has widely spread importance. By using agro-waste based water extract of muskmelon fruit shell ash (WEMFSA) P. B. Hiremath *et al.* came forward with a strategy of one-pot three-component reaction for the synthesis of 2-amino-4*H*-pyran derivatives in 2020 (Scheme I.14).[17] WEMFSA perform the role of catalyst in the absence of an external base or ligand/catalyst/additives. Electron withdrawing and donating group containing systems also performed well.



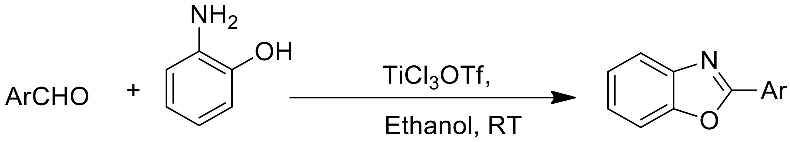
Scheme I.14. Synthesis of 2-Amino-4*H*-pyrans catalyzed by WEMFSA

In the year 2014, A tandem synthesis of 3-halo-5-substituted isoxazoles was carried out by W. Chen *et al.* by reacting 1-copper(I) alkynes and dihaloformaldoximes under base-free conditions (Scheme I.15).[18] The reaction passes *via* selectively nucleophilic addition-elimination. Here the alkyl group can be aryl, alkyl or cyclic.



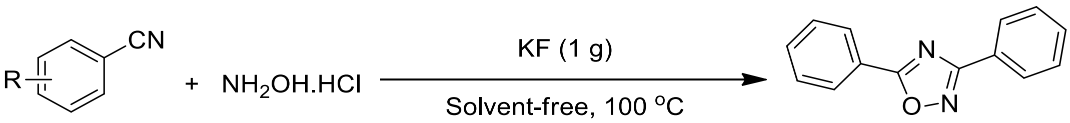
Scheme I.15. Tandem synthesis of isoxazoles from 1-Copper (I) Alkynes

In the year 2016, benzoxazole derivatives were synthesized by J. Azizian *et al.* from the reaction of aldehydes and 2-aminophenol under mild conditions using $TiCl_3OTf$ as a catalyst and ethanol as green media (Scheme I.16).[19]



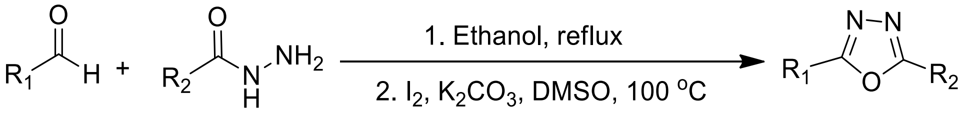
Scheme I.16. Synthesis of benzoxazoles by using $TiCl_3OTf$ as a catalyst

By the reaction of nitriles and hydroxylamine hydrochloride in the presence of potassium fluoride as catalyst S. Rostamizadeh *et al.* has introduced a one-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles *via* solid support under solvent-free condition in the year 2010. The major intermediate formed for this protocol was found to be amidoxime (Scheme I.17).[20]



Scheme I.17. Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles using potassium fluoride under solvent-free conditions

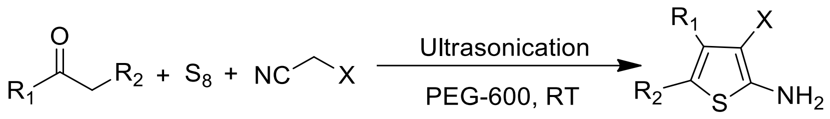
A transition-metal-free oxidative cyclization process of acylhydrazones was developed by W. Yu *et al.* in the year 2013 towards the synthesis of symmetrical and asymmetrical 2,5-disubstituted (aryl, alkyl, and/or vinyl) 1,3,4-oxadiazoles by using iodine in the presence of potassium carbonate (Scheme I.18).[21]



Scheme I.18. Synthesis of 1,3,4-Oxadiazoles from aldehydes and hydrazides using I_2

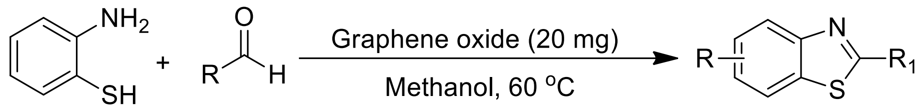
I.3.3. Synthesis of *S*-containing heterocyclic compound

In the year 2017, A. Akbarzadeh *et al.* developed a strategy for the synthesis of functionalized 2-aminothiophene derivatives by using the one-pot three-component reaction procedure from enolizable carbonyl compounds, malononitrile or ethyl cyanoacetate and elemental sulfur using PEG-600 as an eco-benign reaction medium, ultrasonic conditions (Scheme I.19).[22]



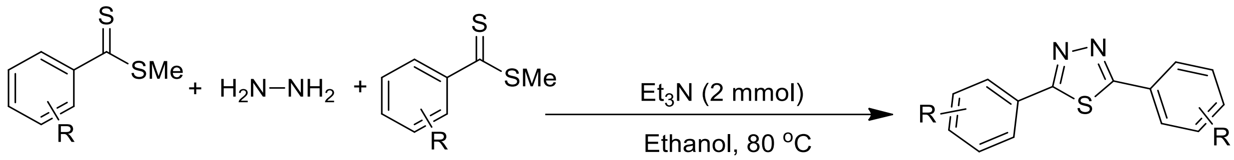
Scheme I.19. Synthesis of 2-aminothiophene moieties by using PEG-600

In the year 2016, K. B. Dhopte *et al.* reported the synthesis of benzothiazoles using graphene oxide, a carbocatalyst by the reaction of 2-aminothiol and aldehyde at 60 °C, under ultrasonic irradiation by using methanol as solvent (Scheme I.20).[23] In this protocol Graphene oxide acts as metal-free acid catalyst as well as an oxidizing agent.



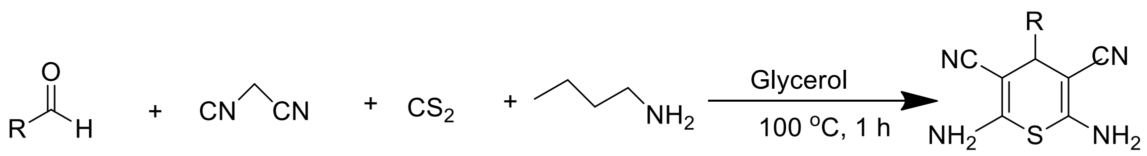
Scheme I.20. GO catalyzed synthesis of benzothiazoles

In the year 2019, H. A. Swarup *et al.* strategized an approach towards the construction of 3,5-disubstituted 1,3,4-thiadiazoles from dithioesters, hydrazine hydrate and triethyl amine under transition-metal free condition by using triethylamine in ethanol media (Scheme I.21).[24]



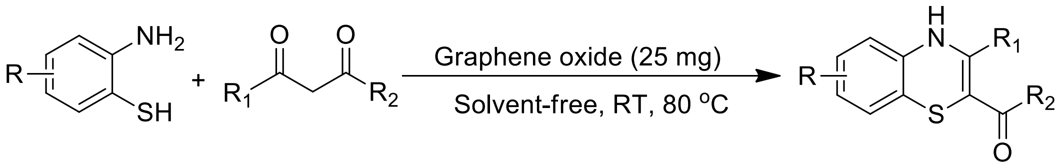
Scheme I.21. Synthesis of 3,5-disubstituted 1,3,4-thiadiazole from dithioesters

In the year 2019, B. Mitra *et al.* came up with one-pot pseudo five-component protocol and contributed to environmental sustainability by using glycerol to design the diverse biologically active 4*H*-thiopyrans (Scheme I.22)[25].



Scheme I.22. Glycerol assisted synthesis of 4*H*-thiopyran

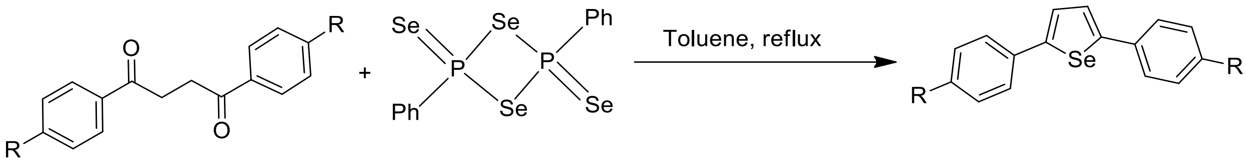
Graphene oxide is widely known to be a recyclable carbocatalyst. So Graphene oxide was used for the construction of 1,4-benzothiazine from 2-aminothiophenol and 1,3-dicarbonyl compound by S. Bhattacharya *et al.* in the year 2017 (Scheme I.23).[26] This method stressed on the large surface area of GO nanosheet also with the presence of acidic and oxidative groups catalyze the oxidative cyclization significantly.



Scheme I.23. GO assisted construction of 1,4-benzothiazine from 2-aminothiophenol and 1,3-dicarbonyl compound

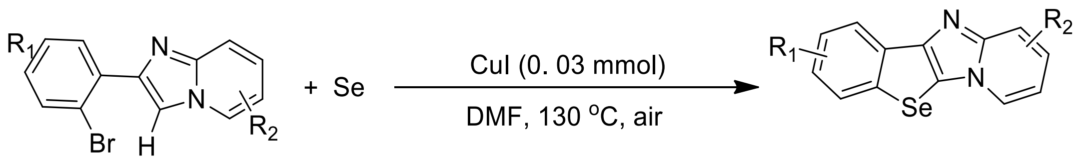
I.3.4. Synthesis of *Se*-containing heterocyclic compound

In the 2010, G. Hua *et al.* formulated a synthetic procedure for synthesis of 2,5-diarylselenophenes by the reaction of 2,4-bis(phenyl)-1,3-diselenadiphosphetane-2,4-diselenide (Woollins'reagent) with one equivalent of 1,4-diarylbutane-1,4-diones under the conditions of refluxing toluene (Scheme I.24).[27]



Scheme I.24. Synthesis of novel 2,5-diarylselenophenes

In 2017, P. Sun *et al.* strategized a protocol for the formation of nitrogen heterocycle-fused imidazo[1,2-*a*]-pyridine and benzo[*b*]selenophenes by using copper-catalyzed direct selenylation of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines through regioselective breaking of C(sp^2)−Br and C(sp^2)−H bonds using readily available selenium powder and the selenylating reagents were found to be under ligand and base-free conditions in air (Scheme I.25).[28]



Scheme I.25. Selenylation of imidazo[1,2-*a*]pyridines by using Copper as a catalyst

I.4. Conclusion

There are so many strategies already reported towards the synthesis of carbocyclic and heterocyclic compounds. From above literature study it is clear that sufficient scope is still there to incorporate new research domain in this field.

I.5. References

References are given in BIBLIOGRAPHY under Chapter I (page 90-91).