

Chapter I

A Concise Review on Synthetic Strategies for Medicinally Active Heterocyclic Compounds

I.1. Introduction

Heterocyclic compounds are cyclic compounds that have at least one atom other than a carbon atom, the atom can be oxygen, nitrogen, sulfur, selenium, phosphorous, etc. Out of a wide range of heterocyclic compounds, oxygen, nitrogen, and sulfur containing heterocycles are the most abundant. Heterocyclic chemistry is one of the major topic in organic chemistry, as most of the synthesized organic compounds are heterocycles. Heterocyclic compounds have been extensively used in the pharmaceutical and medicinal industry; the majority of the commercially available drugs consist of heterocyclic scaffolds as their core. Although heterocyclic compounds containing one or more heteroatom in three to eight-membered rings are well studied by scientists around the globe, among them five and six-membered heterocyclic ring systems have major contributions to heterocyclic chemistry. A few literatures reported five and six-membered heterocyclic scaffolds are shown in Figure I.1.

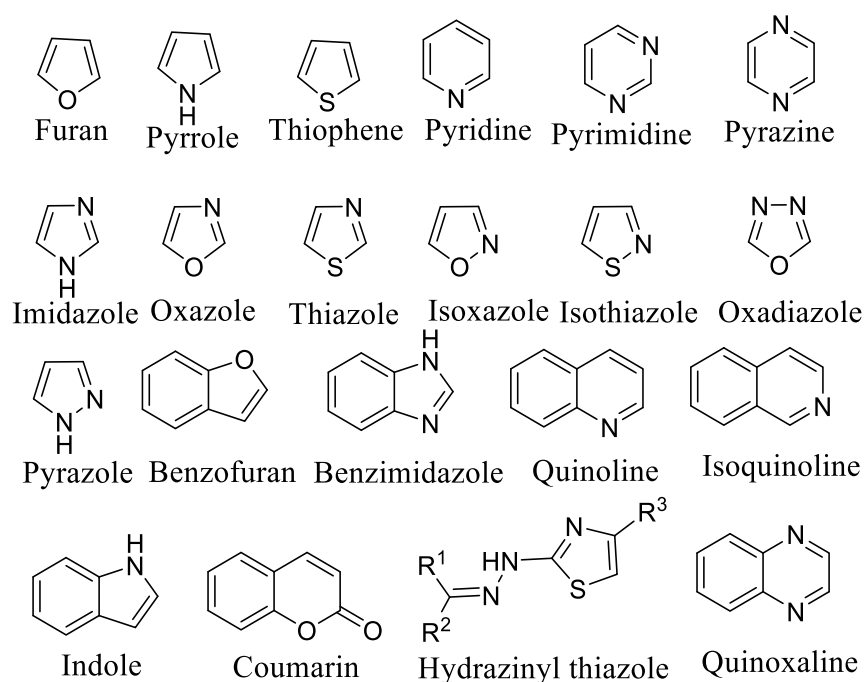


Figure I.1. Some of the literature reported heterocyclic scaffolds

Heterocyclic compounds are the prime moiety that is present in the vast depository of nature. Most of the naturally available compounds consist of heterocycles. Heterocyclic compounds are very crucial for the biochemical process and also a major ingredient for biologically important molecules like nucleic acid, vitamins, etc. Even the major constituents of photosynthesis and hemoglobin are also made up of heterocycles. Besides its biological importance, it is also an active ingredient for the preparation of insecticides, rodenticides,

pesticides, fungicides, and other agrochemical products. With the increase in the development of new drugs, heterocycles are getting more attention from researchers as it is a chief component in the construction of drug molecules. A few medicinally important compounds consisting of heterocycles are shown in Figure I.2.

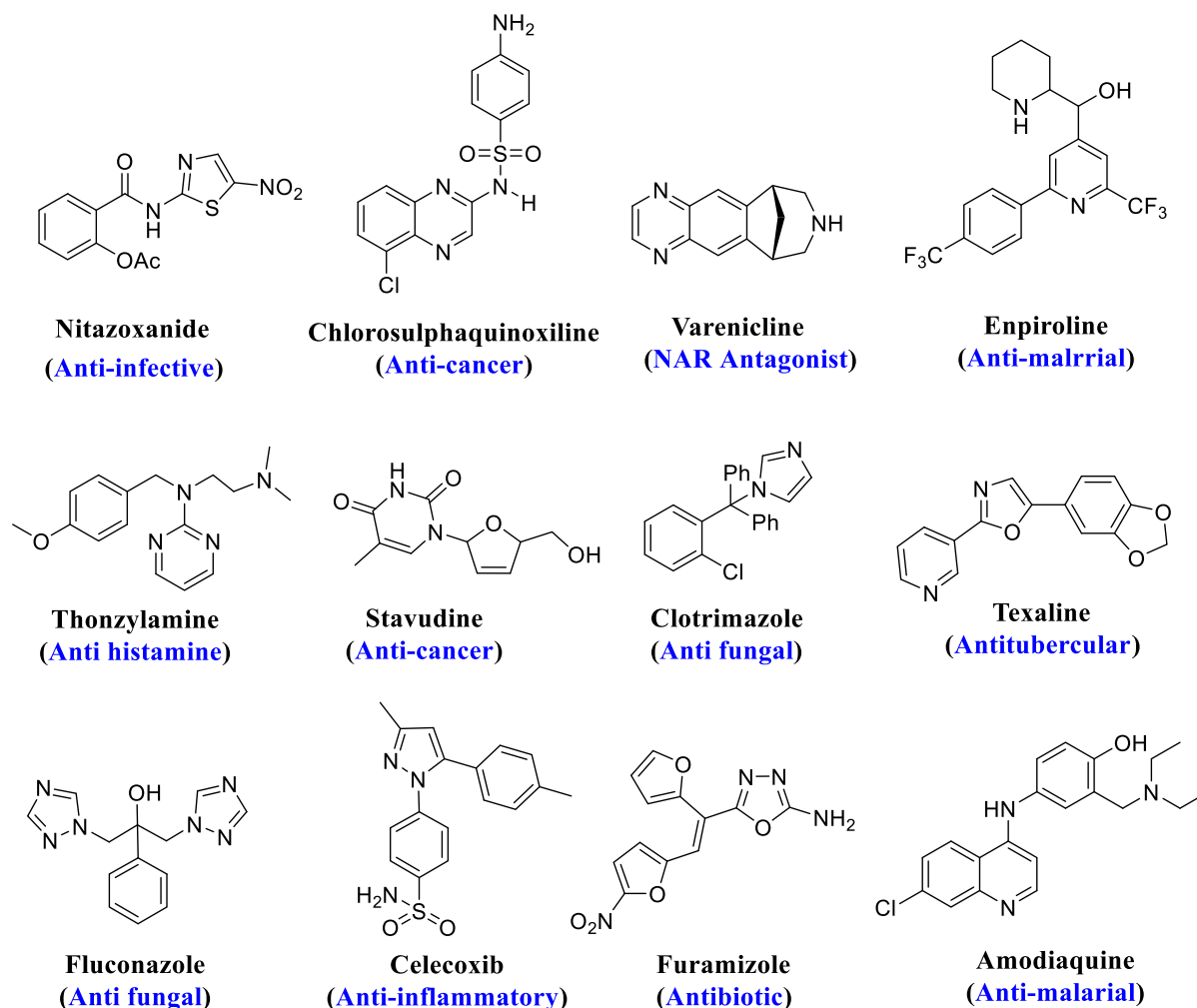


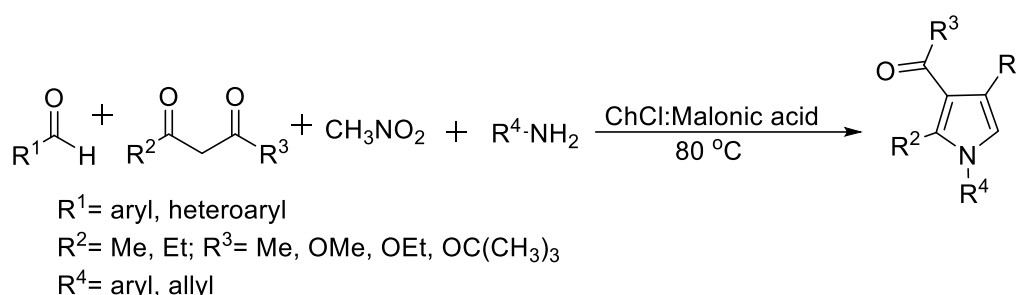
Figure I.2. Medicinally active compounds containing heterocyclic scaffolds

Apart from medicinal importance, it is also used in dye industries and has tremendous application in the preparation of organic light-emitting diodes (OLED), semiconducting materials, fluorescence chemosensors, etc. With the ever-increasing utilities of heterocycles in day-to-day life, the development of new synthetic methodologies for the construction of heterocycles is the need of time. To meet these needs, chemists around the globe are continuously working to develop new and efficient synthetic strategies for the construction of heterocyclic scaffolds.

I.2. Synthetic methodologies for the synthesis of heterocyclic compounds

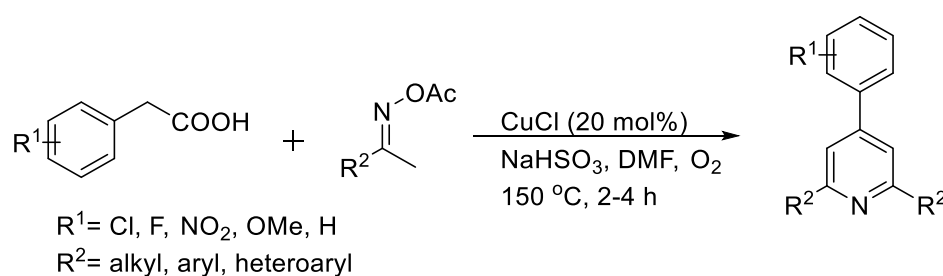
I.2.1. Synthetic methodologies for nitrogen-containing heterocyclic compounds

Hu *et al.* reported¹ ChCl: Malonic acid based deep eutectic solvent (DES) catalyzed one-pot multicomponent synthesis of pyrrole derivatives using aldehydes, amines, 1,3- dicarbonyl compounds, and nitromethane at 80 °C for 1 hour (Scheme I.1.). In this reaction methodology, authors showed the excellent reusability of DES medium up to five cycles without compromising the product yield.



Scheme I.1. ChCl: Malonic acid based DES catalyzed synthesis of pyrrole derivatives

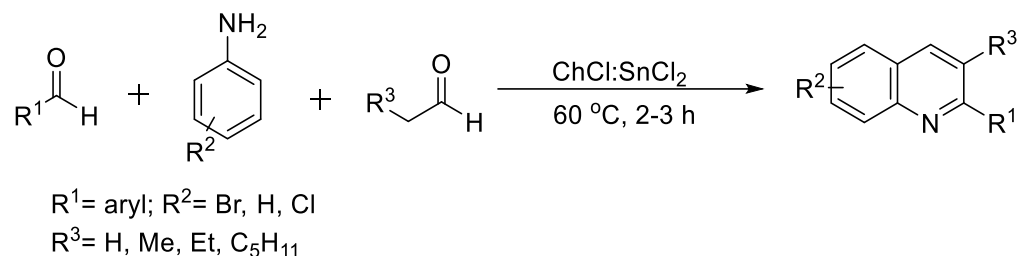
An efficient methodology for the synthesis of 2,4,6- triphenyl pyridine had been demonstrated² by Varaprasad and co-workers. To achieve this target, they utilized aryl acetic acid, oxime acetates, and NaHSO₃ at 150 °C in N, N-Dimethylformamide (DMF) medium in the presence of Copper Chloride as a catalyst under an oxygen atmosphere (Scheme I.2.). Using their developed methodology, authors synthesized a library of 2,4,6- triphenyl pyridine derivatives in moderate to excellent yield (45-94%).



Scheme I.2. Copper catalyzed one-pot synthesis of 2,4,6-triphenyl pyridines

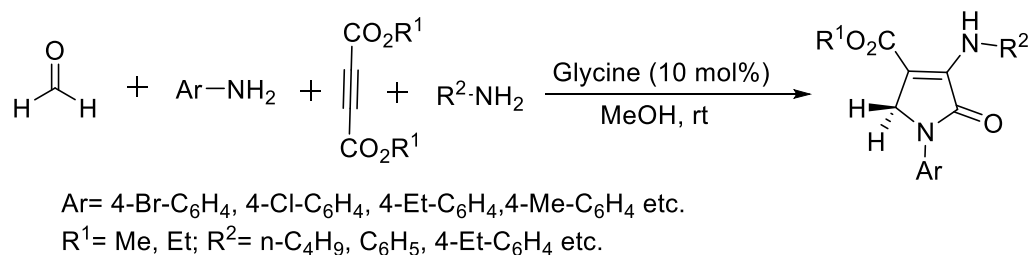
Sahabi *et al.* designed³ a one-pot three-component reaction protocol for the preparation of quinoline derivatives by reacting aldehydes, amines, and enolizable aldehyde in ChCl: SnCl₂ (1:2) deep eutectic solvent at 60 °C (Scheme I.3.). Here ChCl: SnCl₂-based deep eutectic solvent both acts as solvent as well as the catalyst. The authors checked the suitability of their

protocol on a wide range of substrates and found the product yield of corresponding quinoline derivatives in good to excellent yield. Above all DES medium could be reused up to four cycles without any appreciable change in product yield.



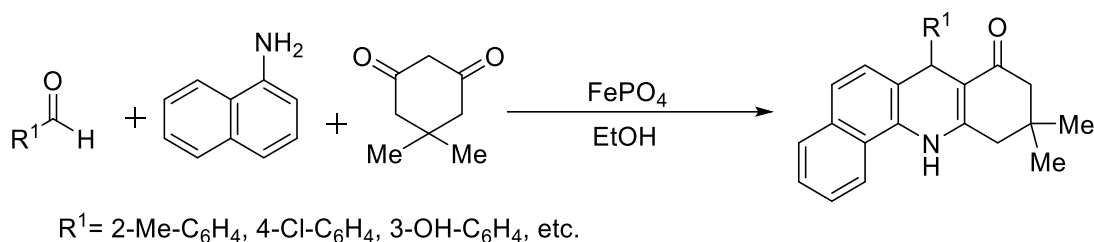
Scheme I.3. ChCl: SnCl₂ based DES catalyzed preparation of quinoline derivatives

Mohamadpour investigated⁴ a multicomponent reaction strategy for the preparation of dihydro-2-oxypyrroles utilizing formaldehyde, amines, and dialkyl acetylenedicarboxylate using glycine as a catalyst at room temperature (Scheme I.4.). In this protocol, different amines and dialkyl acetylene went smoothly to provide dihydro-2-oxypyrroles derivatives in ample amounts (76-96%).



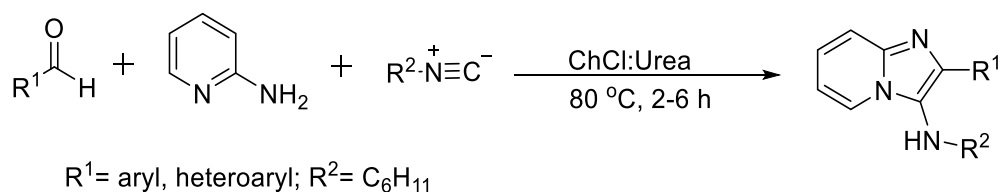
Scheme I.4. Glycine catalyzed one-pot multicomponent synthesis of dihydro-2-oxy pyrrole derivatives

Behabahani and co-workers studied⁵ one-pot synthesis of dibenzo[*c*] acridine derivatives using aromatic aldehydes, 1-naphthylamine, and dimedone in the presence of Iron (III) phosphate as a catalyst (Scheme I.5.). During the preparation of a library of acridine derivatives, authors noticed that the aldehydes group containing the electron withdrawing group took part in the reaction better than the electron donating group containing aldehydes. Mild reaction conditions, easy separation of catalyst, and excellent yield of the product were the major advantages of their protocol.



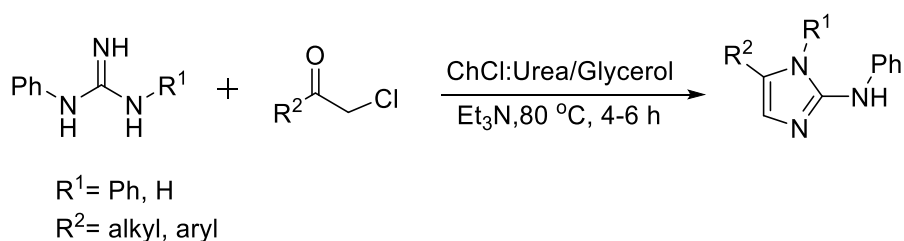
Scheme I.5. Iron (III) phosphate catalyzed preparation of dibenzo[*c*] acridine derivatives

Azizi *et al.* designed⁶ ChCl: Urea (1:2) catalyzed one-pot three-component synthesis of imidazo [1,2-*a*] pyridine from aromatic aldehydes, 2-amino pyridine, cyclohexyl isocyanide (Scheme I.6.). To optimize the reaction condition authors used six different DESs, and also varied the reaction temperature and found Choline Chloride: urea-based deep eutectic solvent at 80 °C gave the best result affording product yield in good to excellent amount (57-87%).



Scheme I.6. ChCl: Urea catalyzed one-pot synthesis of imidazo [1,2-*a*] pyridine derivatives

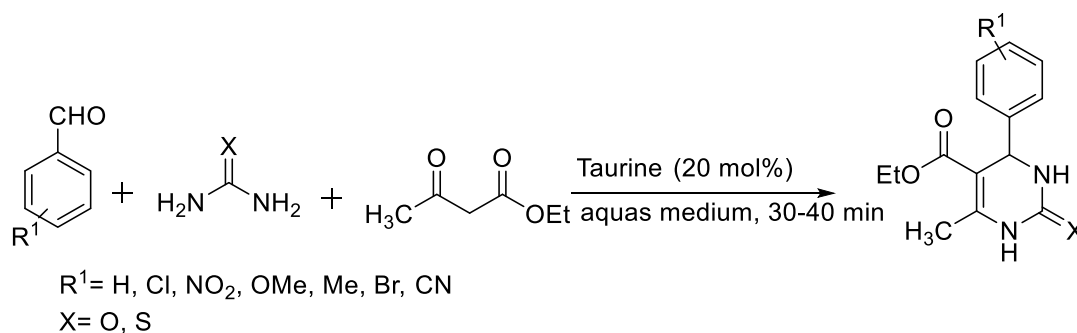
Capua *et al.* investigated⁷ the preparation of 2-amino imidazole in deep eutectic solvent reacting α -Chloro ketone (1 mmol), guanidine (1.3 mmol), and Et₃N (1 mmol) at 80 °C (Scheme I.7.). Authors noticed that among the various DES mixtures, both ChCl: Glycerol and ChCl: Urea and DES mixtures were the best candidates to produce imidazole derivatives in excellent yield (65-80%). Capua and co-workers were able to reuse DES media for up to two cycles successfully, however further attempts to reuse the DES mixtures significantly decreased the product yield.



Scheme I.7. DES catalyzed synthesis of 2-amino imidazole derivatives

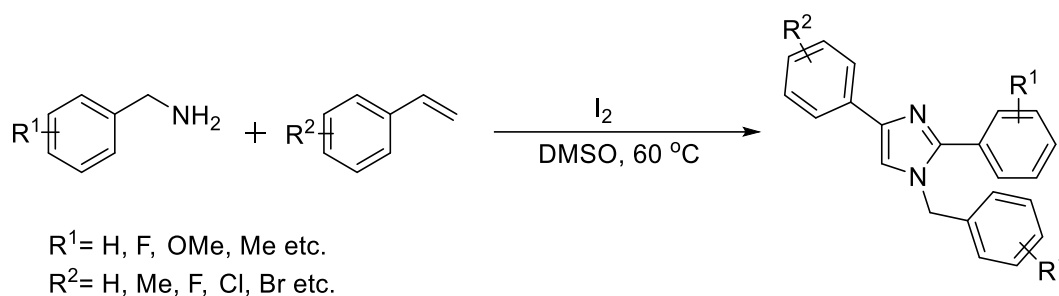
Aleem and co-workers developed⁸ a one-pot multicomponent reaction methodology for the synthesis of 3,4-dihydropyrimidin derivatives using Taurine as an environmentally benign and

bio-organic catalyst (Scheme I.8.). Authors refluxed aromatic aldehydes, ethyl acetoacetate, and urea/thiourea in water: ethanol (1:3) medium in the presence of Taurine catalyst for 30-40 minutes, which gave corresponding 3,4-dihydropyrimidin derivatives in magnificent amount (92-99%).



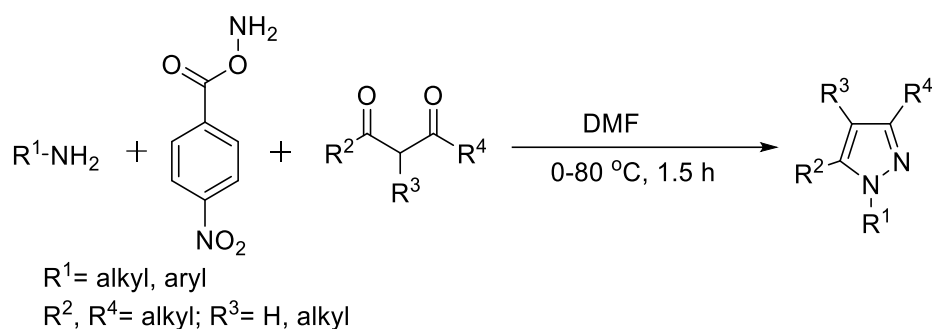
Scheme I.8. Synthesis of 3,4-dihydropyrimidin derivatives using Taurine as a catalyst

Bhukta *et al.* designed⁹ I₂-DMSO mediated an environment friendly strategy for the synthesis of substituted imidazole derivatives by reacting benzyl amines and styrenes at 60 °C (Scheme I.9.). Authors had found no substantial electronic effect of the substrate to alter the yield during the synthesis of a library of imidazole derivatives using this protocol and were also able to synthesize in gram scale. To propose the most plausible mechanism they showed conjugative C-N bond formation followed by oxidative cyclization leading to the formation of imidazole moiety.



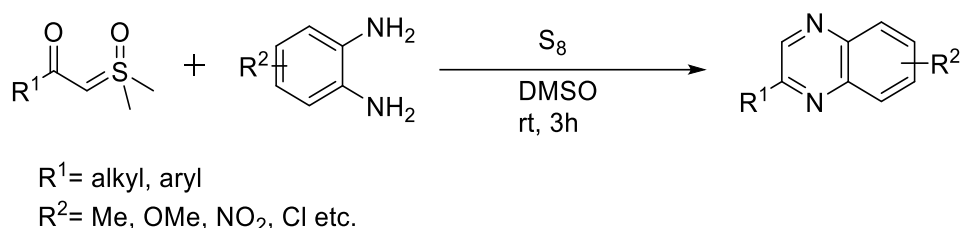
Scheme I.9. I₂-DMSO mediated synthesis of substituted imidazole derivatives

Gulia and co-workers reported¹⁰ a simple methodology for the preparation of N-substituted pyrazole derivatives by reacting primary amines, diketones, and *O*-(4-nitrobenzoyl) hydroxylamine (Scheme I.10.). During the exploration of substrate scope authors introduced a wide range of primary aromatic as well as aliphatic amines, with diketones and *O*-(4-nitrobenzoyl) hydroxylamine, all of them took part in the reaction smoothly to afford corresponding N-substituted pyrrole derivatives in moderate to good yield (27-70%).



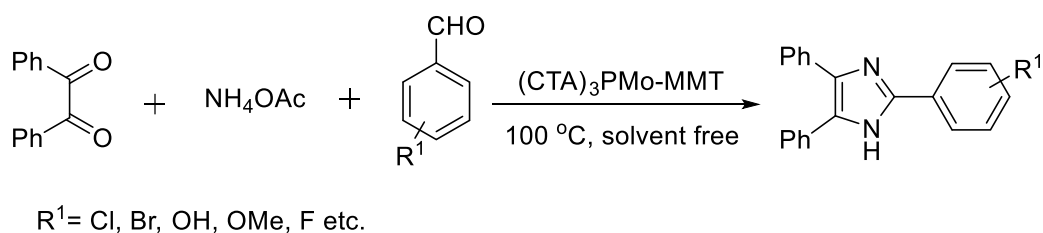
Scheme I.10. One-pot multicomponent synthesis of pyrazole derivatives in DMF medium

An elemental sulfur-mediated one-pot synthesis of quinoxaline derivatives had been reported¹¹ by Chaubey *et al.* (Scheme I.11.). In the presence of sulfur, authors reacted diverse functional groups containing *o*-phenylenediamine with sulfoxonium ylides at room temperature, which gave corresponding quinoxaline derivatives in good to excellent yield (64-90%).



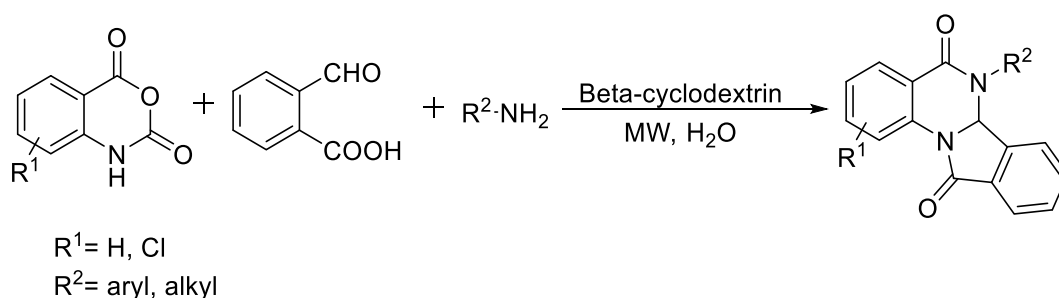
Scheme I.11. Sulfur mediated preparation of quinoxaline derivatives

Farahani *et al.* synthesized¹² cetyltrimethylammonium grafted montmorillonite (MMT) clay-supported phosphomolybdic acid-based nanocomposite (Scheme I.12.). Authors characterized it with Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), and inductively coupled plasma emission spectroscopy techniques. Then they employed this new nanocomposite as a catalyst for the synthesis of 2,4,5-trisubstituted imidazoles by reacting 1,2-diketones, aldehydes, and ammonium acetate at 100 °C. Authors had synthesized a wide range of substituted imidazoles with ample amount of yield (80-97%). Above all this (CTA)₃PMo-MMT can be easily recovered and reused for further conjugative cycles.



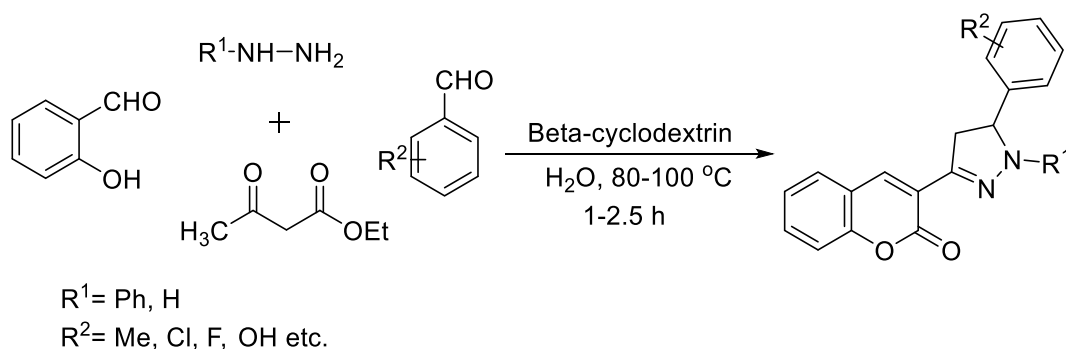
Scheme I.12. One-pot three-component synthesis of 2,4,5-trisubstituted imidazoles

Reddy *et al.* reported¹³ one-pot multicomponent synthesis of dihydroisoindolo[2,1-*a*]quinazoline- 5,11-dione derivatives by reacting amines, isatoic anhydrides and 2-formyl benzoic acid in the presence of β -cyclodextrin catalyst under microwave condition in aqueous medium (Scheme I.13.). Authors were able to synthesize a wide array of dihydroisoindolo[2,1-*a*]quinazoline- 5,11-dione derivatives in pleasing amounts (60-95%) by varying aliphatic as well as aromatic amines, substituted isatoic anhydrides, and formyl benzoic acid.



Scheme I.13. β -cyclodextrin catalyzed synthesis of dihydroisoindolo[2,1-*a*]quinazoline- 5,11-dione derivatives

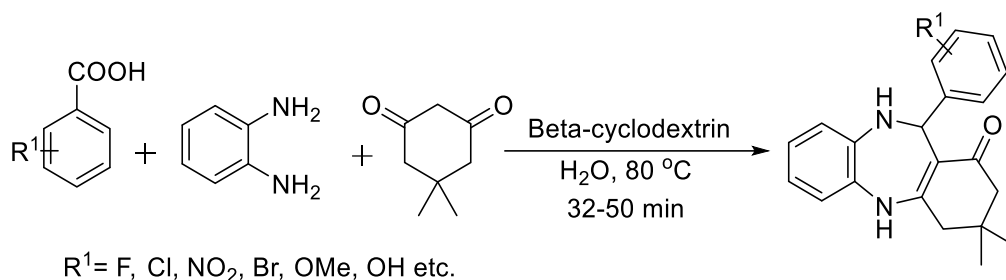
Chate *et al.* reported¹⁴ β -cyclodextrin catalyzed coumarin-pyrazolines synthesis from a one-pot multicomponent reaction of salicylaldehyde, ethyl acetoacetate, hydrazines, and aldehydes in an aqueous medium under refluxing conditions (Scheme I.14.). Authors had synthesized a wide range of coumarin-linked pyrazoline scaffolds in ample amounts (79-97%) by varying aldehydes as well as hydrazine with salicylaldehyde and ethyl acetate. They also observed the antimicrobial properties of this novel coumarin-pyrazolines due to their inhibitory effect against D-alanine-D-alanine ligase.



Scheme I.14. One-pot four-component synthesis of coumarin-pyrazolines using β -cyclodextrin as a catalyst

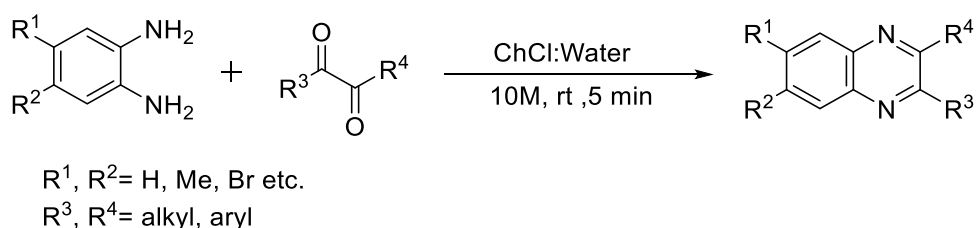
Masram *et al.* reported¹⁵ β -cyclodextrin catalyzed one-pot facile synthesis of 1,5-benzodiazepine derivatives by reacting *o*-phenylene diamine, dimedone, and aldehydes in

aqueous at 80 °C (Scheme I.15.). They proposed a reaction pathway where dimedone reacts with *o*-phenylene diamine to give an imine intermediate which further reacts with aldehydes to give the corresponding benzodiazepine derivatives. Authors had shown that β -cyclodextrin can be easily recovered from the reaction mixture and reused for four to five times without compromising product yield.



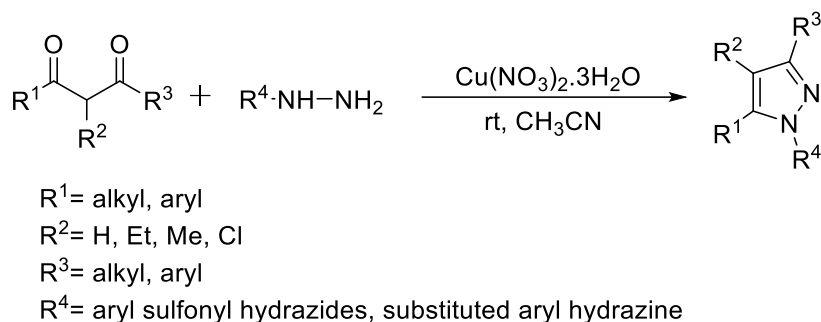
Scheme I.15. β -cyclodextrin catalyzed synthesis of 1,5-benzodiazepine derivatives

Lupidi *et al.* designed¹⁶ a one-pot synthetic strategy for the preparation of densely functionalized quinoxaline derivatives by reacting 1,2-dicarbonyl compound and 1,2-diamino compounds in ChCl: water-based deep eutectic solvent at room temperature (Scheme I.16.). The authors proposed that due to the presence of an extensive hydrogen bonding network in the DES medium, the energy of the transition state for this reaction pathway lowered significantly. Due to the mildness of this protocol, they had successfully employed a protecting group as well as acid-sensitive functional group in the 1,2-diketo compound, all of them went smoothly in the reaction condition leading to the formation of quinoxaline derivatives. To minimize the waste generation authors have reused and recycled DES medium up to six cycles.



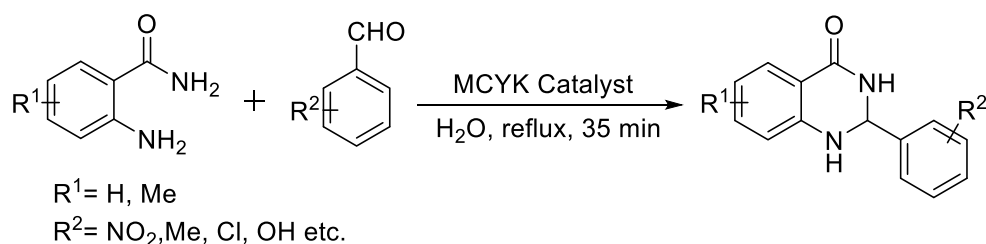
Scheme I.16. DES catalyzed synthesis of quinoxalines

Wang *et al.* investigated¹⁷ Copper catalyzed one-pot preparation of substituted pyrrole derivatives by mixing substituted hydrazines and 1,3-diketo compounds in acetonitrile at room temperature (Scheme I.17.). Authors had successfully synthesized a library of pyrrole derivatives in good to excellent amounts (67-95%) using a wide variety of hydrazines and both symmetrical as well as unsymmetrical 1,3-diketo compounds.



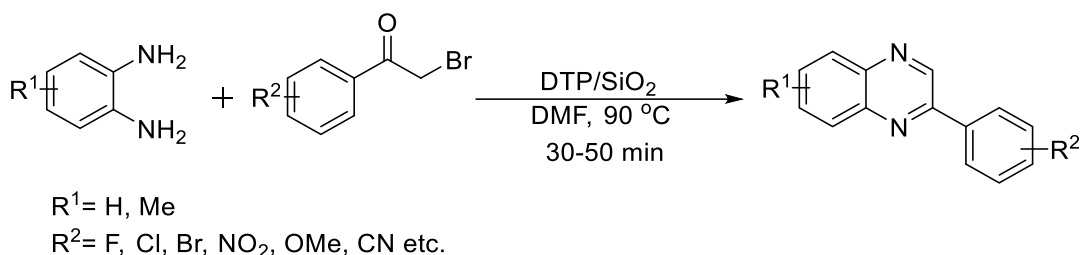
Scheme I.17. Copper catalyzed one-pot multicomponent synthesis of substituted pyrrole derivatives

Lodhi and co-workers synthesized¹⁸ a new heterogeneous catalyst namely micro-meso-composite zeolite (MCYK) by desilication of microporous zeolite H-BEA in the presence of yeast and cetyltrimethylammonium bromide (CTAB) (Scheme I.18.). Authors had also extensively characterized newly formed catalyst via FT-IR, X-ray diffraction, and solid-state magic angle spinning nuclear magnetic resonance techniques. With the fully characterized catalyst in hand, they used it for the preparation of dihydroquinazolinone derivatives by reacting 2-aminobenzamides with aldehydes in aqueous medium at refluxing condition.



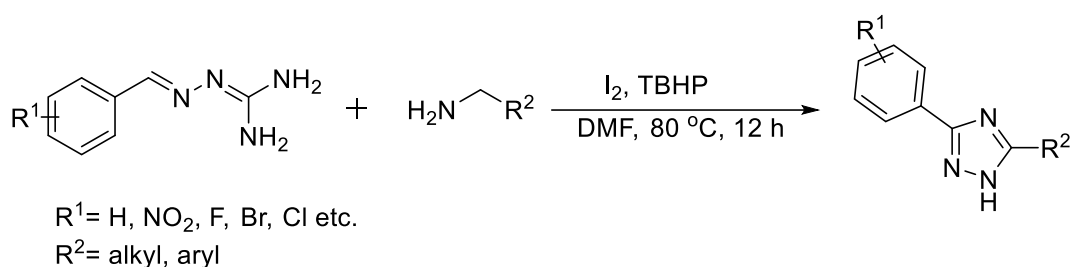
Scheme I.18. One-pot preparation of dihydroquinazolinone derivatives in aqueous medium

Hebade *et al.* reported¹⁹ silica supported dodecatungstophosphoric acid catalyzed one pot two component synthesis of quinoxaline derivatives using *o*-phenylenediamines and phenacyl bromides in DMF medium at 90 °C (Scheme I.19.). Authors had noticed that solvent plays a crucial role in their reaction condition, as polar protic solvent hindered substrates from coming in close proximity to the catalyst thereby decreasing the product yield. So, to overcome this difficulty they employed aprotic solvent which noticeably increases product yield. Authors were also able to easily separate their catalyst by simple filtration and reuse it up to five times without compromising product yield.



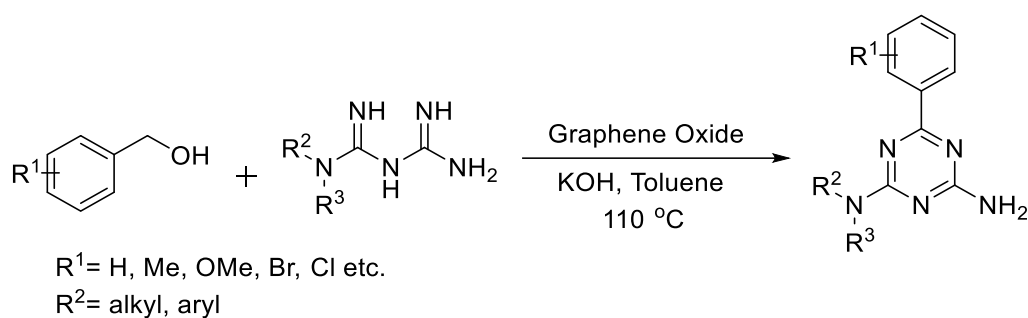
Scheme I.19. Silica supported dodecatungstophosphoric acid catalyzed synthesis of quinoxaline derivatives

Wani *et al.* investigated²⁰ iodine catalyzed synthesis of 3,5-disubstituted-1,2,4-triazoles from benzyl amines and diaminoazines. To achieve this target, they stirred different diaminoazines and benzyl amines at 80 °C in DMF medium in the presence of tert-Butyl hydroperoxide (TBHP) as an oxidant and iodine as a catalyst for 12 hours, which afforded corresponding triazole derivatives in decent amounts (32-77%) (Scheme I.20.). To discuss the possible reaction pathway, they proposed first nucleophilic addition of benzylamine to diaminoazines, followed by oxidation with TBHP and then intramolecular nucleophilic cyclization to give a triazole derivative.



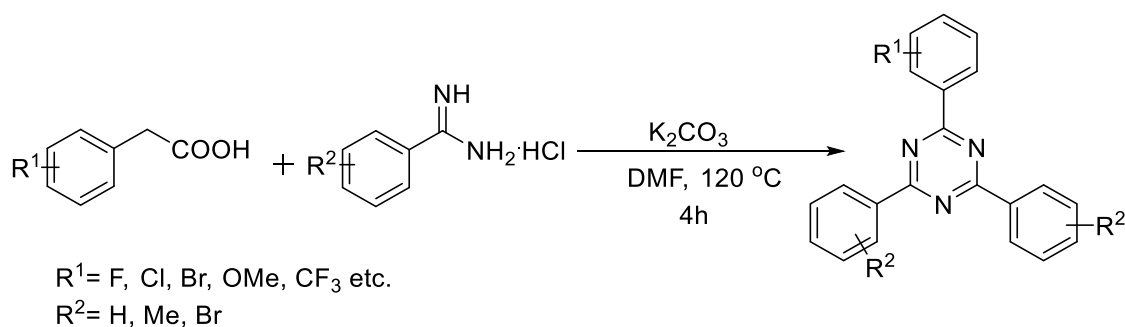
Scheme I.20. Iodine catalyzed preparation of 3,5-disubstituted-1,2,4-triazoles

Chaurasia and co-workers reported²¹ Graphene Oxide (GO) catalyzed one pot multicomponent synthesis of trisubstituted 1,3,5-triazine derivatives by reacting benzyl alcohols with biguanides in toluene medium with the presence of potassium hydroxide (KOH) at 110 °C (Scheme I.21.). While checking the substrate scope authors introduced various substitutions in the ortho, meta, and para position of benzyl alcohol with biguanides and observed all of them went smoothly in reaction conditions to afford corresponding trisubstituted 1,3,5-triazine derivatives in moderate to excellent yield (34-91%). However, they also noticed that substituent at the ortho position of benzyl alcohol gave a lower yield of the product. The authors were also able to successfully recover and reuse the GO catalyst for up to six cycles with a minimal amount of change in product yield.



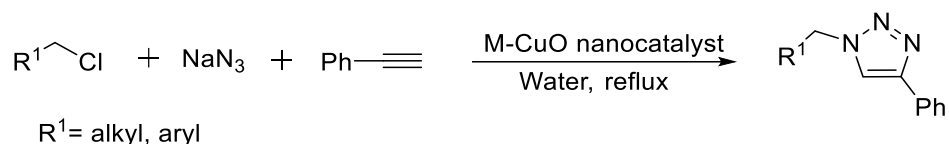
Scheme I.21. Graphene oxide catalyst synthesis of trisubstituted 1,3,5-triazine derivatives

Paredeshi *et al.* also reported²² the metal free synthesis of 1,3,5-triazine derivatives from different synthons (Scheme I.22.). To achieve this target, they reacted different arylacetic acids with benzamidine hydrochloride at 120 °C in DMF medium using K_2CO_3 as a base and got an ample amount (63-94%) of 1,3,5-triazine derivatives. Authors proposed at first arylacetic acids suffer oxidative decarboxylation to produce aldehydes, which react with benzamidine hydrochloride to form the Schiff base. Another molecule of benzamidine hydrochloride undergoes conjugate addition with Schiff base, followed by oxidation to produce 1,3,5-triazine derivatives.



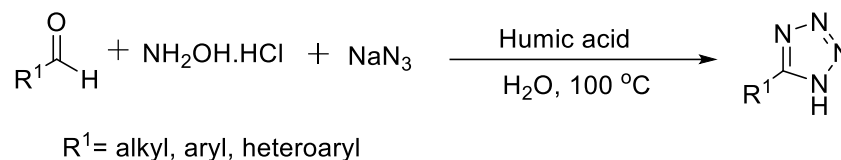
Scheme I.22. One-pot two-component synthesis of 1,3,5-triazine derivatives

Rajabi *et al.* designed²³ a new heterogenous catalyst where copper oxide nanoparticles were supported on melamine (M-CuO nanocatalyst) (Scheme I.23.). The newly made melamine-supported copper oxide nanocatalyst was extensively characterized by XRD, TGA, DSC, EDS, SEM, BET and other techniques. With this novel catalyst in hand, they prepared 1,4-disubstituted-1,2,3-triazole derivatives by reacting benzyl or alkyl halide with sodium azide and phenyl acetylene in an aqueous medium. Above all investigators were also able to easily recover and reuse this new nanocatalyst for up to six cycles without any considerable change in product yield.



Scheme I.23. One-pot preparation of 1,4-disubstituted-1,2,3-triazole derivatives

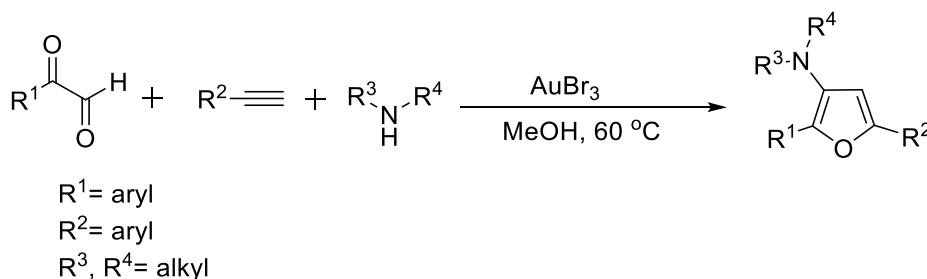
A humic acid catalyzed²⁴ one-pot multicomponent synthesis for 5-substituted 1H-tetrazole had been reported by Wang *et al.* (Scheme I.24.). The authors reacted a wide range of aldehydes, sodium azide, and hydroxylamine hydrochloride in water at 100 °C, Which resulted in the formation of tetrazole derivatives in excellent amount (81-96%). After the synthesis of tetrazole derivatives, they were able to easily recover the catalyst from the reaction mixture by simple filtration and reuse the humic acid catalyst for five successive cycles without compromising product yield.



Scheme I.24. Humic acid catalyzed synthesis of 5-substituted 1H-tetrazole

I.2.2. Synthetic methodologies for oxygen-containing heterocyclic compounds

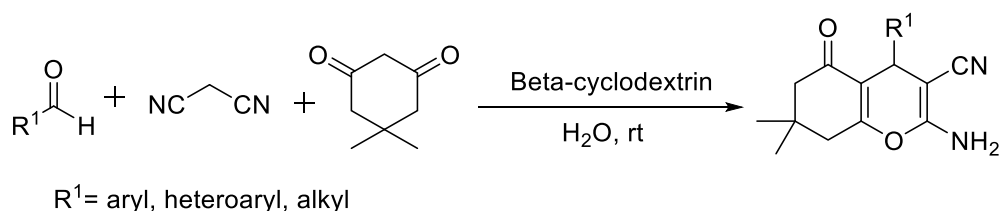
Li and co-workers investigated²⁵ AuBr₃ catalyzed one pot multicomponent synthesis of furan derivatives from phenylglyoxals, terminal alkynes, and secondary amines under a nitrogen atmosphere in a methanol medium (Scheme I.25.). While checking the substrate scope they noticed that the alkynes bearing electron withdrawing group (EWG) gave more amount of furan derivatives than electron releasing group (ERG) containing alkynes.



Scheme I.25. AuBr₃ catalyzed one-pot multicomponent synthesis of furan derivatives

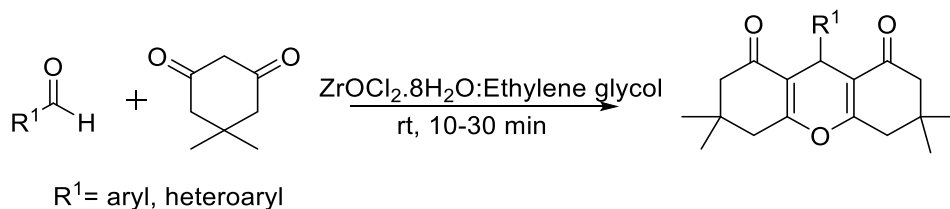
β-cyclodextrin catalyzed one-pot three-component preparation tetrahydrobenzo[*b*] pyran derivatives were reported²⁶ by Lu *et al.* (Scheme I.26.). The investigators stirred different aryl

aldehyde, dimedone, and malononitrile at room temperature in an aqueous medium in the presence of a β -cyclodextrin catalyst, which produced a significant amount (72-94%) of tetrahydrobenzo[*b*] pyran derivatives. They were able to recover and reuse the β -cyclodextrin catalyst for three catalytic cycles with minimal change in product yield.



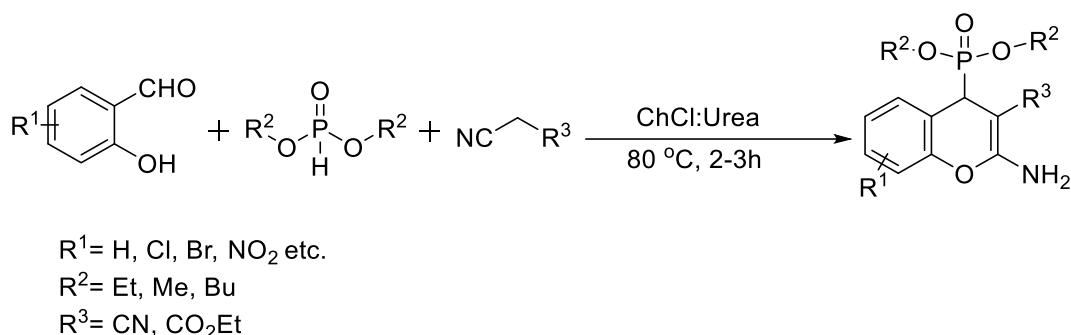
Scheme I.26. β -cyclodextrin catalyzed preparation of tetrahydrobenzo[*b*] pyran derivatives

Deep eutectic solvent-catalyzed 1,8-dioxooctahydroxanthene derivatives had been prepared²⁷ by Shaibuna *et al.* (Scheme I.27.). The investigators reacted different aldehydes with dimedone in $ZrOCl_2 \cdot 8H_2O$ and ethylene glycol-based DES mixture at room temperature afford the corresponding 1,8-dioxooctahydroxanthene derivatives in ample amounts (85-96%). They were able to recover and reuse the DES medium for five catalytic cycles with a slight decrease in product yield.



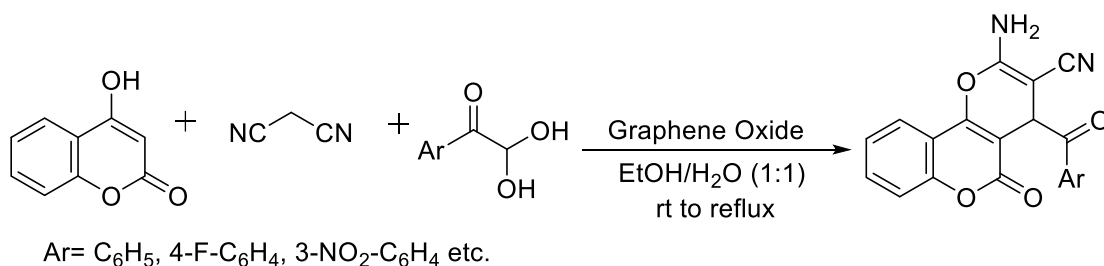
Scheme I.27. Synthesis of 1,8-dioxooctahydroxanthene derivatives in DES medium

Krishnammagari and co-workers designed²⁸ a facile method for the preparation of 2-amino-4H-chromen-4yl phosphonate in $CHCl_3$: Urea-based DES medium utilizing salicylaldehyde, ethyl cyanoacetate or malononitrile, and, dialkyl phosphites at 80 °C. In this protocol, the DES medium acts both as a solvent as well a catalyst (Scheme I.28.). Above all, they were also able to recover DES from the reaction mixture and reuse up to four catalytic cycles.



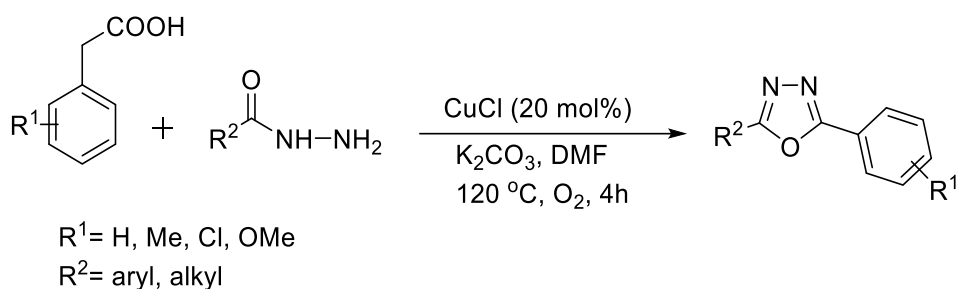
Scheme I.28. ChCl: Urea based DES catalyzed synthesis of 2-amino-4H-chromen-4yl phosphonate

A one-pot three-component reaction had been carried out²⁹ for the preparation of pyranocoumarin derivatives by Khodabakhshi *et al.* (Scheme I.29.). They reacted aryl glyoxals, 4-hydroxycoumarin, and malononitrile in the presence of graphene oxide (GO) catalyst in EtOH-H₂O (1:1) medium to afford the corresponding pyranocoumarin derivatives in excellent amounts (85-95%). Furthermore, the authors were also able to recover and reuse the GO catalyst for four cycles with negligible change in product yield.



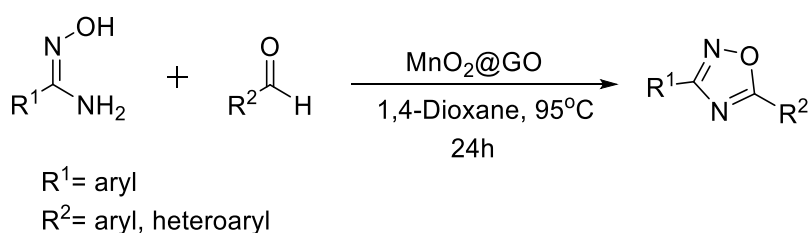
Scheme I.29. One-pot multicomponent synthesis of pyranocoumarin derivatives

Lekkala *et al.* reported³⁰ copper catalyzed one-pot two-component synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by stirring hydrazides and arylacetic acid at 120 °C in DMF medium using K₂CO₃ as a base and O₂ as oxidant (Scheme I.30.). With the optimized condition they synthesized a wide range of 2,5-disubstituted 1,3,4-oxadiazole derivatives and were also able to prepare in gram scale. They have proposed at first arylacetic acid undergoes oxidative decarboxylation to generate aldehyde, which subsequently takes part in a reaction with hydrazide to produce 2,5-disubstituted 1,3,4-oxadiazole derivatives.



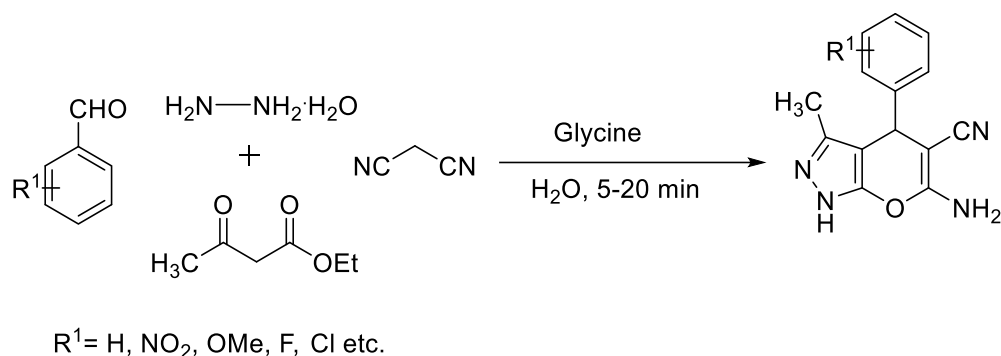
Scheme I.30. Copper catalyzed synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives

Saadati and co-worker designed³¹ a manganese oxide nanoparticle grafted on a graphene oxide (GO) based new heterogeneous catalyst by reacting graphene oxide with KMnO_4 (Scheme I.31.). This newly prepared heterogeneous nanocomposite was widely characterized with FT-IR, Raman spectroscopy, XRD, SEM, TGA, DSC, and other techniques. To check the catalytic utility of the new heterogeneous nanocomposite, investigators employed it for the preparation of 1,2,4-oxadiazole derivatives from aldehydes and amidoximes. They have prepared a library of 1,2,4-oxadiazole derivatives in moderate to excellent yield (45-83%) by varying different aldehydes and amidoximes. They were able to easily recover the nanocomposite by simple centrifugation and reuse it for seven cycles without any significant change in product yield.



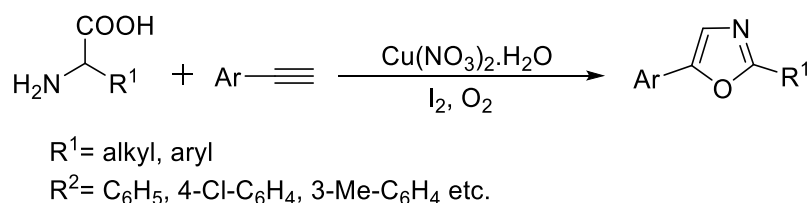
Scheme I.31. One-pot two-component synthesis of 1,2,4-oxadiazole derivatives

Reddy *et al.* investigated³² the one-pot multicomponent synthesis of pyranopyrazoles using glycine as an organocatalyst. To prepare pyranopyrazoles derivatives investigators carried out a reaction between aldehydes, ethylacetoacetate, malononitrile, and hydrazine hydrate in an aqueous medium using glycine as a catalyst at room temperature (Scheme I.32.). While exploring the substrate scope for this reaction protocol authors employed both ERG as well as ERG containing aldehydes and observed all of them went smoothly in reaction conditions to afford an abundant amount (85-95%) of pyranopyrazole derivatives.



Scheme I.32. Glycine catalyzed one-pot multicomponent synthesis of pyranopyrazoles

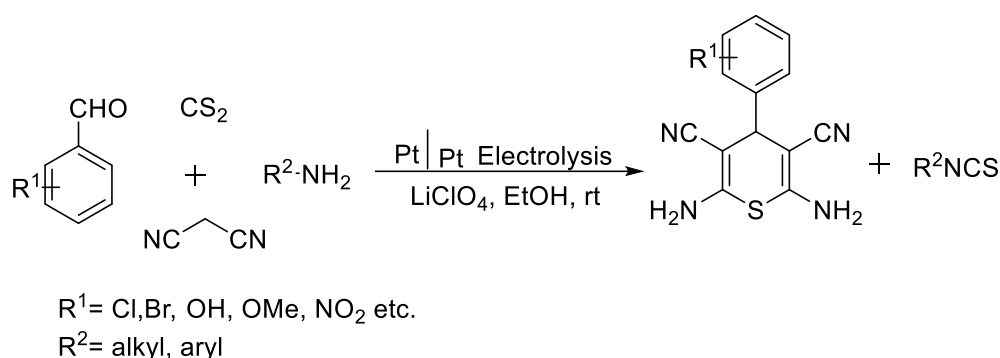
Iodine and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ catalyzed one-pot synthesis of 2,5-disubstituted oxazoles from arylacetylenes and naturally available α -amino acids had been reported³³ by Wang *et al.* (Scheme I.33.). They synthesized a library of oxazole derivatives in excellent amounts (66-83%) by using different α -amino acids like phenylalanine, phenylglycine, valine, leucine, etc. as well as diverse arylacetylenes. Investigators proposed this reaction went through the formation of phenacyl iodide.



Scheme I.33. Iodine and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ catalyzed one-pot synthesis of 2,5-disubstituted oxazoles

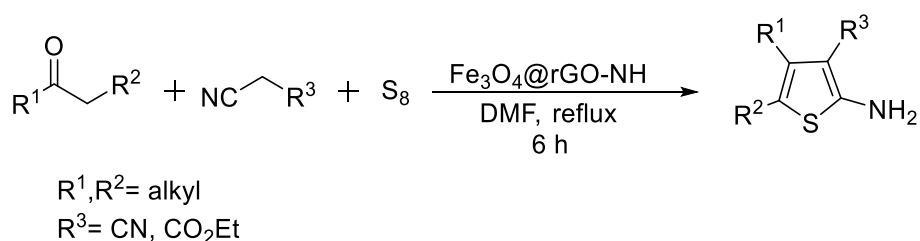
I.2.3. Synthetic methodologies for sulphur-containing heterocyclic compounds

An electro-catalyzed one-pot synthesis of 4H-thiopyran derivatives from aromatic aldehyde, amine, malononitrile, and carbon disulfide had been investigated³⁴ by Dubey *et al.* (Scheme I.34.). They synthesized a wide array of 4H-thiopyran derivatives in room temperature conditions by using different aldehydes in the presence of lithium perchlorate as a supporting electrolyte with constant potential. While describing the reaction pathway investigators proposed this reaction goes via 2-aryllidene malononitrile intermediate.



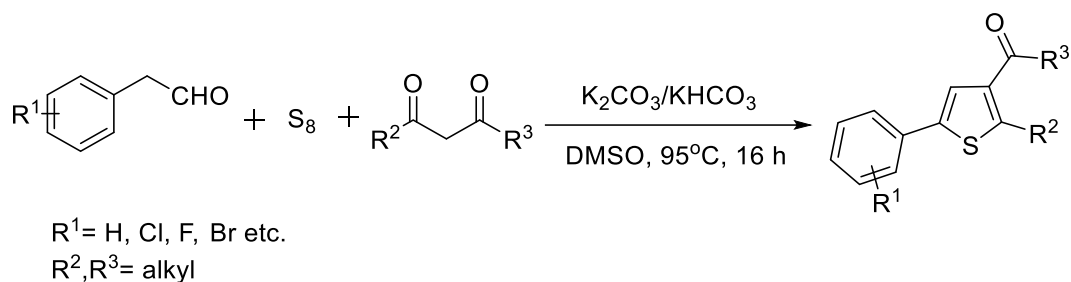
Scheme I.34. Electrocatalyzed one-pot synthesis of 4H-thiopyran derivatives

Rezaei-Seresht *et al.* designed³⁵ piperazine grafted magnetic reduced graphene oxide based ($\text{Fe}_3\text{O}_4@\text{rGO-NH}$) new heterogeneous catalyst (Scheme I.35.). This newly made heterogeneous catalyst had been characterized with FT-IR, TGA, and other techniques. With this fully characterized catalyst in hand, they used it for the preparation of 2-aminothiophenes. Investigators prepared a wide range of 2-aminothiophenes derivatives in ample amounts by varying carbonyl compounds with ethyl acetoacetate or malononitrile and sulfur in a DMF medium under refluxing conditions. This new heterogeneous composite can be easily separated from the reaction mixture by a magnet. A reusability study shows catalyst retains its catalytic potential for up to five cycles with a minimal decrease in product yield.



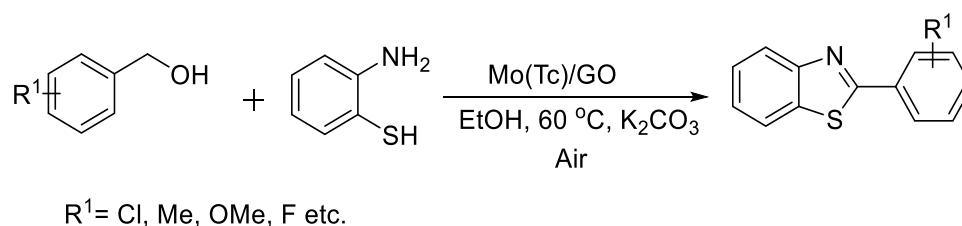
Scheme I.35. One-pot multicomponent synthesis of 2-aminothiophenes derivatives

Wang *et al.* reported³⁶ a facile method for the synthesis of 2,3,5-trisubstituted thiophenes by reacting elemental sulfur, aryl acetaldehyde, and 1,3-dicarbonyl compounds in the presence of potassium carbonate and potassium bicarbonate in DMSO at 95 °C (Scheme I.36.). Utilizing their developed methodology, they synthesized a diverse range of thiophene derivatives in good to excellent yield (36-81%).



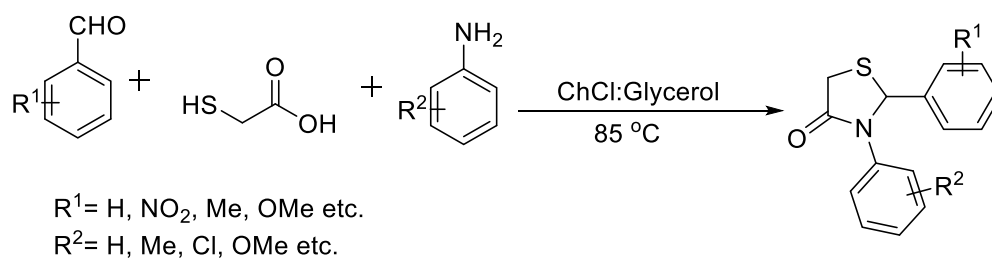
Scheme I.36. One-pot three-component synthesis of 2,3,5-trisubstituted thiophenes

Karami *et al.* designed³⁷ a new heterogeneous catalyst by anchoring thiophene 2-carbaldehyde molybdenum complex on the surface of amine functionalized graphene oxide [MO(TC)/GO] and characterized with TEM, SEM, EDX, TGA, XRD, FT-IR techniques (Scheme I.37.). The author shows the excellent catalytic potential of this new heterogeneous catalyst for the preparation of benzothiazoles from 2-aminothiophenol and benzyl alcohols. They had shown excellent recovery and reusability of the catalyst up to five runs without any noticeable change in product yield.



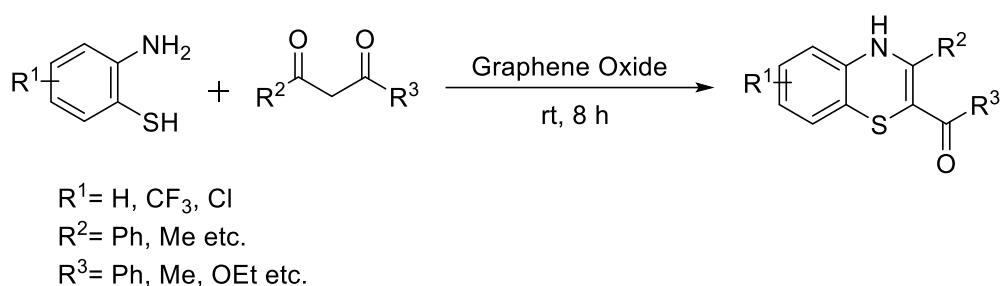
Scheme I.37. One-pot two-component preparation of benzothiazoles

ChCl: glycerol (1:2) based deep eutectic solvent catalyzed one-pot three-component synthesis 1,3-Thiazolidin-4-ones had been demonstrated³⁸ by Yedage *et al.* (Scheme I.38.). Investigators stirred different anilines, aldehydes, and thioglycolic acid in DES mixture at 85 °C and got corresponding 1,3-Thiazolidin-4-ones derivatives in good excellent amounts (85-97%). Above all, they could also synthesize 1,3-thiazolidin-4-ones derivatives in gram scale using this protocol and recover and reuse DES mixture up to five repetitive cycles.



Scheme I.38. ChCl: Glycerol based DES catalyzed synthesis of 1,3-Thiazolidin-4-ones

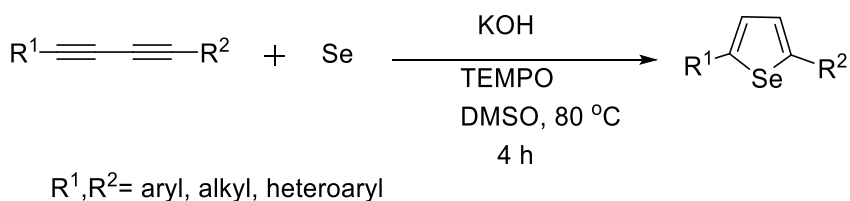
Bhattacharya *et al.* reported³⁹ Graphene oxide (GO) catalyzed one-pot multicomponent synthesis of 1,4-benzothiazine from 2-aminothiophenol and 1,3-dicarbonyl compound under solvent free conditions. Investigators employed a wide range of substituted 2-aminothiophenol with various 1,3-dicarbonyl compounds to check the substrate scope of their newly developed protocol and found reaction went well to afford corresponding 1,4-benzothiazine derivatives in good to excellent yield (75-88%) (Scheme I.39.). However, the authors noticed that using 1,3-di t-butyl ketone, dimethyl malonate, and ethyl cyanoacetate did not lead to product formation. The authors also recovered the GO from the mixture reaction by centrifugation and reused it for five cycles without any considerable change in product yield.



Scheme I.39. Graphene Oxide catalyzed synthesis of 1,4-benzothiazine derivatives

I.2.4. Synthetic methodologies for selenium-containing heterocyclic compounds

Salles *et al.* reported⁴⁰ a facile methodology for the preparation of 2,5-disubstituted selenophene derivatives from 1,3-diynes and selenium in the presence of KOH and TEMPO in DMSO medium (Scheme I.40.). Authors had synthesized a library of selenophene derivatives by varying different EWG as well as ERG containing 1,3-diynes with selenium. To explain the most plausible mechanism authors had proposed in KOH/DMSO superbasic medium elemental selenium produce selenide which undergoes an addition reaction with 1,3-diynes followed by intramolecular cycloaddition occur to form 2,5-disubstituted selenophene derivatives.



Scheme I.40. One-pot synthesis of 2,5-disubstituted selenophene derivatives

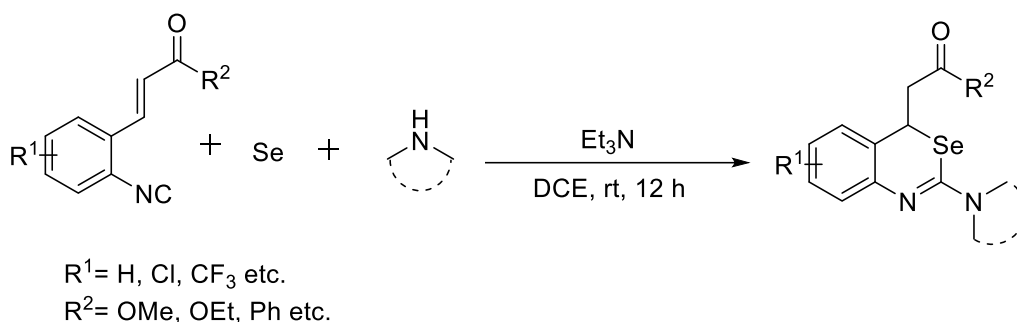
Fang and co-workers reported⁴¹ one-pot multicomponent synthetic strategy for the synthesis of 1,2,4-selenadiazole derivatives by reacting imidamides, isocyanides, and selenium powder in

acetonitrile medium in the presence of N, N-diisopropyl ethylamine (DIPEA) base (Scheme I.41.). Authors successfully synthesized a wide range of 1,2,4-selenadiazoles in moderate to good amounts by varying both ERG and EWG in imidamides and isocyanides. Here investigators were able to prepare one C-Se bond, one N-se bond, and two C-N bonds in one pot.



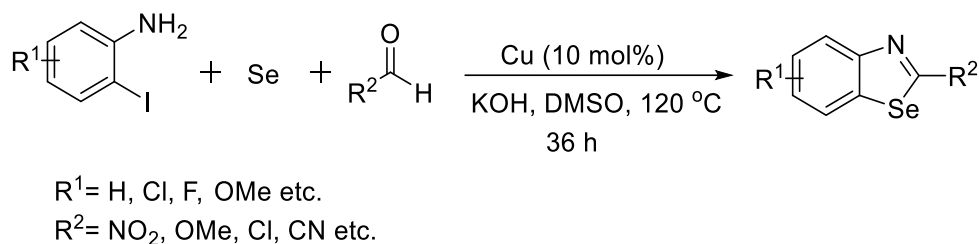
Scheme I.41. One-pot multicomponent synthesis of 1,2,4-selenadiazole derivatives

A one-pot multicomponent synthetic methodology for the preparation of 2-aminobenzo[*d*][1,3] selenazine derivatives had been reported⁴² by Fang *et al.* (Scheme I.42.). Authors had stirred amines, elemental selenium, and o-substituted aryl isocyanides in the presence of triethyl amine as a base in 1,2-dichloroethane (DCE) medium and observed the formation of 2-aminobenzo[*d*][1,3] selenazine derivatives in good to excellent amount (68-95%).



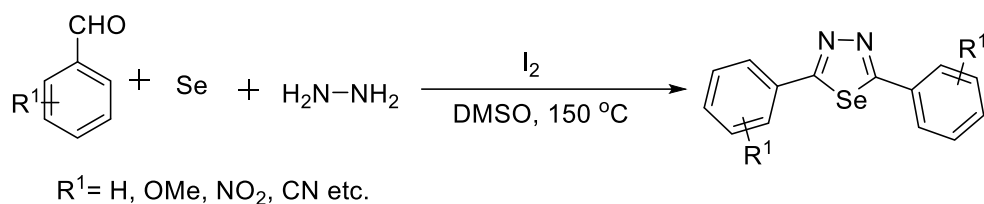
Scheme I.42. Base promoted one pot synthesis of 2-aminobenzo[*d*][1,3] selenazine derivatives

Su *et al.* designed⁴³ copper catalyzed one-pot multicomponent synthetic strategy for the preparation of 2-aryl-1,3-benzoselenazoles in moderate to good amounts (29-75%) by reacting aromatic aldehydes, selenium powder, and 2-iodoanilines at 120 °C in dimethylsulfoxide (DMSO) medium in the presence of potassium hydroxide (KOH) base (Scheme I.43.).



Scheme I.43. Copper catalyzed synthesis of 2-aryl-1,3-benzoselenazoles

Bowroju and co-workers developed⁴⁴ a synthetic methodology for the preparation of 1,3,4-selenadiazoles from aldehydes, hydrazine, and elemental selenium. Investigators stirred ERG as well as EWG containing aldehydes, with hydrazine and elemental selenium at 150 °C in DMSO medium in the presence of iodine as a catalyst which affords corresponding 1,3,4-selenadiazole derivatives in excellent amounts (Scheme I.44.). They also noticed that aldehydes bearing EWG showed better reactivity in reaction conditions as compared to ERG containing aldehyde.



Scheme I.44. One-pot multicomponent synthesis of 1,3,4-selenadiazoles

I.3. Conclusion

From the concise review of different synthetic methodologies for medicinally important heterocyclic compounds, it can be said although there is substantial growth in the development of new protocols but there remains plenty of scope to design and develop new synthetic strategies for greener synthesis of heterocyclic scaffolds.

I.4. References

References are given in the BIBLIOGRAPHY section under chapter I.