Copper Catalyzed Cascade Reaction for the Synthesis of 2-Iminocoumarin Derivative

By

SHRUTHI.S

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In Partial Fulfilment of the Requirements for the Degree of

Master of Philosophy in Chemistry

July, 2019

DECLARATION

I declare that the dissertation entitled **"Copper Catalyzed Cascade Reaction for the Synthesis of 2-Iminocoumarin Derivative"** submitted by me for the degree of **Master of Philosophy (M.Phil)** is the record of work carried out by me during the period from **2018** to **2019** under the guidance of **Dr. V.SHARULATHA, Assistant Professor (SS)** and has not formed the basis for the award of any Degree, Diploma, Associateship, Fellowship, Titles in this University or any other University or other similar Institution of Higher Learning.

Signature of the candidate

CERTIFICATE FROM THE SUPERVISOR

This is to certify that the dissertation entitled **"Copper Catalyzed Cascade Reaction for the Synthesis of 2-Iminocoumarin Derivative"** submitted for the degree of **Master of Philosophy (M.Phil.)** by **S. SHRUTHI** is the record of research work carried out by me during the period from **2018** to **2019** under my guidance and supervision, and that this work has not formed the basis for the award of any Degree, Diploma, Associateship, Fellowship or other Titles in this University or any other University or institution of Higher Learning.

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SHRUTHI.S

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ABBREVIATION

Ac	**Acetyl**
Ar	**Aryl**
Bn	**Benzyl**
Bu	**Butyl**
CH_2Cl_2	**Dichloro methane or methylene chloride**
CH_3CN	**Acetonitrile**
CO_2	**Carbondioxide**
conc.	**Concentration**
Cs_2CO_3	**Cesium carbonate**
Cu	**Copper**
Cu $(OAc)_2$	**Copper(II)acetate**
CuAAC	**Copper catalyzed azide-alkyne cyclo addition**
CuBr	**Copper bromide**
CuCl	**Copper chloride**
CuI	**Copper iodide**
CuOAc	**Copper acetate**
DCC	***n,n'*-dicyclohexylcarbodiimide**
DCM	**Dichloromethane**
DEPT	**Distortionless enhancement of polarisation transfer**
DMF	**Dimethylformamide**
DMS	**Dimethyl sulfide**
DMSO	**Dimethylsulfoxide**
Equiv	**Equivalent**
Et	**Ethyl**
Et_3N	**Triethyl amine**
FT-IR	**Fourier transform infrared spectroscopy**
H	**Hours**
H_2SO_4	**Sulphuric acid**
HCl	**Hydrochloric acid**

HRMS	**High-resolution Mass Spectrometry**
MCRs	**Multicomponent reactions**
Me	**Methyl**
MeCN	**Acetonitrile**
MeOH	**Methanol**
mg	**Milligram**
MnO_2	**Manganese (IV) oxide**
Mol	**Mole**
MOM	**Methoxymethyl**
Mp	**Melting point**
MS	**Molecular sieves**
MW	**Microwave**
NMR	**Nuclear magnetic resonance**
^oC	**Degree of celcius**
Pr	**Propyl**
R_f	**Retention factor**
Rt	**Room temperature**
TBAB	**Tetra-n-butylammonium bromide**
TBACl	**Tetra-n-butylammonium chloride**
TBAI	**Tetra-n-butylammonium iodide**
TBS	**t-butyldimethylsilyl**
Tf	**Trifluoromethanesulfonyl**
TFA	**Trifluoroacetate**
THF	**Tetrahydrofuran**
TiO2	**Titanium dioxide**
TLC	**Thin-layer chromatography**
TMS	**Trimethylsilyl**
Ts	**p-toluenesulfonyl**
TsN_3	**p-toluenesulfonyl azide**

1. INTRODUCTION

1.1 MCRs for Heterocyclic Synthesis

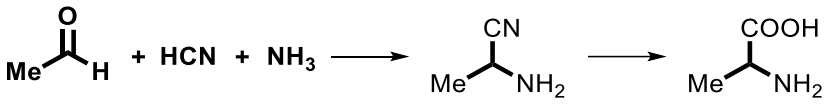
Multicomponent reactions (MCRs) constitute one of the most efficient tools in modern synthetic organic chemistry, since they have all features that contribute to an ideal synthesis viz high atom efficiency, quick and simple implementation, time and energy saving, environment-friendly and they offer a target and diversity-oriented synthesis (**Wender *et.al.*,2014**). Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product. In these reactions most of the atoms contribute to the newly formed product. In an MCR, a product was assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge in conducting an multicomponent reaction was that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The results depend on the reaction conditions such as solvent, temperature, catalyst, concentration and the kind of starting materials and functional groups. Such, considerations of particular importance in connection with the design and discovery of novel MCRs (**Dömling, 2004**).

Multicomponent reactions have been known for over 150 years. The first documented multicomponent reaction was the Strecker synthesis of α-amino cyanides in 1850 from which α-amino acids could be derived. A multitude of MCRs exist today, of which the isocyanide based MCRs are the most documented. Other MCRs include free-radical mediated MCRs, MCRs based on organoboron compounds and metal-catalyzed MCRs.

Isocyanide based MCRs are most frequently exploited because the isocyanide is an extraordinary functional group. It is believed to exhibit resonance between its tetravalent and divalent carbon forms. This induces the isocyanide group to undergo both electrophilic and nucleophilic reactions at the C_2 carbon atom, which then converts to the C_4 carbon form in an exothermic reaction. The occurrence of isocyanides in natural products has also made it a useful functional group. The two most important isocyanide-based multicomponent reactions are the Passerini 3-component reaction to produce α-

acyloxy carboxamides and the Ugi 4-component reaction, which yields the α-acylamino carboxamides.

In **1850, Strecker** synthesized α-amino nitrile via one-pot reaction of aldehyde, hydrogen cyanide and aqueous ammonia. This adduct is one of the important precursors for α-amino acids (Scheme 1).

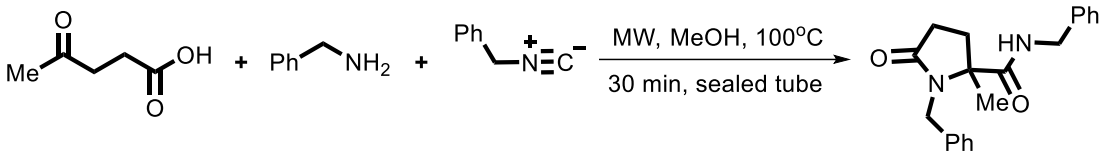


Scheme 1. Synthesis of α-amino nitrile

Hantzsch(1882), reported the synthesis of symmetrical 1,4-dihydropyridines *via* the condensation of two equiv of β-ketoesters with one equiv of ammonia and aldehyde. Subsequently, Hantzsch showed the synthesis of pyrroles using condensation of α-halogenated ketones with β-ketoesters and primary amines. In **1891, Biginelli** reported the synthesis of highly functionalized dihydropyrimidine using acid catalyzed condensation of β-ketoesters with aldehydes and urea. Later, **Mannich** invented the synthesis of β-aminoaldehydes or β-aminoketones *via* the condensation of enolizable carbonyl compounds which generated iminium ions from aldehydes and amines. In **1956, Asinger** described the synthesis of thiozolines using the condensation generated 2-thioaldehydes or 2-thioketones with aldehydes and ammonia. Later, this reaction was successfully generalized to synthesize various five and six membered heterocycles such as imidazolines, oxazolines, oxazines, thiazines and pyrimidines. In **1965, Gewald** reported the synthesis of functionalized thiophenes using the base catalyzed condensation of β-ketoesters, cyanoacetates and elemental sulphur.

In **1921, Passerini** reported three component reaction of acids, carbonyl compounds and isocyanide to furnish α-acyloxycarboxamides. These reactions are highly versatile to synthesis peptide-like linear compounds. By utilizing α-halogenated carbonyl compounds, cyclization can be achieved in one-pot process. In **1959, Ugi** reported the four component reaction of amines, carbonyl compounds, acids and isonitriles to furnish α-acylamino amides. Using bifunctional starting material as a multicomponent partner,

the synthesis of heterocycles could be achieved. (Scheme 2)



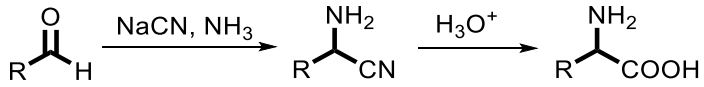
Scheme 2. Synthesis of heterocycles

The use of transition metal (eg., Pd, Cu, Rh, Ru, *etc*.) based catalytic systems for MCRs facilitates the formation of highly functionalized heterocycles with high molecular diversity. Among them, copper(I)-catalyzed MCRs is an efficient strategy for the synthesis of highly functionalized heterocyclic scaffolds with structural diversity using ketenimine intermediates.

1.2 Examples of multicomponent reactions

1.2.1 Strecker reaction

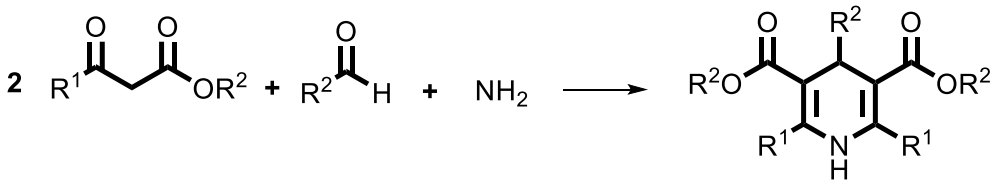
Strecker (1850) reported the famous synthesis of α-amino acids. The reaction of multicomponent reaction which comprises three components of aldehydes, hydrogen cyanide and ammonia as the substrate to give α-amino acids. This reaction was recognized as the world's first multicomponent reaction.



Scheme 3. Strecker reaction

1.2.2 Hantzsch dihydropyridine synthesis

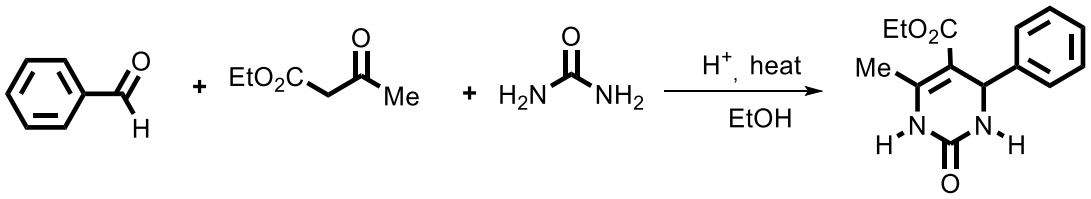
The best-known three component reactions which afforded 1,4-dihydropyridine derivatives using β-keto esters, aldehydes and ammonia was reported by **A.R. Hantzsch (1881).** A calcium channel blocker, "Nifedipine" was synthesized by this reaction.



Scheme 4. Hantzsch dihydropyridine synthesis

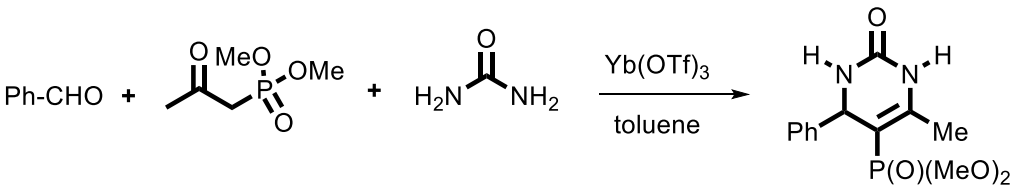
1.2.3 Biginelli condensation

Biginelli condensation involved the reaction of an aldehyde with urea and a β-ketoester under acidic conditions and reflux with ethanol to yield 3,4-dihydropyrimidin-2-one derivatives. (**Biginelli *et.al.*, 1893**)



Scheme 5. Biginelli condensation

Yuan *et.al.*, (2003) developed a modified Biginelli condensation by using ytterbium triflate as a catalyst and the 3,4-dihydropyrimidin-2-one derivatives were formed depending on the structure of the β-ketophosphonate and aldehyde.A aliphatic aldehydes including propionaldehyde and butyraldehyde were found to be resistant to this reaction.



Scheme 6. Modified Biginelli condensation

1.3 Metal-catalyzed multicomponent reactions

The transition metal-catalyzed reaction has become a powerful tool in organic synthesis in the past, which had played an important role in developing chemical science and technology by the discovery and development of new types of chemical compounds and powerful new synthetic methodologies (**Shi *et.al*,2012**). Commonly, transition metal

catalysts were based on metals such as palladium, nickel, copper, cobalt, iron, gold, manganese, rhodium and ruthenium. (**Stanley *et.al.*,2008**). The importance of transition metal chemistry was recently further underlined by the **three Nobel Prizes in Chemistry to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their pioneering work on the palladium-catalyzed cross couplings in 2010.** Before seven other individuals had won Nobel Prizes in Chemistry for their seminal contributions in the field of catalysis**.** Until now, the application of transition metal catalysts for various bond-breaking/forming reactions is well established, however, many important and often unexpected achievements continue unabated.

Transition metals, especially palladium and copper, are well-known catalysts for multicomponent reactions. Carbopalladation reactions of allenes, alkynes and carbon monoxide are very important processes in multicomponent syntheses. Additionally, copper-catalyzed multicomponent reactions such as azide–alkyne cycloadditions and various A^3-coupling reactions were useful procedures in heterocyclic chemistry. However, several methods based on these protocols have also been developed for the synthesis of heterocyclic phosphonates.

1.4 Heterocyclic compounds

Heterocyclic rings found in many naturally occurring compounds and they compose the core structures of many biologically active scaffolds as well as some industrial compounds. The most common heterocycles are those having five- or six-membered rings and containing heteroatoms of nitrogen, oxygen, or sulfur. The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene. A molecule of pyridine contains a ring of six atoms—five carbon atoms and one nitrogen atom. Pyrrole, furan, and thiophene molecules each contain five-membered rings, composed of four atoms of carbon and one atom of nitrogen, oxygen, or sulfur, respectively. (**Thomas J. J. Müller, 2017**). Heterocyclic compunds have a wide range of application. They are predominantly used as pharmaceuticals, as agrochemicals and as veterinary products. They also find applications as sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dye stuff. They are used as vehicles in the synthesis of other organic compunds. Some of the natural products e.g. antibiotics such as penicillin's,

cephalosporin; alkaloids such as vinblastine, morphine, reserpine etc. have heterocyclic moiety. (**Pragi Arora, et.al., 2012**). The important methods for synthesizing heterocyclic compounds can be classified under five headings.

1.4.1 Nucleophilic ring closure

To prepare compounds containing one heteroatom, an open-chain hydrocarbon derivative containing two halogen element atoms—specifically, chlorine, bromine, or iodine either as halides (in which the halogen atoms are attached directly to the hydrocarbon chain) or as acyl halides (in which the halogen atoms belong to derivatives of carboxylic acids) is reacted with the dihydro form of the heteroatom (ZH_2, or an equivalent reagent) to give nonaromatic heterocycles.

1.4.2 Electrophilic ring closure

Heterocyclic ring-forming reactions in which the heteroatom acts as an electrophile—an electron-seeking atom or molecule—are rare, because nitrogen, oxygen, and sulfur atoms are themselves electron-rich centres that act generally as nucleophiles.

1.4.3 Ring closure by way of cyclic transition states

A most important method for the synthesis of carbocyclic six-membered rings is the Diels-Alder diene reaction, named for its Nobel Prize-winning discoverers, the German chemists Otto Diels and Kurt Alder.

1.4.4 Conversion of one heterocyclic ring into another

Although there are many reactions of theoretical importance in which one heterocyclic ring is converted into another, few are of practical use. The preparation of pyridine from tetrahydrofurfuryl alcohol and ammonia and the conversion of pyrylium salts into pyridinium salts are good examples of such transformations.

1.4.5 Modification of an existing ring

Dehydrogenation of saturated or partially saturated heterocyclic rings to thermodynamically more-stable heteroaromatic compounds by heating with sulfur or by

treatment with a palladium catalyst is analogous to similar reactions involving carbocyclic compounds. Therefore, the development of new multicomponent reactions towards biomedical and industrial scaffolds is inevitable at the present time. Furthermore, the combination of established multicomponent reactions with post-reaction transformations opens the way towards a vast number of diverse and complex products. Some of these post-MCR transformations are:

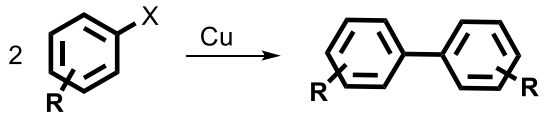
- **Intramolecular cycloaddition reactions**
- **Knoevenagel condensations**
- **Metathesis reactions**
- **Aza-Wittig reactions**
- **Mitsunobu reactions, etc. (Zhu *et.al.*,2005**)

1.5 Chemistry of Copper Catalysis

Copper salts as catalysts have been known for more than one century and served well for C–N, C–S, C–O and other bond formation reactions **(Hassan *et.al.*,2002)**. After the discovery of palladium-catalyzed cross-coupling reactions, copper chemistry was somewhat neglected for an extended period of time. To date, being capable of catalyzing the reactions for the synthesis of arylamines, palladium catalysts have been also employed in many other bond formations **(Zhu *et.al.*,2011**). Despite many advantages of its use in organic synthesis, palladium chemistry itself has some drawbacks, including its cost, high toxicity and restrictions in scope. Therefore, chemists have started to reconsider other metal catalysts as an alternative for palladium. In the past years, copper has again received increasing attention for the construction of various bonds in organic synthesis.

Copper catalysts fascinate chemists for several reasons. First of all, copper is very cheap compared to palladium and the total amount of copper on earth is vast. Furthermore, copper salts generally present a low toxicity. More importantly, copper can take part in cross-coupling chemistry in a way strikingly similar to palladium and possesses unique

chemoselectivity and reactivity. Copper is a very versatile transition metal that has been used as a building material by human civilizations for over 6000 years. Some of the most highly cited papers of all time on this topic are reviews on conjugate addition, cross-coupling, and [3 + 2] "Click" reaction applied to bioconjugation. The growth in copper-catalyzed organic reactions may be driven by a couple of factors. First, copper chemistry is incredibly diverse. Depending on its oxidation state, this metal can efficiently catalyze reactions involving both one and two-electron (radical and polar) mechanisms, or both. Copper coordinates easily to heteroatoms and to π-bonds and is well-known to activate terminal alkynes. The **Ullman and Goldberg C–C and C–N cross-coupling** reactions were discovered over a century ago and their development has really blossomed over the past twenty years. Second, copper is an earth-abundant metal, making its use more cost effective and more sustainable than precious transition metal catalysts.



Scheme 7. Ullmann reaction

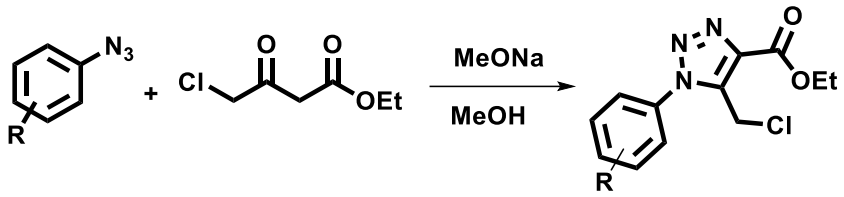
The copper either as metal or in salt form (ionic or complex) has been employed as a most effective catalyst to promote the 1,3- dipolar addition reaction-click chemistry.

1.5.1 Copper halide catalysis

Among copper halide catalysts, copper iodide is being frequently used in various transformations. Few reports of copper bromide catalysis are also available. Copper (I) combined with copper (II) salts, other metal complexes or ionic liquids are also used as effective catalytic systems. Most of the reactions proceed smoothly at room temperature. However, there are many reports, which require traditional heating and some are facile upon application of unconventional energy sources like microwave (MW) irradiation and ultrasound/sonication conditions. Use of co-solvent systems also promotes the reactions efficiently.

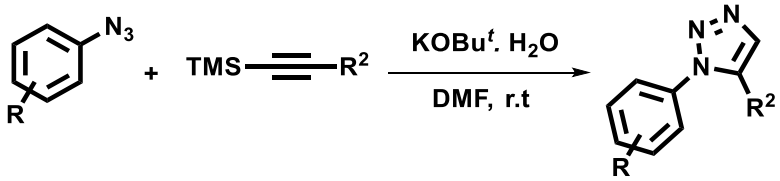
1.5.2 Use of other non-copper catalysts

Limitations of copper-catalyzed click methods mainly arise in the field of bioconjugation and in vivo imaging due to the toxic nature of copper. The reaction between azides and alkynes in biological environment is rarely observed due to their inertness in absence of copper. Therefore, the importance of copper-free click reactions has been realized.



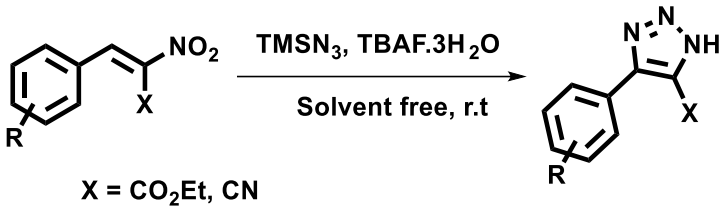
Scheme 8. Dipolar additions

Synthesis of substituted 1H-1,2,3-triazole-4-carboxylic ester have been performed by the reaction of aryl azides , ethyl 4- chloro-3-oxobutanoate and either O- or S-nucleophiles in the presence of a base catalyst. It has been observed that the reaction most probably proceeds via [3+2] cyclocondensation between aryl azide and ethyl 4-chloro-3-oxobutanoate followed by nucleophilic substitution of chlorine in the chloromethyl group.



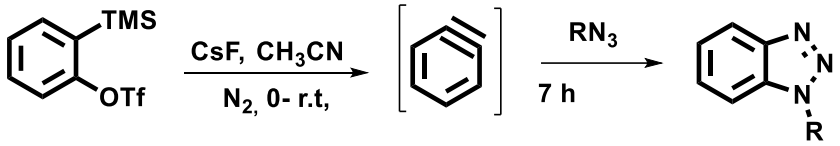
Scheme 9. Synthesis of 1H-1,2,3-triazole-4-carboxylic ester

Wu *et.al.*, (2012) carried out a base-promoted cycloaddition reaction between aryl azide trimethylsilyl alkynes to generate 1,5- disubstituted 1,2,3-triazoles regioselectively in good yields at ambient temperature.



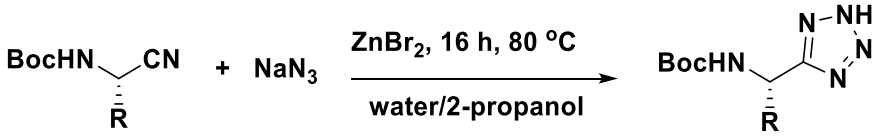
Scheme 10. 1,5- disubstituted 1,2,3-triazoles

4-Aryl-5-cyano- or 4-aryl-5-carbethoxy-1H-1,2,3-triazoles were synthesized by [3+2] cycloaddition reactions of 2-aryl-1-cyanoor 2-aryl-1-carbethoxy-1-nitroethenes with $TMSN_3$ under solvent-free conditions in presence of TBAF catalyst .



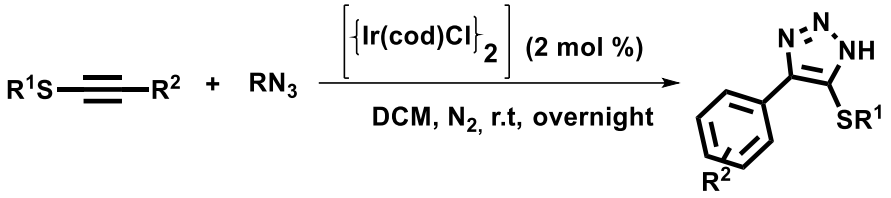
Scheme 11. 4-aryl-5-carbethoxy-1H-1,2,3-triazoles

Numerous 1-alkyl benzotriazoles were synthesized in good yields by the reaction of various alkyl azides with 2-(trimethylsilyl) phenyl triflate in the presence of CsF in acetonitrile via fluoride triggered azide-benzyne cycloaddition (Scheme 19).



Scheme 12. 1-alkyl benzotriazoles

Schmidt *et.al.*, (2007), applied click chemistry in ionic liquids based on alkylated imidazoles combined with microwave heating to remove the hazards with volatile azides in intermolecular reactions and the problem of removal of zinc salts from the acidic product. **Beccalli and co-workers (2008)** performed totally regioselective cycloadditions of 1,3-dipoles nitrile oxide and azide with *N, N*-disubstituted propargyl amines leading to the formation of polyheterocyclic systems. Zinc bromide has been used as catalyst to develop a simple route for the synthesis of Boc-protected tetrazole analogs of amino acids starting from *N*-Boc amino acids in a [2+3] cycloaddition of Boc-α-amino nitrile and sodium azide .

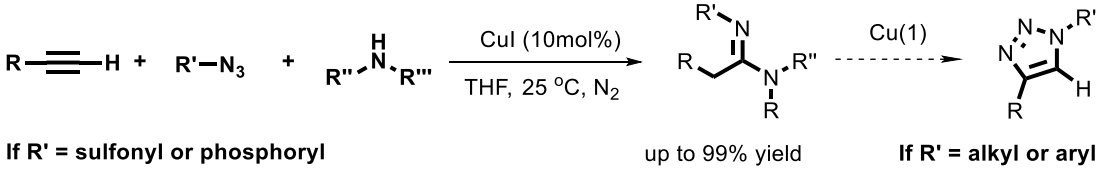


Scheme 13. Iridium-catalyzed 1,3-DC of azides and alkynes

Sun *et.al.*, (2014) reported an iridium-catalyzed intermolecular cycloaddition of azide with electron-rich internal thio-alkynes (IrAAC) which can be a complementary to the well-known CuAAC and RuAAC click reactions.

1.6 Cu-Catalyzed MCRs for Heterocycle Synthesis

Meldal and Sharpless (2002) independently reported Copper(I)-catalyzed cycloaddition of alkyl or aryl azides with terminal alkynes. Since these prominent reports, versatility of these reactions are widely explored in the area of bioconjugation, material science and drug discovery. Classically, thermally induced Hüisgen cycloaddition afforded 1:1 mixture of 1,5-disubstituted and 1,4-disubstituted 1,2,3-triazoles. On the other hand, copper(I)-catalyzed cycloaddition of organic azides with terminal alkynes lead to the formation of 1,4-disubstituted-1,2,3-triazoles. **Chang *et.al.*, (2005)** reported an unprecedented copper(I)-catalyzed three component synthesis of amidines with high yields via the coupling of sulfonyl azide and terminal alkyne (Scheme 13).



Scheme 14. Synthesis of amidines

In case of phosphoryl and sulfonyl azides, the cycloaddition products are converted into ketenimine, which can be reacted in situ with variety of nucleophiles to furnish diverse structural scaffolds. Copper(I) with alkyne produces copper(I)-acetylide. Copper acetylide may undergo reaction with sulfonyl azides to produce *N*- sulfonyl (1,2,3-triazolyl) copper species *via* intermediates. Triazolyl copper species may convert into the

ketenimine *via* the intermediate. The active ketenimine may be reacted with nucleophiles or the combination of nucleophile and electrophile coupling partners.

1.6.1 Copper-Catalyzed Multicomponent Reactions for Heterocycle Syntheses

In chemical syntheses, most of the important biological heterocyclic scaffolds are often synthesized divergently or sequentially in many steps, which vary on the complexity of target molecules rather than convergent methods. Optimization of each and every steps of divergent process leads to the lower yield of the target molecule, which associates costs, time, efforts, resources, selectivity and environmental impact. The "ideal synthesis" in organic chemistry should lead to the desired target molecule in a single step with high yield and 100% selectivity using the readily accessible starting materials (Figure 1). The synthetic variables towards ideal synthesis need to be optimized in terms of cost and time to improve the yield of the product. (**Wender *et.al.*,1997**). The preparative complexity in multistep synthesis increases proportionally to the number of steps involved in the reaction towards the target product. This reflected in product isolation and purification such as crystallization, extraction and distillation.

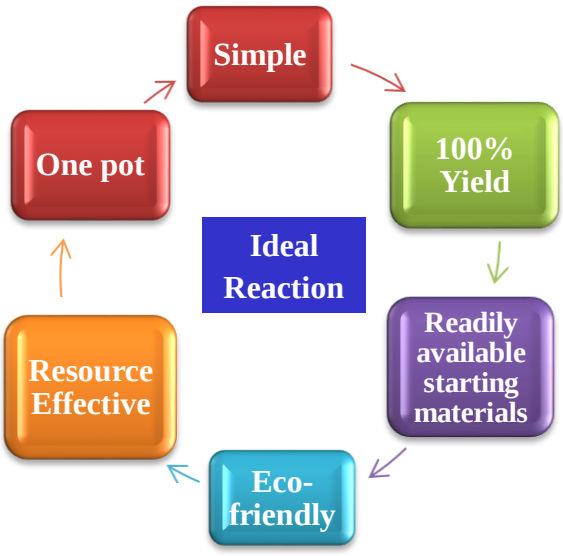


Fig.1. The ideal chemical synthesis

MCRs afford powerful synthetic tool for the transformation of three or more readily available simple substrates into a library of highly functionalized molecules. (**Zhu *et.al.*,**

2005). The products are widely used in biological, medicinal and material sciences. In addition, MCRs are highly flexible, selective and atom efficient with high exploratory power (*EN*), which is commonly identified as sub-class of domino or tandem reactions. MCRs can be broadly classified by the number of reaction component involved (Figure 2). They can also be classified on the mechanistic pathway as three types: type I in which the reaction substeps are in equilibria (eg., Strecker rand Mannich reactions), type II in which final step towards the product formation is irreversible (eg., Ugi and Passerini reactions) and type III in that the substeps are irreversible (one-pot multicomponent synthesis of heterocycles). (**Ugi *et.al.*, 1997**)

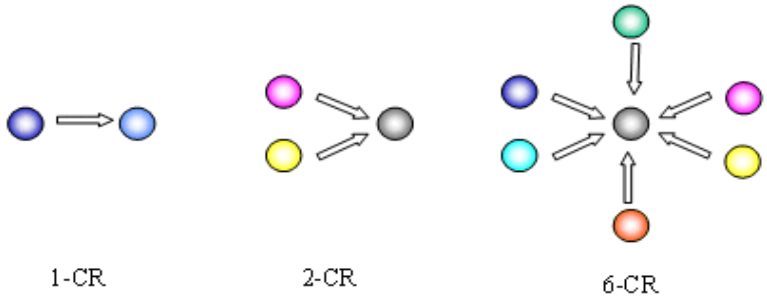


Fig.2. Multi component reactions

1.7 Copper catalysis in click chemistry

During the past years, a variety of scientific and methodological developments have been achieved, which urge chemists to increase the tools to improve the ease and practicality of synthesis and related separation and purification processes. Huisgen 1,3-dipolar cycloaddition between organic azides and alkynes is one among many synthetic tools that became quite well-known over the recent decade, mainly due to its key improvement in terms of rate and regioselectivity. The revolutionary idea was independently introduced by **Sharpless and Meldal (2002)** through the introduction of copper(I) catalysis termed as 'Click Chemistry'. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) is a type of Huisgen 1,3-dipolar cycloaddition based on the formation of 1,4-disubstituted 1,2,3-triazoles between a terminal alkyne and an aliphatic azide in the presence of copper, and is classified as a 'click reaction'. Click chemistry promotes the use of organic reactions that allow the connection of two molecular building blocks in a facile, selective, high-yielding reaction under mild reaction conditions with few or no byproducts.

Furthermore, this chemistry has the capacity to promote bioconjugation and peptide ligation, stemming from the properties of the triazole linkage as a peptide mimetic.

The tremendous synthetic potential of initial protocols for Huisgen 1,3-dipolar cycloaddition reaction between organic azides and alkynes was limited by the markable disadvantages like heating requirement, prolonged reaction time and formation of structural isomers due to the lack of selectivity. The wonderful copper(I)- catalyzed modification introduced at the dawn of last decade, allowed the cycloaddition to occur at room temperature or with moderate heating leading to the exclusive formation of 1,4-disubstituted triazole with shortest workup and purification steps. In 2005, another analogous RuAAC was reported by Fokin group, which led to the selective formation of 1,5-disubstituted triazole. Therefore, these remarkable modifications turned azidealkyne click method a practically quantitative, robust, insensitive and general orthogonal ligation reaction that is suitable in all aspects of drug discovery, combinatorial chemistry, target-templated in situ chemistry, material chemistry, proteomics and DNA research using bio-conjugation reactions.

Mechanistic overview

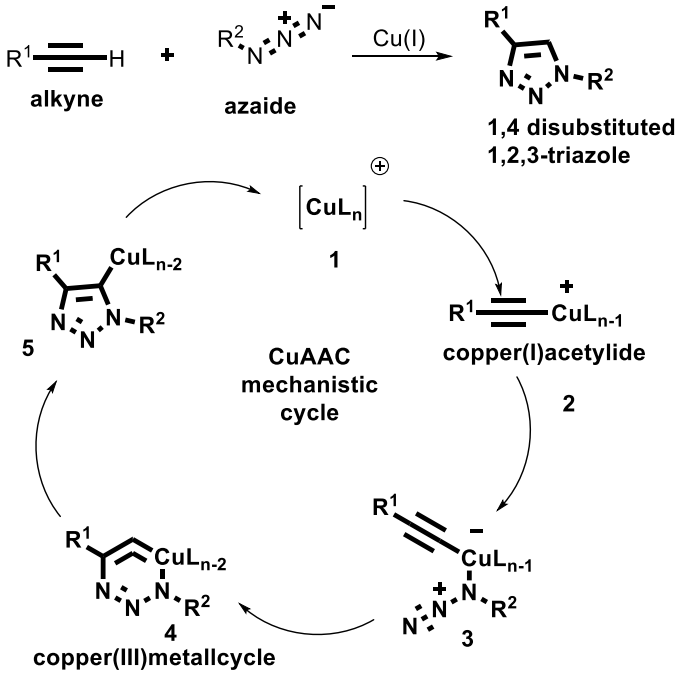


Fig. 3. Proposed mechanism for copper-catalyzed azide-alkyne cycloaddition (CuAAC)

The classical Huisgen 1,3-dipolar cycloaddition of organic azide with dipolarophiles is a one-step process, whereas its copper(I)- catalyzed variant **(figure.3)** is considered to be a step-wise process involving copper in the intermediate steps. In the initial step, copper forms acetylide via coordination with alkyne. In the next step, azide binds to the copper followed by the formation of an unconventional copper(III)metallacycle. The energy calculation showed a considerable low energy barrier for the step justifying the higher rate of the reaction than its uncatalyzed version. The intermediate then undergoes ring contraction to give copper triazolyl derivative, which upon protonolysis gives the desired 1,2,3-triazole product (Fig. 3).

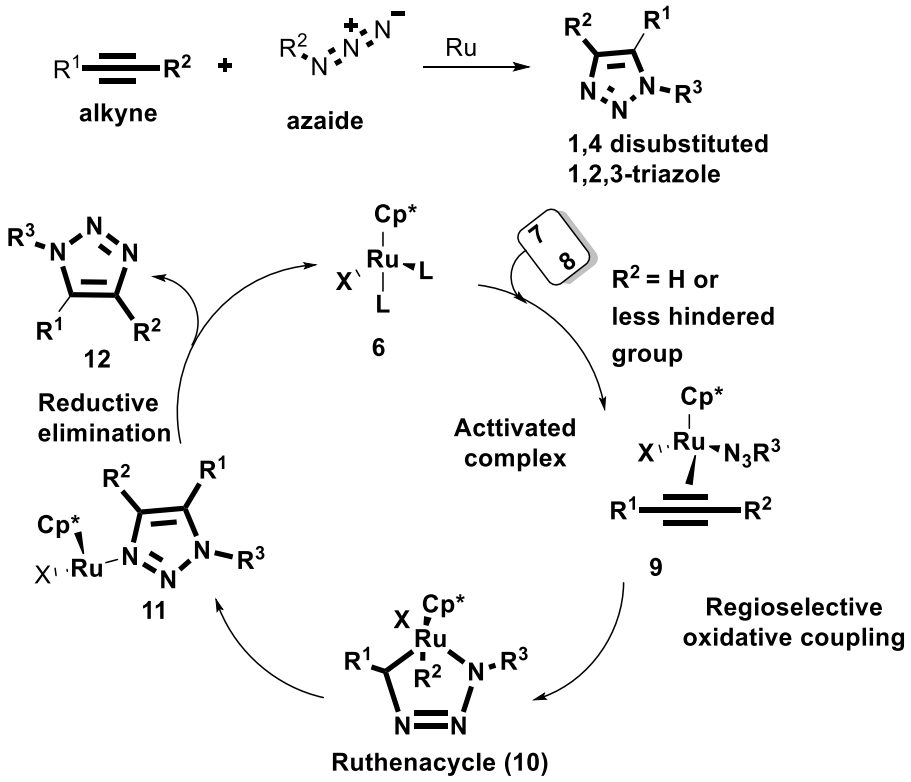


Fig. 4. Proposed mechanism for ruthenium catalyzed azide-alkyne cycloaddition (RuAAC)

The analogous RuAAC does not involve a ruthenium acetylide intermediate like copper, since it applies to both terminal as well as non-terminal alkynes. In the first step, the spectator ligands get displaced to form activated complex. This is followed by oxidative coupling between terminal nitrogen of azide and more electronegative less sterically

demanding carbon of the alkyne to form a Ruthenacycle. The Ruthenacycle then undergoes reductive elimination to release 1,2,3-triazole compound regenerating the active complex for the next cycle **(Fig. 4).**

1.8 Cascade Reaction

A **cascade reaction**, also known as a **domino reaction** or **tandem reaction**, include multiple transformations in a single pot. In single pot, single set of conditions was maintained. Each transformation is dependent on the preceding transformation. Cascade reactions are useful method for constructing polycyclic skeletons, which are important biological scafolds. A variety of cascade reactions, carried out under multiple reaction conditions, such as pericyclic, polar, radical and transition metal-catalyzed reaction conditions have been investigated.

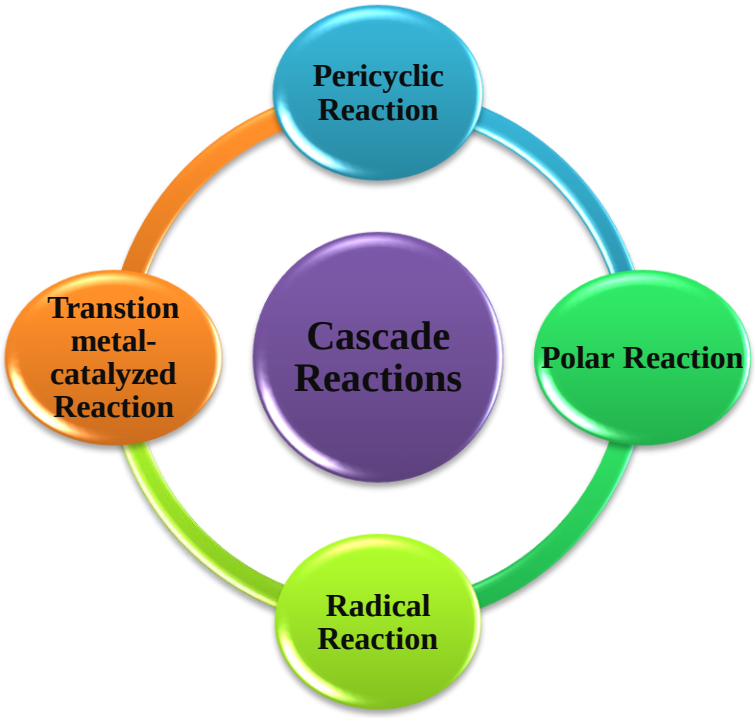


Fig.5. Cascade reactions

1.9 Iminocoumarin

Coumarins are an important organoleptic heterocyclic scaffold and widely exist in nature with numerous applications in the field of material and medicinal sciences.

Coumarin derivatives exhibit various medicinal properties, such as anticoagulant, anti-cancer, anti-microbial, anti-HIV, anti-inflammatory, anti-oxidant, antibiotic, anti- diabetic and anti-Alzheimer properties. In addition, the compounds containing coumarin motifs showed potent inhibitors of HIV integrase, Heat Shock Protein 90, Casein Kinase 2 (CK2), Human Monoamine Oxidases and Cholinesterase. Further, coumarin as plant sources are utilized in perfumes. They also find applications as dyes in food flavoring stuffs. In addition, coumarins serve as an excellent fluorescent probes in biology and medicine as well as dyes in laser technology. **(Rohini .K, *et.al.*, 2014)**

Iminocoumarins are a group of chemicals consisting of a coumarin with an attached imine group. Iminocoumarins are important heterocyclic scaffolds and find broad applications in biological and material sciences. For examples, the compounds having iminocoumarin structural motif exhibit anticoagulant, anticonvulsant, anti-inflammatory, antimicrobial, antioxidant and antitumor properties. In addition, they are found to be inhibitors of lymphocyte protein-tyrosine kinase and human carbonyl reductase. Furthermore, iminocoumarins are utilzied as dyes and fluorescent probes for metal senors, anionic sensors and biological probes. As a result, development of effective methods for the construction of iminocourmain derivatives is highly desirable. **(P.K.Jain, *et.al.*, 2012)**

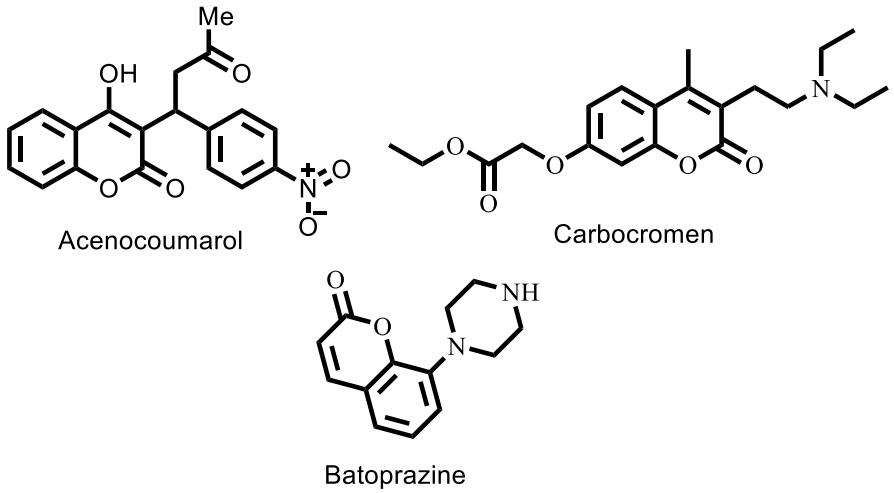


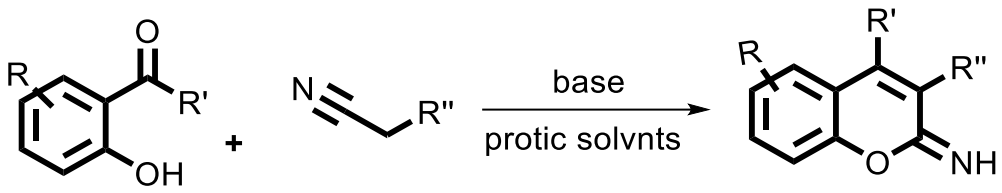
Fig.6. Examples of biologically important coumarin derivatives

1.10 Strategies for Synthesis of Iminocoumarins

Iminocoumarins are prepared by various methods such as Knoevenagel condensation, annelation of ketenimine with salicylaldehydes, cascade condensation and copper-catalyzed azide-alkyne cycloaddition reactions.

1.10.1 Knoevenagel Condensation

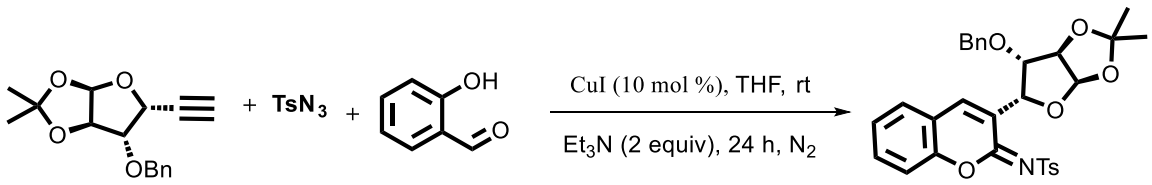
The classical methods for synthesis of iminocoumarin take an advantage of Knoevenagel condensation reaction. In the presence of base such as metal hydroxides, piperidine *etc.*, condensation of salicylaldehydes with active methylene nitrile compounds in protic solvents afford iminocoumarin derivatives.



Scheme 15. Knoevenagal condensation

1.10.2 Annelation of Ketenimine

Kaliappan *et.al.*, (2012), reported Cu(I)-catalyzed MCR of sugar-derived alkynes, tosyl azide and salicylaldehydes to provide 3-C-linked glycosyl iminocoumarin



Scheme 16. Annelation of Ketenimine

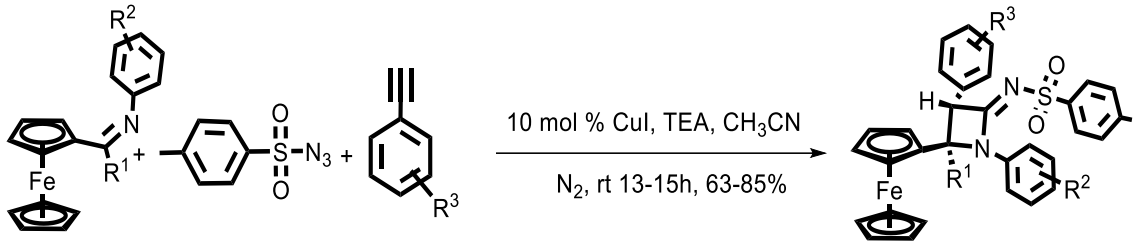
OBJECTIVE

After the development of copper(I) catalyzed synthesis of heterocycles using MCRs remarkably over the last decade and now has engulfed almost every section of chemistry and applied sciences. The MCRs using copper catalysis finds application in different scientific fields like carbohydrate chemistry, polymer, drug discovery, etc. Realizing the importance and practical applicability of copper catalysis in the MCRs and the significance of 2-iminocoumarin the work has been targeted with the aim

- To develop a efficient route for the synthesis of 2-iminocoumarin derivative in presence copper catalyst *via* cascade reaction
- To prepare the starting compounds 2-(prop-2-yn-1-yloxy)benzaldehyde and p-toluene sulfonyl azide
- To optimize the reaction conditions using different bases like Et_3N, K_2CO_3, Na_2CO_3, Cs_2CO_3 and K_3PO_4 for better yield
- To characterize the synthesized 2-iminocoumarin using FT-IR, ^1H NMR, ^{13}C NMR and HRMS

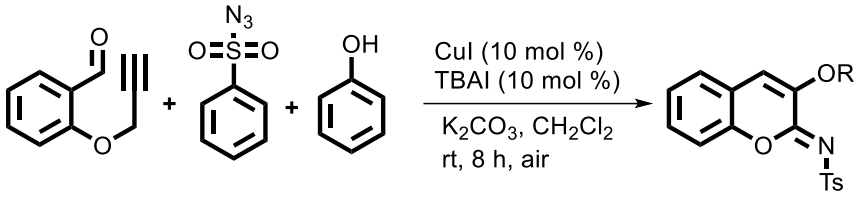
2. REVIEW OF LITERATURE

❖ **Gouthaman.S, *et.al.*, (2013)** reported the one-pot diastereoselctive synthesis of highly functionalized ferrocenyl azetidinimines by using copper as catalyst and four component reactions of ferrocenealdehyde, aromatic amines, tosyl azide and aryl alkynes to give the high yields.



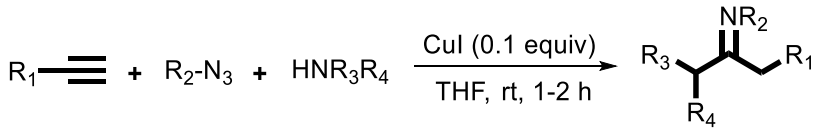
Scheme 17

❖ The reaction copper(I)-catalyzed ynal , *p*-toluenesulfonyl azide (TsN_3) and phenol as the model substrates in the presence of different copper(I) sources, bases, additives and solvents at room temperature *via* cycloaddition, intramolecular ketenimine rearrangment and cyclization reactions was reported by **Murugavel (2016)**.



Scheme 18

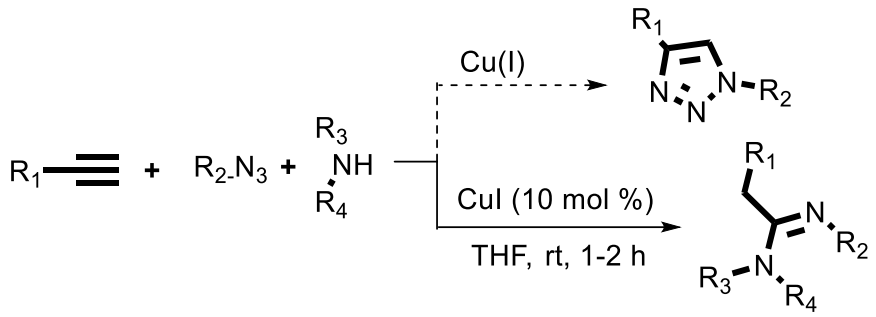
❖ **Imhyuk Bae *et.al,* (2005)** reported the synthesis of highly efficient one-pot synthesis of N-sulfonylamidines with sulfonyl azide, alkyne and amine using copper as catalyst.



Scheme 19

❖ **Chang *et.al,* (2006)** reported the cycloaddition of azides and alkynes which was found to

be very useful method in the preparation of triazoles and can be considered a click reaction. The copper catalyzed reaction between terminal alkynes and azides resulted in 1,4-disubstituted 1,2,3-triazoles with high yields.

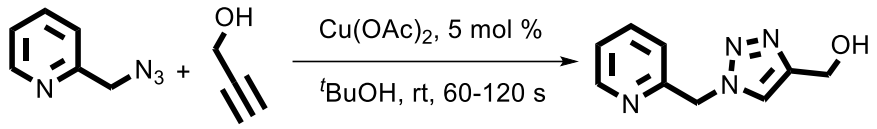


Scheme 20

- **Meldal and Sharpless (2002),** independently reported copper(I)-catalyzed cycloaddition of alkyl or aryl azides with terminal alkynes. Because of the, versatility of these reactions they were widely explored in the area of bioconjugation, material science and drug discovery. Thermally induced Hüisgen cycloaddition normally affords 1:1 mixture of 1, 5-disubstituted and 1,4-disubstituted 1,2,3-triazoles. On the other hand, copper(I)-catalyzed cycloaddition of organic azides with terminal alkynes lead to the formation of 1,4-disubstituted-1,2,3-triazoles.

- **Chang *et.al,*(2006)** reported three component synthesis of amidines with high yields via the coupling of sulfonyl azide and terminal alkyne using copper(I) as catalyst. In case of phosphoryl and sulfonyl azides, the cycloaddition products were converted into ketenimine, which can be reacted in situ with variety of nucleophiles to furnish diverse structural scaffolds.

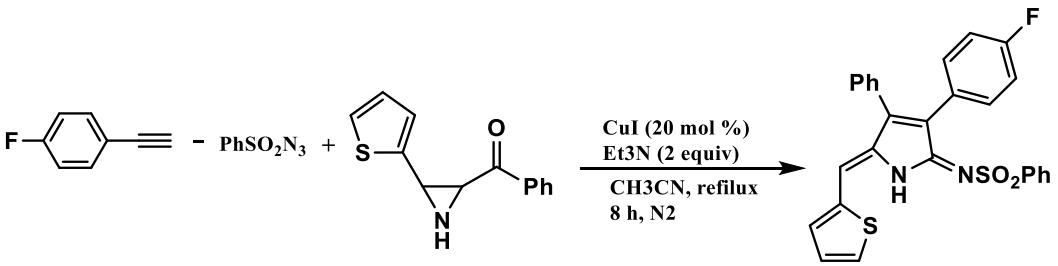
- **Wendy S. Brotherton, *et.al,*(2006)** reported the synthesis of copper(II) salt accelerated azide-alkyne cycloaddition reaction in alcoholic solvents without reductants such as sodium ascorbate. The reaction of 2-picolylazide and propargyl alcohol in the presence of 1 % of Cu $(OAc)_2$ proceede with good yields.



Scheme 21

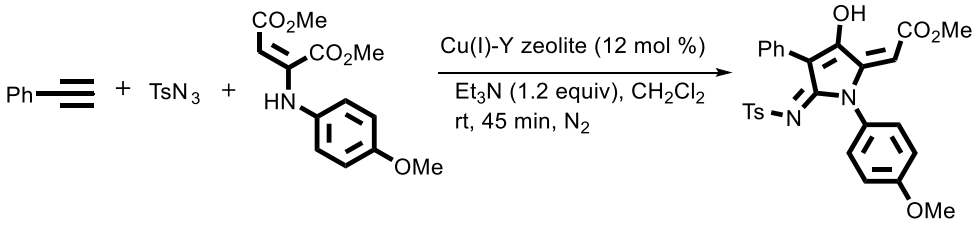
Reaction of Nitrogen Nucleophiles

❖ **Wang *et.al,*(2007)** reported the synthesis of 5-arylidene-2-imino-pyrrolines from 2-acylaziridines, sulfonyl azides and alkynes using 10 mol % CuI in the presence of 2 equiv of Et_3N in CH_3CN at reflux under nitrogen atmosphere. The reaction proceeded *via* nucleophilic addition to generate ketenimine followed by cleavage of C-N bond of aziridine to afford the target products. No product was formed with aliphatic alkynes under same conditions.



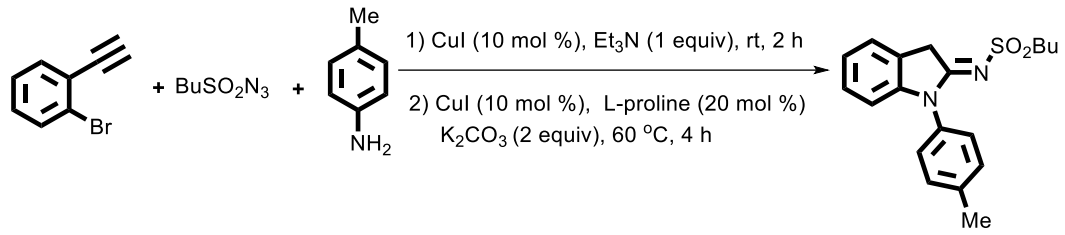
Scheme 22

❖ The synthesis of functionalized pyrrolidines from alkyne, sulfonyl azide and dimethyl 2-(phenylamino)maleate using Zeolite-Copper(I)-catalysts was carried out by **Pitchumani *et.al.*, 2015.** In this reaction, alkyne with sulfonyl azide generated ketenimine underwent reaction with dimethyl 2-(phenylamino)maleate followed by intramolecular [1,3]-H shift to yield the products.



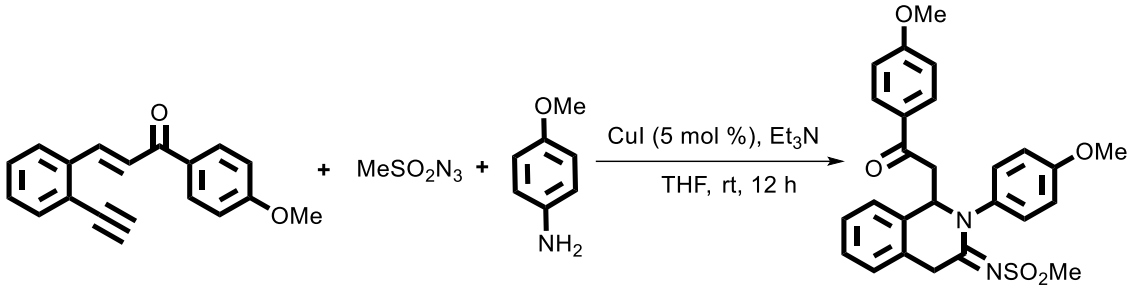
Scheme 23

❖ **Wang *et.al.*,(2011)** showed copper-catalyzed three component synthesis of 2-(N-sulfonylimino)indolines from 2-bromo-phenylacetylene, sulfonyl azides and amines. The reaction proceeded *via* C-N bond cross-coupling reaction sequence to afford indoline derivatives with moderate to good yield.



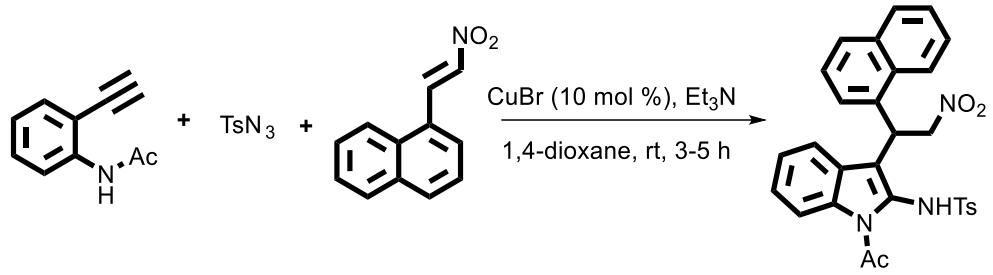
Scheme 24

❖ Synthesis of 1,2-dihydroisoquinolin-3(4H)-imines from 2-ethylphenylchalcone, sulfonyl azide and amine using 5 mol% CuCl in the presence of Et_3N in high yield was reported by **Wu *et.al.*,(2011).** This reaction proceeded *via* double nucleophilic addition of amine nucleophile to both chalcone as well as azide which generated ketenimine and Michael acceptor.



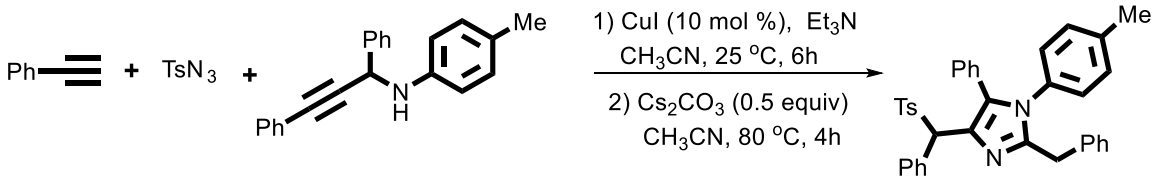
Scheme 25

The authors also subsequently developed a new method for the synthesis of indole derivatives using copper catalyzed three component reaction of 2-ethynylaniline, sulfonyl azide and nitrostyrene *via* nucleophilic addition to which generated ketenimine followed by Michael addition to the styrene. Some of the derivatives were found to be HCT-116 inhibitor from the preliminary biological screening.



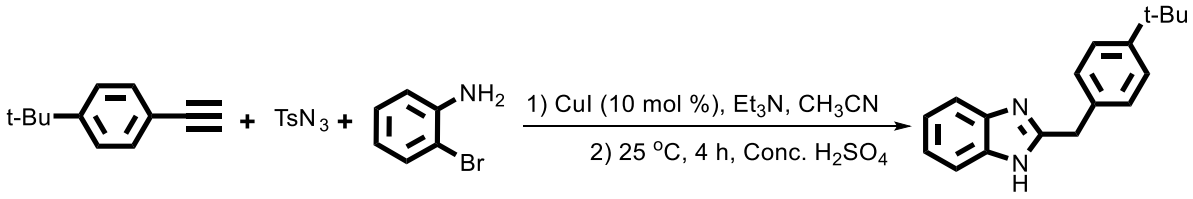
Scheme 26

❖ Copper(I)-catalyzed three component reaction of alkyne, sulfonyl azide and propargylamine using 10 mol % CuI in the presence of Et_3N in CH_3CN was carried out. The reaction proceeded *via* cascade nucleophilic addition of amine to which generated ketenimine, through 6π-electrocylization reaction and intramolecular [1,3] migration of sulfonyl substituents to furnish tetra-substituted imidazole.(**Wang *et.al.*, 2012**)



Scheme 27

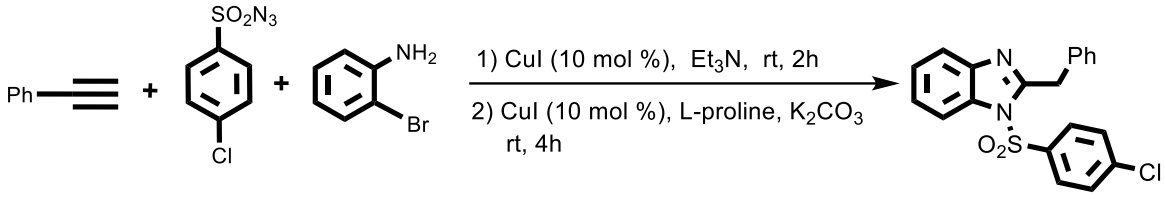
❖ The three-component reaction of 1,2-diamino benzene, alkyne and azide using 10 mol % of CuI in the presence of Et_3N in CH_3CN followed by reflux with conc. H_2SO_4 afforded benzimidazoles.



Scheme 28

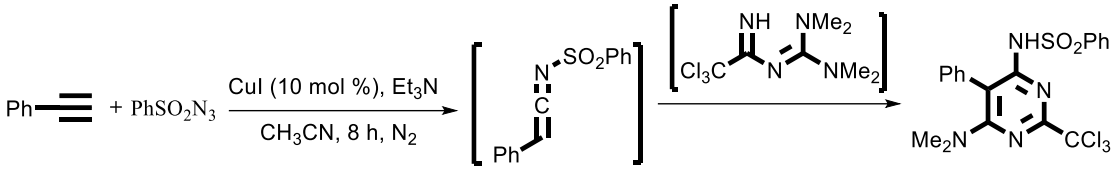
❖ **Wang *et.al.*,(2010)** reported the synthesis of functionalized *N*-sulfonyl substituted benzimidazole derivatives from 2-bromoaniline, sulfonyl azide and alkyne *via* one-pot

copper(I)-catalyzed three component reaction. The reaction proceeded *via* nucleophilic addition of aniline to generated ketenimine followed by C-N cross- coupling reaction.



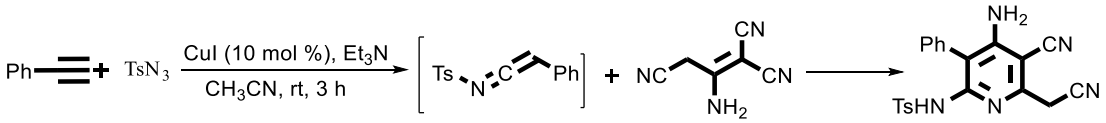
Scheme 29

- A new approach for the synthesis of polysubstituted pyrimidines using copper(I)-catalysed cycloaddition of alkyne with sulfonyl azide followed by the reaction of ketenimine with tetramethylguanidine derivative derived from trichloroacetonitrile and quinidine was carried out by **Yavari *et.al*.,(2013).**



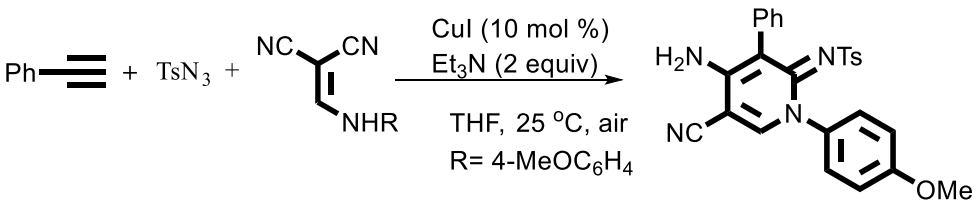
Scheme 30

- The same group subsequently demonstrated the synthesis of pyridine derivatives from ketenimine and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**2014**).



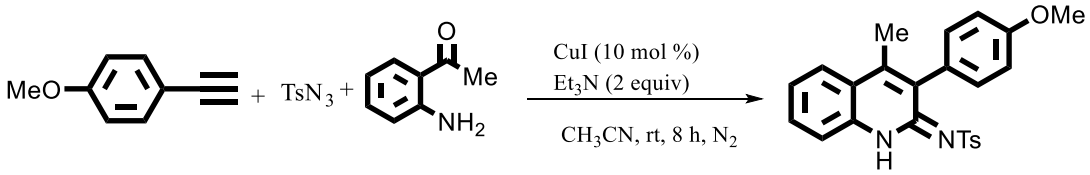
Scheme 31

- Synthesis of functionalized 4-amino and 6-amino-2-iminopyridines from alkyne, sulfonyl azides and 2,2'-dicyano substituted enamine using 10 mol% CuI in the presence of 2 eqiuv Et_3N was carried out by **Dong *et.al*.,(2013)**. When the reaction was performed in THF at 25 ^oC, 4-amino-2-iminopyridine derivatives was predominantly formed. On the other hand, 2-amino-2-iminopyridine was found to be formed preferably in DMF at 50 ^oC under nitrogen atmosphere *via* an intramolecular nucleophilic vinylic substitution.



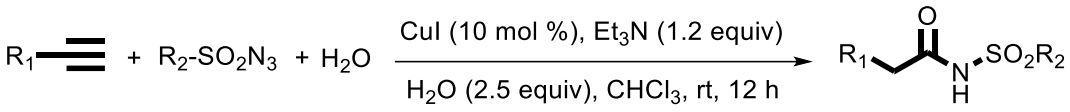
Scheme 32

- Synthesis of 2-imino-1,2-dihydroquinoline from terminal alkyne, sulfonyl azide and acetylene using 10 mol% CuI in the presence of 2 eqiv Et_3N and CH_3CN under nitrogen atmosphere was reported by **Wang *et.al.*,2008.** This reaction proceeded *via* cascade nucleophilic addition to which generated ketenimine followed by cyclization.



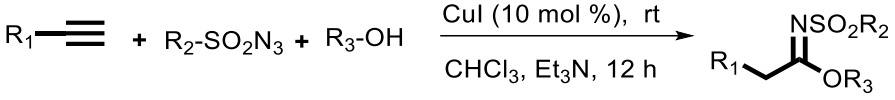
Scheme 33

- **Chang and Fokin (2009)** reported the alternate synthesis of amide, with the reactions of terminal alkynes and sulfonyl azides in the presence of triethyl amine and a catalytic amount of copper(I) iodide delivered the N-sulfonyl amides under aqueous conditions. **Fokin (2006).** simultaneously reported the same sequence with different conditions. For example, the addition of 2 mol % of TBTA accelerates the reaction.



Scheme 34

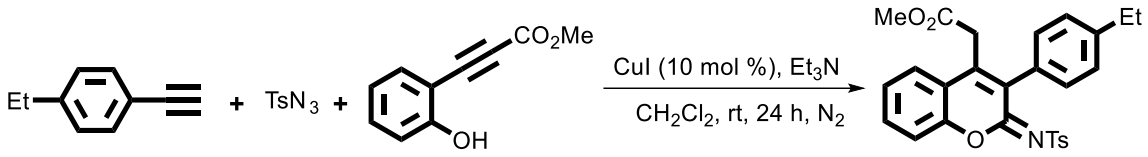
Synthesis of amide compounds in high yields under mild conditions by the reaction of the terminal alkynes, sulfonyl azides and alcohols with triethylamine and catalytic amounts of copper(I) iodide was carried out by (**Chang, 2010**).



Scheme 35

Reaction of Oxygen Nucleophiles

❖ **Wang *et.al.*,(2013)** developed copper(I)-catalyzed three- component synthesis of functionalized iminocoumarin derivatives from terminal alkyne, sulfonyl azide and salicylaldehyde, the reaction proceeded *via* addition with the generation of ketenimine with oxygen nucleophile followed by cyclization. Later, these authors showed the synthesis of 2-iminocoumarin from 2-hydroxyphenylpropiolates.

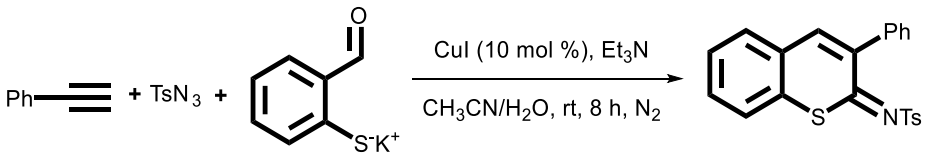


Scheme 36

The synthesis of functionalized 2-iminodihrdrocoumarin is demonstrated using copper(I)-catalyzed three-component reaction of 2-hydroxychalcone, terminal alkyne and sulfonyl azide. The reaction proceeded *via* ketenimine generated by nucleophilic addition followed by an intramolecular Michael addition.

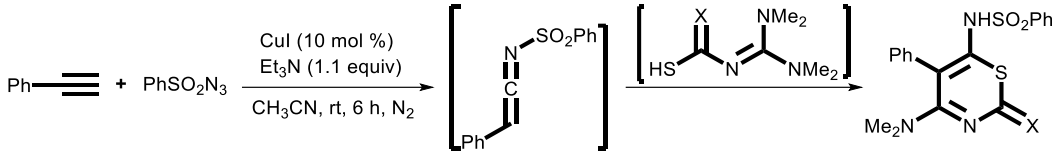
Reaction of Sulphur Nucleophiles

❖ Synthesis of 2-iminothiocoumarins were achieved by copperr(I)-catalyzed three component reaction of alkynes, sulfonyl azides and potassium salt of 2-mercapto-benzaldehyde was carried out by **Wang *et.al.*,(2008)**.The cascade process involved the trapping of iminocoumarin generate ketenimine.



Scheme 37

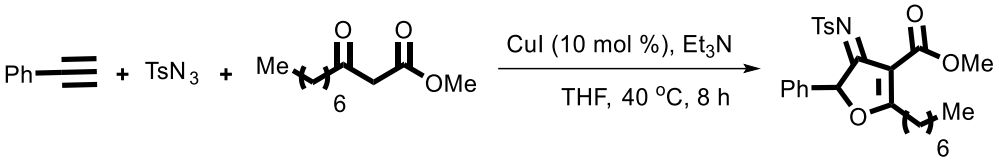
❖ **Yuvari *et.al.*,(2013)** reported the synthesis of 2-thioxo-2*H*-1,3-thiazines from alkyne and sulfonyl azide which generated adduct of carbondisulphide with tetramethylquanidine using 10 mol % CuI in the presence of 1.1 equiv Et_3N in CH_3CN at room temperature . In addition, 2-arylimino-2*H*-1,3-thiazines were also synthesized using the same protocol.



Scheme 38

Reaction of Carbon Nucleophiles

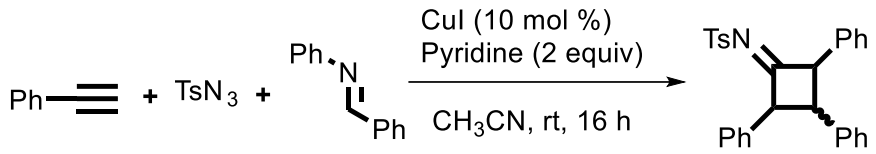
❖ Synthesis of 4-arysulfonylimido-4,5- dihydrofuran derivatives from terminal alkyne, sulfonyl azide and alkyl acetoacetate using 10 mol % CuI in the presence of 2 equiv Et_3N in THF was demonstrated. The reaction proceeded *via* carbon nucleophilic addition which generated ketenimine.(**Zhang *et.al.*,2010**).



Scheme 39

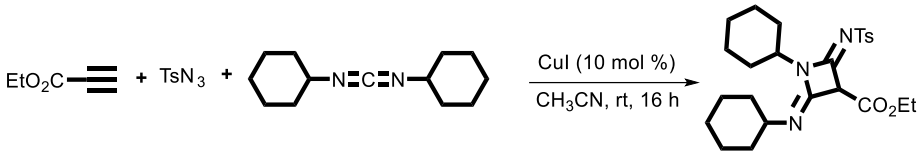
[2+2] Cycloaddition Reaction

❖ **Fokin *et.al.*,(2006)** showed the synthesis of diastereoselective azetidines from terminal alkyne, sulfonyl azide and imine using 10 mol % CuI in the presence of pyridine in CH_3CN at room temperature. These transformations take place *via* [2+2]-cycloaddition which generated ketenimine with imine to afford azetidines with good diastereoselectivity.



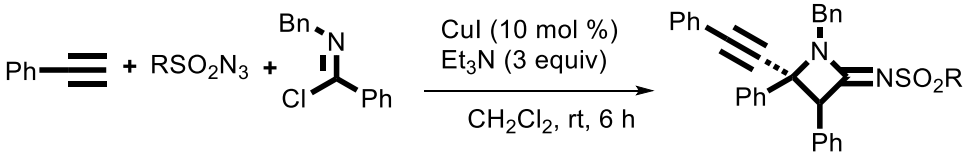
Scheme 40

❖ Synthesis of 1,4-diimino-azetidines from alkyne, sulfonyl azide and dicyclohexylcarbodiimide using 10 mol % CuI in CH_3CN at room temperature was reported by **Xu *et.al.*,(2007)**. This reaction proceeded *via* [2+2] cycloaddition of ketenimine with DCC to provide the corresponding heterocycles in good to high yields.



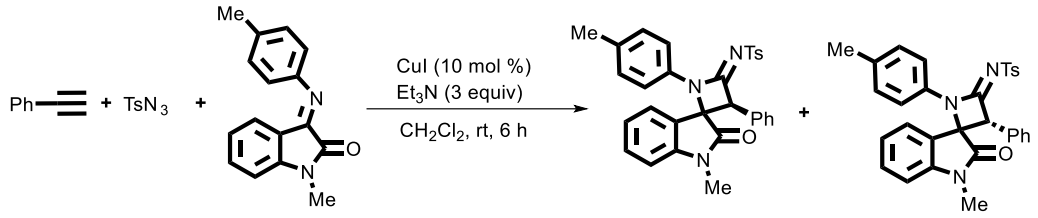
Scheme 41

❖ Synthesis of highly substituted azetidine-2-imine derivatives from sulfonyl azide, alkyne and imidoyl chloride has been accomplished using 10 mol % CuI in the presence Et_3N in CH_2Cl_2 in good yields. The transformation occured *via* intermolecular [2+2] cycloaddition which generated ketenimine with ynimine to afford the target with high diastereoselectivity. (**Xing *et.al.*,2013**)



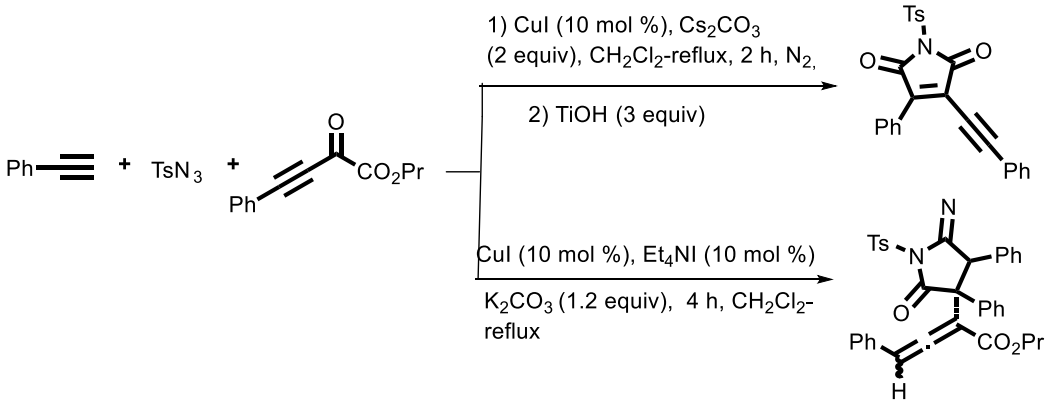
Scheme 42

❖ **Shanmugam *et.al.*,(2014)** reported the reaction of terminal alkyne, sulfonyl azide and 2-aryliminoindolin-2-one using 10 mol % CuI in the presence of 2 equiv Et_3N in CH_3CN under nitrogen atmosphere. The reaction took place *via* [2+2] cycloaddition which generated ketenimine with 2- aryliminoindolin-2-one with high diastereoselectivity.



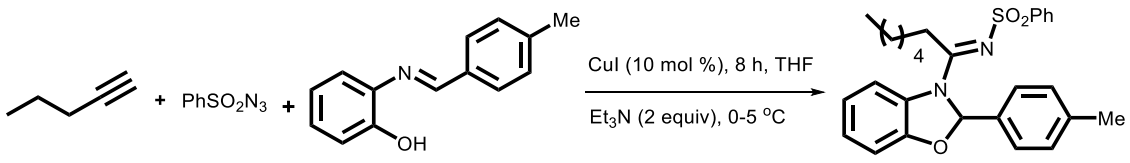
Scheme 43

❖ **Ma *et.al.*,(2009)** developed a new method for the functionalized 2-iminooxetanes from terminal alkynes, sulfonyl azides and aromatic 2-oxobut-3-ynoates using copper(I)-catalyzed multicomponent [2+2] cycloaddition reaction of aromatic 2-oxobut- 3-ynoates which generated ketenimine. The rearrangements of 2-iminooxetane reaction afforded pyrrolidinones and maleimide derivatives.



Scheme 43

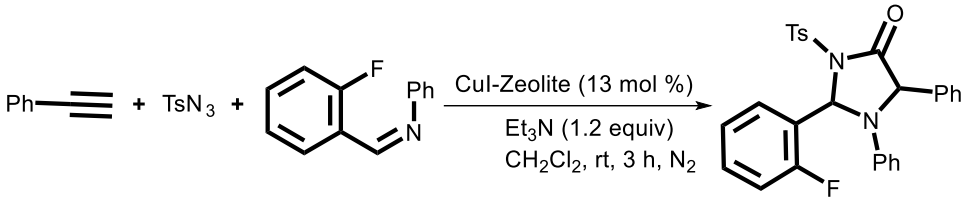
❖ Synthesis of functionalized benzaxozoline-amidine derivatives from terminal alkyne, sulfonyl azides and Schiff base of salicylaldehyde using 10 mol % CuI in the presence of Et_3N was reported by **Zhang *et.al.*,(2009)**. The reaction proceeded *via* [2+2]-cycloaddition reaction of which generated ketenimine with Schiff base followed by skeletal reorientation to afford the corresponding heterocycle in good yields.



Scheme 44

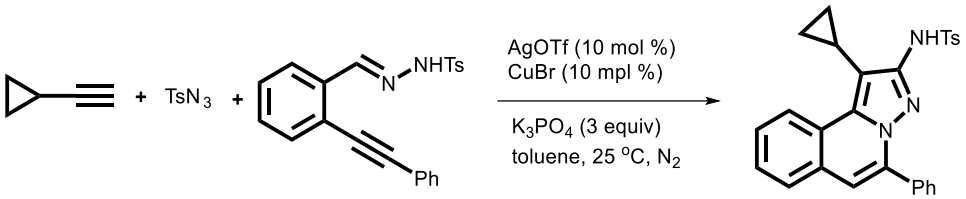
[3+2] Cycloaddition Reaction

- Synthesis of functionalized diasteroselective imindazoline-4-ones from alkyne, sulfonyl azide and nitrone using 13 mol % copper(I)- zeolite in the presence of 1.2 equiv Et_3N in CH_2Cl_2 under nitrogen atmosphere was reported. This transformation took place *via* [3+2] cycloaddition which generated ketenimine with nitrone followed by skeletal rearrangement.(**Pitchumani *et.al.*,2011**)



Scheme 45

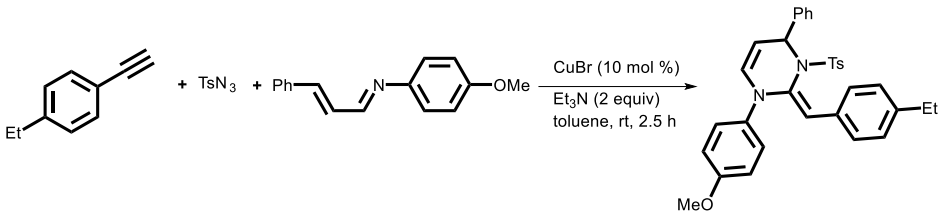
- The synthesis of functionalized 2-amino-*H*-pyrazolo[5,1-*a*]-isoquinolines was reported by **Li *et.al.*,(2011)** through an intermolecular [3+2]-cycloaddition which generated ketenimine with isoquinolinium-2-yl-amide in good yields.



Scheme 46

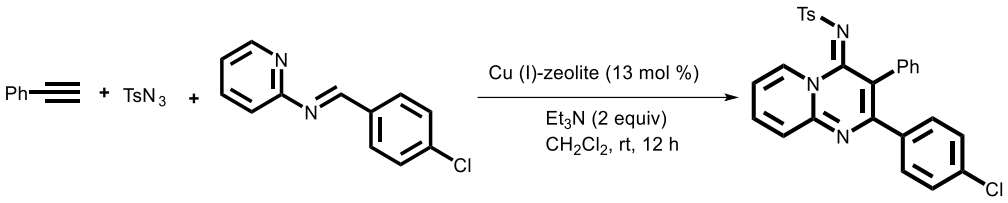
[4+2] Cycloaddition Reaction

- **Wang *et.al.*,(2009)** reported copper(I)-catalyzed three-component synthesis of tetrahydropyrimidines from terminal alkynes, sulfonyl azides and *α,β*-unsaturated imine. At room temperature, tetrahydropyrimidine is selectively formed *via* formal [4+2] cycloaddition with the generation of ketenimine with *α,β*-unsaturated imine. On the other hand, under reflux, [2+2] product was obtained.



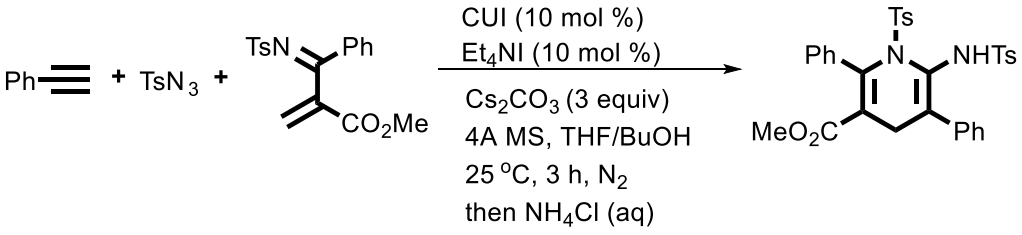
Scheme 47

❖ **Pitchumani *et.al.*,(2013)** accompolished chemo- and regioselective synthesis of pyrido[1,2-*a*]pyrimidin-4-imines from sulfonyl azide, alkyne and N-arylidenepyridine-2-amine using 13 mol % copper(I)-Zeolite in the presence of 2 eqiv Et_3N in CH_2Cl_2 at room temperature obtained the yield. This transformation proceeds *via* formal [4+2] Cycloaddition of which generated cesium stabilized ketenimine with N-arylidenepyridine-2-amine.



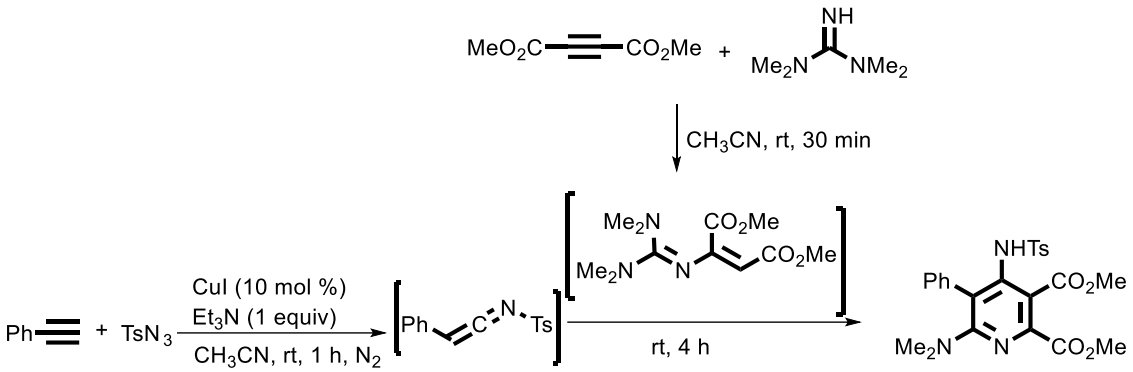
Scheme 48

❖ A new protocol for the synthesis of dihydropyridones *via* copper catalyzed three-component inverse electron-demand hetero Diels Alder reaction of which generated cesium stabilized ketenimine intermediate with electron demand conjugate *α,β*-unsaturated tosylimine was found by **Ma *et.al.*,(2015).**



Scheme 49

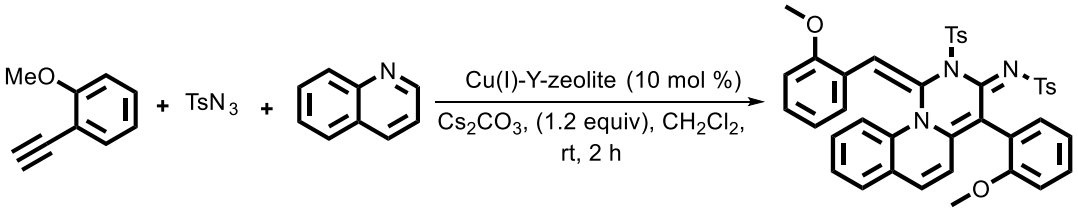
❖ **Yuvari *et.al.*,(2015)** developed new method to access polysubstituted pyridine from ketenimine which formed stabilized adduct between dialkyl propiolate and quinidine *via* one-pot copper catalyzed three-component reaction to the products.



Scheme 50

[2+2+2] Cyclomerization Reaction

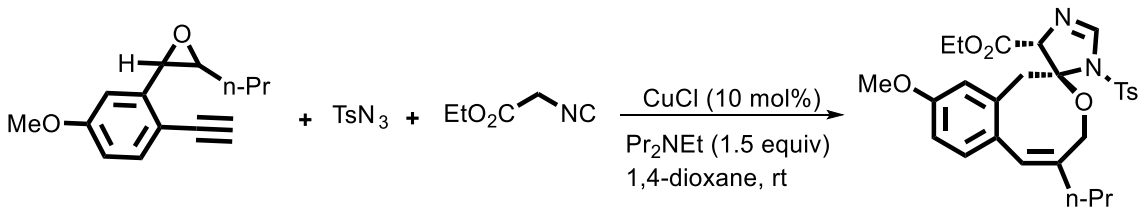
- **Pitchumani *et.al.*, (2015)** reported Copper-Zeolite catalyzed three-component synthesis of pyrimido-[1,6-*a*]quinolone derivatives from terminal alkynes, sulfonyl azides and quinoline using 10 mol % copper(I)-Y Zeolite in the presence of 1.2 equiv Cs_2CO_3 in CH_2Cl_2 at room temperature. This reaction proceeded *via* tandem [2+2+2] trimerization of two equiv ketenimine with one equivalent of quinolone to yield the corresponding heterocycles with good yields.



Scheme 51

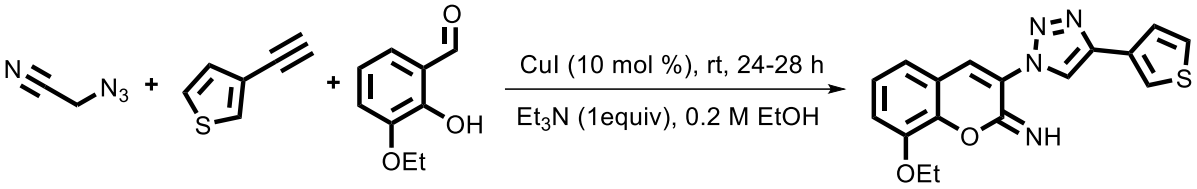
Miscellaneous Reactions

- Synthesis of highly functionalized fused spirocycles from 2-(2-ethylphenyl)oxirane and sulfonyl azide using 10 mol % CuCl in the presence of 1.5equiv Pr_2EtN in 1,4-dioxane at ambient temperature was rereported by **Wu *et.al.*,(2012)** with good yields.



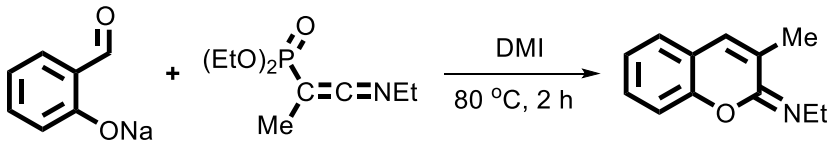
Scheme 52

❖ Copper catalyzed cycloaddition of sulfonyl azides with terminal alkynes proceeded *via* reactive ketenimine that can be readily reacted with diverse nucleophiles to afford highly functionalized structural scaffolds. This strategy provided a potential route for the construction of highly functionalized heterocyclic compounds utilizing suitable coupling partners. Copper-catalyzed three-component synthesis of 3- triazolyl-2-iminocoumarins was reported by **Qian *et.*al., (2013)** from azide-alkyne cycloaddition between 2-azidoacetonitrile and acetylene. The activated methylene group of triazole then underwent an aldol-cyclization-dehydration with salicylaldehyde to furnish iminocoumarin. This reaction was subsequently extended for synthesis of glycosylated iminocoumarin derivatives.



Scheme 53

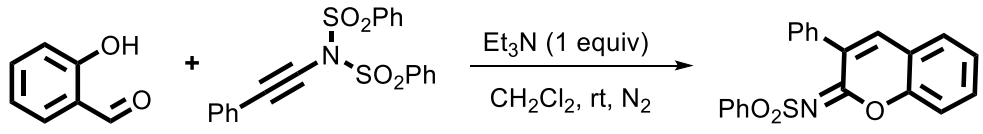
❖ **Motoyoshiya *et.al.*, (1979)** reported the synthesis of iminocoumarin *via* annelation of stable C-phosphono-ketenimine with sodium salt of salicylaldehyde.



Scheme 61

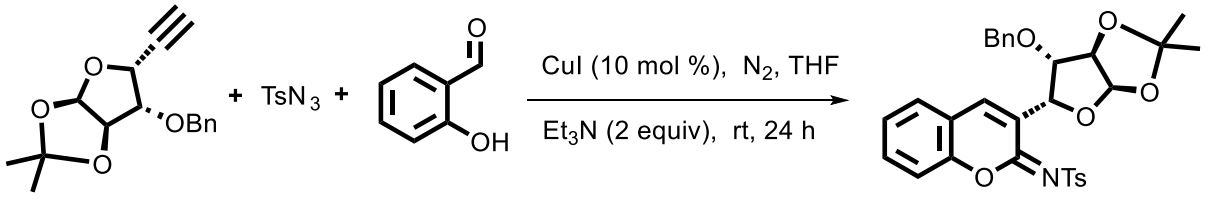
❖ Et_3N-mediated synthesis of iminocoumarin from *N, N*- disulfonylnamides and

salicylaldehydes was carried out. In this reaction, the annulation of reactive ketenimine intermediate with salicyladehyde afforded the target heterocycles. (**Cao *et.al.*,2014**)



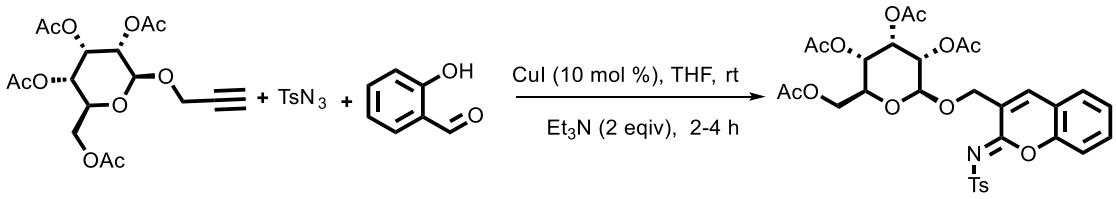
Scheme 54

- Copper(I)-catalyzed multicomponent reaction of sugar-derived alkynes, tosyl azide and salicylaldehydes to provide 3-C-linked glycosyl iminocoumarin was reported by **Kaliappan *et al.*,2012.**



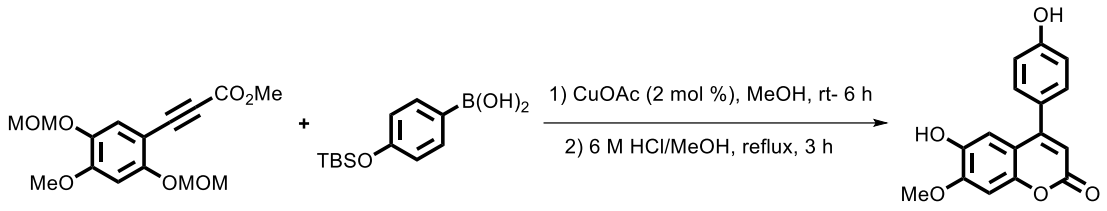
Scheme 55

- **Mandal (2014)** extended strategy for the synthesis of glycosylated iminocoumarins *via* copper(I)-catalyzed multicomponent reaction of sugar alkynes, sulfonyl azides and salicyaldehydes to give the product.



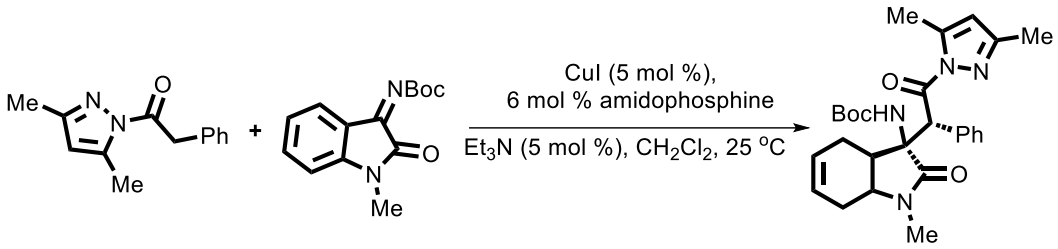
Scheme 56

- Copper-catalyzed hydroarylation of aryl boronic acids with MOM-protected methyl 3-(2-methoxymethoxy)aryl)propiolates using 2-10 mol % CuOAc in MeOH, followed by refluxing with 6 M HCl afforded coumarins. (**Yamamoto and Kirai, 2008**)



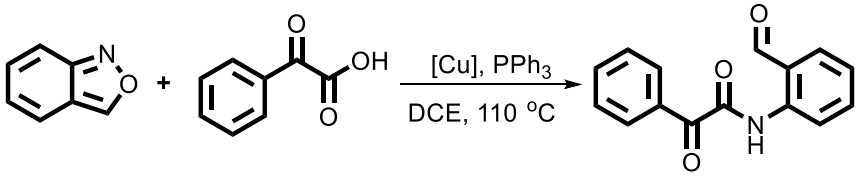
Scheme 57

- The enantioselective mannich raction between *N*-acylpyrazoles and isatin 5 mol % $Cu(CH_3CN)_4PF_6$ and 6 mol % of chiral amidophosphine produced excellent yield. (**Jian Lu *et.al.*,(2012**)



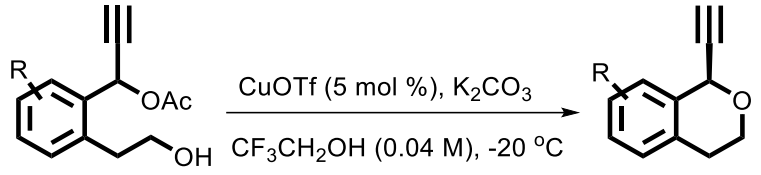
Scheme 58

- **Ping-Gui Li *et.al.*,(2013)** reported the synthesis of α-ketoimides with aldehyde group by using copper as a catalyst under redox-neutral conditions, in which cleavage of C-O bond was favoured but normal C-C bond cleavage was suppressed.



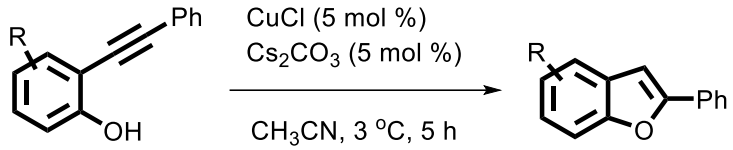
Scheme 59

The enantioselective intramolecular etherification of propargylic esters with copper catalyst and potassium carbonate (10 mol %) at 20 °C was reported by **Shiyao Liu *et.al.*,(2019)** to yield (R)-1-ethynylisochromane.



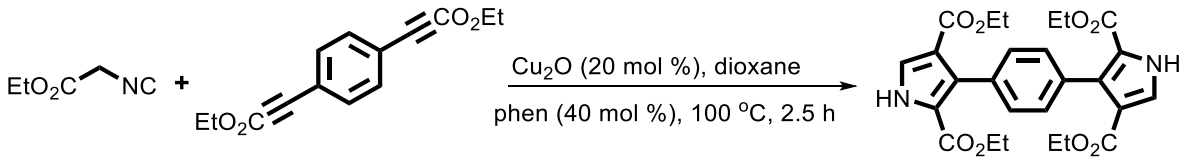
Scheme 60

- Synthesis of 2-substituted benzo[b]furans and indoles using copper as catalyst *via* intra molecular cyclisation of 2-alkynyl phenols and tosyl amine was demonstrated by **Zhouting Rong *et.al.*,2019.**



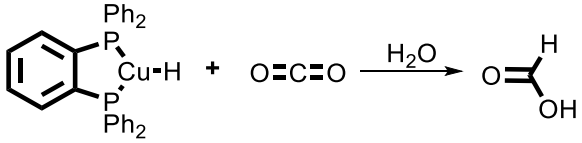
Scheme 61

- **Shin Kamijio *et.al.*,(2005)** accomplished the reaction of alkynes with isocyanides in the presence of copper catalyst and phen at 100 °C to synthesize the substituted pyrroles.



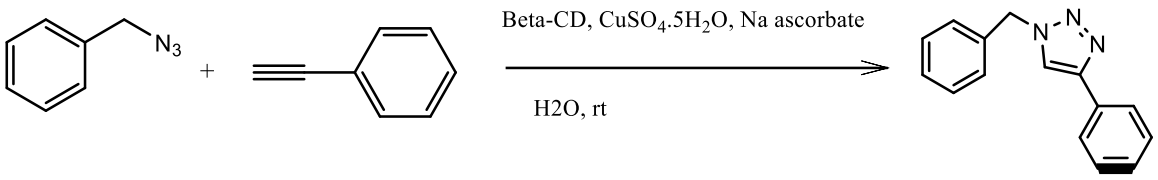
Scheme 62

- The simple and most important formation of formic acid was explained by **Ken Motokura *et.al.*,(2007)** *via* the reaction of carbon dioxide with hydrosilanes and using $Cu(OAc)_2 \cdot H_2O$–1,2-bis(diphenylphosphino)benzene system as catalyst. It was highly effective for the formic acid synthesis under 1 atm of CO_2.



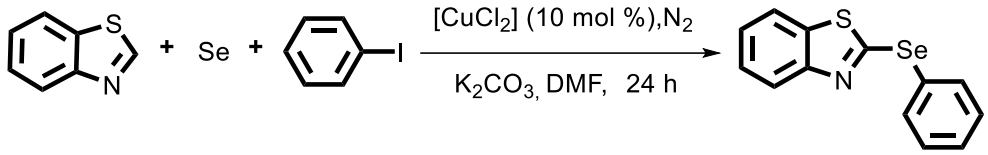
Scheme 63

❖ **Jung-Ah Shin *et.al.*,(2009)** accomplished the synthesis of 1,4-disubstituted-1,2,3-triazoles from the reaction between benzyl azides and phenyl acetylene in water in the presence of catalytic amount of β-cyclodextrin, copper sulphate pentahydrate and ascorbate in good yields.



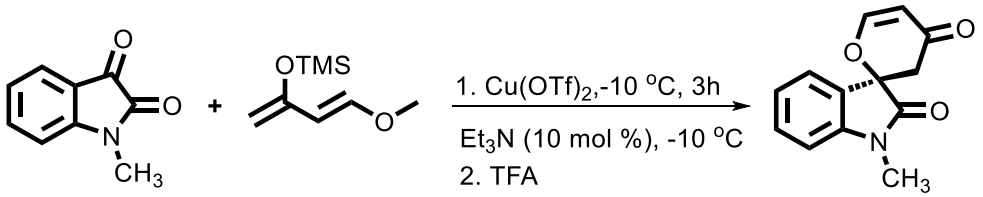
Scheme 64

❖ Copper catalyzed three component coupling reaction for the first time was carried out benzo thiazole, selenium powder and iodobenzene in the presence of 10 mol % of $CuCl_2$ and potassium carbonate as solvent under nitrogen atmosphere at 24 h to yield of 2-(phenylselanyl)benzo[d]thiazole yield. (**Chao Gao *et.al.*,2016**)



Scheme 65

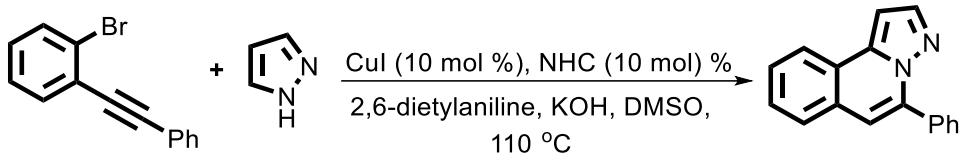
❖ **Yanan Li *et.al.*,(2016)** explained an highly enantioselectie hetero-Diels-Alder reaction of Danisishefsky's diene (1-methylindoline-2,3-dione) with glyoxal with chiral copper catalyst. This transformation provided way for the synthesis of a wide range of biologically active dihydropyrones with high level of enantioselectivity.



Scheme 66

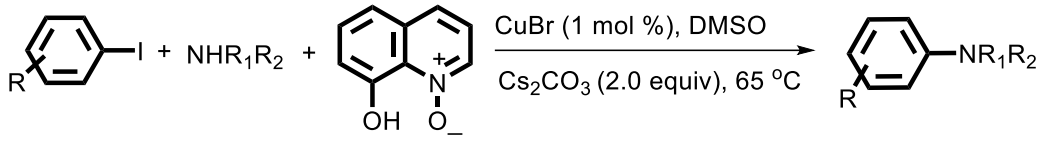
❖ The reaction of 2-alkylbromobenzene and pyrazole in the presence of CuI facilitated the

preparation of [5, 1-a]isoquinolines in good yield as described by **Xiaolin Pan *et.al.*,(2013**). The reaction involved hydroamination and C-H activation.



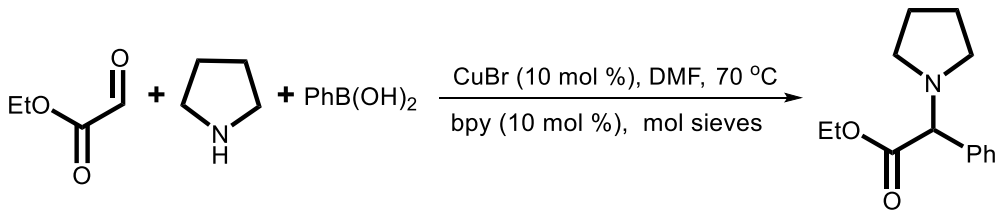
Scheme 67

- The copper catalyzed Ullman C-N coupling reactions of iodobenzene and amine group with 8-hydroxyquinoline *N*-oxide in the presence of CuBr (10 mol %) and Cs_2CO_3 (2.0 equiv) and DMSO as solvent at 65 ^oC the yield was reported by **Kai Yang *et.al.*,2011.**



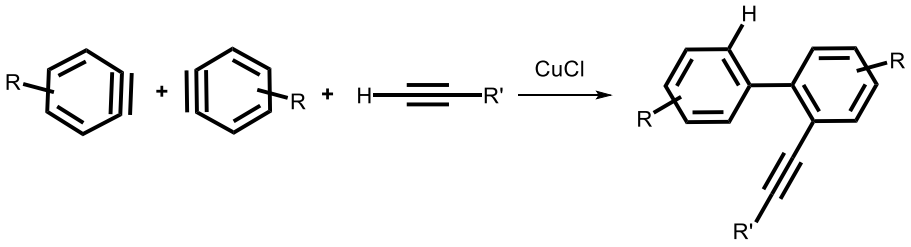
Scheme 68

- **Robin Frauenlob *et.al.*,(2012)** reported petasis reaction for the synthesis of tertiary amines and amino esters using copper catalyst. The reaction proceeded *via* coupling of aldehydes, amines and boronic acids. This process involved transmetalation from boron to copper.



Scheme 69

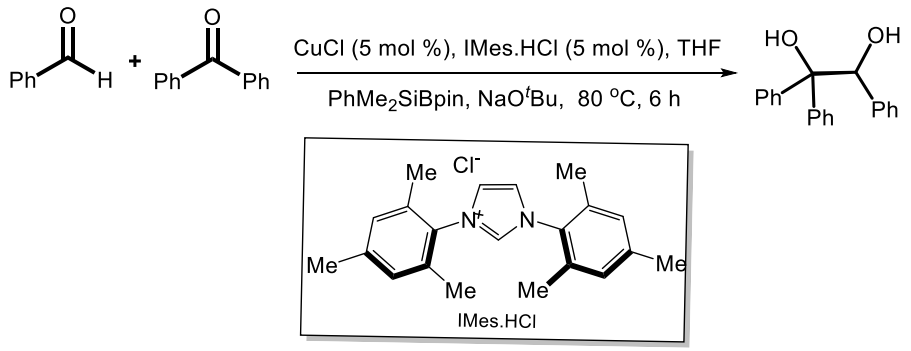
- The formation of 2-alkynylbiaryls an one step reaction with two molar amounts of arynes into a C-H bond of terminal alkynes was prepared by using copper (II) catalyst was reported by **Hiroto Yoshida *et.al.*,(2009)** to give the good yield.



Scheme 70

- **Paul E. Weston *et.al.*,(1928)** reported that the addition of aryl amines or N-acyl aryl amines to form N-aryl aryl amines and the salts of phenols with aryl halides to form di-aryl ethers. In this reaction nitro benzene or phenol (high boiling point solvent) was used and potassium carbonate was added to neutralize halogen acid formation. However, in some cases other form of copper or copper compounds was used to give equally good yields.

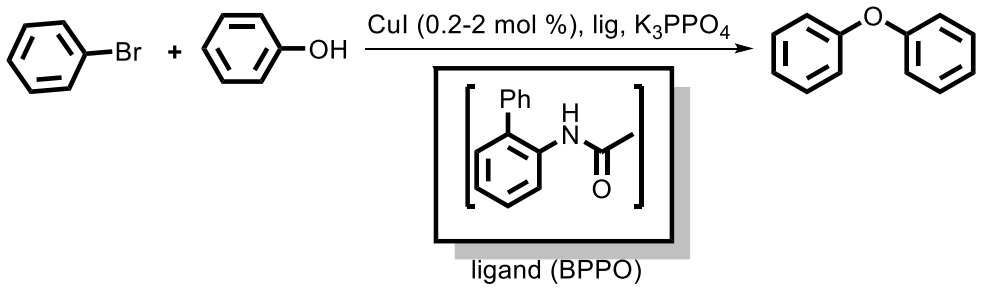
- The reductive coupling of two different carbonyl compounds has been obtained in the reaction between aldehydes and arylketones with a silylboronate in the presence of catalytic amount of a CuCl-N-heterocyclic carbine (NHC) complex and stoichiometric amount of alkoxide base which yielded cross-coupled 1,2-diol derivatives. It was proposed that involves the catalytic formation of nucleophilic α-silyloxybenzylcopper(I) species from a aromatic aldehyde and its subsequent coupling with arylketone. This copper catalyst reaction enabled coupling between aromatic aldehydes and imines. **(Mitsutaka Takeda *et.al.*, (2019).**



Scheme 71

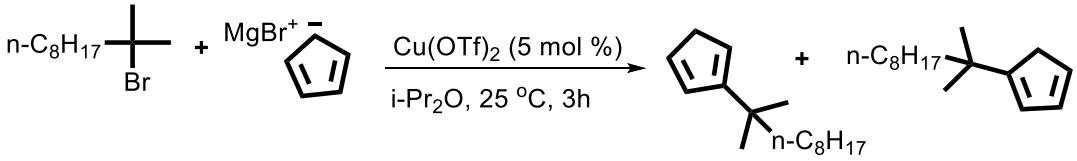
- **Yuntong Zhai *et.al.*,(2017)** reported the formation of diaryls from phenols and hetero

aryl halides in the presence of very low loading of CuI and *N*,*N*'-bis(2-phenylphenyl)oxalamide (BPPO) as ligand and DMF or MeCN as a solvent at 90 ^{o}C for 24 hours.



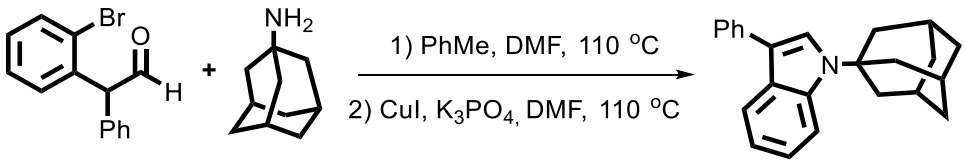
Scheme 72

- **Masahiro Sai *et.al.*, (2008)** accomplished the copper catalyzed reactions of alkyl halides with organometallic reagent. The reaction of cyclopentadienyl Grignard reagent proved to react with tertiary alkyl halides under copper catalysis gave the coupling products. The treatment of 2-methyl-2-bromodecane with cyclopentadienyl magnesium bromide in the presence of catalytic amount of copper (II) triflate in diisopropyl ether yielded the mixture of coupling products in high yield.



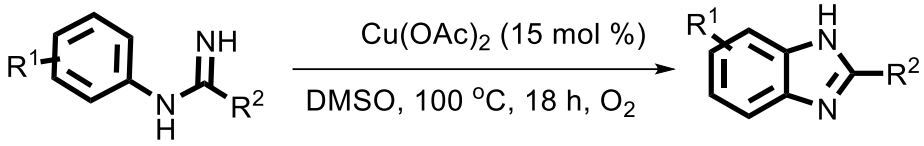
Scheme 73

- *N*-Substituted indoles were synthesized from primary amines through copper iodide as catalyst under refiux, DMF was used as a solvent at 110 ^{o}C yields of the reaction was found to be high. (**Ronald Besandre *et.al.*,2013**)



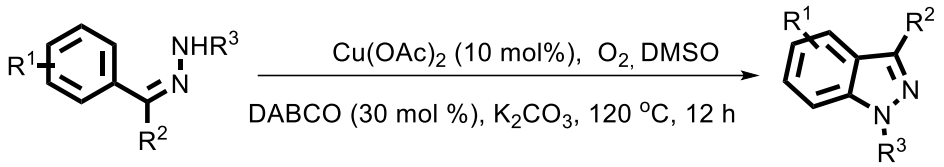
Scheme 74

❖ **Brasche *et.al.*,(2008)** reported the synthesis of efficient heterocycles via copper-catalyzed C-H functionalisation reaction towards the nitrogen containing species. The intramolecular reaction of amidines afforded to yield benzimidazoles in high yields in the presence of copper catalyst and using molecular oxygen as oxidant.



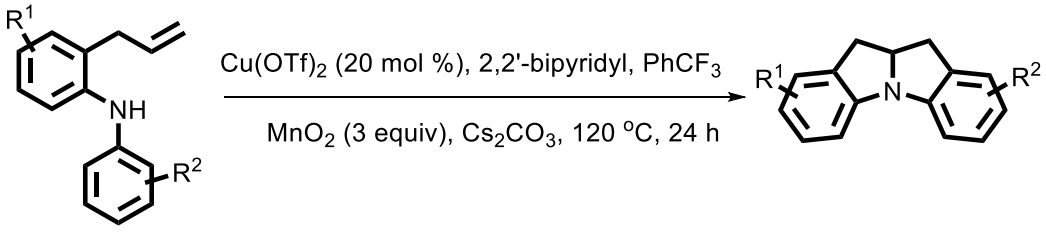
Scheme 75

❖ **Jiang *et.al.*,(2017)** developed the synthesis of five membered *N*-heterocycles of indazoles in the presence copper catalyzed aryl C-H functionalisation of $Cu(OAc)_2$ at 10 mol % and DMSO as a solvent at 120 ^oC with high yields.



Scheme 76

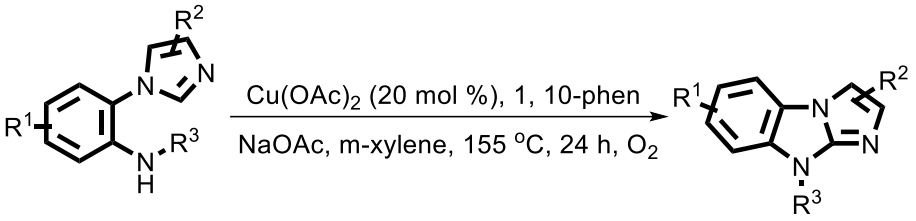
❖ N-Heterocycles *viz* 11-dihrdro-10H-indolo [1,2-a] indoles was prepared by copper-catalyzed intramolecular carboamiantion of alkene using 3 equiv of MnO_2 as the oxidant. (**Sherman and Chemler *et.al.*, (2009).**



Scheme 77

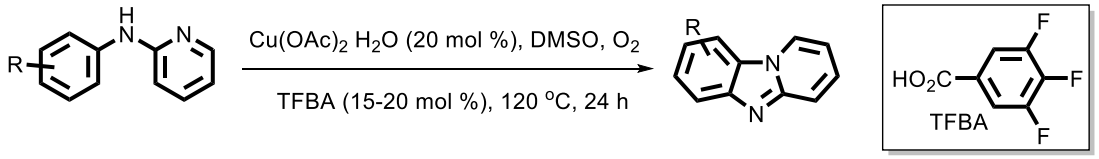
❖ **Hirano *et.al.*,(2014)** explained an efficient picolinmide-directed, copper-catalyzed synthesis of carbozoles via aryl C-H functionalization. In this reaction of a copper catalyzed via intramolecular C-H amination of 2-aminobiphenyls is the introduction of

picolinamide-based directing group removing the coupling constant.



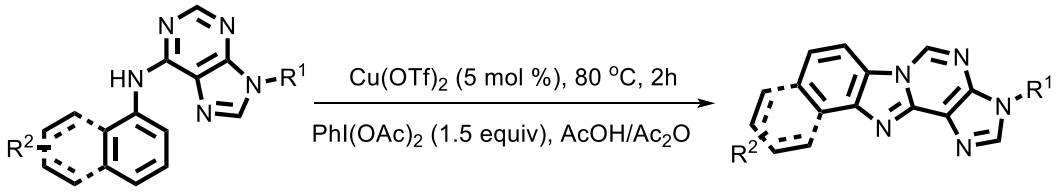
Scheme 78

❖ Synthesis of N-heterocycles of pyrido [1,2-a]benzimidazoles via copper-catalyzed aryl C-H functionalisation with an hetero-aromatic compounds TFBA and DMSO used as a solvent at 120 °C for 24 h was reported by **Maes *et.al.*,(2011).**



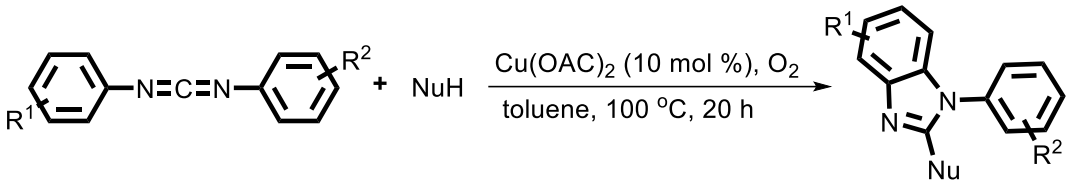
Scheme 79

❖ Synthesis of purine-fused polycycles in the presence $Cu(OTf)_2$ at 80 °C for 2 h in high yields was reported by **Guo *et.al.*,2012.** The reaction proceeded *via* intramolecular aryl C-H activation of anilinopurine nucleosides using $PhI(OAc)_2$ as an oxidant.



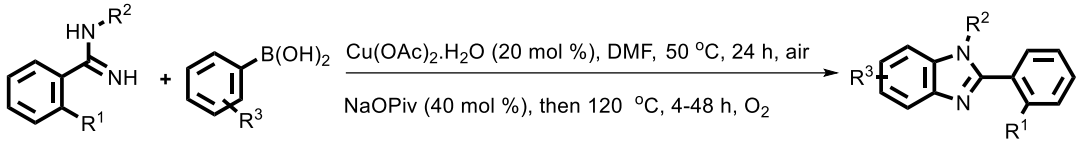
Scheme 80

❖ **Bao *et.al.*, (2010)** developed the synthesis of five-membered *N*-heterocycles by benzimidazoles copper-catalyzed aryl C-H functionalization in moderate to good yields. The copper-catalyzed addition of nucleophiles to arylcarbodiimides used molecular oxygen as an oxidant.



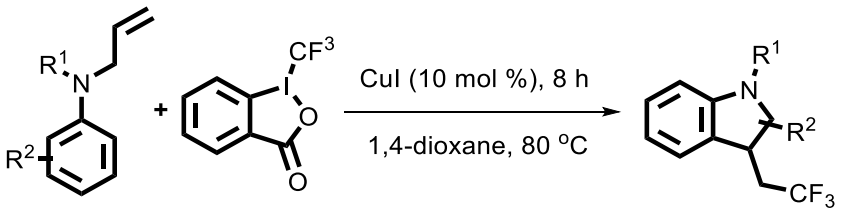
Scheme 81

- **Neuvile, Zhu *et,al.*,(2012)** reported the one pot synthesis of substituted benzimidazoles catalyzed by copper between the reaction of benzimidines with aryl boronic acids in good yields. This reaction proceeds via an intermolecular C-N bond formation and an intramolecular aryl C-H functionalization.



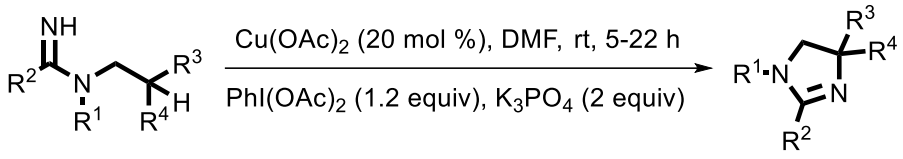
Scheme 82

- Copper-catalyzed carbotrifluoromethylation of *N*-protected allylanilines with Togni'S reagent resulted in the prepation of trifiuromethylated indoline derivatives with high yields. (**Sodeoka *et.al.*,2013**)



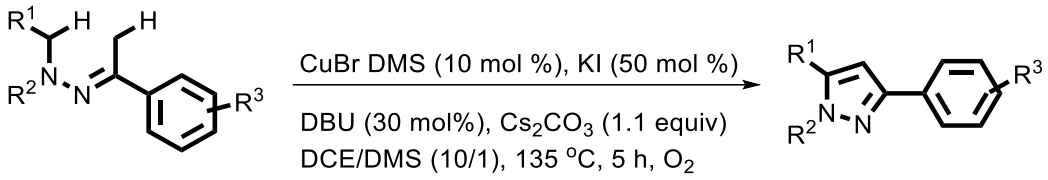
Scheme 83

- The reaction of amidine-directed copper-catalyzed C-H functionalization for the synthesis of five-membered *N*-heterocycles dihydroimidazoles were explained from intermolecular amination of C-H bonds of *N*-alkylamidines using $Cu(OAc)_2$ and $PhI(OAc)_2$ as an oxidant. (**Navado *et.al,*.2013**)



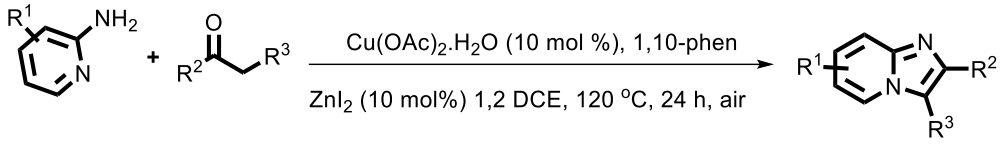
Scheme 84

❖ **Ge *et.al.*,(2013)** reported an efficient copper catalyzed intramolecular dehydrogenative cyclization reaction for the formation of *N*-heterocycles of pyrazoles were prepared in the presence of copper bromide and the intramolecuar reaction of *N,N*-disubstituted hydrazones. In this reaction the addition of dimethyl sulfide (DMS) was used as cosolvent to improved the reaction efficiency.



Scheme 85

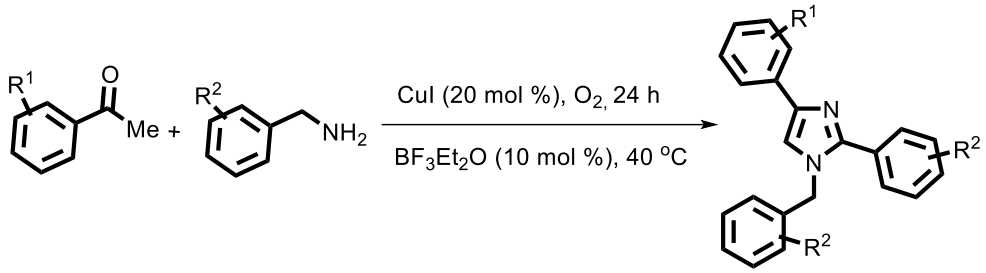
❖ A novel method for the for the synthesis of imidazo[1,2-a]pyridines from commercially available compounds was reported by **(Hajra *et.al.*,2013).** The reaction of 2-aminopyridines and ketones gave imidazo[1,2-a]pyridines in high yields. The reaction was carried out in the presence of copper as catalyst. Also, a new catalytic system of CuI/air was developed to synthesize imidazo[*1,2-a*]pyridines from the same starting materials. The reaction of 2-aminopyridines and ketones in the presence of $CuCl_2$/nano-TiO_2 catalytic system was carried out



Scheme 86

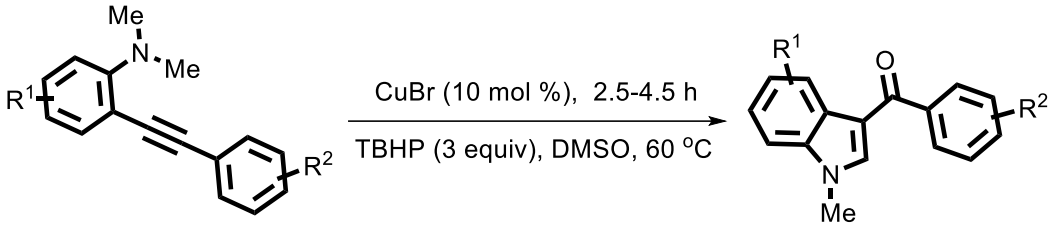
❖ **Cai *et.al.*, (2012)** developed the reaction of ketones and benzylamines with CuI as catalyst for the oxidative dehydrogenation to yield substituted imidazoles in moderate

yields.



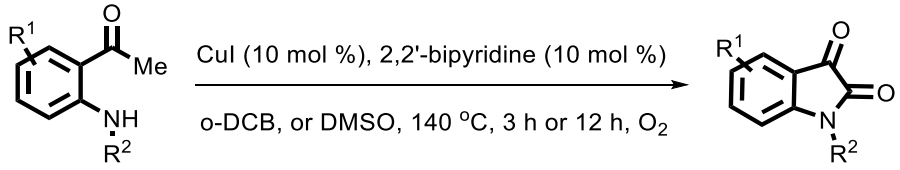
Scheme 87

- Reaction of copper catalyzed intramolecular oxidative functionalization of o-alkynylated N,N-dimethylamines using TBHP as an oxidant by C-C and C-O bond formation for the preparation of 3-arylindoles in moderate yield was reported by **Patel *et.al.*,(2013)**



Scheme 88

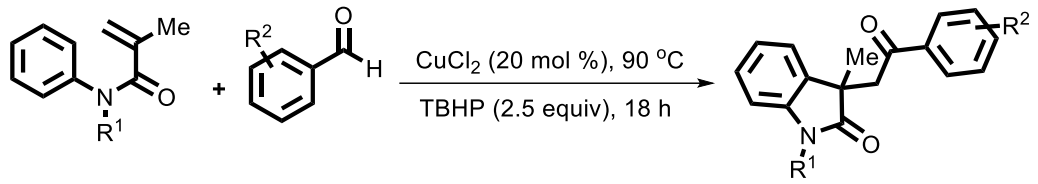
- **Cheng *et.al.*, (2013)** reported the reaction of intramolecular oxidative C-H amination of 2'-amino-acetophenone in the presence of CuI as the catalyst and molecular oxygen as the oxidant. The reaction provided isatins in good yield.



Scheme 89

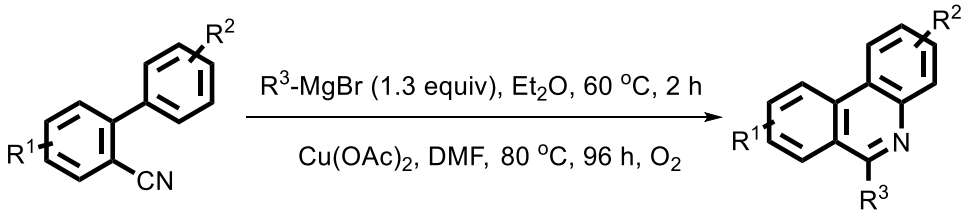
- The coupling reaction of *N*-arylacrylamides and aldehydes proceeded through aryl C-H and formyl C-H functionalization in the presence of $CuCl_2$ as a catalyst and TBHP as an oxidant to synthesize oxindoles was reported by **Zhou *et.al.*, (2012).** The first step was

the generation of an acyl reaction from the reaction of TBHP and aldehydes in the presence of copper species. This reaction proceeded by the addition followed by cyclization to yield the desired products.



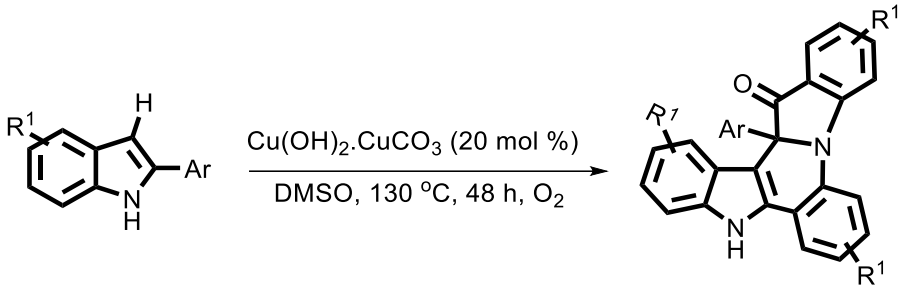
Scheme 90

- **Chiba *et.al.*, (2010)** explained six-membered *N*-heterocyclic species, particularly phenanthridine derivatives were great importance because of their potent biological activities and optoelectronic properties. The synthesis of phenanthiridine derivaties from C-H functionalization were carried out by the reaction of biaryl-2-carbonitriles and Grignard reagents via copper catalyzed C-N bond formation under an O_2 atmosphere. This reaction proceeded via N-H imine formation by the nucleophilic addition of Grignard reagent to biaryl-2-carbonitrile followed by copper catalyzed intramolecular aryl C-H functionalization.



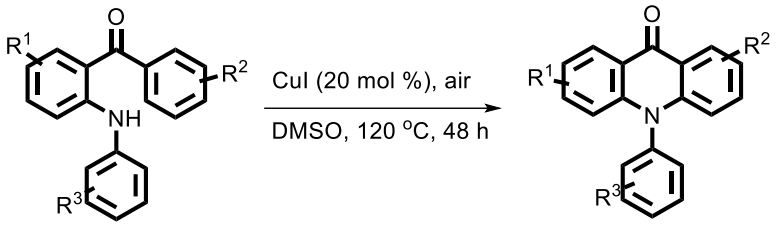
Scheme 91

- The formation of six membered ring fused heterocycles via Cu-catalyzed C-H functionalization of oxidative dimerization of 2-arylindolines with molecular oxygen as an oxidant afforded six-ring-fused heterocycles containing indole and quinoline skeletons. In this reaction molecular oxygen was added not only for oxidant but also for reactant. This method was novel route for the preparation of *N*-heterocycles. **(Zou *et.al.*,2012)**



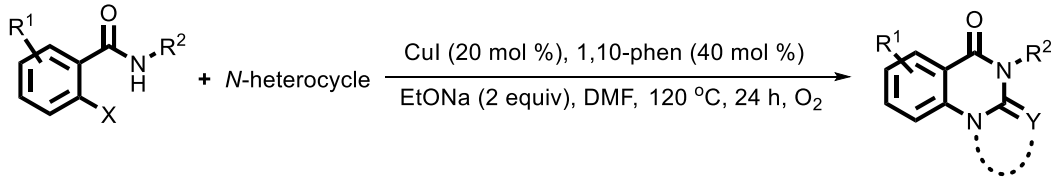
Scheme 92

❖ **Zhou *et.al.*, (2012)** reported copper catalyzed intramolecular aryl C-H functionalization for the synthesis of *N*-aryl acridones. The reaction proceeded *via* intramolecualr amination in the presence of 20 mol % of CuI and air as an oxidant under neutral conditions.



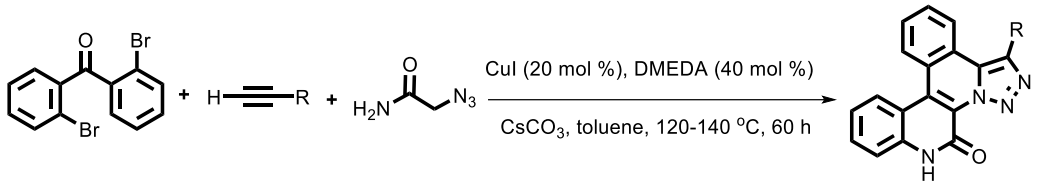
Scheme 93

❖ The reaction of one-pot synthesis of 2-halobenzaides and *N*-heterocycles in presence of molecular oxygen as an oxidant in the preparation of azoquinazolinones was reported by **Chen *et.al.*,(2013).**



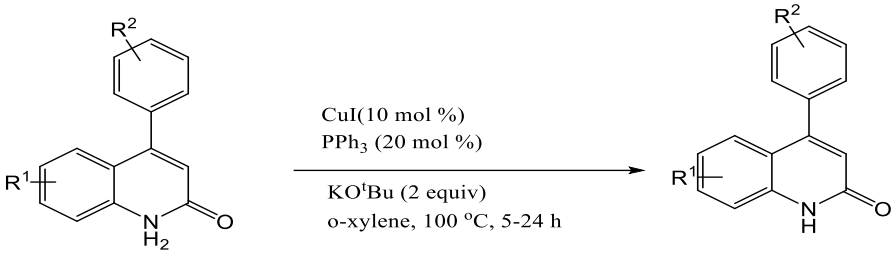
Scheme 94

❖ **Qian *et.al.*,(2013)** reported the synthesis of *N*-polyheterocycles *via* the reaction of bis(2-bromophenyl)methanone, terminal alkynes and 2-azidoacetamides in the presence of CuI as catalyst.



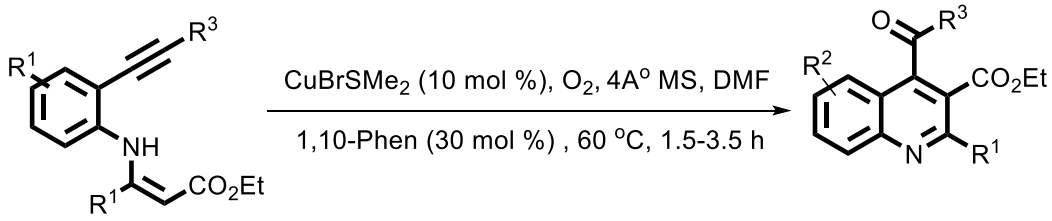
Scheme 95

❖ An simple method for the synthesis of 4-aryl-2-quinolines was reported by **Cacchi *et.al.*,(2012).** The reaction proceeded in the presence of copper catalyzed intramolecular cyclization of 3,3'-diarylacrylamides used air as an oxidant and KO^{t}Bu as the base.



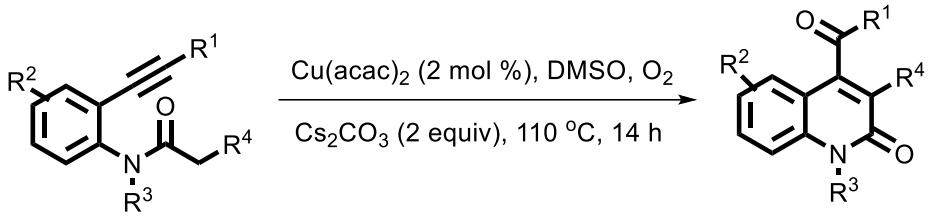
Scheme 96

❖ An efficient method for the synthesis of six-membered *N*-heterocycles using copper catalyzed oxidative functionalization of alkynes. The desired products was obtained by intramolecular reaction of *N*-(2-alkynylaryl)enamine carboxylates using copper catalyst and molecular oxygen as an oxidant.**(Chiba *et.al.*,2012)**



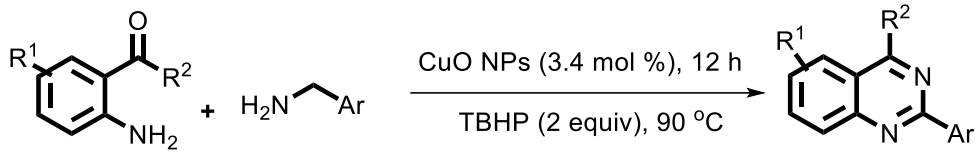
Scheme 97

❖ **Li *et.al.*,(2013)** reported the intramolecular copper catalyzed C-H functionalization for the synthesis of quinilinones, which proceeded by the oxidative cyclization of *N*-(2-ethynylaryl)acetamides and molecular oxygen as an oxidant.the products were obtained in high yields.



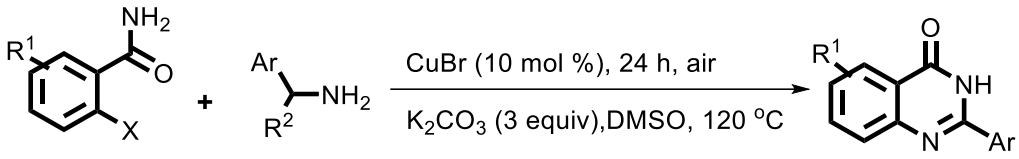
Scheme 98

❖ **Wang *et.al.*,(2013)** reported the synthesis of quinazolines by the reaction of 2-aminobenzophenones and benzylamines in the presence of copper catalyst and TBHP as the oxidant in high yields.



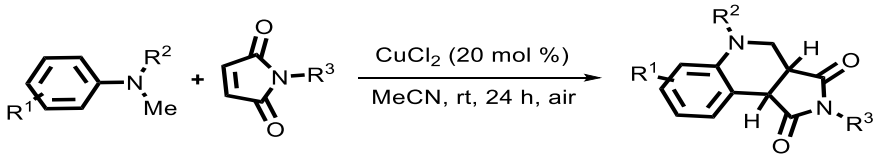
Scheme 99

❖ The reaction of substituted 2-halobazamides and benzylamines using CuBr as the catalyst and air as an oxidant yielded quinazolinones was reported by **Yu *et.al.*,(2010)**



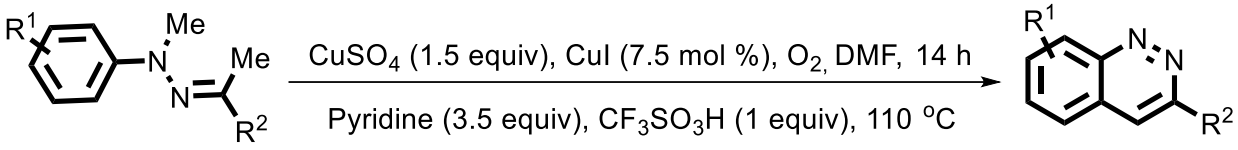
Scheme 100

❖ **Hirano *et.al.*,(2011)** reported the synthesis of tetrahydroquinolines by the copper catalyzed oxidative direct cyclization of *N*-methylanilines with electron deficient alkenes in the presence of $CuCl_2$/air system. The *N*-methylanilines reacted with maleimides to form tetrahydroquinolines.



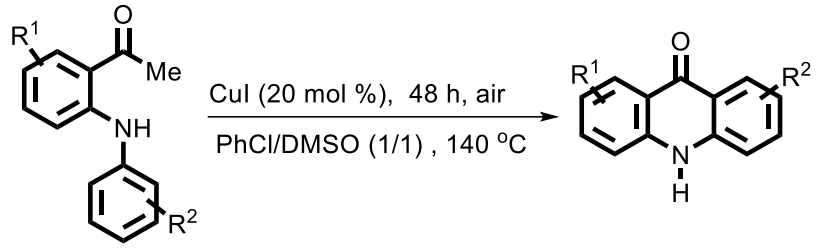
Scheme 101

❖ Synthesis of cinnolines were synthesized from copper catalyzed intramolecular aerobic dehydrogenative cyclization of *N*-methyl-*N*-phenylhydrazoness with molecular oxygen used as oxidant to form the product was reported by **Ge *et.al.*, 2012.**



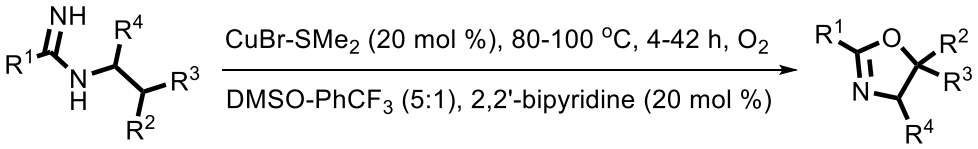
Scheme 102

❖ Synthesis of acridones using copper catalyzed C-C bond cleavage and intramolecular cyclization of 11-[2-(arylamino)aryl]ethanones occurred to give yield was reported by **Zhou and Fu *e.al.*,(2013)**



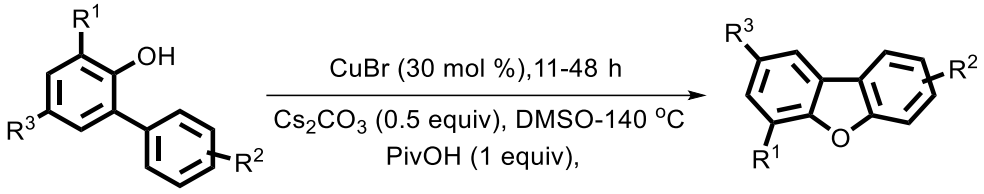
Scheme 103

❖ A reaction for the synthesis of dihydrooxazoles via copper catalyzed C-H functionalization and C-H oxygenation of *N*-alkylamidines under oxygen atmosphere give dihydrooxazoles. **(Chiba *et.al.*,2012)**



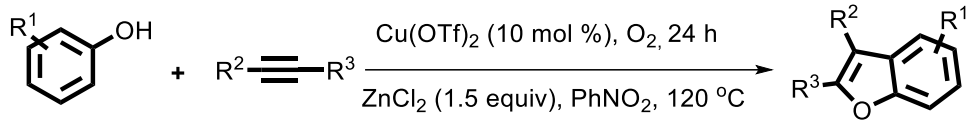
Scheme 104

❖ **Zhu *et.al.*,(2012)** reported the reaction of intra-molecular oxidative C-H cyclo-etherification of *O*-arylphenols with 30 mol % CuBr as a catalyst and air as an oxidant in the preparation of dibenzofurans as the product.



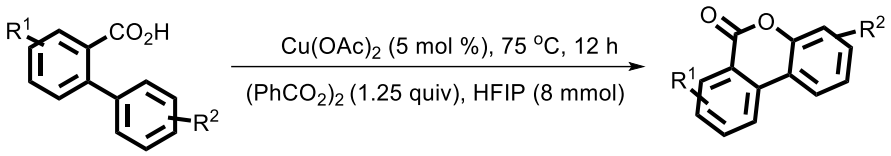
Scheme 105

- The reaction of phenols and alkynes in the presence of $Cu(OTf)_2$ and molecular oxygen as an oxidant in the intermolecular nucleophilic addition and intramolecular copper catalyzed aryl C-H functionalization was reported by **Jiang *et.al.*,(2013)** to give the product of benzofurans.



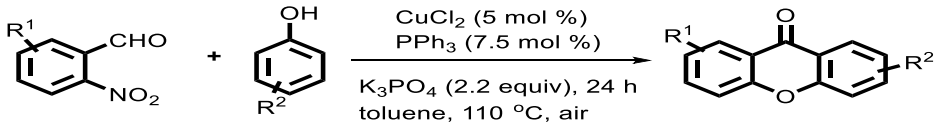
Scheme 106

- **Gallardo-Donarie and Martin (2013)** reported an efficient method to synthesize benzolactones by intramolecular C-H hydroxylation of 2-arylbenzoic acids and $Cu(OAc)_2$ as the catalyst, $(PhCO_2)_2$ as oxidant to give the yield.



Scheme 107

- One step method for the preparation of xanthones from phenols and aryl aldehydes using $CuCl_2$ as a catalyst and air as an oxidant to give the product of xanthones. (**Wang *et.al.*,2012**)



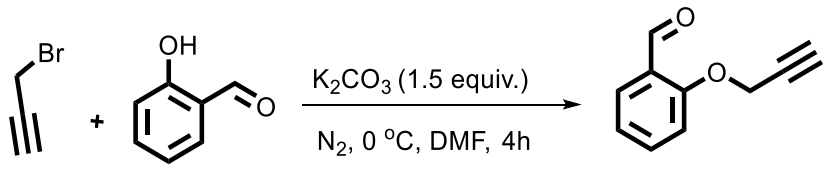
Scheme 108

3. MATERIALS AND METHODS

3.1 GENERAL

- The Fourier transform infrared (FTIR) spectra were recorded by ART technique in a SHIMADZU spectrophotometer. Absorption frequencies were quoted in reciprocal centimeter
- Nuclear Magnetic Resonance (^{1}H-NMR, ^{13}C NMR, DEPT-135 NMR) spectra were determined by Bruker modern 400MHz FT NMR instrument in d-$CDCl_3$ as solvent with tetra methyl silane as the internal reference. Chemical shift were quoted in parts per million (ppm)
- High Resolution Mass Spectroscopy was determined by Thermo Exactive Orbitrap
- Thin Layer Chromatography (TLC) was performed using glass plates coated with silica gel G to monitor and check the completion of each reaction
- Petroleum ether (60-80^{0}C); ethyl acetate; were used as the developing solvents. Spots were detected with iodine
- The solvents and reagents used for the synthesis were of reagent grade and were purified by standard methods.
- Column Chromatography was prepared by silica gel (60-120 mesh). The solvents used for column chromatography was petroleum ether (0%, 5%, 10%, 15%) and ethylacetate and dichlorometane (DCM)

Synthesis of 2-(prop-2-ynyloxy) benzaldehydes

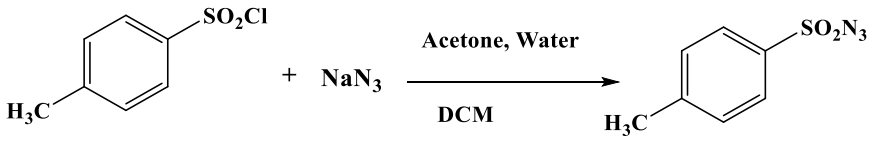


Scheme 109. Synthesis of 2-(prop-2-ynyloxy) benzaldehydes

10 mmol of 2-hydroxybenzaldehyde was dissolved in DMF taken in 250 ml round bottom flask. Then 1.5 equiv 3-bromoprop-1-yne and 1.5 equiv potassium carbonate were added to the above mixture. The reaction mixture was flushed with nitrogen and stirred magnetically for 4 h at room temperature. After the reaction was over, the reaction mixture was poured into ice cold water and was evaporated under reduced pressure and the residue was adsorbed onto small amounts of silica to afford the desired product. The purification was performed by column chromatography on silica gel (eluent: EtOAc/petroleum ether = 1:10), affording product in 97% yield.

Preparation of p-toluene sulfonyl azide (Tosyl azide)

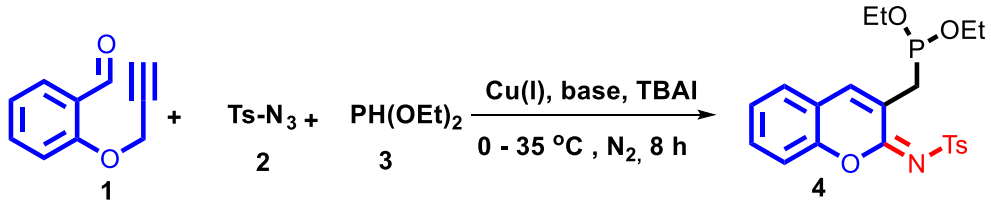
9.5 g of tosyl chloride and 25 ml of acetone was taken in a 250 ml round bottom flask and stirred magnetically using magnetic stirrer. Then 3.5 g of sodium azide and 10 ml of water was taken in a beaker and mixed thoroughly. This solution was added to the magnetically stirred solution of tosyl chloride and acetone and stirring was continued for 2-3 hours. After the completion of the reaction acetone was removed using rotary evaporator. To the solution 10-15 ml of DCM was added and transferred to a separatory flask (250 ml). The organic layer was collected and dried over sodium sulphate because of the absorbing water impurities. DCM from this concentrated solution was evaporated using rotary evaporator and the solution was refrigerated for 24 hours, to afford a desired tosyl azide, in pure form.



Scheme 110. Preparation of p-toluene sulfonyl azide

Synthesis of 2-Iminocoumarin Derivatives

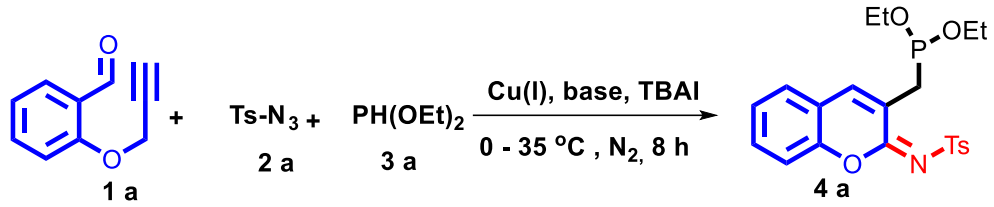
To a double-neck round bottom flask fitted with nitrogen adapter for purging nitrogen gas and septum. 1 g of 2-(prop-2-ynyloxy) benzaldehyde, 166mg of dimethylaminopyride (DMAP) and 250 mg of copper iodide was flushed under reduced pressure and stirred magnetically at 0 ^{o}C. Nitrogen gas was passed through the reaction mixture using ballon technique. After 10 minutes, 5 ml of acetonitrile, 2.7 ml of diethylphosphite and 1.7 ml of tosyl azide was added using syringe through septum. The reaction was stirred for 24 hours. After the completion of the reaction, the mixture was washed through celite pad using DCM as solvent. The solvent was removed using rotary evaporator. After the removal of solvent DCM and water mixture in the ratio (4:3) was added and organic layer was separated using separatory flask (250 ml). The collected organic layer was dried over sodium sulpahte. The crude product was purified using coloumn chromatography. (eluent: EtOAc/petroleum ether = 4:3), affording the product in 83% yield.



Scheme 111. Synthesis of 2-iminocoumarin

4. RESULTS AND DISCUSSION

4.1 The synthesis of 2-iminocoumarin derivative was accomplished in one pot using 2(prop-2-yn-1-yloxy)benzaldehyde **1a**, tosyl azide **2a**, and diethyl phosphonite **3a** as the model substrates in presence of copper iodide via cascade reaction **(Scheme 112)**



Scheme 112

The reaction was carried out under nitrogen atmosphere at 0^0 -35^0C with constant stirring for 24hours.The crude product obtained after workup was purified by column chromatography. The coupling of 2-(prop-2-yn-1-yloxy)benzaldehyde **1a**, tosyl azide **2a** and diethyl phosphonite **3a** readily took place to afford diethyl ((2-(tosylimino)-2H-chromen-3-yl)methyl)phosphonite **4a** as the sole product with the yield of 83%.

Optimization of the reaction was carried out by employing 2-(prop-2-yn-1-yloxy)benzaldehyde **1a**, tosyl azide **2a**, and diethyl phosphonite **3a** using a series of copper salts in the presence of different bases **(Table 1)**. First, our investigation started with 2-(prop-2-yn-1-yloxy)benzaldehyde **1a**, *p*-toluenesulfonyl azide (TsN_3) **2a** and diethyl phosphonite **3a** as the model substrates for the scrutinization of the reaction conditions, which was carried out using different Cu(I) sources, bases, additives, and solvents at room temperature under air **(Table 1).** Gratifyingly, the reaction proceeded to afford the iminocoumarin phosporyl methyl ether **4a** in 30% yield, when the substrates **1a, 2a**, and **3a** were reacted with 10 mol % CuI and 2.2 equiv of K_2CO_3 in CH_3CN under ambient conditions **(entry 2)**. However, increasing the reaction temperature to reflux for 24 h led to the coupling of all the substrates to afford coumarin **4a** in 30% respectively. Subsequent screening of the base led to an increase in the formation of **4a** to 50% using K_2CO_3, while Cs_2CO_3 exhibited inferior results **(entries 3-4)**.

TABLE 1. Optimization of the reaction condition

Entry	Catalyst	Base	Additive	Solvent	yield (%)[b]
1	CuI	Et_3N	-	CH_3CN	n.d.
2	CuI	K_2CO_3	-	CH_3CN	30
3	CuI	K_2CO_3	TBAB	CH_3CN	76
4	CuI	K_2CO_3	TBAC	CH_3CN	71
5	CuI	K_2CO_3	TBAI	CH_3CN	83
6	CuI	K_2CO_3	TBAI	CH_2Cl_2	42
7	CuI	K_2CO_3	TBAI	$(CH_2Cl)_2$	74
8	CuI	K_2CO_3	TBAI	THF	28
9	CuI	K_2CO_3	TBAI	Toluene	60
10	CuI	Na_2CO_3	TBAI	CH_3CN	35
11	CuI	Cs_2CO_3	TBAI	CH_3CN	n.d.
12	CuI	K_3PO_4	TBAI	CH_3CN	n.d.
13	CuBr	K_2CO_3	TBAI	CH_3CN	67
14	CuCl	K_2CO_3	TBAI	CH_3CN	71
15	Cu_2O	K_2CO_3	TBAI	CH_3CN	41
16	-	K_2CO_3	TBAI	CH_3CN	n.d.

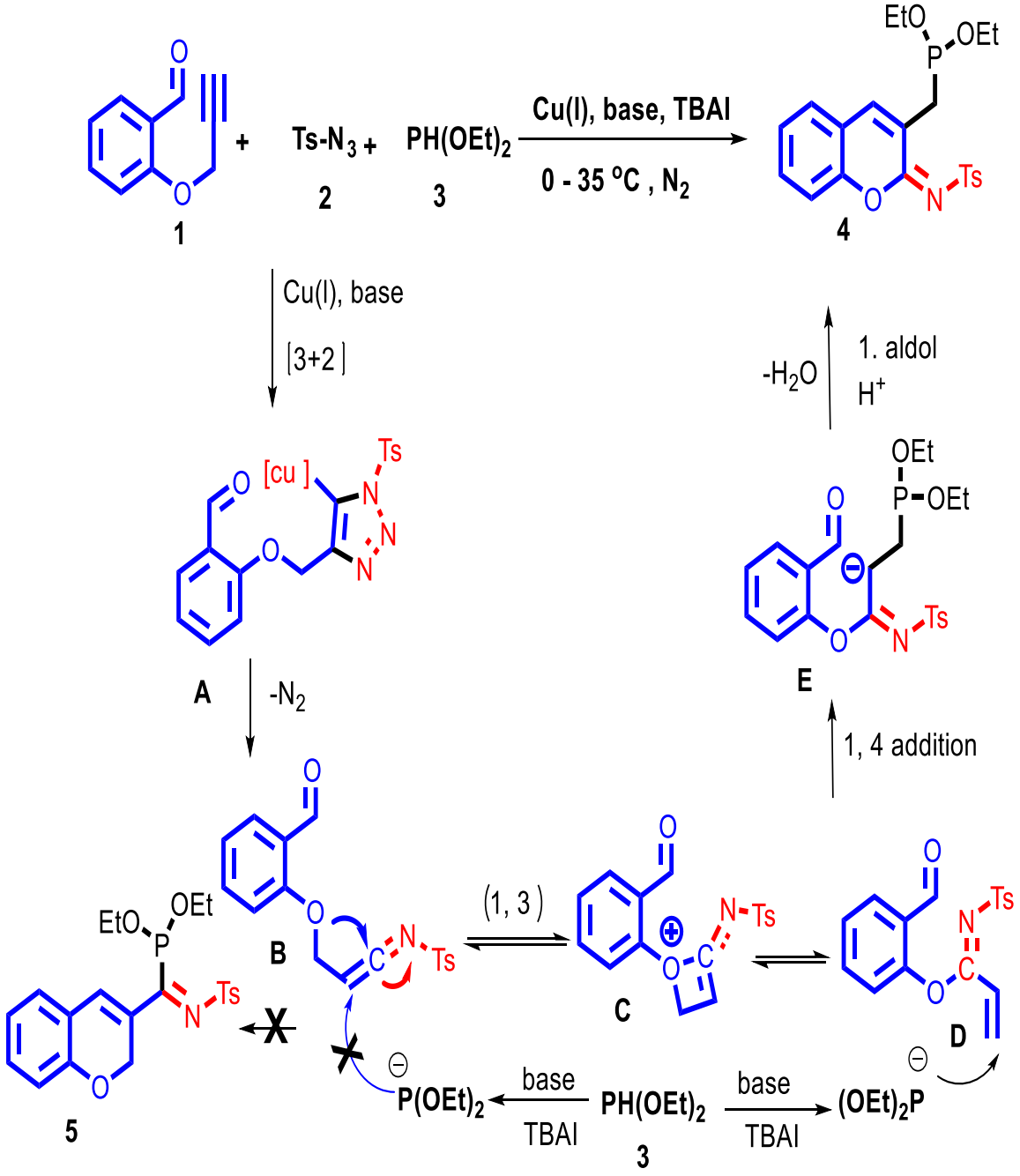
[a] Ynal **1a** (0.5 mmol), azide **2a** (0.6 mmol), diethyl phosphonite **3a** (0.6 mmol), catalyst (10 mol %), base (1.1 mmol), additive (10 mol %), solvent (3.0mL), 8 h, air. [b] Determined by 400MHz ^{1}HNMR. n.d.= notdetected.

Surprisingly, the use of tetrabutylammonium iodide (TBAI) as an additive led to an increase in the yield to 83%, whereas tetrabutylammonium bromide (TBAB) and tetrabutylammonium chloride (TBAC) afforded a 76% and 71% yield, respectively. In a set of bases screened, K_2CO_3 furnished the best results, while Na_2CO_3 resulted in a moderate yield. In contrast, Cs_2CO_3, K_3PO_4 and Et_3N showed no effect for the target reaction. CuI provided a superior yield compared to the other copper (I) salts such as CuBr, CuCl, and Cu_2O that were tested. Consequently, CH_3CN was found to be the solvent of choice. Other solvents such as toluene, THF, CH_2Cl_2 and 1,2-dichloroethane has no appreciable effect on **4a**, as it resulted in a sluggish conversion. A control experiment confirmed that, without the Cu source, the target reaction was not observed. In contrast, the organic bases such as DBU, Et_3N and 2,6-lutidine failed to produce the target heterocycle 4**a**. In a set of copper sources screened, CuI, CuCl, CuBr and $Cu(acac)_2$, the former gave the best results (entries 8-10). While the reactions using dioxane, DMSO, toluene and DMF gave inferior results (**entries 11-13)**.

Likewise, lowering the catalyst loading (5 mol%) or the reflux reaction temperature or increasing the quantity of the base (2 equiv) led to drop in yield to <70%. A control experiment confirmed that without the copper source the coupling reaction was not observed.

4.2 Proposed Catalytic Cycle and plausible mechanism (Murugavel *et.al., 2016*)

The Cu(I)-catalyzed azide-alkyne cyclo-addition (CuAAC) of alkyne **1** with azide **2** may generate ketenimine **B** via intermediate **A**, which may undergo the pseudo pericyclic [1,3]-migration of 2-formylaryloate through the four membered cyclic zwitterionic transition state **C** to give the intermediate **D**. The 1,4-conjugate addition of the diethyl phosphite anion ion with **D** may lead to the formation of the intermediate **E**. The aldol-type condensation dehydration of **E** could yield the target product **4**. The absence of the formation of **5** suggests that this protocol involves the rearrangement of the ketenimine **B** to afford **D** compared to the direct intermolecular reaction of the ketenimine **B** with the diethyl phosphite anion ion that could lead to **5**. Followed by having the optimized reaction conditions, the substrate scope was explored with a series of substituted salicylaldehydes **(Scheme 113)**.



Scheme 113. The proposed catalytic cycle

4.3 Spectral Charactesiation of the synthesized compound (4a)

4.3.1 FT-IR

The structure of final diethyl ((2-(tosylimino)-2H-chromen-3-yl)methyl)phosphonite derivative **4a** was arrived based on spectroscopic analysis. Presence of (2-(tosylimino)-2H-chromen-3-yl) was confirmed by a strong absorption at 1720 cm^{-1} in the IR spectrum. **(Figure 7)**. Out-of-phase P-O-C stretch 1088-920 cm^{-1} strong in IR, In-phase P-O-C stretch was observed at 845-725 cm^{-1}, rocking vibrations for P-O-Et occurred at 1190-1170 cm^{-1} and 1167-1155 cm^{-1} respectively. Asymmetric S=O stretch was seen at 1420-1300 cm^{-1}, which was very strong. Also a strong stretch at 1200-1000 cm^{-1} was seen confirming the presence of S=O group.

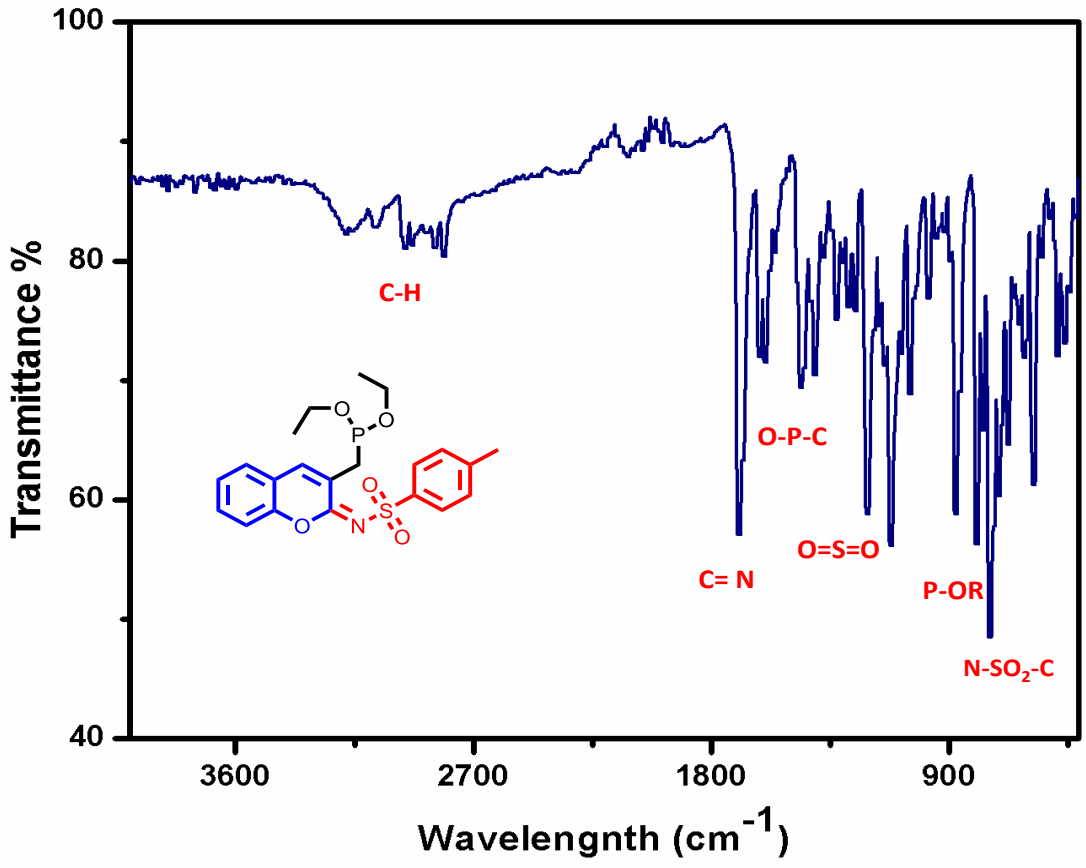


Figure.7 FT-IR spectrum of compound diethyl((2(tosylimino)2Hchromen3yl)methyl)phosphonite

4.3.2 ^{1}H NMR

In the ^{1}H NMR spectrum of ((2-(tosylimino)-2H-chromen-3-yl)methyl)phosphonite displayed six sets of protons labelled **a, b, c, d, aromatic and e** (**Figure 8).** Labelled (**a)**-6-methyl protons showed doublet of doublet at 1.48 ppm (coupling constant J = 7.1, 6.0 Hz). The tosyl-methyl (**d)** -3 protons showed singlet at 2.49, (**b)** 4-methylene protons near the oxygen atom appeared as multiplet at 5.08 - 4.83 ppm and (**c)**. The peak corresponding to methylene 2-protons were near of the phosphorus atom observed at 3.30 - 2.72 ppm as multiplet. The peak corresponding to eight aromatic protons in the region 7.26-6.70 ppm. Finally the (2H-chromene of 4-H) **e**-labelled methine proton is observed at 7.56 ppm as doublet of doublet. All the signals were found to be in the expected region, in consistent with the assigned structure.

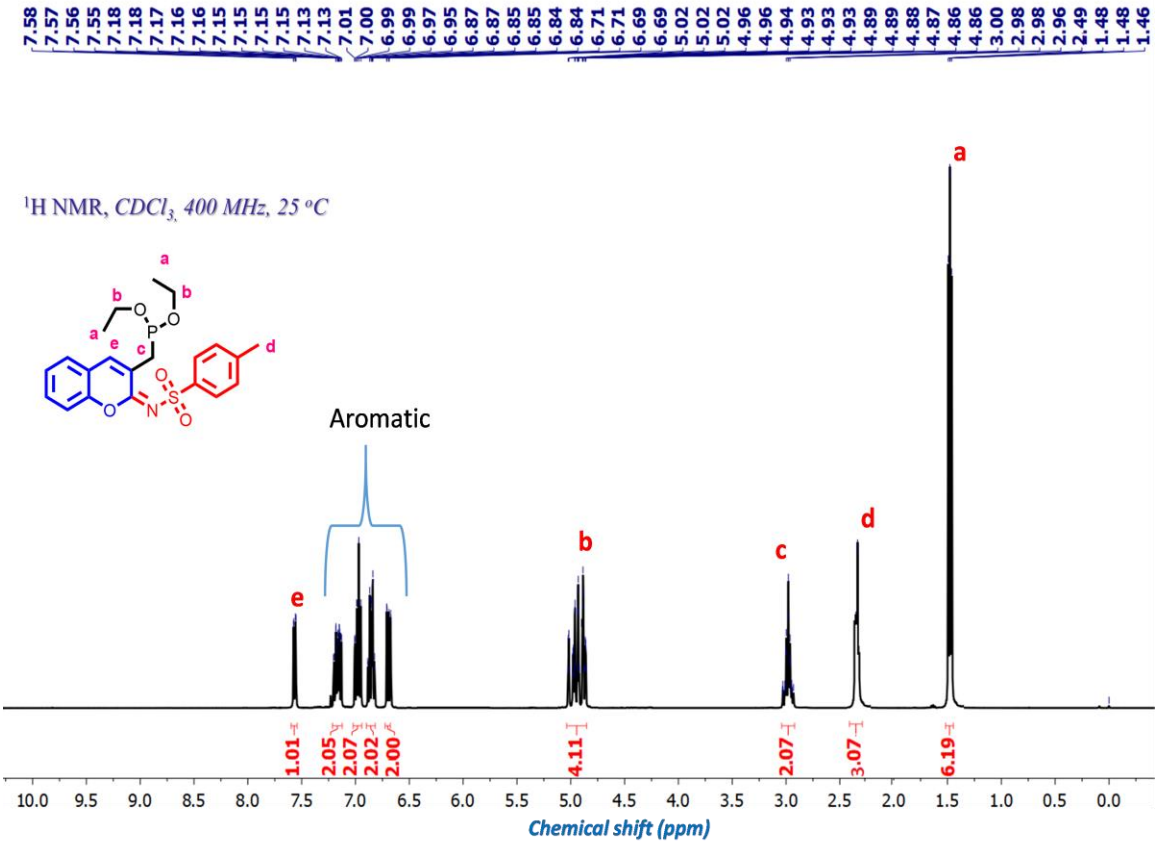


Figure.8 ^{1}H NMR spectrum of compound diethyl((2(tosylimino)2Hchromen3yl)methyl)phosphonite

4.3.3 ^{13}C NMR

The ^{13}C NMR spectroscopy of **(Figure 9)** positioned imine signals at δ 178.3 (C=N) ppm. Among the 2H-chromen-2-ylidene skeletal carbons, the substituted methine and aromatic carbons were observed at 156-110.3 ppm. The ring methylene carbon was visible at δ 48.8 and 44.4 ppm. The diethyl phosphonite methylene carbons appeared at δ 25.7, tosyl and diethyl phosphonite methyl carbons were observed at 22.7 and 19.7 ppm respectively and were confirmed by DEPT-135 spectral analysis **(Figure 10)**. Among the ring adjacent methylene carbons was visible at δ 48.8 and 44.4 ppm while the phosphonite methylene carbon was visible at δ 25.7 ppm of the negative signals observed. The rest of the positive signals observed were in agreement with the proposed structure.

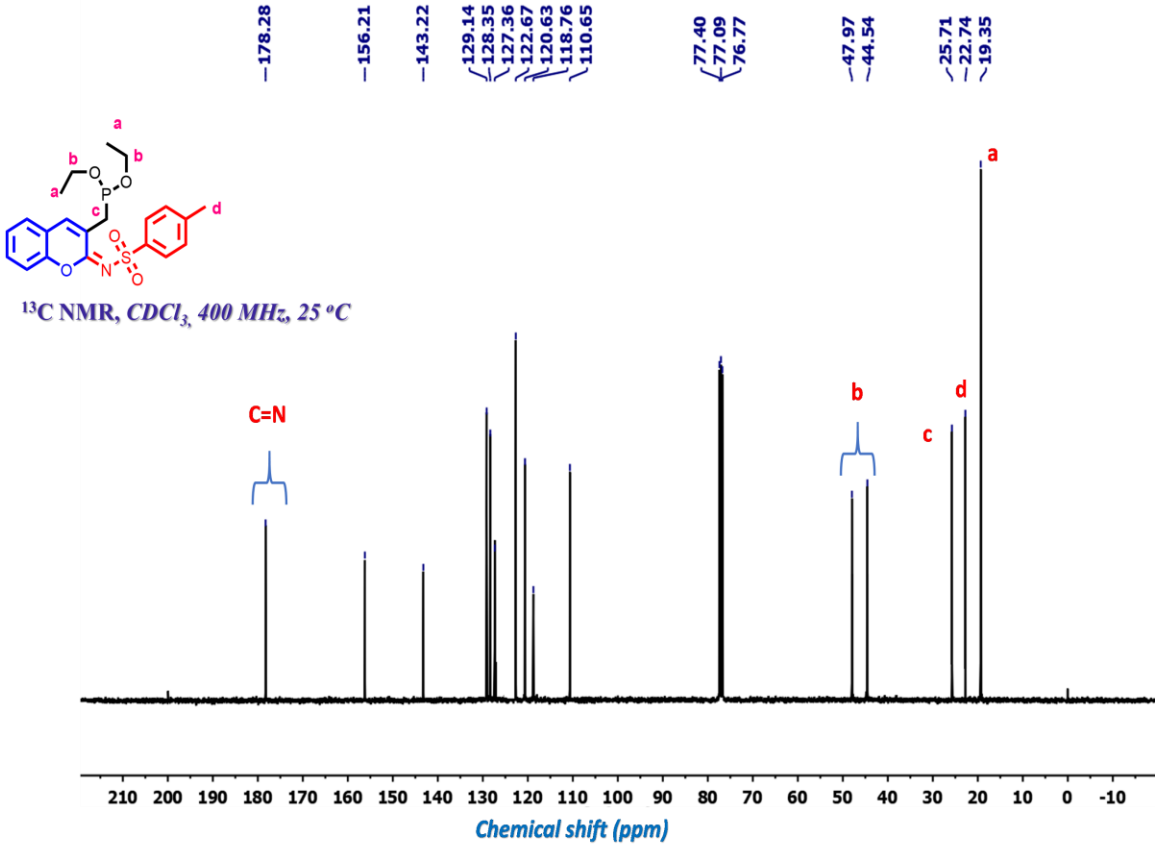


Figure.9 ^{13}C NMR spectrum of compound diethyl((2(tosylimino)2Hchromen3yl)methyl)phosphonite

DEPT-135

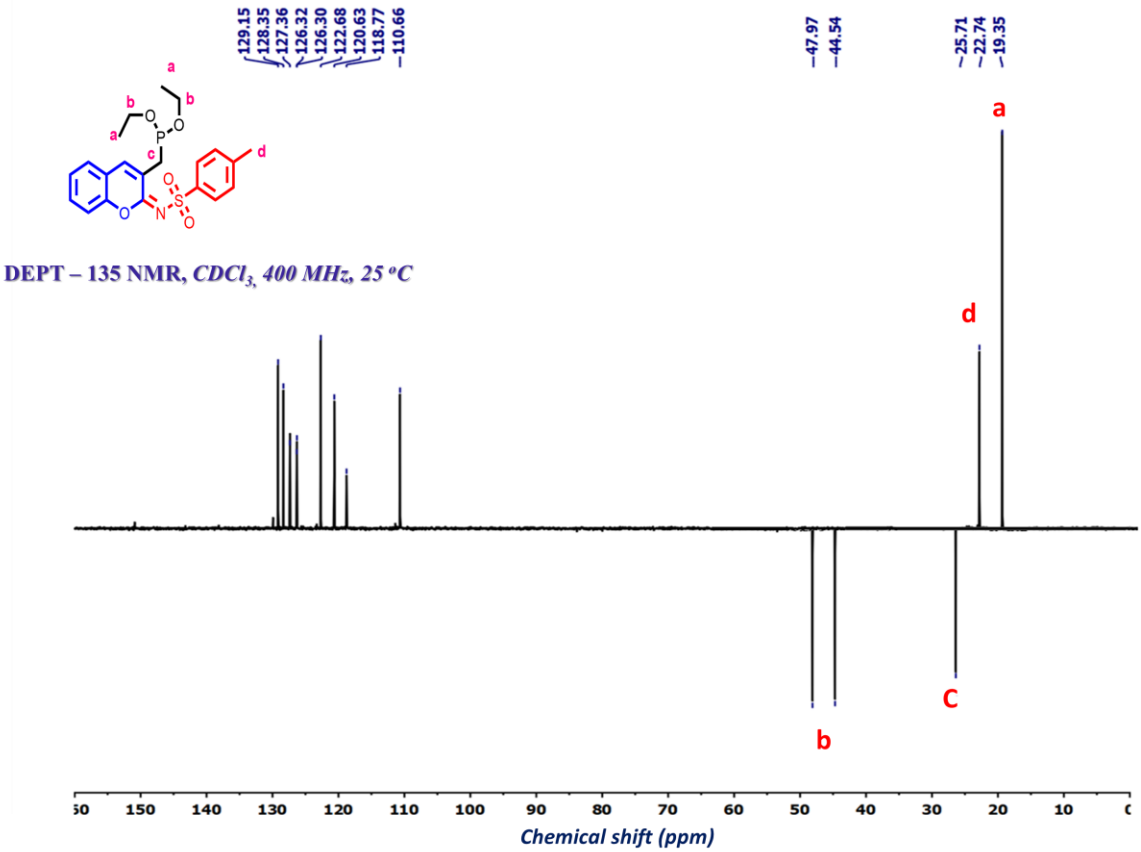


Figure.10 DEPT-135 NMR spectrum of compound diethyl((2(tosylimino)2Hchromen3yl)methyl)phosphonite

4.3.4 HRMS

Further evidence for the structure was obtained from high resolution mass spectrum which showed a molecular ion peak at *m/z* = 433.46**(Figure 11).** Hence the assigned structure of the diethyl ((2-(tosylimino)-2H-chromen-3-yl)methyl)phosphonite is confirmed.

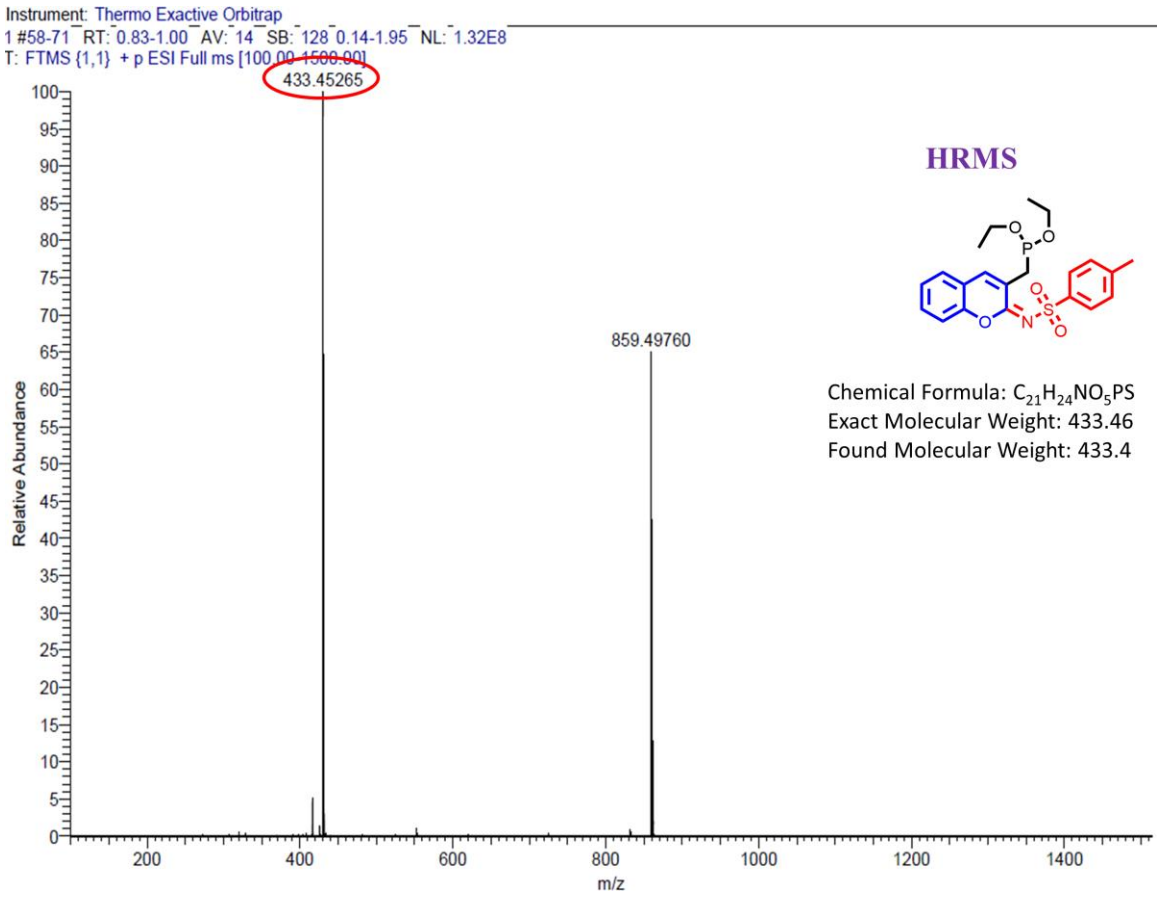


Figure.11 HRMS of compound

diethyl ((2-(tosylimino)-2H-chromen-3-yl)methyl)phosphonite

5. SUMMARY AND CONCLUSION

The results of the present study viz synthesis of 2-iminocoumarin is summarized below,

- The reaction employing 2-(prop-2-yn-1-yloxy)benzaldehyde, tosyl azide and diethyl phosphonite took place smoothly to afford diethyl ((2-(tosylimino)-2H-chromen-3-yl)methyl)phosphonite as the sole product with the yield of 87%.
- Optimization of reaction conditions with different combinations of solvents, additives, bases and catalyst was carried out.
- The best combination of solvent, additive, base and catalyst for the high yield of the compound was found to be acetonitrile, TBAI, K_2CO_3 and CuI respectively.
- The structure of the compound was confirmed by ^{1}H, ^{13}C, DEPT and HRMS.

In summary the work has demonstrated the applicability CuI as catalyst for one pot cascade reaction. The title compound 2-iminocoumarin derivative in was obtained in higher yield using the present strategy. The work will be a major breakthrough in the area of synthesis of 2-iminocoumarin derivatives with phosphorus substitution which may have potent biological activity. The same set of reaction conditions may also be applied for the further preparation of 2-iminocoumarin substituted at the 3rd position.

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