COPPER BASED NANOPARTICLES AS AN INEXPENSIVE CATALYST FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS: REVIEW

Sneha Naik[1], Padmini C. Panjikar[2], Sonia Chahar Srivastava[3], Palvi Jindal[4], Anupama Sharma[5], Manmohan Singh Chauhan[6], Narendra Pal Lamba[7]

Article History: Received: 13.05.2023 **Revised:** 22.06.2023 **Accepted:** 18.07.2023

Abstract

Heterocyclic scaffolds play a vital role in the structures of numerous drugs and natural products, owing to their wide range of pharmaceutical and biological activities. Copper has the ability to undergo redox processes and hence plays a pivotal role in catalytic activity and versatility in organic synthesis. Nowadays, Copper based nanoparticles have been extensively investigated as a novel class of catalysts for various chemical transformation. This review focuses on the application of copper-based nanoparticles as catalysts in the synthesis of potential heterocyclic moiety that offers several advantages, that includes low catalyst loading, high atom economy, improved yields, easy separation, cost effective, shorter reaction times, recyclability and reusability of the catalyst.

Keywords: copper nanoparticles, catalysis, nano-catalyst, heterocycles, heterogenous

[1,4,6,7]Amity University Rajasthan, Jaipur, India – 303002
[2]Dept. of Chemistry, Parvatibai Chowgule College of Arts and Science, Goa, India - 403601
[3]S. S. Jain Subodh PG (Autonomous) College, Jaipur, India - 302007
[5]St., Wilfred's College, Jaipur, India- 302020

DOI: 10.31838/ecb/2023.12.si6.669

1. INTRODUCTION:

The field of chemistry that focuses on carbon compounds is referred to as organic chemistry Earlier the chemical compounds were broadly classified with respect to their sources, into two classes: inorganic and organic. Inorganic compounds are those derived from mineral, whereas organic compounds are obtained from living organisms. Until 1850 many chemists believed that organic compounds could never be synthesised in the laboratory as they were obtained from living species. Today most of the organic compounds are synthesised in the laboratory either by isolating them from natural source and modifying it or from simple organic compounds derived from petroleum products[1]. In the year 1815, Berzelius assumed that organic compounds were produced under the influence of a vital force-the essence of life, and they could not be prepared artificially. In 1828 Wohler converted an inorganic compound-ammonium cyanate to urea, a chemical that is only obtained from animal sources. His work led to laboratory routes towards synthesis of more organic compounds such as acetic acid synthesised by Kolbe in 1845 and methane synthesized by Berthelot in 1856.[2] In today's day and age millions of organic compounds have been synthesised in the laboratory that have never been found in nature, which includes synthetic fabrics, plastics, synthetic rubber, medicines, and even things like photographic film and Super glue.[3]

Organic chemistry has revolutionized our lives by providing accessible comforts and essential resources that were once inaccessible or limited to the privileged few. In the past few decades, we have seen an enormous increase in life span of an individual and this could be achieved moreover due to the isolation and synthesis of new drugs to combat infections and the availability of vaccines.[4] Our agricultural output has also been increased with quality enhancement all because of fertilizers, pesticides, and herbicides. The numerous products derived from organic chemistry have significantly shaped our modern lives, and without them, our existence would be notably altered. Within the realm of organic chemistry, their exist several branches that includes medicinal chemistry, polymer chemistry, heterocyclic chemistry, natural product chemistry, stereochemistry, organometallic chemistry, pericyclic chemistry, and so on. Among them, heterocyclic chemistry has made significant contributions to the field of chemical sciences and continues to be highly valued in current research.

Heterocyclic compounds

Heterocyclic compounds, a significant area of study in organic chemistry, belong to a broad category of compounds that feature at least one heteroatom (such as nitrogen, oxygen, or sulfur) alongside carbon atoms in a cyclic structure. These compounds hold great significance in modern times due to their diverse applications in biochemistry, medicine, agriculture, and industry. Their utility contributes to the well-being of human society and the environment, making them highly valuable in various fields.[5] About majority of organic chemistry work comprises of heterocyclic compounds. In nature these compounds are widely distributed in plants and animals and play a vital role in the metabolism of all living cells. Chlorophyll and heme, which belong to the porphyrin ring system are necessary components for photosynthesis and for oxygen transport in animals. They both are heterocyclic compounds. Essential dietary ingredients such as riboflavin (vitamin B2), thiamine (vitamin B1), pyridoxol (vitamin B6), riboflavin (vitamin B2), nicotinamide (vitamin B3) and ascorbic acid (vitamin C) do possess heterocyclic moiety in their structure. Deoxyribonuclic acid (DNA)- a molecule that carries genetic information for the development and functioning of an

organism is also composed of heterocyclic compounds-pyrimidines and purines namely adenine, guanine, pyrimidine, thymine, and cystosine.[6] Even some of the naturally produced compounds such as penicillin's, cephalosporin; vinblastine, morphine, reserpine, nicotine, atropine, papaverine etc. have heterocyclic moiety. Besides being a part of natural products, heterocycles include their use as sensitizers, antioxidants, corrosion inhibitors, copolymers, and dyestuff. Heterocyclic compounds are considered as important precursor compound in synthetic organic chemistry as well as in natural product synthesis. The synthetic research on heterocyclic compounds have been one of the significant aspect due to their variety of bioactive properties such as antifungal, anti-inflammatory, antibacterial, anticonvulsant, antiallergic, herbicidal, anticancer, and so on. Most pharmaceutical products that mimic natural products with biological activity are heterocycles. The synthesis of heterocycles has always been a highly significant research area in synthetic chemistry, driven by widespread interest in these compounds.[7,8] As a result, numerous classic named reactions have been developed, reflecting the importance and focus placed on this field of study. While classic syntheses have traditionally been reliable for producing heterocyclic compounds, they no longer meet the environmental and safety standards of today. As a result, there is a pressing need for contemporary advancements in discovery and process chemistry to focus on developing sustainable and environmentally friendly synthetic routes. These alternatives must be rapid and meet the high standards of environmental acceptability, replacing the classic methods that are no longer deemed appropriate.

Catalysis:

Considering the 12 principles of green synthesis towards sustainable production of chemicals, as outlined by Anastas and Warner, researchers have developed a range of innovative and environmentally friendly approaches. To tackle these challenges, energy efficient techniques like microwave irradiation and sonochemistry have been employed over the conventional heating. Also, the use of environmentally benign solvents and catalysis has emerged as key tools in green synthesis and engineering. Catalysis is indeed a key player in chemical transformations and plays a crucial role in various chemical protocols, spanning from academic research at laboratory level to industrial applications. By utilizing catalytic reagents, it becomes possible to lower the required reaction temperature, minimize waste produced by reagents, and enhance the selectivity of reactions. This not only contributes to the development of more sustainable practices but also helps avoid undesirable side reactions, leading to greener and more efficient technologies. Catalysis enables us to achieve more efficient and environmentally friendly chemical processes across different sectors of the chemical industry.

The absence of catalysts would have hindered the synthesis of various essential products for humans. While heavy metal catalysts are commonly used, they are often not recoverable from the system. In contrast, softer catalysts like zeolites and phase transfer catalysts, such as crown ethers, have found more industrial applications. The three well-known categories of catalysis—homogeneous, heterogeneous, and enzymatic—each have their own advantages and disadvantages. Enzymatic catalysis, found in nature, is considered the most efficient and environment friendly form of catalysis. However, both homogeneous and heterogeneous catalysis possess unique merits and demerits. Consequently, there is an urgent need for a new catalytic system that combines the activity of homogeneous

catalysis with the easy recoverability of heterogeneous catalysts.

Nano-catalysts offer a promising solution as they incorporate the advantages of both homogeneous and heterogeneous catalytic systems. Nano-sized catalysts have a high surface area, which significantly increases the contact between reactants and catalysts—like homogeneous catalysis. Furthermore, their insolubility in the reaction solvent makes them heterogeneous catalysts, allowing for easy separation from the reaction mixture—like heterogeneous catalysis.

One of the most crucial characteristics of any catalyst for acceptance in green chemical manufacturing processes is the ability to recover it from the system. Nano-catalysts, with their small size and high surface area, enable rapid and selective chemical transformations with excellent product yields. Moreover, their insolubility in the reaction solvent facilitates the separation and recovery of the catalyst from the reaction mixture. This unique combination of properties makes nano-catalysts highly attractive for green and efficient industrial catalysis in the recent years.[9]

Nanoparticles in organic chemistry

In recent years Nanoparticles (NPs) have emerged as a highly valued resource as a catalyst in many chemical reactions at industrial level as well as in research. Due to their wide range of applications in various fields such as energy conservation and storage, environmental remediation, chemical manufacturing, and biological sciences, there has been a huge research interest in synthesis of various highly functionalized NPs. The unique properties at the nanoscale make these nanoparticles a versatile tool for various organic transformations and applications. As catalysts, nanoparticles have contributed immensely to a wide range of organic reactions. Their high surface area-to-volume ratio enhances catalytic activity, allowing for more efficient and selective transformations. Nanoparticle catalysts have been utilized in various categories of reactions such as hydrogenation, oxidation, coupling reactions, and carbon-carbon bond formation. Metal nanoparticles functionalized with ligands can provide unique reactivity and selectivity in organometallic catalysis. Additionally, these nanoparticles can be used as supports for immobilizing organic catalysts or reagents, improving their stability and recyclability. Functionalized nanoparticles can encapsulate and protect organic molecules, allowing controlled release and targeted delivery to specific sites in the body. This enables improved drug efficacy and reduced side effects. Nanoparticles can be used as sensors in organic chemistry to detect and quantify various analytes. By modifying the surface properties of nanoparticles, they can selectively interact with specific molecules, resulting in changes in their optical, electrical, or magnetic properties. These changes can be easily measured and used for sensing applications.

The use of nanoparticles in organic chemistry continues to evolve, enabling novel synthetic strategies and applications. Their tunable properties and compatibility with organic systems make them valuable tools for advancing the field and addressing various challenges in organic synthesis and molecular design. But the main challenge in the development of catalytic nanoparticles is to prepare nanomaterials that are highly active, selective, stable, robust, and inexpensive. Over the past decade, significant research efforts have been directed towards the synthesis of metal oxide nanoparticles, including titanium, zinc, iron, and magnesium. Among these metal oxides, copper nanoparticles have garnered considerable attention and have been extensively studied.

Copper [10,11]

Copper (Cu)-a chemical element, having atomic number 29, belongs to the 3d

transition metal series and is known for its distinct red-orange colour. It is obtained from various sources that includes a) Copper Ores and minerals such as chalcopyrite, bornite, malachite, and chalcocite. b) discarded electrical wires, plumbing materials, and electronic waste. c) from industrial by-products, such as copper slag, copper ash, and copper scrap from manufacturing processes. d) from electrorefining-a process where impure copper is purified using electrolysis. Cu commonly exhibits two oxidation states: +1 (cuprous) and +2 (cupric). Copper(I) compounds are typically more reactive and tend to be unstable in air, while copper (II) compounds are more stable. Copper has the ability to undergo redox processes and hence plays a pivotal role in catalytic activity and versatility in organic synthesis. In coordination chemistry, copper has the tendency to form complexes with various ligands, including monodentate ligands (e.g., water, ammonia), polydentate ligands (e.g., ethylenediamine, EDTA), and organometallic ligands to form distinct complexes. Copper complexes often exhibit diverse geometries and can possess unique electronic and magnetic properties. Besides its exceptional characteristics in scientific research and various applications, copper also fulfils vital functions within biological systems. It is an essential trace element involved in various biological processes, such as electron transfer reactions in enzymes (e.g., cytochrome c oxidase) and oxygen transport in hemocyanin. The coordination chemistry and redox properties of copper are critical for its biological functions. This element covers a wide range of fields, extending from the fundamental principles of coordination chemistry to its practical uses across diverse industries. The distinctive properties and adaptable nature of copper render it highly valuable in both academic and industrial settings.

In the past few years Cu and Cu based nanocatalyst have emerged as a new tool for the synthetic chemist in catalytic organic transformations, electrocatalysis, and photocatalysis of which its contribution in organic synthesis have been greatly appreciated. It is due to their small size, large surface area, and unique reactivity that makes them attractive for promoting a wide range of transformations. Copper nanoparticles have demonstrated significant utility in the synthesis of heterocyclic compounds. There have been many reports on synthesis of numerous biologically active heterocycles such as benzoxazoles, benzofuran, triazoles, tetrazoles, indolizines, pyrroles, quinoline, quinzolines, chromenes, coumarin derivatives catalysed by copper-based nanoparticles. Copper catalysed reactions offers various advantage over the conventional methods as it requires mild reaction conditions, improved reaction rates, enhanced catalytic activity, increased selectivity, and simple synthetic techniques.

The primary aim of this review article is to provide an overview of recent research focusing on the utilization of copper nanoparticles as catalysts in the synthesis of diverse heterocyclic compounds over the past decade.

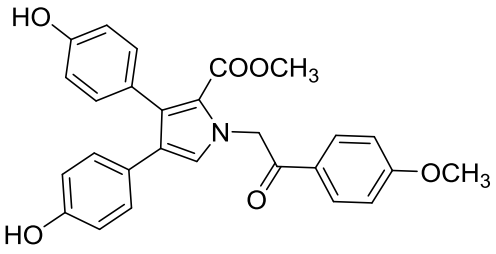
Nano-copper based particles as catalysts in the synthesis of heterocyclic scaffolds

In recent times, there have been numerous reports highlighting the effectiveness of metallic copper (Cu) or its oxide nanoparticles, either alone or when supported on different materials, as highly promising catalysts for the synthesis of important heterocyclic compounds.

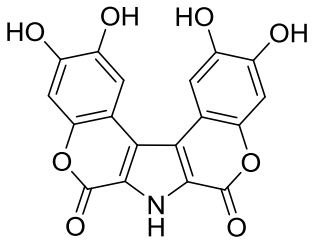
Pyrroles, pyrrolidine and piperidine

Pyrrole is a significant heterocycle known for its crucial role in various natural products and drugs. It is widely utilized as a fundamental structure in organic synthesis and finds applications in fields

like materials science, medicinal chemistry, and pharmacology[12,13,14].



Lamellarin O

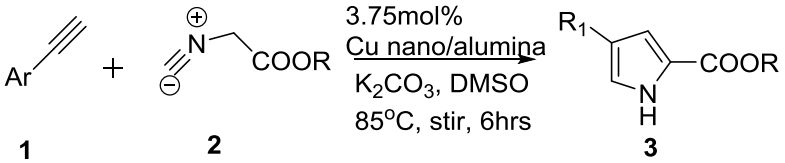


Ningalin A

Figure 1 natural products containing pyrrole nucleus.

Substituted pyrroles serve as intermediates[15] in organic synthesis and are also used as conducting materials[16,17] in the organic domain. In recent decades, numerous sophisticated techniques have been developed for synthesizing pyrroles. Among them various methods, the metal-catalyzed [3+2] cycloaddition of isocyanides and alkynes has emerged as a highly reliable and promising approach for accessing substituted pyrroles. This method is advantageous due to its efficient use of atoms. However, most of the reported reactions involve activated alkynes, resulting in the formation of either oligo (2,3-disubstituted) pyrroles or polysubstituted pyrroles. The challenge lies in synthesizing regioselective 2,4-disubstituted pyrroles from unactivated alkynes and isocyanides, and finding a solution to this problem remains elusive.[18,19].

The research team of Tiwari[20] has reported a regioselective synthesis of 2,4-disubstituted pyrroles (3) from inactivated terminal aromatic/ aliphatic alkynes (1) and isocyanides (2) catalysed by nano copper (0) stabilized on alumina prepared from Cu-Al hydrotalcite (scheme 1). Phenyl acetylene and methyl 2-isocyanoacetate were chosen as the initial substrates for optimization in the synthesis process. Through various optimization attempts, it was determined that using 3.75 mol% of catalyst and 1.5 equivalents of K2CO3 as a base in DMSO at 85°C under a nitrogen atmosphere provided the best conditions. Different isocyanides, including methyl 2-isocyanoacetate, ethyl 2-isocyanoacetate, tert-butyl isocyanoacetate, and diethylphosphonoacetonitrile, were successfully incorporated, yielding satisfactory results. Moreover, the reaction was expanded to include a range of aryl-substituted terminal alkynes, encompassing both electron-donating and electron-withdrawing groups on the phenyl ring, and yielded the corresponding pyrrole derivatives in moderate yields.



1 **2** **3**

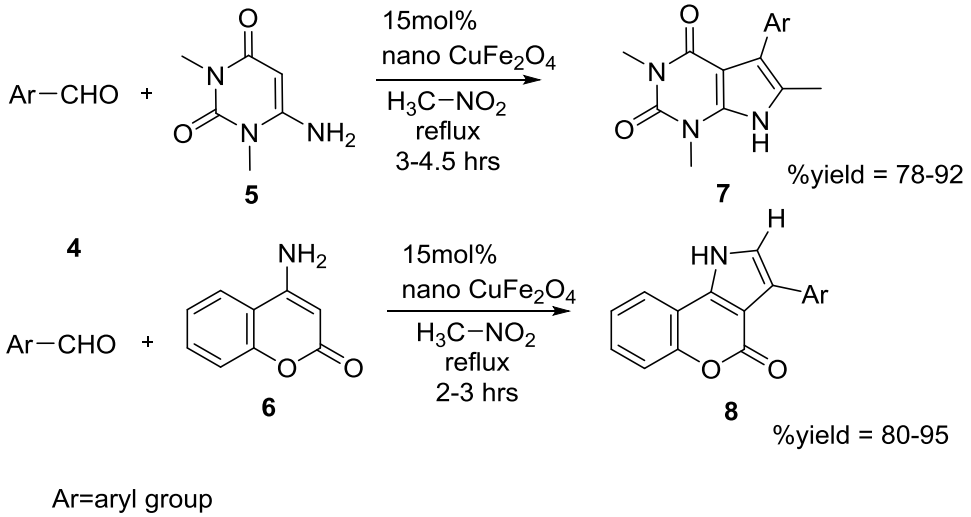
R= Me, Et, t-Bu, P(O)OEt$_2$

% yield=65-75

Scheme 1

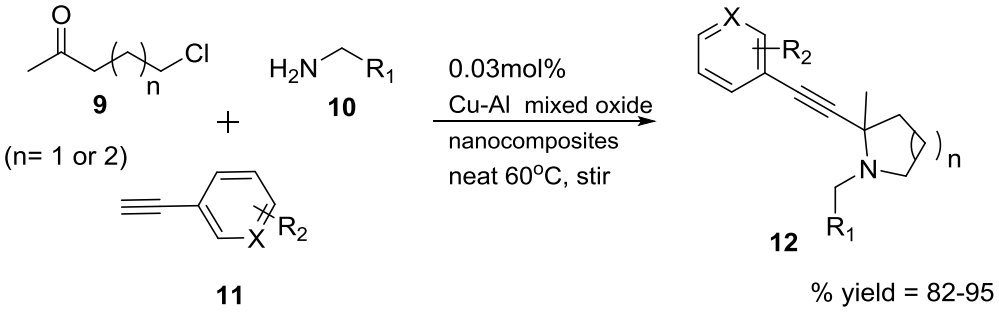
In another work, Paul and his co-workers reported[21] a one-pot three-component domino coupling of 6-aminouracil (5)/4-aminocoumarin (6), aldehydes (4) and

nitromethane in presence of nano CuFe2O4 as catalyst to yield highly substituted coumarin (8) and uracil (7) fused pyrrole derivatives (scheme 2). To evaluate the efficiency and potential of various catalysts, a model reaction using 1,3-dimethyl-6-aminouracil, p-methoxybenzaldehyde, and nitromethane as substrates were employed. Different catalysts were tested in this three-component reaction to assess their performance and effectiveness in promoting the desired transformation. After numerous optimization attempts, it was established that the most effective conditions for the synthesis involved using a catalyst loading at 15 mol% under reflux condition. These optimized conditions resulted in the formation of the desired heterocyclic molecules with excellent yields.



Scheme 2

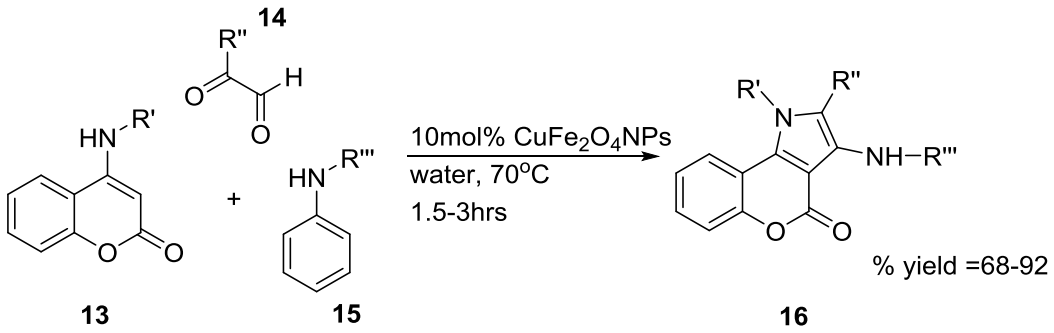
Purohit and. Rawat[22] in their work utilized reusable calcinated copper-aluminum mixed oxide nanocomposites (Cu-Al-MO NCs) for the highly efficient and selective one-pot green synthesis of substituted pyrrolidines/piperidines (12). This was achieved through a coupling reaction (scheme 3) involving a ketone (9), substituted amine (10), and alkyne derivative (11). The CuAl-MO nanocomposites exhibited excellent catalytic efficiency, enhanced by their stability and the ease of retrieving the catalyst for subsequent reuses. Remarkably, the catalyst maintained its activity and selectivity throughout multiple cycles without significant degradation. In the initial stage, a model reaction involving 5-chloropentan-2-one, n-propylamine, and phenylacetylene was conducted. The reaction employed a very low concentration of 0.03 mol% CuAl-MO nanocatalyst and was carried out at a temperature of 60°C. Various solvents were tested, including toluene, DMF, DMSO, acetonitrile, as well as greener solvents such as H2O, PEG, and DEG. Among the solvents tested, the polar aprotic solvent acetonitrile was found to be the most suitable solvent, giving the substituted pyrrolidine/piperidine.



Scheme 3

Another interesting observation was found that catalysts used in the study exhibited excellent recyclability, retaining their activity for at least five cycles without significant loss. The total turnover number (TTN) reached a remarkable value of over 5172, highlighting the efficiency of the catalysts. Additionally, the stability of the catalytic sites in the CuAl-MO nanocomposites was confirmed using the hot filtration method, which showed low levels of leaching during the reaction.

In another work reported by Saha[23] and team synthesis of chromeno[4,3-b]pyrrol-4(1H)-one derivatives) was achieved from one pot three component reaction of aromatic amine (15), glyoxal monohydrate (14) and 4-aminocoumarin (13) using nanocrystalline CuFe2O4 in aqueous media (scheme 4). After performing series of efforts to optimise the reaction condition it was found that 10mol% catalyst loading in water leads to good - excellent yield of the desired heterocyclic scaffold. The easy recovery and reusability of the catalyst and operational simplicity of the process makes the protocol attractive, sustainable, and economic.



Scheme 4

Furans

Furans are aromatic heterocycles that play a significant role in various pharmacological activities. They are also fundamental components of many natural products and are utilized as flavour and fragrance compounds.

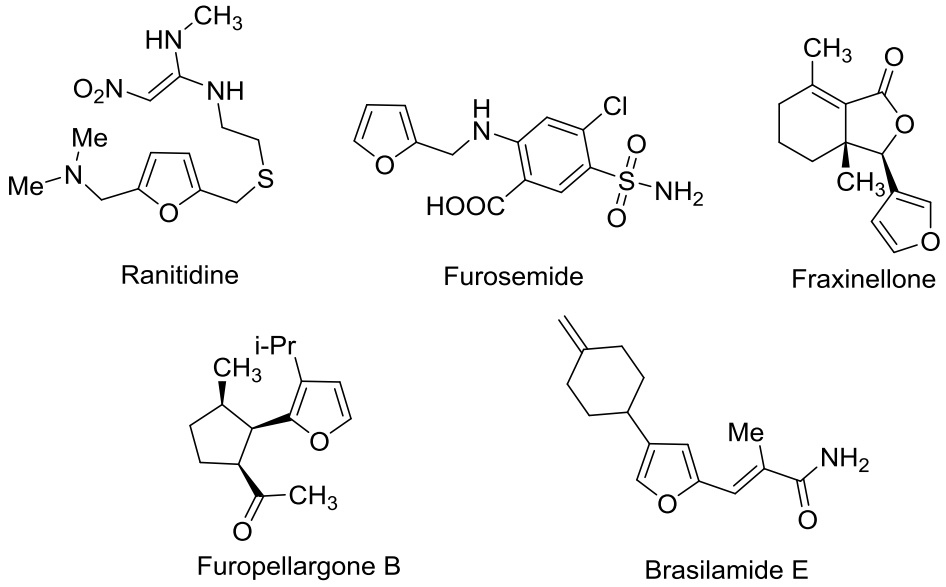
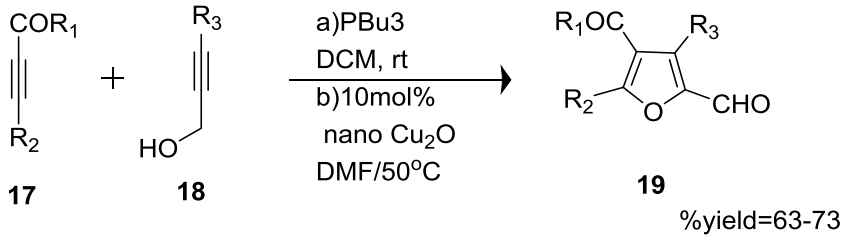


Figure 2 Some furan-based medicines and natural products

Furans serve as intermediate compounds in diverse processes within synthetic organic chemistry and materials science. The significant utility of furans has led to the development of various synthetic methods for producing functionalized furans. These methods include the Paal-Knorr synthesis, Feist-Benary synthesis, cyclization of alkynyl-substituted divinyl ketones, and cyclization of allenyl ketones, among others. These synthetic approaches have been extensively studied and reviewed in the literature to provide a comprehensive understanding of the different strategies available for synthesizing furans with specific functional groups or modifications.[24]



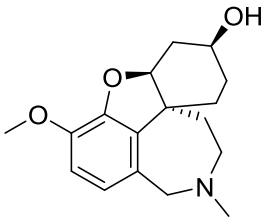
Scheme 5

In a recent study conducted by Hua Cao[25] and their team, they reported a novel and effective one-pot domino process (scheme 5) catalysed by nano-Cu_2O for the regioselective synthesis of 2,4,5-trisubstituted α-carbonyl furans (19). The process involved a series of electron-deficient alkynes (17) reacted with 2-yn-1-ols (18), resulting in moderate to good yields of the desired furan products. Importantly, the reactions were carried out under atmospheric pressure in the presence of air. To establish the optimal reaction conditions, the authors used phenyl propionate and propargyl alcohol as model substrates. They found that the best results were obtained using 10 mol% of nano-Cu_2O particles at a temperature of 50°C under atmospheric pressure.

Benzopyrimidoazepines

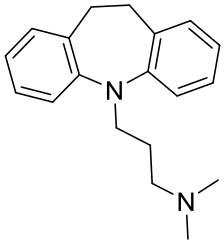
Azepines are a significant structural motif found in various natural products that exhibit notable biological activities and have been utilized in drug development.

Benzoazepine, in particular, is a well-known pharmacophore present in several drugs because of its diverse biological activities, including antibacterial, anticonvulsant, anti-HIV-1, and antihypertensive properties.[26,27,28,29,30]. Its presence in these compounds highlights the importance and potential therapeutic value of the benzoazepine moiety in medicinal chemistry.



Lycoramine

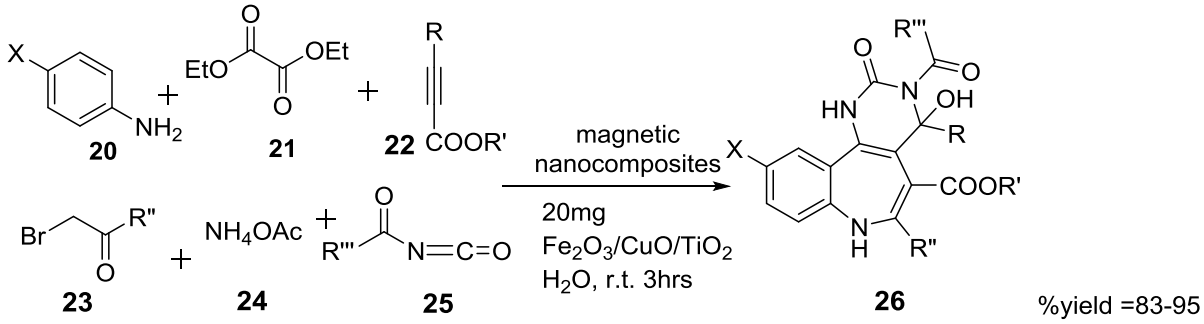
Figure 3 natural product containing azepine structure.



Imipramine-an antidpressant

Figure 4 pharmaceutical drug containing azepine nucleus.

The Meybodi[31] and group developed an effective, green, and environmentally synthesis of new derivatives of benzopyrimidoazepines (scheme 6) that includes reaction of substituted anilines (16), diethyl oxalate (17), activated acetylenic compounds (18), alkyl bromides (19), ammonium acetate (20), and aryl/alkyl isocyanates (21) in aqueous media at ambient temperature in the presence of new organometallic nanocatalyst $Fe_3O_4/TiO_2/CuO$@MWCNT-MNC.



Scheme 6

In this study, the synthesis of benzopyrimidoazepines was achieved through a series of reaction steps. Anilines (20) and diethyl oxalate (21) were mixed in the presence of Fe3O4/TiO2/CuO@MWCNT catalyst (0.02 g) for 30 minutes. Subsequently, activated acetylenic compounds (22) and α-haloalkanes (23) were added to the mixture and stirred for an additional 15

minutes. Ammonium acetate (24) and isothiocyanates (25) were then introduced and stirred for 30 minutes. The reaction proceeded for 3 hours, and its completion was confirmed by TLC analysis. To isolate the final product (26), the catalyst was separated using an external magnet, and the solid benzopyrimidoazepines was subsequently filtered and purified using solvent extraction. The overall synthesis process involved the combination of various starting materials and reagents, employing the catalyst and conducting several reaction steps to achieve the desired product in an excellent yield.

Benzimidazole

Benzimidazoles have demonstrated a wide range of biological activities, including anti-bacterial, anti-fungal, anti-inflammatory, anti-viral, and anti-cancer properties.[32,33,34] These significant characteristics have led to the development of numerous synthetic methods for benzimidazole synthesis. In recent years, there has been a growing emphasis on the development of green and sustainable protocols for their synthesis.

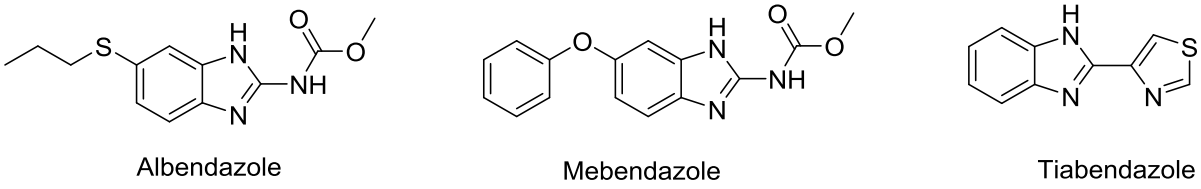
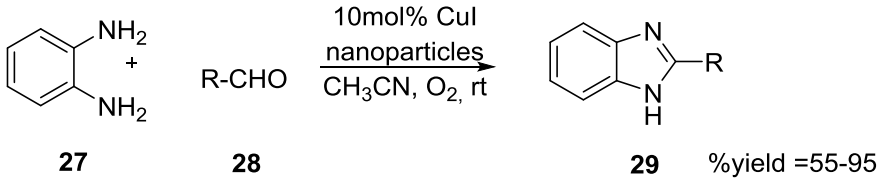


Figure 5 some of the pharmaceutical drugs containing benzimidazole nucleus

The traditional strategy for synthesizing benzimidazoles involves the condensation of o-phenylenediamines with carboxylic acids or their derivatives in the presence of strong acids at high temperatures. Although various catalysts and microwave irradiation have been employed to reduce reaction times, the harsh conditions associated with these methods limit their synthetic applicability.[35,36,37] As an alternative, the oxidative cyclization of Schiff-base derivatives derived from o-phenylenediamine and aldehydes has emerged as a more favourable route for obtaining 2-substituted benzimidazoles.

A recent work by Reddy[38] and et al reported CuI nanoparticles as a heterogeneous catalyst for the synthesis of several benzimidazole derivatives (29) via oxidative cyclization of various o-phenylenediamines (27) with substituted benzaldehydes/aldehydes (28) (scheme 7).

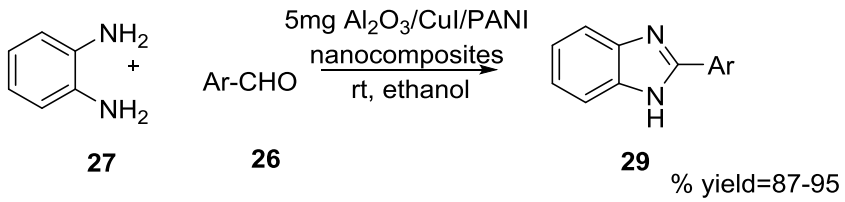


Scheme 7

At the beginning of the work, screening process to evaluate the effectiveness of different catalysts and solvents for the coupling reaction was carried out between o-phenylenediamine and benzaldehyde to produce 2-phenyl-1H-benzimidazole. The catalysts tested included ferrites, TiO2, CuI, and CuI nanoparticles (CuI Nps). Among the various catalysts examined, the 10mol% CuI nanoparticles demonstrated the highest yield of the desired benzimidazole product. Furthermore, it was found that using acetonitrile as the solvent was optimal for this reaction.

Remarkably, the reaction proceeded smoothly and efficiently at room temperature without the need for a base or additional heating, giving the expected cyclized product in moderate to excellent yield.

Kohli and their research group conducted a study in which they successfully synthesized a heterogeneous Al2O3/CuI/PANI nanocatalyst. This nanocatalyst was employed in a one-pot synthesis of 2-substituted benzimidazoles (29) (Scheme 8). The synthesis involved the condensation reaction between o-phenylenediamine (27) and aldehydes (30) using ethanol as a green solvent. The initial experiments involved the reaction of o-phenylenediamine and 4-methylbenzaldehyde using the Al2O3/CuI/PANI catalyst (5 mg) under various conditions. Different solvents were tested at room temperature, including toluene, THF, DMF, acetonitrile, ethylene glycol, methanol, ethanol and DMSO including neat conditions. Ethanol was determined to be the most suitable solvent for the reaction. Based on these findings, the optimal reaction conditions were determined to be 5 mg of the Al2O3/CuI/PANI nanocatalyst in ethanol as the solvent at room temperature for 1 hour. Under these conditions, a series of 2-benzimidazole derivatives were synthesized with excellent yields using differently substituted benzaldehydes.



Scheme 8

Indazolines

Indazole is a heterocycle that comprises benzene ring fused with pyrazole ring. Although this heterocycle is rare in nature but present in a variety of synthetic compounds that possesses diverse pharmacological activities such as anti-inflammatory, antiarrhythmic, antitumor, antifungal, antibacterial, and anti-HIV properties. compounds containing Indazole nucleus with various substituents and functional groups are known to exhibit significant pharmacological activities and often serve as important structural motifs in drug molecules.[39,40]

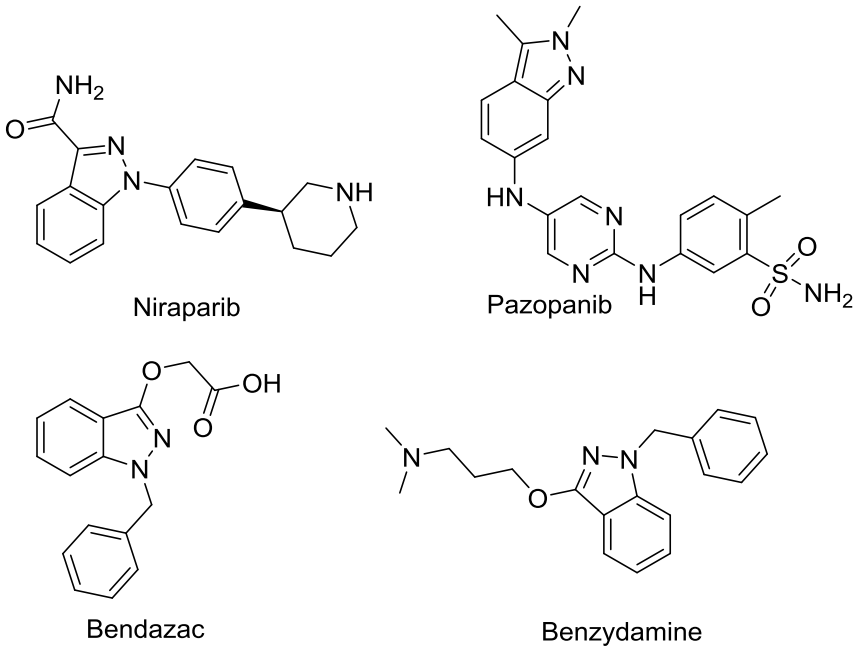
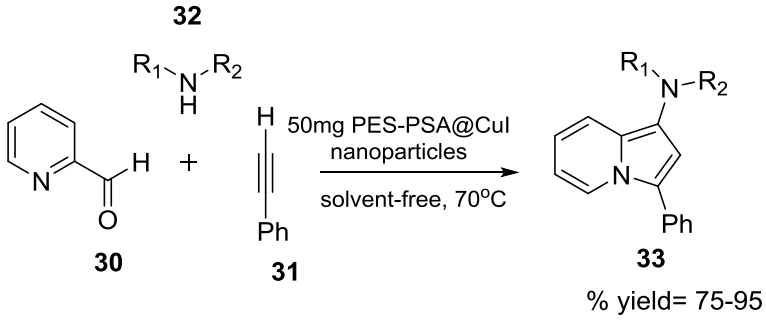


Figure 6 a) Niraparib anticancer drug for the treatment of recurrent epithelial ovarian, *fallopian tube or primary peritoneal, breast, and prostate cancer.b) Pazopanib is a tyrosine kinase inhibitor for renal cell carcinoma treatment. c)Bendazac and Benzydamine are commercially available anti-inflammatory drugs*

Solgi and team reported CuI NPs supported on porous cross-linked poly(ethyleneamine)– polysulfonamide (PEA–PSA@CuI) as an effective and recyclable nanocatalyst for the synthesis of indolizine derivatives. This three-component reaction (scheme 9) involved condensation of 2-pyridine carbaldehyde (30) with phenylacetylene (31) and second-order amines (32) in the presence of PEA–PSA@CuI as catalyst under solvent-free conditions resulting amino indolizine derivatives (33) as products in good to excellent yields. after optimizing the reaction conditions with respect to differential solvents and catalyst loading, the results showed that the best condition is stirring at 70℃ and 50 mg of catalyst concentration under solvent-free condition. Also, it is worth mentioning that the secondary amines chosen for this reaction were dibenzylamine, dibutylamine, N-methylaniline, morpholine, piperidine, 4-methylpiperidine, 1-methylpiperazine, piperazine and pyrrolidine, reacted efficiently and obtained aminoindolizines in good to excellent yield.

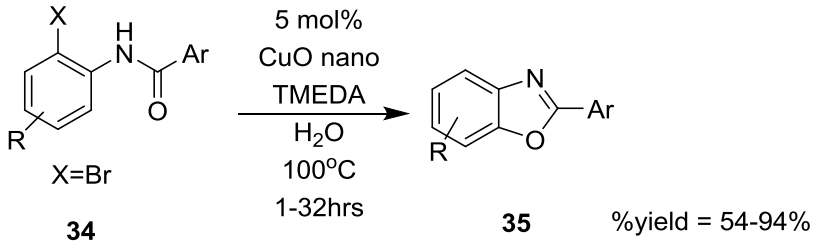


Scheme 9

Benzoxazoles

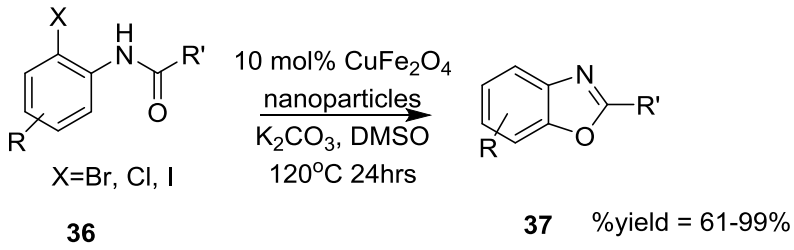
Benzoxazole are an important subclass of heterocycles that occur widely in bioactive molecules and are important targets in drug discovery. The traditional method for the synthesis of benzoxazoles involves condensation of 2-aminophenol with a carboxylic acid in the presence of an acid, or with an aldehyde under oxidative conditions. Another approach is intramolecular cyclization of 2-haloanilides into benzoxazoles.

In a recent work Nilufa Khatun[41] and et al reported a method wherein o-haloanilides (31) in the presence of 5mol% CuO nanoparticles and TMEDA in water at 100℃ to provide the substituted benzoxazoles (32) in a moderate to excellent yield (scheme 10). The presence of the ligand/base TMEDA changes the selectivity, giving exclusively the desired heterocyclic compound.



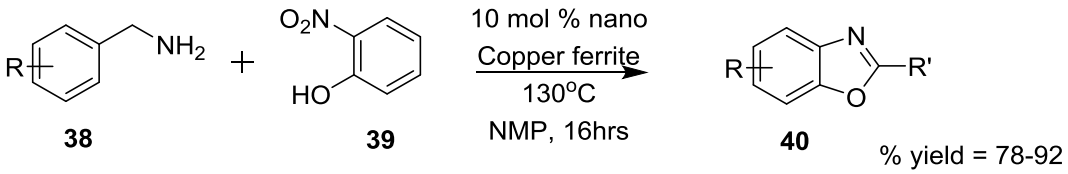
Scheme 10

In another work reported by Daoshan Yang[42] and team, substituted benzoxazoles (37) were synthesised from substituted N-(2-halophenyl) benzamides (36) in presence copper (II) ferrite serves as a nanocatalyst (scheme 11). Under the optimized conditions N-(2-halophenyl) benzamides with 10 mol% catalyst, two equivalents of potassium carbonate as the base and dimethyl sulfoxide as the solvent at 120°C under an atmosphere of nitrogen gave the corresponding benzoxazole in good to excellent yields. According to their report, 2-iodoanilides showed higher reactivities than the 2-bromoacetanilides, in terms of intramolecular O-arylation to produce benzoxazole.



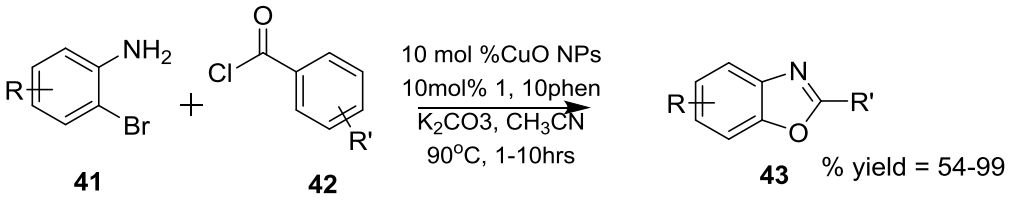
Scheme 11

Sarode[43] and team reported a new, green and sustainable approach for the synthesis of 2-substituted benzoxazole (40) by using a one pot redox cascade condensation reaction (scheme 12) of benzyl amine (38) and 2-nitro phenol (39), catalysed by Cu Ferrite NPs. For optimisation of reaction conditions, important parameters such as Solvent, temperature and catalyst loading were taken into consideration and found that NMP as solvent gave maximum yields of the desired product at a temperature of 130℃ and 10mol% catalyst amount.



Scheme 12

Recently Wang[44] and group developed a practical one-pot synthetic strategy for substituted benzoxazoles (43) (scheme 13) by using copper nanoparticles as a catalyst with o-bromoanilines (41) and acyl chlorides (42) as starting materials. The copper nanoparticles catalyst showed highly catalytic activity under the influence of 1,10-phenanthroline ligand. With the optimized reaction conditions that includes 10 mol % of Cu NPs, 10 mol % of 1,10-phen as promotor and 2 equivalent of K2CO3 in presence of acetonitrile as solvent under nitrogen at 90℃ gave the desired heterocycle in good to excellent yields. Overall, this methodology is considered to be an effective for wide variety of functional groups. Furthermore, the solid catalyst could be recovered and reused conveniently several times with satisfactory yields.

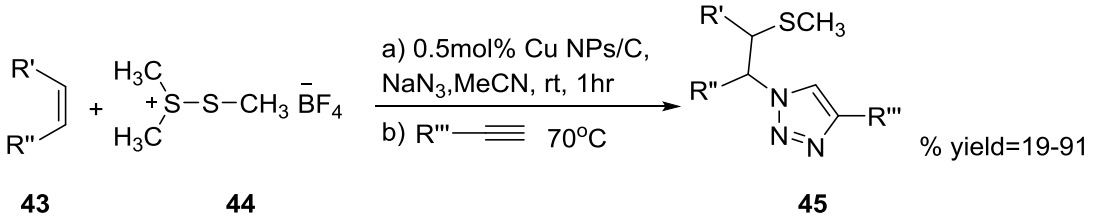


Scheme 13

Triazoles

Triazole heterocyclic compounds have garnered significant attention due to their potential applications as medicinal agents, agrochemicals, man-made materials, artificial acceptors, supramolecular ligands, and biomimetic catalysts. The extensive research conducted on these compounds has made them an extremely attractive area of study.[45]

In a recent work, Alonso[46] and team reported a one-pot for the synthesis of 1,2,3-triazoles (45) from inactivated alkenes (43), dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) (44) and sodium azide with phenylacetylene via click reaction in presence of CuNPs/C at room temperature (scheme 14). After an optimization of the reaction conditions (i.e, solvent, catalyst, temperature, and reaction time), the authors' discovered alkene mixed with 0.5mol% CuNPs/C, DMTSF, and sodium azide in acetonitrile at room temperature; were the best condition to produce the corresponding methylsulfanyl azide which further reacted with phenyl acetylene to give the desired triazole derivative.



43 **44** **45**

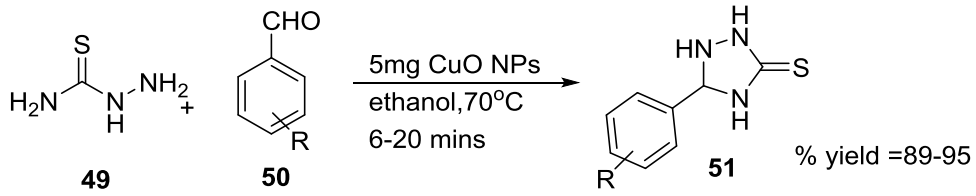
Scheme 14

In another work , Bonyasi[47] and coworkers reported A new magnetic catalyst comprising starch supported CuFe2O4 NPs as heterogeneous catalyst for click chemistry in the multicomponent synthesis of 1,2,3-triazole derivatives (48) in water at room temperature (scheme 15). Initially, the authors selected benzyl bromide, sodium azide, and phenylacetylene was selected as a model substrate for optimization. Effects of different reaction conditions such as solvent and amount of catalyst were studied and evaluated that Using water as solvent, the reaction was carried out with 0.06 and 0.04 mol% loadings affording the corresponding triazole in 73 and 64% yield, respectively. The scope of the reaction was studied with different alkyl halides and acetylenes giving the corresponding triazole in good to excellent yields. The catalyst is separated magnetically and can be used for at least 11 runs with small decrease in activity.

46 **47** **48**

Scheme 15

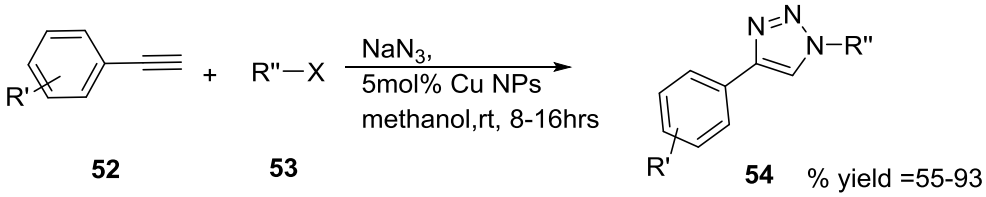
Shreyas. S[48] and team in their work reported green CuO nanoparticles for one-pot synthesis of 5-aryl-1,2,4- triazolidine-3-thione derivatives from thiosemicarbazide (49) and substituted aldehydes (50) (scheme 16). To optimize the reaction condition, the synthesis of 5-phenyl-1,2,4-triazolidine-3-thione (51) from thiosemicarbazide and benzaldehyde was selected as a model substrate. After screening different solvents and catalyst loading it was discovered that 5mg of catalyst in ethanol at 70℃ gave excellent results. To check the practicability and generality of the optimised conditions the authors explored several substituted aromatic aldehydes containing electron donating and withdrawing groups as well as five or six membered heterocyclic aldehydes containing one heteroatom were explored and gave the corresponding 5-phenyl 1,2,4-triazolidine 3-thione in brilliant yields. Also, the catalyst can be reused for six cycles without any appreciable drop in the catalytic activity.



49 **50** **51**

Scheme 16

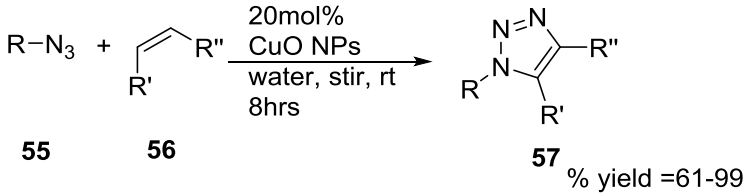
Huang[49] and team reported a three-component reaction of alkyl halides (53), sodium azide with terminal alkynes (52) can be catalysed by nano-copper particles under ambient conditions to give 1,4-disubstituted-1,2,3-triazoles (54) (scheme 17). In their initial study phenyl acetylene, benzyl bromide, and sodium azide were chosen to optimize the reaction conditions. It was evaluated that catalyst loading of 5mol% in water gave the best output. To check the efficiency of the optimised condition different substituted phenylacetylenes and benzyl halides were used in this click reaction and a series of 1,4-disusbstituted 1,2,3-triazoles were synthesized smoothly in good to excellent yields. The catalyst can reused for at least 3 consecutive runs without any loss in catalytic activity.



52 **53** **54**

Scheme 17

In recent work Gangaprasad[50] and team reported a heterogeneous CuO nanoparticles catalysed oxidative [3+2] cycloaddition of organic azides (55) with a variety of activated olefins (56) to give differently substituted triazoles (57) (scheme 18). At first the authors started investigation with methyl vinyl ketone and benzyl azide as model substrates for optimizing reaction. the study included screening of various solvents, different catalyst and catalyst loading. From their study they inferred that water, and 20 mol% of CuO nanoparticles gave the optimum result. The scope of the reaction was studied by utilizing the optimised condition on various benzyl, aromatic and aliphatic azides with methyl vinyl ketone. A diverse array of 1,2,3-triazoles were obtained in moderate to excellent yields. Moreover, the catalyst can be recovered and reused upto for runs.

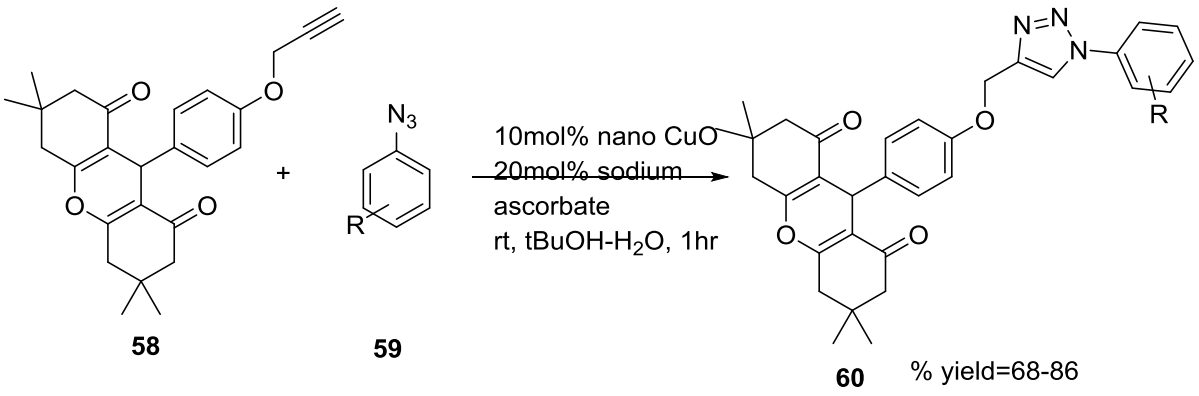


55 **56** **57**

Scheme 18

P. Iniyavan[51] and team reported, synthesis of xanthene substituted triazoles catalyzed by copper oxide nanoparticles. Initially the authors selected 3,3,6,6-tetramethyl-9-(4-

(prop-2-ynyloxy) phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (58) and phenyl azide as the model substrates to find out the optimized condition (scheme 19). After optimization it was found that 10mol% of catalyst along with 20mol% sodium ascorbate as promoter in tertiary butanol–water (1:1) mixture at room temperature gave the good result. The scope of the reaction was checked with differently substituted xanthenes and azides bearing electron-withdrawing and electron-donating substituted aromatic azides to give the corresponding substituted triazole (60) in good yields. The catalyst is recyclable and can be used upto 4 runs without affecting its activity.

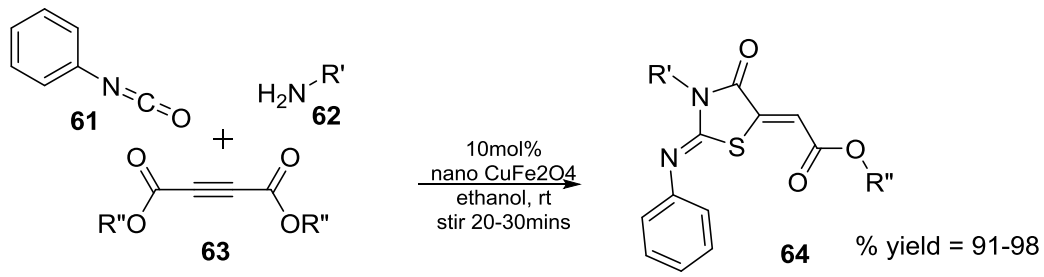


Scheme 19

Thiazolidinone

Among the Sulfur containing compounds thiazolidinone scaffolds, are widely recognized as nuclei of great value for obtaining molecules possessing various biological activities, including analgesic, anti-inflammatory, antidiabetic, antitumor, and antimicrobial.[52]

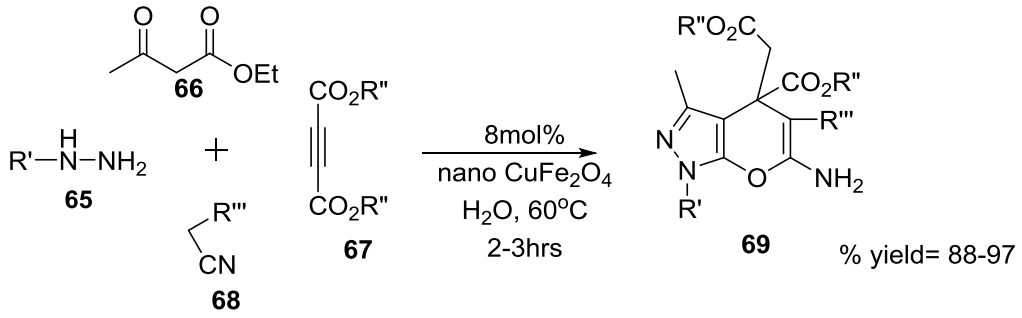
In a recent paper, Pal and team reported[53] that nano-$CuFe_2O_4$ exhibits a strong catalytic activity in the cascade reaction involving 1,4-addition and intramolecular electrophilic cyclization (scheme 20). This reaction generates a series of functionalized 4-oxo-2-(phenylimino) thiazolidin-5-ylideneacetate derivatives (64). To optimise the procedure, the authors investigated the reaction between phenyl isothiocyanate (61), aniline and diethyl acetylenedicarboxylate (63) under of a variety of catalysts, solvents, and amount of catalyst load. As per their finding 10mol% of Nano-CuFe2O4 as catalyst in ethanol as solvent gave the best results. The efficiency of the catalyst was also evaluated and found that large variety of electronically and structurally divergent aromatic amines responded quite well to the optimised reaction conditions.



Scheme 20

Dihydropyrano[2,3-c]pyrazoles

Dihydropyranopyrazoles are very fascinating compounds and have received considerable attention in synthetic research due to their biological activity like antimicrobial, insecticidal, and anti-inflammatory and its ability as precursor compounds in the field of medicinal chemistry. Synthesis of this heterocycle via classical approach often produce significant amounts of waste, placing the chemical industry pressured to minimize waste generation. Considering the limitations involved, multi-component reactions (MCRs) have emerged as an important synthetic tool in a present-day drug discovery as it offers advantages such as high efficiency, good atom economy, and the ability to generate structurally diverse products.[54,55]



Scheme 21

Pradhan[56] and coworkers reported a method for the one pot synthesis dihydropyranopyrazole (69) derivatives using substituted hydrazine derivatives (65), ethyl acetoacetate (66), dialkyl acetylenedicarboxylates (67) and alkyl nitrile derivatives (malononitrile and ethyl cyanoacetate) (64) in water media using nano CuFe2O4 as a magnetically separable catalyst (scheme 21). Initially the reaction was carried out by varying the amount of the catalyst and it was observed that the conversion to dihydropyrano[2,3-c] pyrazole derivative increased with the catalyst load upto 8 mol% in aqueous medium at 80℃condition leading to expected heterocyclic molecules in excellent yield.

The scope of the CuFe2O4-mediated synthesis of dihydropyrano[2,3-c]pyrazole derivatives was explored with various hydrazine derivatives possessing different functional groups such as aryl-halo, aryl-nitro, and arylcyano, as well as ethyl acetoacetate, dialkyl acetylenedicarboxylates, and alkyl nitriles and it is worthy to mention that the reaction resulted the respective dihydropyrano[2,3-c]pyrazole derivatives in good to excellent yields. Also, the catalyst could be reused and utilized for upto six cycles without changing its catalytic activity.

Tetrazoles

Tetrazoles-a five-membered ring containing four nitrogen have gained significant popularity as a functional group due to their versatile applications in the field of heterocyclic chemistry. Besides bearing a wide range of biological properties such as antiviral, anticonvulsant, anti-inflammatory, antimicrobial, antifungal, anti-HIV, antiulcer, antiallergic, antiproliferative, analgesic and anticancer[57], this functionality has been frequently used as lipophilic, spacers, ligands, precursors of a variety of nitrogen containing heterocycles in coordination chemistry and in material sciences including photography, information recording systems, and explosives.[58]

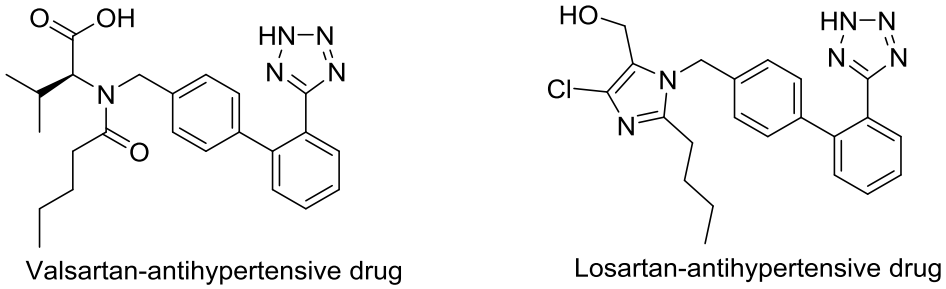
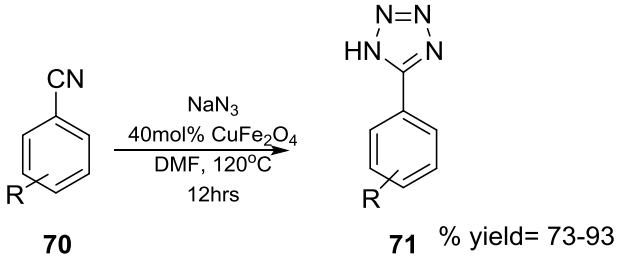


Figure 7 medicinal drugs containing tetrazole stucture

Recently B. Sreedhar[59] and group reported a synthetic route for substituted tetrazoles (71) using various nitriles (70) and sodium azide in presence of CuFe2O4 nanoparticles as catalyst (scheme 22). At first benzonitrile and sodium azide were chosen as the model substrate for the optimization. After several efforts it was observed that 40mol% of catalyst in DMF as solvent at 120℃ generated tetrazoles in good to excellent yields. The catalyst was successfully separated magnetically and reused for a total of five cycles, signifying minimal loss of catalytic activity.

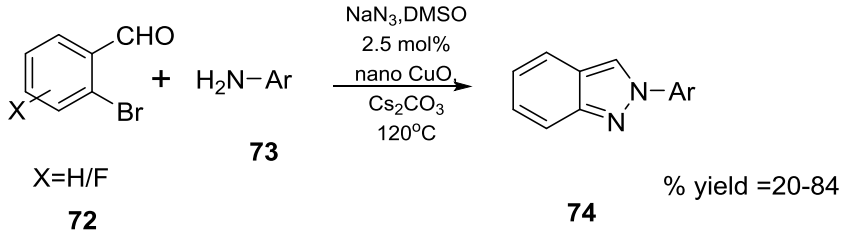


Scheme 22

Benzindazoles

In the past years, 2H-indazole derivatives of have gained significant importance in the field of modern drug discovery. Indazoles are bioisosters of indoles and benzimidazoles and have to possess potential biological activities that includes anti-tumour properties, anti-HIV effects, antimicrobial activity, anti-inflammatory effects, antidepressant properties, anticancer potential, anti-platelet activity, and even contraceptive effects.[60]

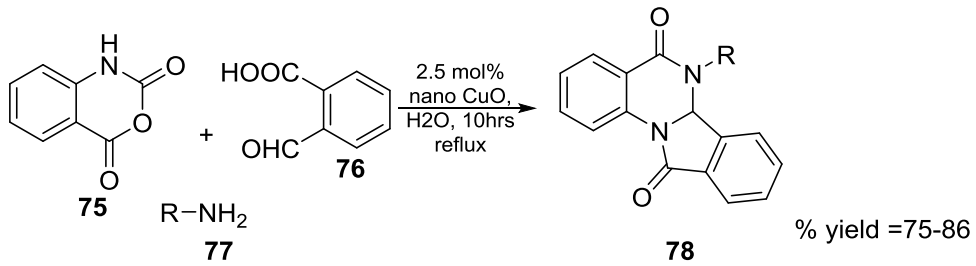
Recently Nilufa Khatun[61] and coworkers reported one-pot synthesis of 2H-indazoles (74) from 2-bromobenzaldehydes (72), primary amines (73) and sodium azide using nano CuO as catalyst under basic conditions (scheme 23). The optimization of reaction was carried by choosing 2-bromobenzaldehyde, aniline and sodium azide as model substrates.at first the reaction was performed at room temperature which did not give any product. The contents were then heated and found that at 120℃ the conversion was excellent. On further optimising the procedure with respect to catalyst loading and effect of addition of different base, the authors concluded that 2.5mol% of nanocatalyst in DMSO in presence of CS2CO3 as base gave the best results. Also, the catalyst could be recycled up to three times, with slight decreases in the yields each time.



Scheme 23

Isoindoloquinazolines

Quinazolines and related compounds are class of heterocycles that encompasses a range of highly effective substances utilized in agriculture, including fungicides, bactericides, defoliants, and plant growth stimulants. Besides these properties, quinazolines exhibit diverse pharmacological activities, making them important compounds in medicinal drug development. In a recent work Sougata Santra[62] and team reported one-pot synthesis of isoindolo[2,1-a] quinazolines by a three-component coupling (scheme 24) of isatoic anhydride, 2-carboxybenzaldehyde and amines using nano CuO catalyst under aqueous conditions. Initially the authors commenced their work by taking isatoic anhydride (75), 2-carboxybenzaldehyde (76) and aniline as the model substrates to check for optimised condition. It was observed that 2.5mol% of CuO in water under refluxing conditions provided the corresponding desired product in excellent yield. To check for the effectiveness of the procedure, the reaction was investigated on variety of amines and found that the corresponding Isoindoloquinazolines derivatives (78) were formed in good to excellent yields. It is worth mentioning that water helps to accelerate this transformation through hydrogen bond mediated 'electrophile–nucleophile dual activation'. The catalyst can be reused several times without significant loss of catalytic activity. The present approach generates less waste and demonstrates an environmentally friendly synthetic procedure.

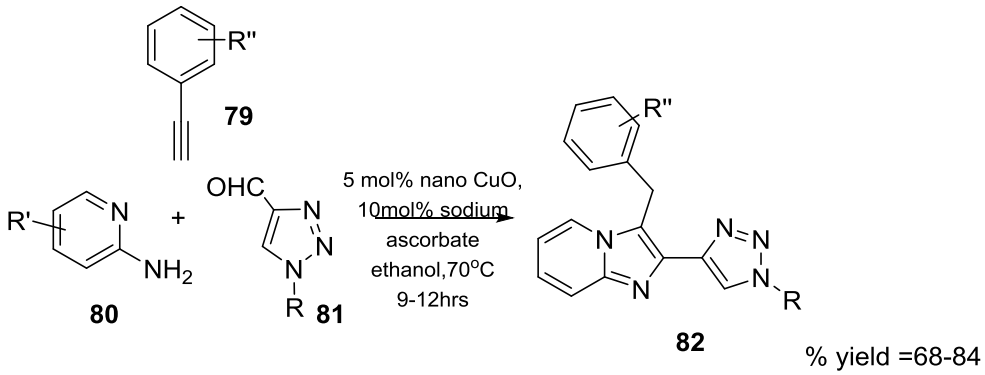


Scheme 24

Triazolyl-imidazo[1,2-a] pyridine

Imidazo[1,2-a] pyridines are important fused heterocycles known for their wide range of biological activities, such as antibacterial, antipyretic, anticancer, antituberculosis, and as GPR39 agonists and calcium channel blockers. Several drugs incorporate the imidazo[1,2-a] pyridine scaffold, that includes Saripidem, Zolimidine, Zolpidem, and Olprinone.[63,64] Recently Bagdi[65], and team reported a synthetic route to 2-triazolyl imidazo[1,2-a] pyridine derivatives (82) via three component A3 coupling followed by 5-exo dig cyclisation by employing 1-alkyl-1,2,3-triazole4-carbaldehyde (81), amidine (80) and terminal alkynes (79) using 5 mol% nanocopper oxide together with 10 mol% sodium ascorbate as click-catalyst in ethanol at 70 ˚C (scheme 25). This

synthetic methodology offers several advantages, that includes recyclability of the catalyst, high yields of the desired product, and a broad range of compatible substrates. The catalyst demonstrates the potential for multiple reuses and can be employed for up to five cycles with a slight reduction in the product yield.

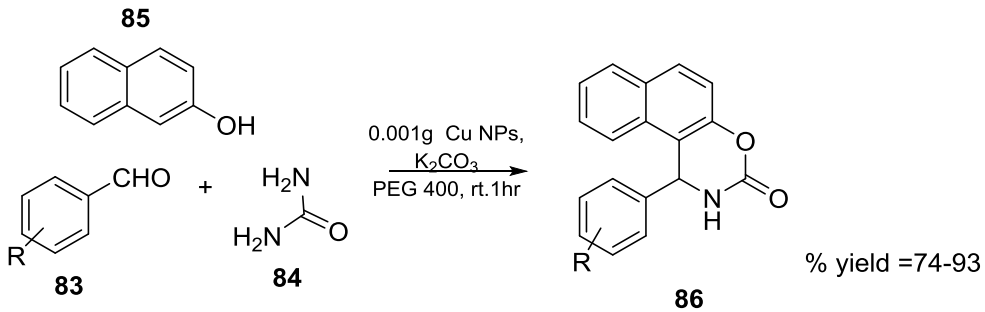


Scheme 25

Oxazinones

Oxazinone derivatives have gained significant attention in the field of pharmacology due to their appealing heterocyclic scaffold and associated pharmacological and biological properties that includes anti-inflammatory, antiulcer, antipyretic, antihypertensive, antifungal, as ligands for 5-HT receptors, DP receptor antagonists, integrin antagonists, platelet fibrinogen receptor antagonists, calmodulin antagonists, inhibitors of the TGF-b signalling pathway, soybean lipoxygenase inhibitors, inhibitors of Janus kinases and other protein kinases, potassium channel openers, immunomodulating agents, thus making them important components of pharmacologically relevant heterocyclic compounds.[66, 67,68]

Recently, Kumar[69] and team developed efficient methodology for the preparation of 2-naphthol condensed 1,3-oxazinone derivatives (86) by employing copper nanoparticles in PEG in the presence of K2CO3 (scheme 26). Various metal nanoparticles in different solvents were evaluated for the optimum synthesis of the naphthalene-condensed oxazinone derivatives by reacting b-naphthol (85), benzaldehyde and urea (84). After evaluating the parameters such as catalyst loading and effect of various solvents, the authors inferred that 0.001g of catalyst in PEG as solvent showed the best activity for conversion. The catalyst could be recovered by separating them from the reaction mixture by mild centrifugation and reused for upto five cycles without losing the catalytic activity.

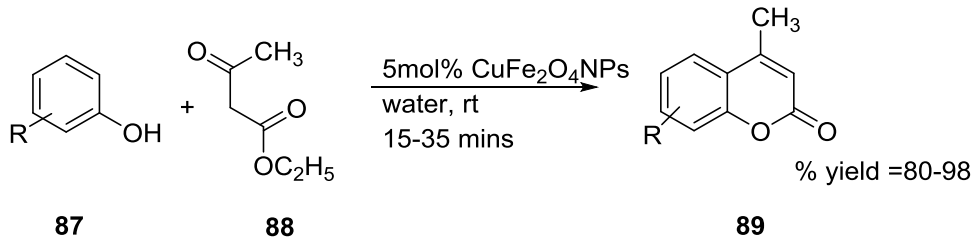


Scheme 26

Coumarines

Coumarin and its derivatives belong to a crucial category of benzo-pyrones that occur naturally and exhibit noteworthy biological activities. These compounds have demonstrated significant effects in various areas, including antitumor, anti-HIV, antioxidative, antimicrobial, and anticancer activities.[70,71,72]

Baghbanian and team reported a synthesis of coumarin derivatives (89) via pechamann condensation using magnetic CuFe2O4nanoparticles as catalysts in water at room temperature (scheme 27). To find the optimized condition, initially resorcinol and ethylacetoacetate (88) in water as model substrate. After series of efforts the authors found that the polar protic solvents such as water and 5mol% of the catalyst loading gave the best results. To assess the generality of this approach for the synthesis of coumarins, various phenols containing a variety of functional groups such as ether, hydroxy, nitro, alkyl, and amino groups were reacted with ethyl acetoacetate under optimized conditions and found that the respective coumarins were produced with good yields and in short reaction time. The catalyst was separated magnetically and could be reused for upto six runs without affecting the catalytic activity.



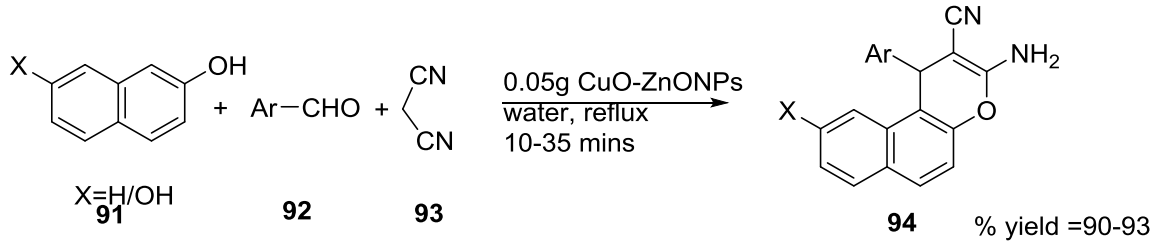
87 **88** **89**

Scheme 27

Chromenes

2-Amino-4H-chromenes are a significant group of heterocyclic compounds that possess a diverse array of biological properties. These compounds are known for their spasmolytic, diuretic, anticoagulant, anticancer, and antisterility activities. Their wide range of biological properties makes them important and versatile molecules in various fields.[73, 74]

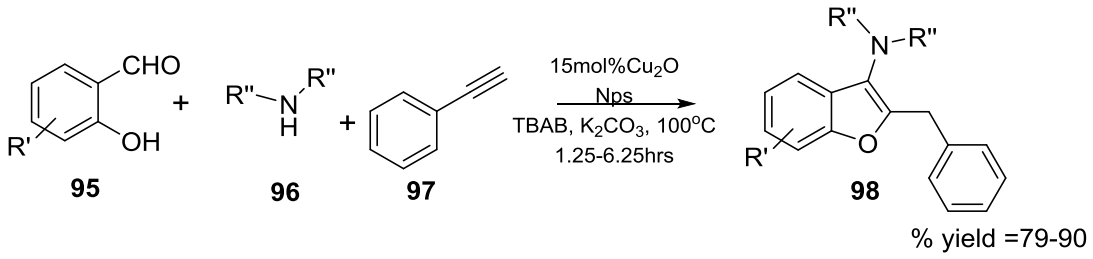
In a recent work Jalal Albadi[75] and team reported one-pot synthesis of 2-amino-4H-chromenes (94) from aromatic aldehydes (92), hydroxynaphthalene derivatives (91), and malononitrile (93) in water at reflux conditions using a novel metal oxide composites of CuO-ZnO nanoparticles as catalyst (scheme 28). To optimize the reaction conditions for the synthesis of 2-amino-4H-chromene, 2-naphtol, malononitrile, and benzaldehyde were selected as model substrates. The authors studied various reaction parameters including solvents, temperatures, and amount of catalyst. After several evaluation process it was found that using 0.05 g of the catalyst in refluxing water was sufficient for the reaction completion and the best results were obtained by carrying out the reaction of model substrates in the presence of 0.05 g of the catalyst under reflux conditions in water. Also it is noteworthy to mention that CuO-ZnO nanocatalyst can be recycled up six times without any significant loss of its catalytic activity.



Scheme 28

Benzofuran

The benzofuran scaffold has emerged as a crucial component in the discovery of bioactive molecules. By making structural and substitution modifications to this oxygen-containing heterocyclic building block, researchers have frequently identified compounds with diverse biological activities.[76,77,78] In recent reported, Sharghi[79] and coworkers developed a new method for the synthesis of 2,3- disubstituted 1-benzofuran derivatives (98) via a tandem alkyne–aldehyde–amine (A3) coupling followed by cyclization under mild conditions and high reaction rate, by using Copper(I) oxide nanoparticles (CONPs) reusable catalyst (scheme 29). This conversion involved a multicomponent coupling/cycloisomerization reactions between various 2-hydroxybenzaldehydes (95), secondary amines (96), and nonactivated alkynes (97) to give 2,3-disubstituted 1-benzofurans (96). After optimization of the reaction, it was found that 15mol% of catalyst concentration in TBAB and K2CO3 at 100 °C in air gave the excellent outcome. The scope and generality of the Mannich base O-annulation reaction catalysed by CONPs were investigated using a diverse range of substrates. The reactionsproceeded successfully in all cases. The desired products were obtained in excellent yields, indicating the high efficiency of the reaction. Additionally, the regioselectivity of the reaction was found to be consistently high, further highlighting the effectiveness of the catalytic system This procedure eliminates the need for propargylamine derivatives, uncyclized intermediates that make purification difficult. The CONPs and tetrabutylammonium bromide were reused successfully for up to five times.

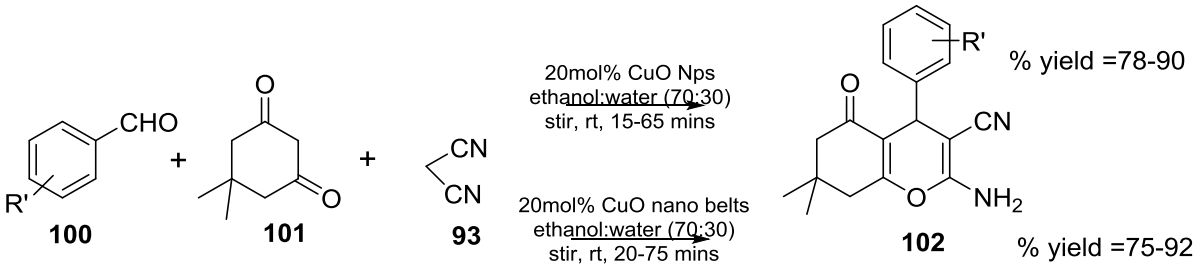


Scheme 29

Benzopyrans

Benzopyran derivatives have been found to possess significant relaxant activity on blood vessels, cardiac muscle, and other smooth muscles. The pyran moiety, in the structure, plays a crucial role in their pharmacological activities.[80,81,] Recently Mulik[82] and coworkers reported a one pot synthesis of benzopyran derivatives (102) from dimedone, aromatic aldehydes and malononitrile using CuO nanobelts as well as nanoparticles as catalyst in water (scheme 30). First dimedone (101) malonitrile (93) and

benzaldehyde (100) were selected as model substrate for optimisation. The solvent effect was checked using different combinations of water–ethanol mixture using CuO nanoparticles and found that 70–30% water–ethanol (v/v) mixture was the best combination depicted by the excellent yield obtained. Quantity of catalyst required for the reaction was also checked by varying the mol % of CuO nanoparticles on the model reaction and found that found that 20 mol % catalyst is sufficient for the reaction, beyond which an increase in catalyst quantity doesn't alter yield and reaction time. The Catalytic activity of these nanocrystals is explored by synthesizing a series of by reaction of dimedone, aryl aldehydes and malononitrile in a water:ethanol (70:30) mixture and generating the desired heterocycle in good to excellent yields. The catalyst CuO Nps and nanobelts can be recycled up three times without any significant loss of its catalytic activity.



Scheme 30

2. Conclusion

Heterocyclic compounds are considered as highly valuable molecules as they exhibit diverse biological activities. In this review, we have tried to report a maximum collection of research work focusing on the application of copper nanoparticles as versatile catalysts in heterocyclic compound synthesis. These reports highlight that copper nanoparticles exhibit exceptional catalytic properties and can effectively promote a diverse range of synthetically relevant reactions. The utilization of these catalysts has revealed to us that a large number of potential heterocycles such as triazoles, tetrazoles, oxazinones, pyrroles, benzoxazoles, imidazopyridines, quinazolines, and other heterocyclic compounds can be readily synthesized efficiently.

This review aims to inspire and encourage further research in the captivating and highly beneficial field of metal nanocatalysis. By highlighting the versatility and promising applications of metal nanoparticles as catalysts, we hope to stimulate scientific exploration and investigation in this area. The potential advancements and discoveries that can emerge from continued research in metal nanocatalysis hold great promise for the development of novel catalytic systems and the advancement of various industries and scientific disciplines.

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