# Chapter I

# A brief review on approaches towards the synthesis of bioactive heterocyclic compounds

## I.1. Introduction

A cyclic organic compound comprising all carbon atoms in ring formation is designated as carbocyclic compound, while the cyclic compounds consisting of at least one hetero atom that is non-carbon atom in the ring are known as heterocyclic compounds. The most common heteroatoms are nitrogen, oxygen and sulphur but heterocyclic ring containing other heteroatoms such as selenium, tellurium and phosphorus are rarely known. Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide and is also recognized as the ubiquitous of conventional organic synthesis. They play imperative role in various processes and industries, as well. It is well known that more than 90% of new drugs consist of heterocyclic framework which plays a vital role as interface between chemistry and biology. Most of the innovation and progress of new scientific approach consists of heterocyclic compounds. Some heterocyclic moieties with both five and six member ring skeleton with one and more than one hetero atoms reported in literature is given in Figure I.1.

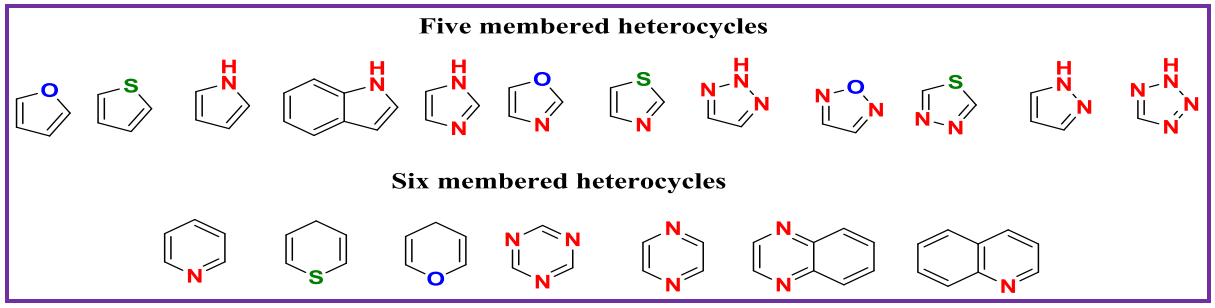



**Figure I.1.** Some known heterocyclic skeleton

Furthermore, heterocyclic moieties have gained enormous significance not only biologically and industrially but also in the implementation of any urbanized human society as well. The bulk of pharmaceutical products that mimic natural products with biological activity are heterocycles. Consequently, researchers are on a continuous exploration to invent and construct better pharmaceuticals, pesticides, insecticides, rodenticides and weed killers by following natural models. Heterocyclic compounds play a prime role in biochemical processes and are also essential constituents of living cells. Other significant convenient applications of these compounds are their use as additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants and vulcanization accelerators. Apart from this, they are considered to be powerful starting materials for construction of naturally occurring biologically active compounds like amino acids, glycosides, naturally occurring heterocyclic compounds, etc.

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 including heterocyclic compounds.

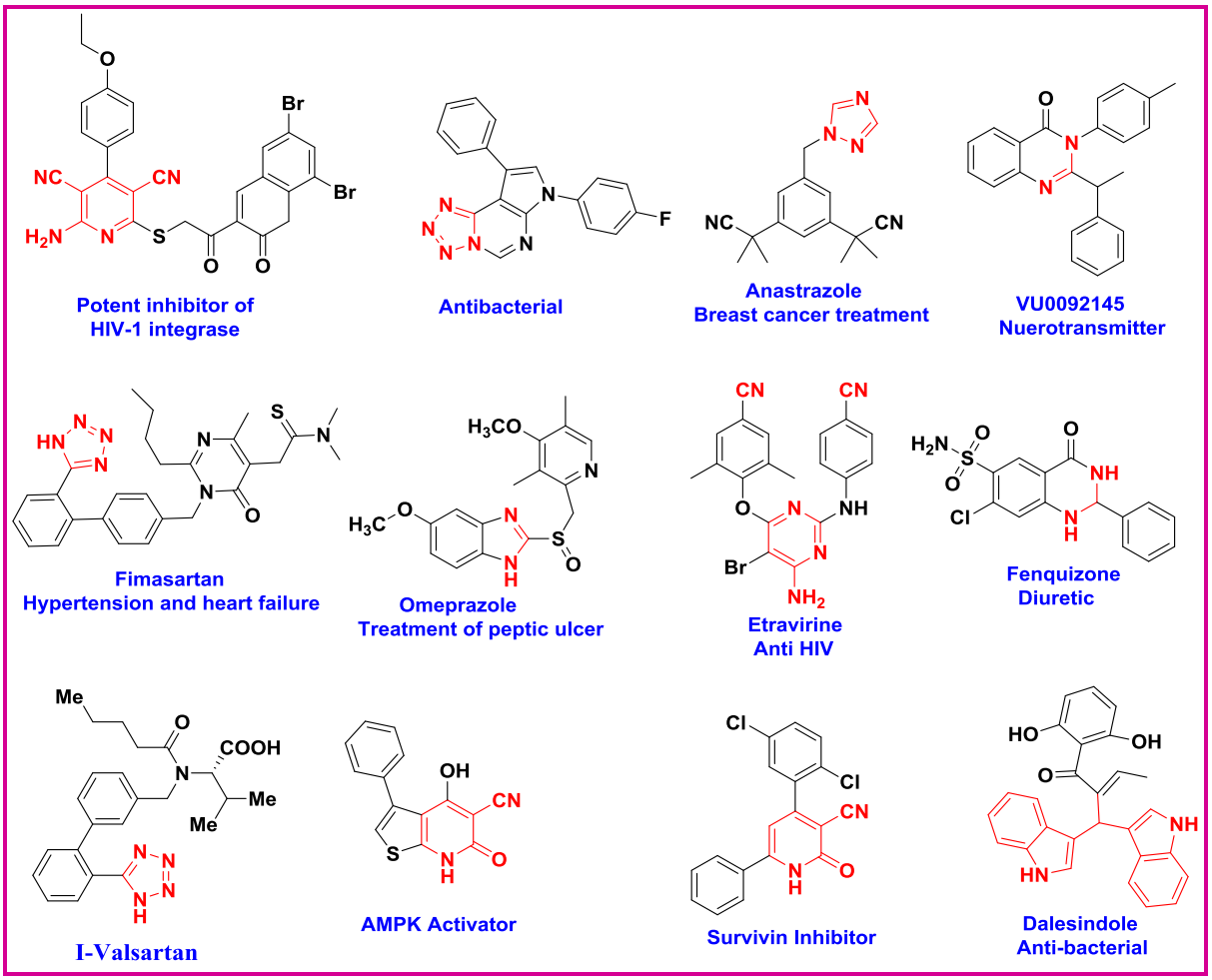



**Figure I.2.** Biologically active molecules having heterocyclic moiety

Heterocyclic derivatives have been extensively used as important tool in skeleton construction for synthesis of numerous drugs in pharmaceutical industries (Figure I.2). There is always an important thing about an efficient methodology for synthesizing of new heterocyclic moiety. Now literature survey reveals that more than 85-95% new drugs containing heterocyclic which has bright scientific insight in the biological system. A vast number of combinations of carbon, hydrogen and hetero atoms can be designed, providing compounds with the most diverse physical, chemical and biological properties. Among 20 million chemical compounds identified by the end of second millennium, more than two-thirds are fully or partially aromatic and approximately one-half are heteroaromatic. It is, therefore, easy to understand why both the development of new methods and the strategic deployment of known methods

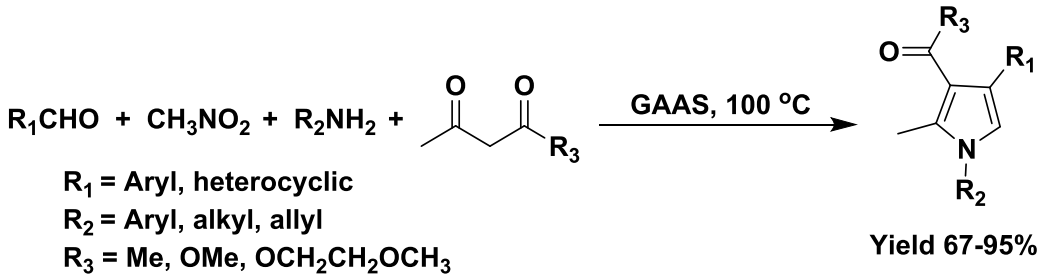
for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations.

**I.2. Approach towards the synthesis of heterocyclic compounds**

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

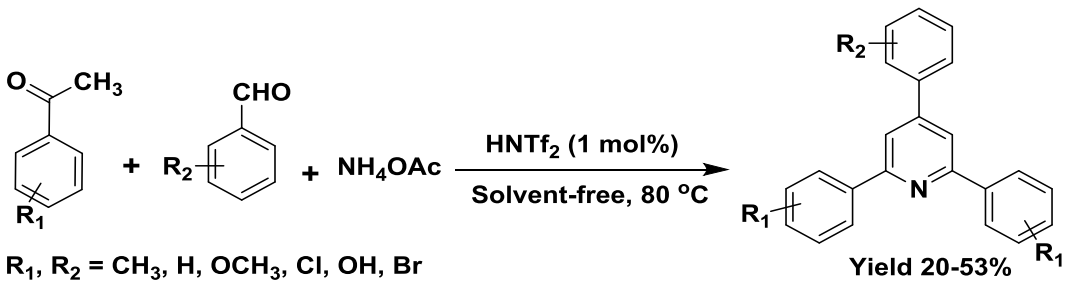
**I.2.1. Synthesis of *N*-containing heterocyclic compounds**

One-pot four-component reaction of amines, aldehydes, 1,3-dicarbonyl compounds and nitromethane was carried out in 50% GAAS to synthesize functionalized polysubstituted pyrroles by B.-L. Li *et al.* (Scheme I.1).[1] This reaction proceeds without any added catalyst and the solvent used could be recycled and reused several times without significant loss of its efficiency. The structures of the prepared products were identified from their IR, $^{1}$H NMR, $^{13}$C NMR spectra, mass spectra and elemental analysis.



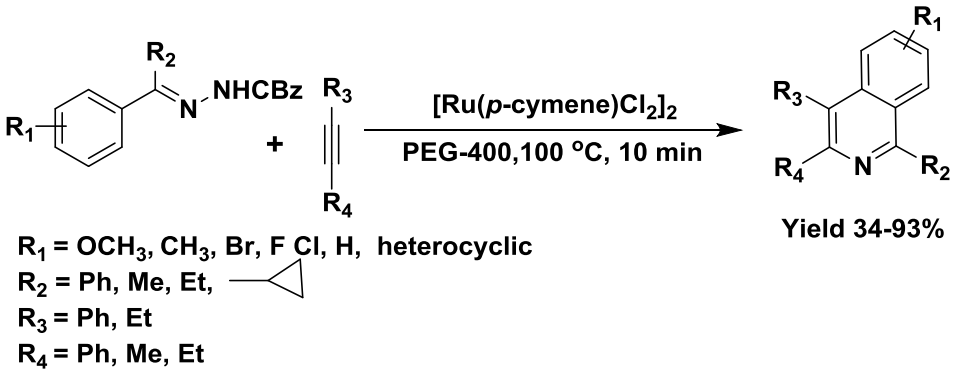

**Scheme I.1.** Synthesis of functionalized pyrroles in gluconic acid aqueous solution

In 2019, H. Wang *et al.* developed one-pot three-component synthesis for preparation of 2,4,6-triarylpyridines from aromatic aldehydes, substituted acetophenones and ammonium acetate using the versatile super brønsted acid, triflimide as an effective catalyst under metal and solvent-free conditions (Scheme I.2).[2]



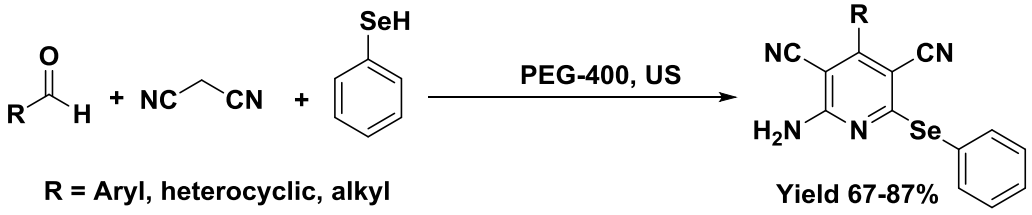

**Scheme I.2.** One-pot three-component synthesis of 2,4,6-triarylpyridines using triflimide

D. S. Deshmukh *et al.* in 2019 employed *N*-Cbz hydrazone as a rarely explored directing group for the synthesis of isoquinolines through annulations with internal alkynes *via* C-H/N-N activation using Ruthenium catalyst. In this work, additive as well as external oxidant-free methodology has been used for the synthesis of isoquinolines using microwave (Scheme I.3).[3] The scope of symmetrical and unsymmetrical substituted internal alkynes for the stated methodology was investigated by them.




**Scheme I.3.** Ruthenium catalyzed annulation of *N*-Cbz hydrazones *via* C–H/N–N bond activation for synthesis of isoquinolines

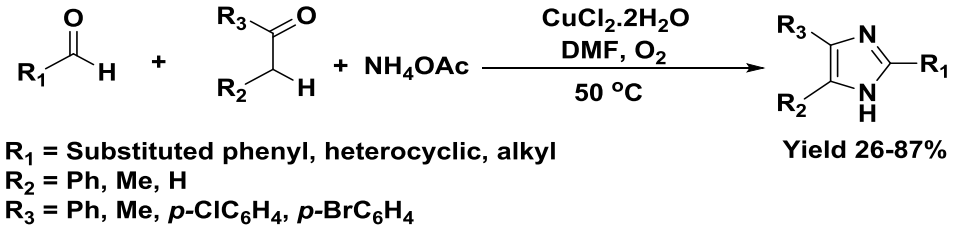
In 2015, Md. N. Khan *et al.* demonstrated one-pot three-component protocol for synthesis of 2-aminoselenopyridine derivatives from aldehydes, malononitrile and benzeneselenol in PEG-400 using ultrasound (Scheme I.4).[4] In this process, total four new bonds, one C–N, one C–Se and two C–C are formed by one pot mechanism. Molecules having pyridine moiety with selenium may be useful in medicinal chemistry.




**Scheme I.4.** Synthesis of selenopyridines in PEG-400 from aldehydes

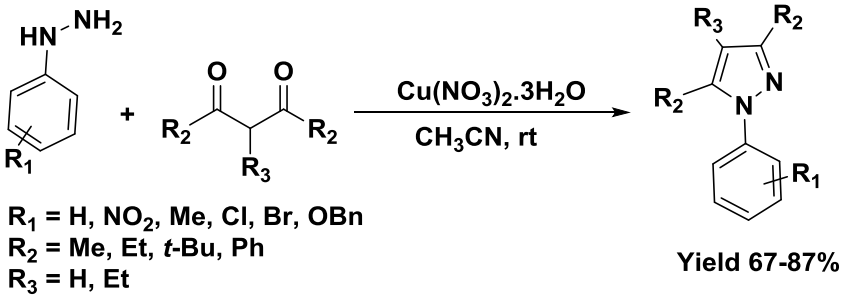
In 2017, J. Jayram *et al*. introduced one-pot multi-component protocol for synthesis of imidazole derivative from aldehydes, α-methyleneketones and ammonium acetate using copper chloride in presence of molecular oxygen (Scheme I.5).[5] In this protocol, ammonium acetate is the source of nitrogen of imidazole moiety and molecular oxygen as oxidant. This

reaction proceeds *via* aerobic benzylic $sp^3$ C-H oxidation to produce a diketone moiety. A radical mechanism was proposed by J. Jayram *et al*.



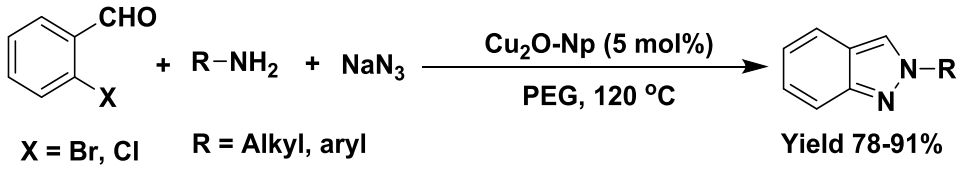

**Scheme I.5.** Copper catalyzed aerobic synthesis of 2,4,5-trisubstituted imidazoles

H. Wang *et al.* developed a strategy for synthesis of pyrazoles using copper catalyst. In this protocol, copper catalyzed condensation reaction was described for synthesis of pyrazole derivatives at room temperature under acid-free conditions in 2018 (Scheme I.6).[6]




**Scheme I.6.** Copper catalyzed synthesis of substituted pyrazoles at room temperature

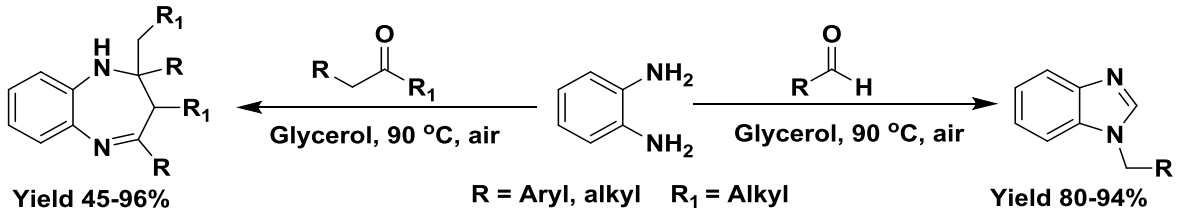
Synthesis of 2*H*-indazole derivatives based on one-pot three-component reaction of 2-chloro and 2-bromobenzaldehydes, primary amines and sodium azide is described by H. Sharghi *et al.* in 2014 (Scheme I.7).[7] The reaction is catalyzed by copper (I) oxide nanoparticles ($Cu_2O$-Np) under ligand-free conditions in PEG-300.




**Scheme I.7.** Synthesis of 2*H*-indazole derivatives catalysed by $Cu_2O$-Np

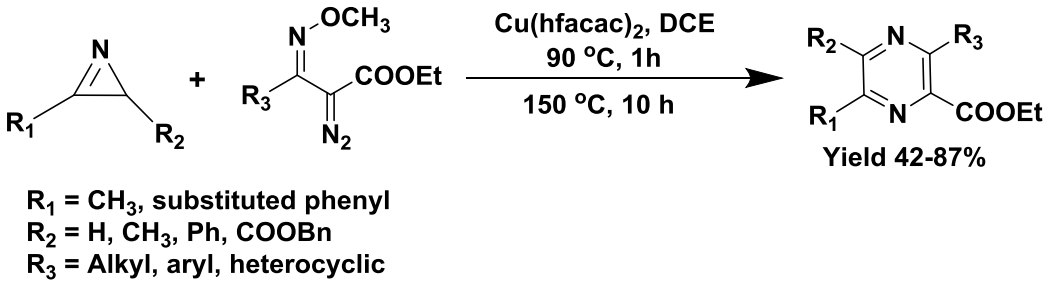
In 2011, C. S. Radatz *et al.* promoted glycerol as a reaction medium for the metal and catalyst-free synthesis of benzodiazepines and benzimidazoles in absence of any supplementary catalyst. These were straightforward approach for synthesis of the corresponding 1,5-benzodiazepines and disubstituted benzimidazoles by the condensation of

*o*-phenylenediamine with several ketones and aldehydes respectively in glycerol (Scheme I.8).[8]



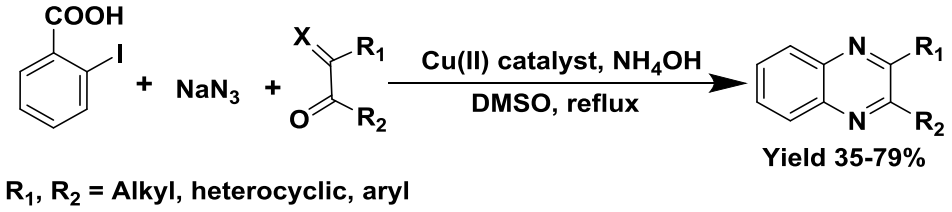

**Scheme I.8.** Catalyst-free synthesis of benzodiazepines and benzimidazoles using glycerol

N. S. Y. Loy *et al.* reported a different, new and innovative strategy for the construction of unsymmetrical substituted pyrazine derivatives using copper salt as catalyst in 2015 (Scheme I.9.).[9] In this method, unsymmetrical substituted pyrazines were designed from α-diazo oxime ethers with 2*H*-azirines using copper hexafluoroacetylacetonate in DCE medium.

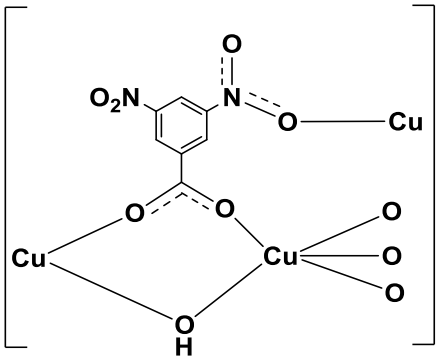



**Scheme I.9.** Synthesis of unsymmetrical pyrazines from α-diazo oxime ethers

In 2018, B. Mitra *et al.* published a one-pot three-component protocol for the synthesis of diverse array of quinoxaline moiety from some substituted *vic*-diketone/α-hydroxy ketone, sodium azide, ammonium hydroxide and 2-iodobenzoic acid using a copper (II) catalyst poly [($\mu_3$-3,5-dinitrobenzoato$k^3$ $O^1$:$O^{1'}$:$O^3$)($\mu_2$-hydroxido-$k^2$O:O)-copper (II)] in DMSO (Scheme I.10).[10] In this methodology, both sodium azide and ammonium hydroxide was used as the source of nitrogen. The synthesized Cu(II) catalyst was characterized by mass, SEM and XRD analysis.



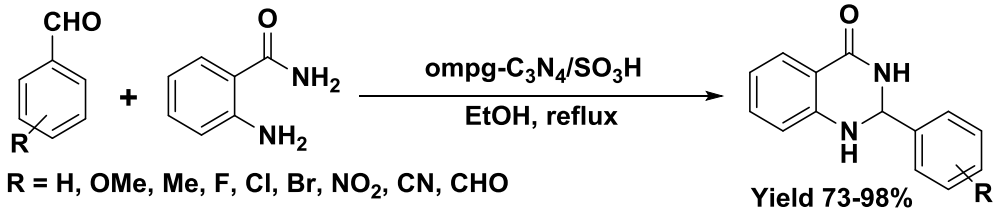

$R_1$, $R_2$ = Alkyl, heterocyclic, aryl




Poly [($\mu_3$-3,5-dinitrobenzoato $k^3$ $O^1$:$O^{1'}$:$O^3$) ($\mu_2$-hydroxido-$k^2$O:O)-copper (II)]

**Scheme I.10.** Synthesis of quinoxaline from 2-iodobenzoic acid using organo Cu(II) catalyst

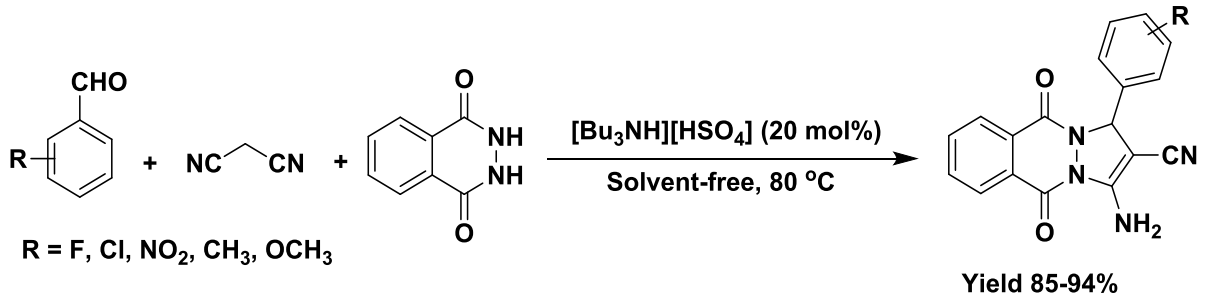
H. Ghafuri *et al.* in 2019 were successful to synthesize sulfonated highly ordered mesoporous graphite carbon nitride (ompg-$C_3N_4$/$SO_3H$) organocatalyst. Then they characterized the catalyst using FT-IR, SEM-EDX, XRD, TGA, differential thermal analysis and BET surface area. The organocatalyst was then employed in one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by condensation of anthranilamide with aldehydes or ketones in ethanol (Scheme I.11).[11]




R = H, OMe, Me, F, Cl, Br, $NO_2$, CN, CHO

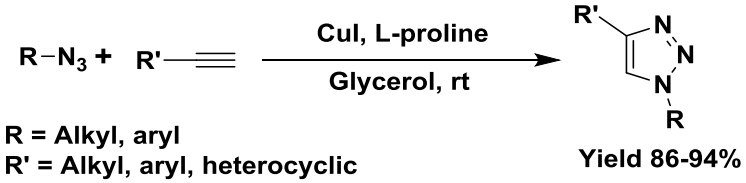
**Scheme I.11.** Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives in ethanol

An acidic ionic liquid, [$Bu_3NH$][$HSO_4$] catalysed one-pot multi-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones by using various aldehyde, malononitrile and phthalhydrazide in absence of solvent was described by M. A. Shaikh *et al.* in 2018 (Scheme I.12).[12] Further, the catalyst was characterized by different techniques such as FT-IR, $^1$H-NMR, $^{13}$C-NMR and TG, DTG and DTA analyses.



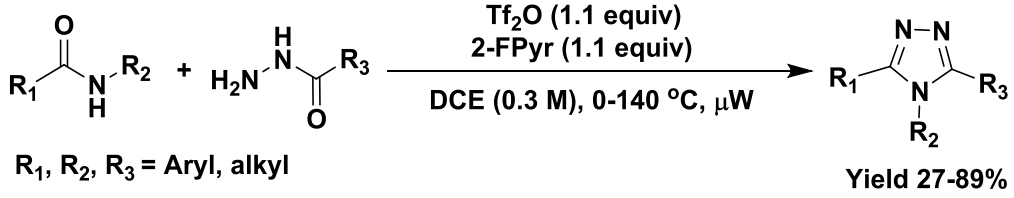

**Scheme I.12.** Acidic ionic liquid [$Bu_3NH$][$HSO_4$] catalysed synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

Synthesis of 1,4-disubstituted-1,2,3-triazoles through CuAAC reaction is known as click reaction. In such conversion, the catalytic species, Cu(I) getting converted to thermodynamically more stable Cu(II) through aerial oxidation or disproportionation is a major issue. To stabilize the Cu(I) species, the reaction is ideally carried out under an inert atmosphere in presence of additives such as alcohols, amines, thiols and aldehydes. To overcome this drawback, B. G. Pasupuleti *et al.* in 2019 reported the first CuI catalyzed click reaction without an inert atmosphere by employing the CuI/L-proline system in glycerol (Scheme I.13).[13]




**Scheme I.13.** Synthesis of 1, 4-disubstituted-1,2,3-triazoles

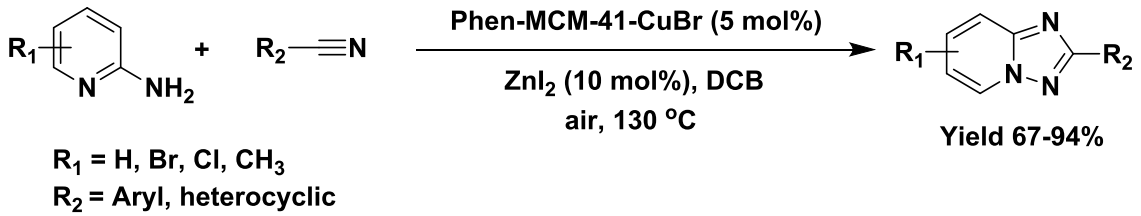
In 2015, W. S. Bechara *et al.* published a methodology for one-pot synthesis of 3,4,5-trisubstituted-1,2,4-triazoles from secondary amides and hydrazides *via* triflic anhydride activation followed by microwave-induced cyclo-dehydration (Scheme I.14).[14]




**Scheme I.14.** One-pot synthesis of 1,2,4-triazoles from hydrazides and secondary amides

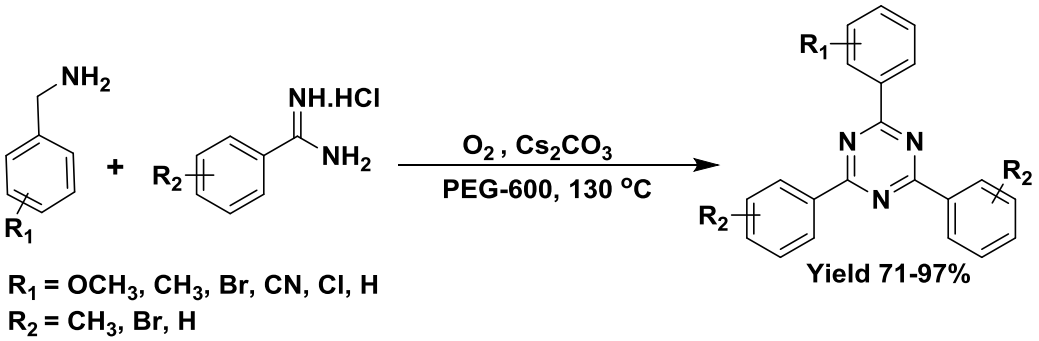
A heterogeneous cascade addition-oxidative cyclization of nitriles with 2-aminopyridines or amidines was achieved in 1,2-dichlorobenzene by using a 1,10-phenanthroline-functionalized

MCM-41-supported copper (I) complex [Phen-MCM-41-CuBr] catalyst and air as the oxidant by J. Xia *et al.* in 2019 (Scheme I.15).[15] This heterogeneous copper (I) catalyst was reported to be easily prepared in two-step procedure from commercially or readily available and inexpensive reagents and exhibited higher catalytic activity. Phen-MCM-41-CuBr was also easy to recover and recyclable up to eight times with almost consistent activity.



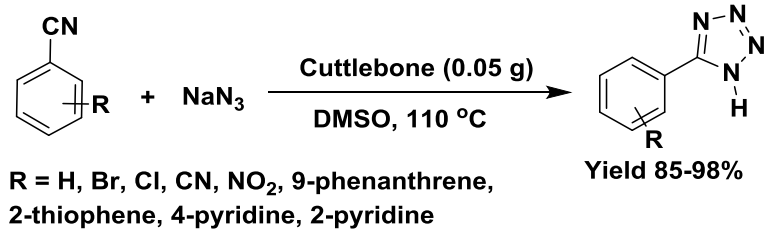

**Scheme I.15.** Copper (I)-catalyzed cascade addition-oxidative cyclization for synthesis of 1,2,4-triazoles

Synthesis of 1,3,5-triazines from substituted benzylamines and amidines in PEG-600 has been demonstrated by A. R. Tiwari *et al.* in 2016. This protocol is free from transition metal, phosphine ligand and explores molecular oxygen as an oxidant (Scheme I.16).[16] A series of 1,3,5-triazines derivatives were synthesized in good yields. PEG-600 was recovered three times without any lost in efficiency.



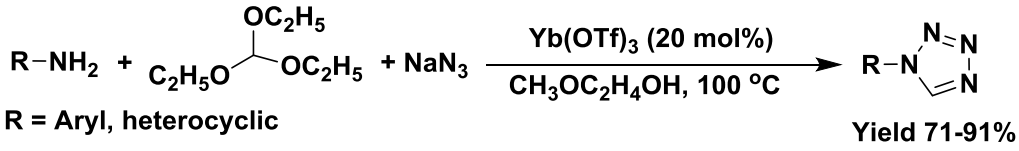

**Scheme I.16.** PEG-600 as a reusable solvent system for synthesis of 1,3,5-triazines

In 2015, S. S. E. Ghodsinia *et al.* reported [3+2] cyclo-addition reaction for synthesis of 5-substituted-1*H*-tetrazoles from nitriles and sodium azide in absence of any metal catalyst (Scheme I.17).[17] The reaction was catalyzed by mesoporous cuttlebone, a natural low cost heterogeneous catalyst in DMSO through "electrophilic activation" of nitriles *via* hydrogen bond formation between cuttlebone and nitrile.




**Scheme I.17.** Synthesis of tetrazoles from nitrile using cuttlebone

A series of tetrazole compounds have been synthesized from amines, triethyl orthoformate and sodium azide through the Lewis acid catalyst $Yb(OTf)_3$ by W. –K. Su *et al.* in 2006 (Scheme I.18).[18] Some of the 1-susbstituted-1*H*-1,2,3,4-tetrazole compounds showed strong phytocidal activity.

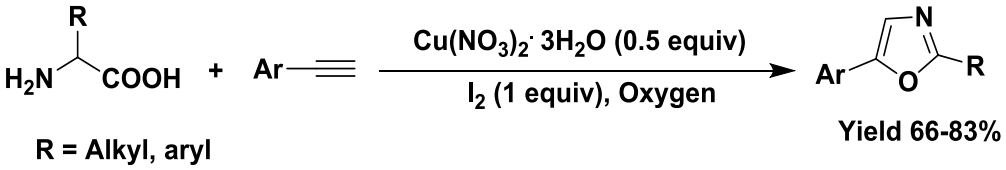



**Scheme I.18.** Synthesis of 1-susbstituted 1*H*-1,2,3,4-tetrazole from amine and orthoformate

### I.2.2. Synthesis of *O*-containing heterocyclic compounds

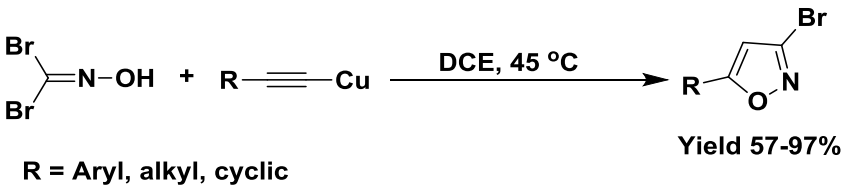
Some examples of synthesis of heterocyclic compounds containing oxygen are given below.

A new strategy has been developed for the synthesis of 2,5-disubstituted oxazoles from easily available arylacetylenes and α-amino acids in the presence of $Cu(NO_3)_2.3H_2O$ and iodine by J. Wanga *et al.* in 2019 (Scheme I.19).[19] This reaction process involves the $I_2/Cu(NO_3)_2.3H_2O$ assisted transformation of arylacetylene to α-iodo acetophenone.



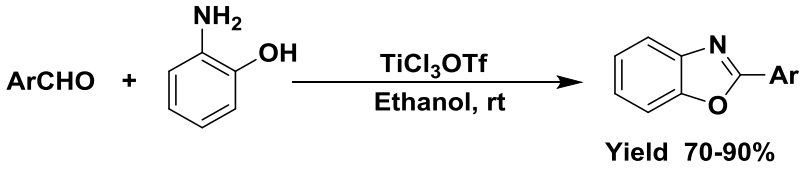

**Scheme I.19.** Synthesis of 2,5-disubstituted oxazoles

In 2014, W. Chen *et al.* reported a tandem synthesis of 3-halo-5-substituted isoxazoles from 1-copper (I) alkynes and dihaloformaldoximes under base-free conditions (Scheme I.20).[20] The reaction proceeds through selectively nucleophilic addition-elimination. Thus, they showed that the drawbacks of the production of this type compound can be avoided completely.



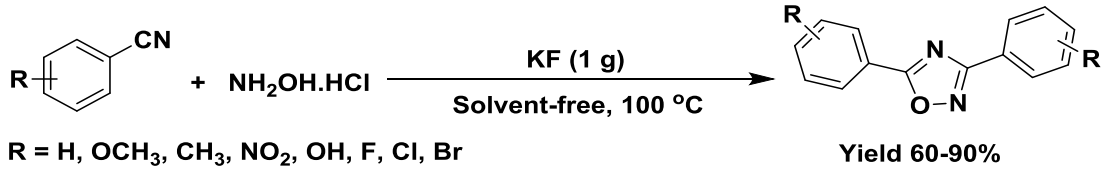

**Scheme I.20.** Tandem synthesis of isoxazoles from copper (I) alkynes

In 2016, benzoxazole derivatives were designed by J. Azizian *et al.* from the reaction of aldehydes and 2-aminophenol under mild conditions exploring $TiCl_3OTf$ as catalyst and ethanol as green solvent (Scheme I.21).[21]



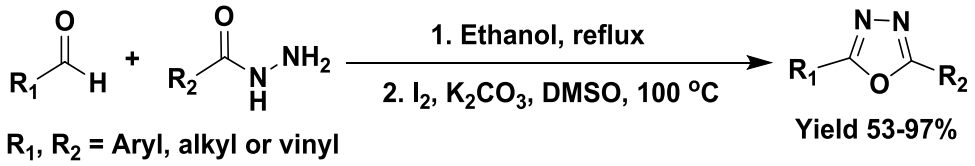

**Scheme I. 21.** Synthesis of benzoxazoles in ethanol at room temperature

S. Rostamizadeh *et al.* described a one-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituent directly from the reaction of nitriles and hydroxylamine hydrochloride in presence of potassium fluoride as catalyst and solid support under solvent-free condition in 2010. The main intermediate formed for this protocol was amidoxime (Scheme I.22).[22]



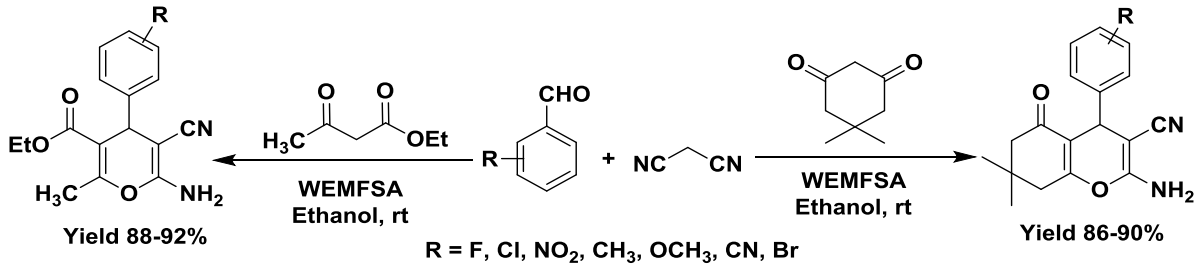

**Scheme I.22.** One-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles using potassium fluoride

In 2013, W. Yu *et al.* demonstrated a transition metal-free oxidative cyclization of acylhydrazones into a series of symmetrical and unsymmetrical 2,5-disubstituted (aryl, alkyl and vinyl) 1,3,4-oxadiazoles by employing stoichiometric molecular iodine in presence of potassium carbonate (Scheme I.23).[23] The acylhydrazone substrates were obtained from *in situ* condensation of aldehydes and hydrazides.



**Scheme I.23.** $I_2$ mediated synthesis of 1,3,4-oxadiazoles from aldehydes and hydrazides

A one-pot three-component reaction for synthesis of 2-amino-4*H*-pyran derivatives was established using agro-waste based water extract of muskmelon fruit shell ash (WEMFSA) by P. B. Hiremath *et al.* in 2020 (Scheme I.24).[24] WEMFSA perform the role of catalyst in absence of an external base or ligand/catalyst/additives.

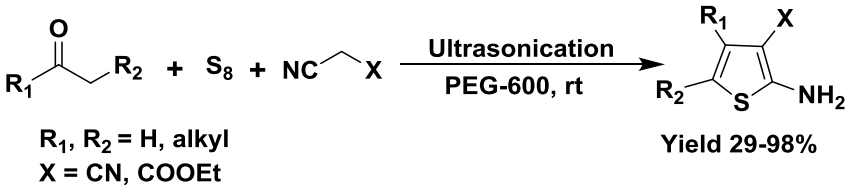



**Scheme I.24.** Synthesis of 2-amino-4*H*-pyrans catalyzed by WEMFSA

### I.2.3. Synthesis of *S*-containing heterocyclic compounds

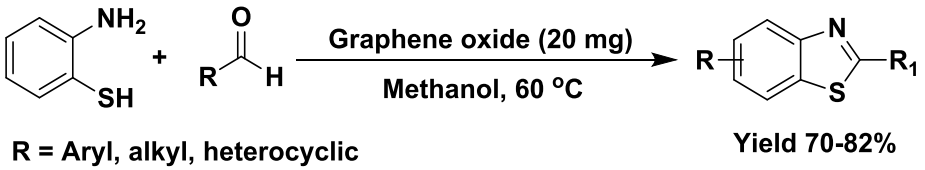
Heterocyclic compounds comprising sulphur are also admired and have gained significance day by day. Some of the examples are given below.

In 2017, A. Akbarzadeh *et al.* reported a method for synthesis of densely functionalized 2-aminothiophene derivatives through one-pot three-component reaction from enolizable carbonyl compounds, malononitrile or ethyl cyanoacetate and elemental sulfur using PEG-600 as an eco-friendly reaction medium, without any basic catalyst under ultrasonic conditions. The recovery and reusability of the solvent was reported to be at least five times without significant loss of its activity (Scheme I.25).[25]



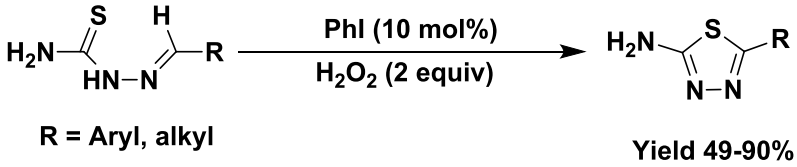

**Scheme I.25.** PEG-600 mediated synthesis of 2-aminothiophene derivatives

In 2016, K. B. Dhopte *et al.* described the synthesis of benzothiazoles using graphene oxide, a carbocatalyst by the reaction of 2-aminothiol and aldehyde at 60 °C as well as under ultrasonic irradiation at 35 °C with methanol as solvent (Scheme I.26).[26] Graphene oxide played dual role of metal-free acid catalyst as well as an oxidizing agent.



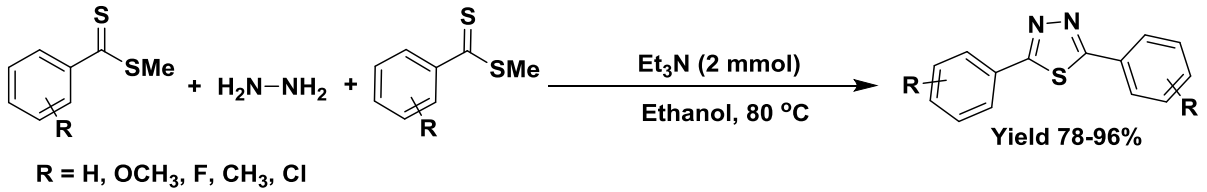

**Scheme I.26.** Synthesis of benzothiazoles using graphene oxide

Y. Han *et al.* demonstrated a new methodology for synthesis of thiadiazole derivatives *via* intramolecular oxidative coupling of thiosemicarbazide, using *in situ* generated hypervalent iodine (III) reagents in 2018 in absence of any transition-metal (Scheme I.27).[27]



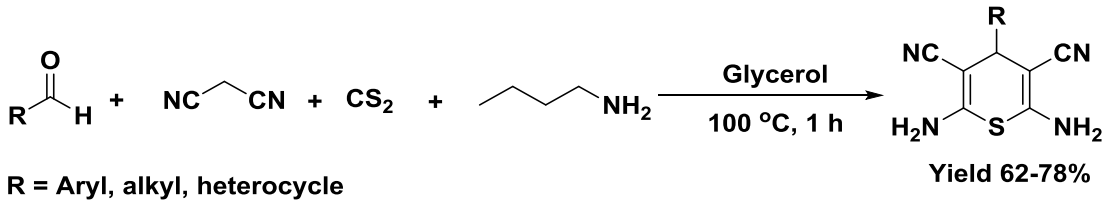

**Scheme I.27.** PhI catalyzed intramolecular oxidative coupling for synthesis of 2-amino-1,3,4-thiadizoles

In 2019, H. A. Swarup *et al.* developed a synthetic approach for construction of 3,5-disubstituted 1,3,4-thiadiazoles from dithioesters, hydrazine hydrate and triethylamine under transition metal-free condition only using triethylamine in ethanol (Scheme I.28).[28]



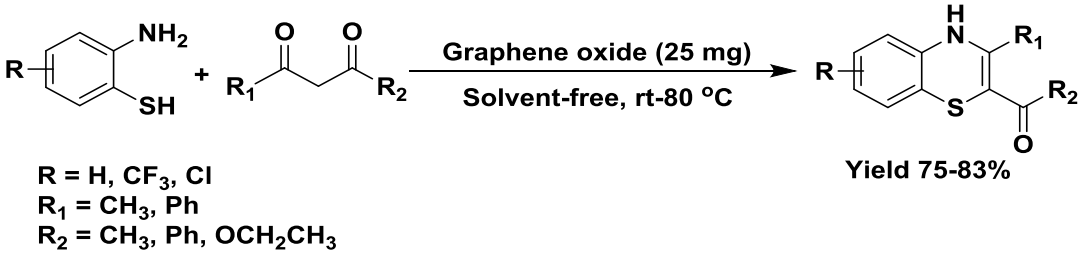

**Scheme I.28.** One-pot synthesis of 3,5-disubstituted 1,3,4-thiadiazole from dithioesters

B. Mitra *et al.* promoted one-pot pseudo five-component strategy and contributed to sustainability by exploring glycerol to design the diverse biologically imperative scaffold 4*H*-thiopyran (Scheme I.29)[29] in 2019 without any supplementary catalyst and the reaction time for this approach was also shorter.




**Scheme I.29.** Glycerol assisted one-pot pseudo five-component synthesis of 4*H*-thiopyran

Graphene oxide had been established to be recyclable carbocatalyst for construction of 1,4-benzothiazine from 2-aminothiophenol and 1,3-dicarbonyl compound by S. Bhattacharya *et al.* in 2017 (Scheme I.30).[30] It is proposed that the large surface area of GO nanosheet along with the presence of acidic and oxidative groups catalyze the oxidative cyclization effectively.

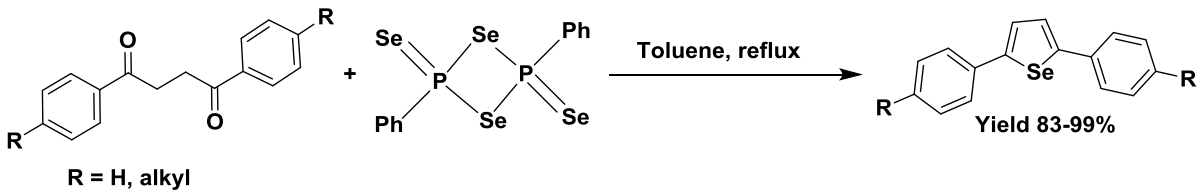



**Scheme I.30.** Graphene oxide (GO): A carbocatalyst for the synthesis of 1,4-benzothiazines

### I.2.4. Synthesis of *Se*-containing heterocyclic compounds

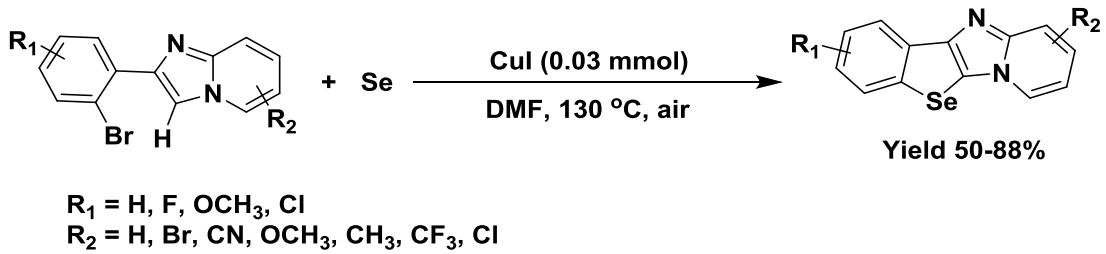
Heterocyclic compounds containing selenium are rarely known and these areas are explored day by day. Some of the examples are given below.

In 2010, G. Hua *et al.* demonstrated a synthetic procedure for preparation of 2,5-diarylselenophenes *via* 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 in refluxing toluene (Scheme I.31).[31] The first X-ray structure of 2,5-diarylselenophenes is presented along with characterization of their redox properties.



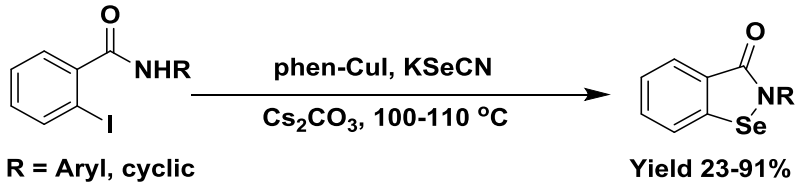

**Scheme I.31.** Synthesis of novel 2,5-diarylselenophenes using Woollin's reagent

P. Sun *et al.* in 2017 developed an approach for the formation of nitrogen heterocycle-fused imidazo[1,2-*a*]-pyridine and benzo[*b*]selenophenes through copper-catalyzed direct selenylation of readily available 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines *via* regioselective cleavage of C($sp^2$)-Br and C($sp^2$)-H bonds using readily available selenium powder as the selenylating agents under ligand and base free conditions in air (Scheme I.32).[32]



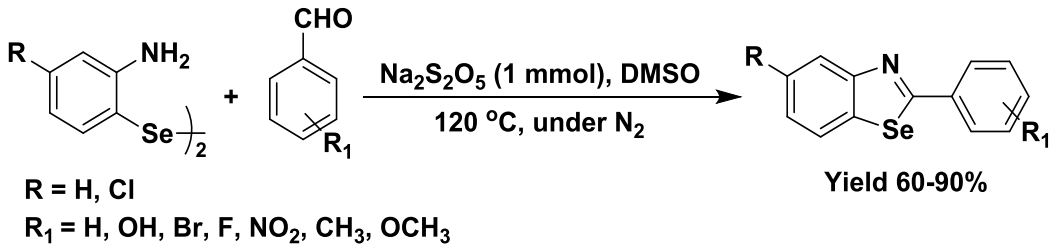

**Scheme I.32.** Copper catalyzed selenylation of imidazo[1,2-*a*]pyridines with selenium powder

2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones containing a C-Se-N bond were prepared through both thermal and photoinduced copper-mediated cross-coupling between potassium selenocyanate and *N*-substituted ortho-halobenzamides by S. Thanna *et al.* in 2017 (Scheme I.33).[33] The copper ligand (1,10-phenanthroline) facilitates C-Se bond formation during heating *via* a mechanism that likely involves atom transfer (AT). Whereas, in absence of ligand, photoinduced activation likely proceeds through a single electron transfer (SET) mechanism.




**Scheme I.33.** Copper promoted synthesis of 2-alkyl-1,2-benzisoselenazol-3(2*H*)-ones

In 2013, C. S. Radatz *et al.* presented a method for synthesis of several 2-aryl-1,3-benzoselenazoles from the reaction of bis(2-aminophenyl)diselenides with different aryl aldehydes, promoted by inorganic reducing agent sodium metabisulfite in DMSO (Scheme I.34).[34]




**Scheme I.34.** Synthesis of 2-aryl-1,3-benzoselenazoles by reaction of bis(2-aminophenyl) diselenides with aldehydes

## I.3. Conclusion

Thus we see that various synthetic methods are developed for synthesis of biologically potent heterocyclic compounds. From the above discussion it is clear that there remains ample scope to develop new reaction methodologies in this field.

## I.4. References

References are given in BIBLIOGRAPHY under Chapter I (page 169-170).