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Mini-Review

Copper Catalyzed Synthesis of Heterocyclic Molecules via C−N and C−O Bond Formation under Microwaves: A Mini-Review

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Cite This: *ACS Omega* 2023, 8, 23240−23256

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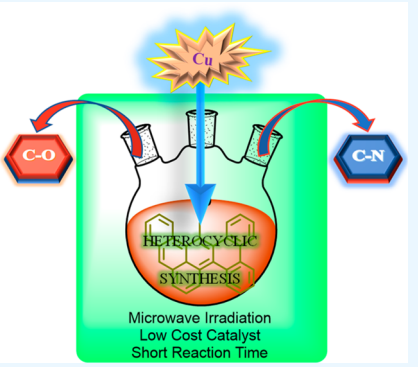
ABSTRACT: Heterocyclic moieties play a significant role in the field of drug discovery. C−N and C−O bond formation reactions are the primary synthetic sequence for the generation of heterocyclic molecules. The generation of C−N and C−O bonds involves the use of mostly Pd or Cu catalysts although other transition metal catalyst's are also involved. However, in C−N and C−O bond formation reactions, several problems were faced such as catalytic systems containing costly ligands, lack of substrate scope, lots of waste generation, and high temperature conditions. So it is imperative to uncover new eco-friendly synthetic strategies. In view of enormous drawbacks, it is important to develop an alternate microwave-assisted synthesis of heterocycles via C−N and C−O bond formation, which provides a short reaction time, tolerance for functional groups, and less waste production. Numerous chemical reactions have been accelerated using microwave irradiation which provides a cleaner reaction profile, lower energy consumption, and higher yields. This review article highlights a comprehensive overview on the potential application of microwave assisted synthetic routes for the synthesis of diverse heterocycles via mechanistic pathways covering the year ranges from 2014 to 2023, along with possible biological interests.



1. INTRODUCTION

C−N and C−O bonds are the most omnipresent and important bonds found in organic materials, natural products, drugs, and agricultural chemicals.[1a] Almost 80% of marketed drugs contain either C−N or C−O bond. Nitrogen and oxygen containing heterocycles stand out among the many types of heterocyclic compounds due to their diverse nature. Further these heterocycles are particularly important in the pharmaceutical industry due to their excellent solubility and salt forming capacity. To synthesize nitrogen and oxygen containing heterocycles, one important step is the formation of C−N or C−O bonds, for which many synthetic strategies have been developed using transition metal catalysts.[1b,c] For the first time the Ullmann group,[2a] and the Goldberg group[2b] discovered the Cu-catalyzed C−N and C−O bond forming reactions. Later on, Buchwald[2c] and Hartwig groups[2d] demonstrated the Pd catalyzed C−N bond formation reaction. Of late the Chan and Lam group achieved a major breakthrough on the Cu-catalyzed C−N bond formation reactions.[2e,f] It has been noticed that other than palladium or copper, several other transition metals such as nickel, zinc, iron, cobalt, and manganese are also used for C−N and C−O bond forming reactions.[3] However, all those methods suffer various drawbacks such as the high reaction temperature, use of costly ligands, lack of substrate scope, and lots of waste generation, etc. Consequently, the development of environmentally friendly, simple, and straightforward C−N or C−O bond forming procedures is advantageous for a wide range of organic synthesis applications.

In heterocyclic chemistry, palladium is one of the most popular metal catalysts employed for the generation of C−N and C−O bonds. These catalysts are costly and unstable, and have poor functional group compatibility. Given the requirement to provide versatile, affordable, multipurpose, and eco-friendly catalytic systems, copper has become an attractive and diverse catalysts. More prominently, Cu-catalyzed reactions are widely used in organic synthesis because of their accessibility, safety, and cost-effectiveness. Copper has been shown to be a viable substitute for costly noble metals like palladium in catalysis. The relevance of copper in transition metal catalysis has been shown by the reports of several new processes during the past decade.[4] Being the most versatile and efficient catalyst among transition metals, copper is a very good redox catalyst. Both Cu(I) and Cu(II) species react efficiently with chemicals for the formation of diverse heterocycles. In addition to their traditional uses as metals, copper salts and complexes are now widely used for their exceptional catalytic properties in a wide range of chemical processes. Further, there is a huge urgency to develop organic synthesis in sustainable pathways. Microwave chemistry is an

Received: March 27, 2023
Accepted: May 22, 2023
Published: June 20, 2023

https://doi.org/10.1021/acsomega.3c02041
ACS Omega 2023, 8, 23240−23256

established field with several well-established applications and a number of benefits in terms of reaction rate and yield. As a result, microwave assisted organic synthesis has become a handy tool for sustainable organic synthesis because of its reliability and efficiency. Researchers were given newfound freedom to make significant advances in the design and development of cutting-edge heterocyclic molecules, thanks to microwave aided chemistry. Starting from heterocyclic synthesis, metal-mediated chemistry, and industrial preparation of aromatic compounds using microwaves, this technology has been extended to continuous-flow organic synthesis also. Lastly the wide application of microwaves in organic synthesis can enhance its value for the synthesis of high-value organic chemicals, polymers, and nanomaterials in much less time than would be required using conventional heating methods.[5] Recently, Szostak and his group reviewed the synthesis of privileged heterocyclic moieties which could be amenable to microwave irradiation also.[6]

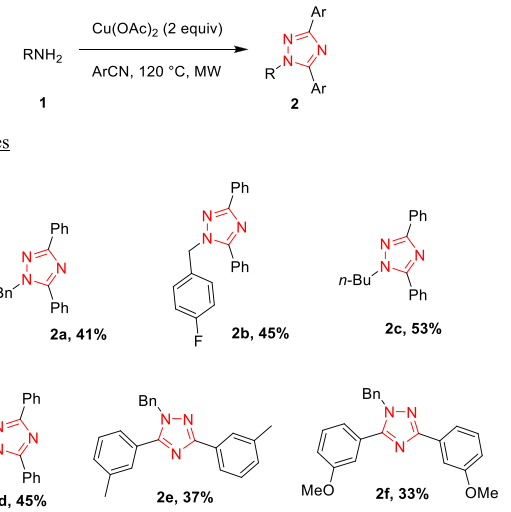
To the best of our knowledge, no specialized review has been focused on highlighting the advancements in Cu-catalyzed synthesis of heterocycles via C−N and C−O bond formation under microwaves, despite numerous reviews about Cu-catalyzed C−N and C−O bond forming reactions published until date. In this review, we have covered the synthesis of five and six membered heterocycles such as triazoles, tetrazoles, isoxazoles, pyrroles, napthofuranones benzofuran linked amino-thiazoles, lactones, furoquinoxalines, quinolones, quinazolinones, 2-iminopyrans, and fused quinazoline, respectively. The review focuses particularly on the mechanism of these microwave-assisted copper-catalyzed heterocyclisation to ignite readers' curiosity about the creation of greener and more useful C−N and C−O bond forming methods covering the year ranges from 2014 to 2023.

2. SYNTHESIS OF CU-CATALYZED HETEROCYCLIC MOIETIES VIA MICROWAVE ASSISTED C−N BOND FORMATION REACTION

Among the nitrogen-containing heterocyclic compounds, five-membered triazoles are known for their greater pharmaceutical applications. Structurally, 1,2,3-triazole and 1,2,4-triazole are the two types of five-membered triazoles with profound bioactivity. Numerous synthetic protocols have been devised for their preparation. In 2014, Ma and his group hypothesized the synthesis of 1,2,4-triazoles via a tandem double addition-oxidative cyclization method using Cu catalysts. The synthetic sequence involved the reaction of two molecules of aryl nitrile and an amine **1** to form 1,2,4-triazoles **2** in the presence of $Cu(OAc)_2$ at 120 °C in microwaves for 30 min (Scheme 1). Here interestingly aryl nitrile was used as solvent and reagents. Using primary amines and aryl nitriles as the starting ingredients, this method has the advantage of forming simultaneously C−N and N−N bonds in one single reaction. A variety of aryl amines and *n*-alkyl amines were used to generate the corresponding substituted 1,2,4-triazoles in low to moderate yields. The anticipated product was not detected when alkyl nitriles were used which specifies that aromatic nitrile is critical for this transformation. Here the microwave irradiation reduced the reaction time drastically.[7]

Mechanistically, aryl nitrile activated by $Cu(OAc)_2$ reacts with amine to form the imidamide **A** by Cu^{2+} mediated direct addition. Addition of another molecule of aryl nitrile activated by $Cu(OAc)_2$ generated intermediate **B**. The intermediate **B** was converted to the cyclic intermediate **C** upon releasing one

Scheme 1. Microwave-Assisted Synthesis of 1,2,4-Triazoles Using Cu(II) Catalyst



molecule of acetic acid followed by the reductive cyclization to generate the 1,2,4-functionalized triazoles **2** (Figure 1). In the

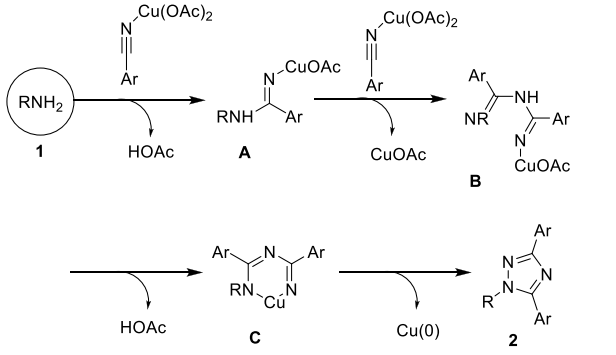


Figure 1. Plausible mechanism for the formation of 1,2,4-triazoles under microwaves.

same year, Narender et al. reported a $Cu(OTf)_2$ catalyzed multicomponent coupling reaction to produce biologically important polysubstituted furoquinoxalines under microwaves. Here, the synthetic protocol demonstrated an effective method for producing good to exceptional yields of furoquinoxalines **6** from *o*-phenylenediamine **3**, and keto esters **4**, and alkynes **5** using $Cu(OTf)_2$ as the catalyst at 80 °C under microwaves for 10 min (Scheme 2). In optimization studies, the importance of temperature and catalyst concentration for increased yield was noted. The yields of the electron-rich diamines were only moderately greater than those of diamines with low electron density. The target furoquinoxalines **6** were smoothly and efficiently generated by both the electron rich and electron withdrawing aromatic alkynes. The synthetic scheme created an easy, unique, and effective approach for the single-step, Cu(II)-catalyzed synthesis of compound **6** using the A^3-coupling reaction in moderate to exceptional productivity under microwaves.[8]

Mechanistically in the A^3-coupling reaction, the *o*-phenylenediamine **3a** reacts with ketoester **4a** to result in an imine intermediate **A** which upon reaction with Cu-acetylide **B** forms the propargylamine **C**. The intermediate **C** subsequently transformed to cyclized intermediate **E** via 5-endo-dig

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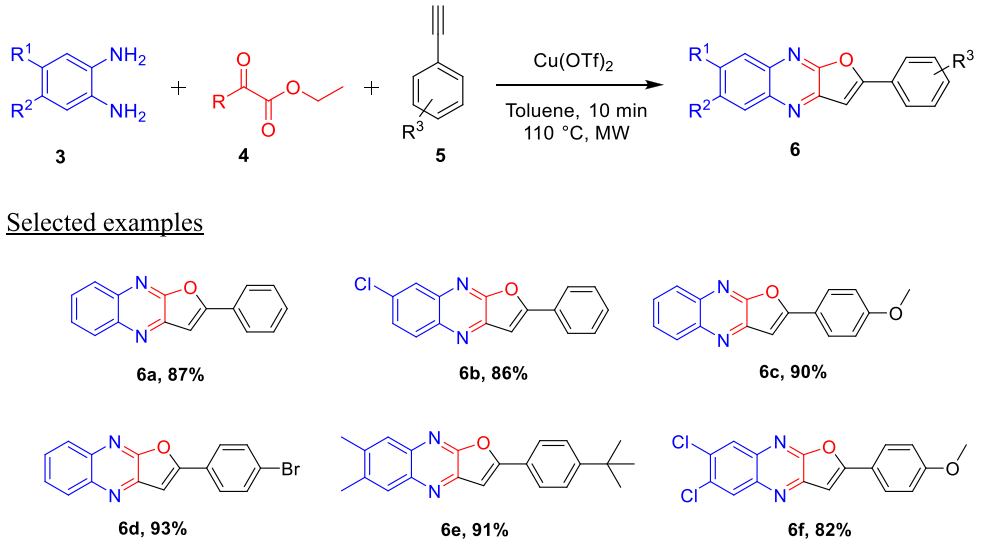
Scheme 2. Microwave-Assisted Synthesis of Furoquinoxalines Using Cu(II) Catalyst



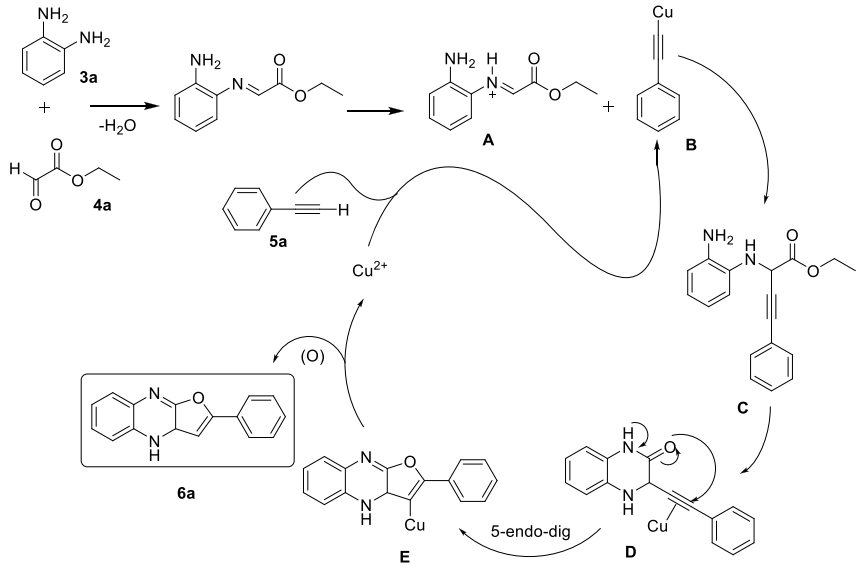


Figure 2. Plausible mechanism of synthesis of furoquinoxalines via intermediates **A**–**E**.

cyclization followed by oxidation of the resulting furoquinoxaline **6a** (Figure 2).

In 2015, Singh and his group developed a simple one-pot sequential method for the production of thiazolidinone-linked 1,2,3-functionalized triazole **10** using Cu (I) catalysis. Thaizolidinones linked triazoles **10** were synthesized from propargyloxybenzaldehyde **7**, aryl azide **8** using $CuSO_4{\cdot}5H_2O$ as catalyst and D-glucose as reducing agent in H_2O-THF (1:2) solvent in microwaves at 70 °C for 55 min followed by reacting thioglycollic acid and aniline **9** (Scheme 3). Both EDG and EWG groups on anilines were found to generate moderate to good yield (62–87%).[9]

Subsequently in 2016, Cui et al. proposed a synthetic protocol for completely functionalized pyrroles via microwave-assisted copper-catalyzed synthesis. In this regard, β-enamino compounds **11** and propargyl acetates **12** underwent microwave irradiation at 150 °C for 20 min in the presence of 5 mol % of $Cu(OTf)_2$ in toluene to form substituted pyrroles **13** (Scheme 4). Moreover, expected products were obtained in 70–80% yield using both electron-donating and electron-withdrawing substituents on the aromatic ring system of β-enamino ester. Similarly, propargyl acetates with terminal alkyne and aryl or heteroaryl groups as substituents yielded pyrroles in moderate to excellent results (54–75%).[10]

Initially, Cu(II) activated propargyl esters reacted with compound **11** to form an intermediate **A** which upon electron reorganization followed by 5-exo-dig intramolecular cyclization resulted in the intermediate **B**. The intermediate **B** underwent isomerization to obtain substituted pyrrole derivatives **13** as shown in Figure 3.

In 2016, Miura and his co-worker reported an intramolecular Cu-catalyzed benzylic sp^3 C–H amination of ortho-methyl-benzamides to develop isoindolinones synthesis, which had significant importance in medicinal chemistry. Isoindolinones **15** was obtained from 2,6-disubstituted benzamide **14** after treatment with $Cu(OAc)_2$ (20 mol %), 1-AdCOOH (40 mol %), and MnO_2 in diglyme for 2 h at 200 °C under microwave irradiation (Scheme 5). It was found electron-donating

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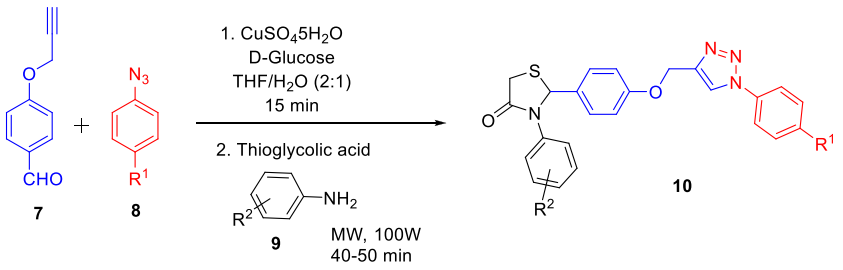
Scheme 3. Microwave-Assisted Synthesis of Thiazolidinone-Linked 1,2,3-Triazole Using Cu(II) Catalyst



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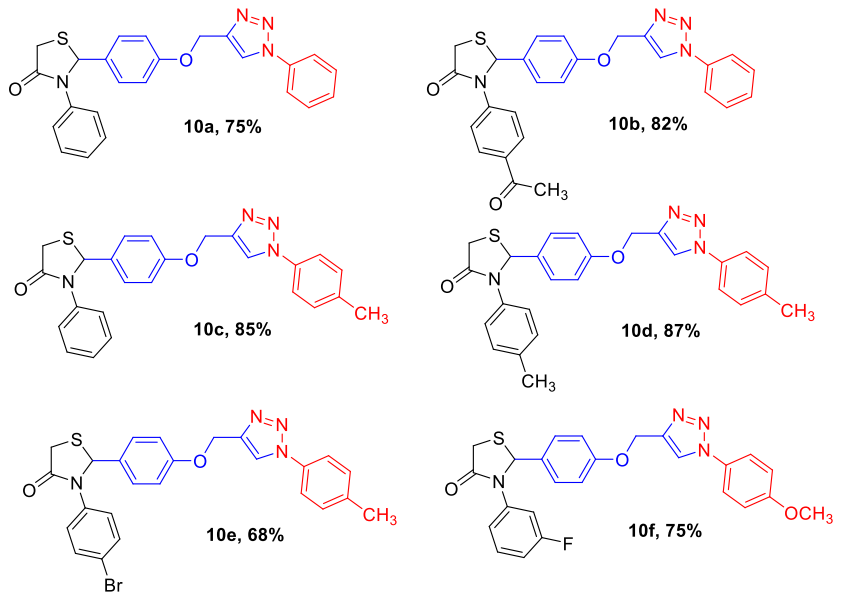
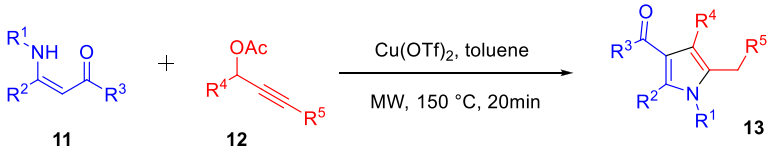


Scheme 4. Microwave-Assisted Synthesis of Pyrroles under Microwaves



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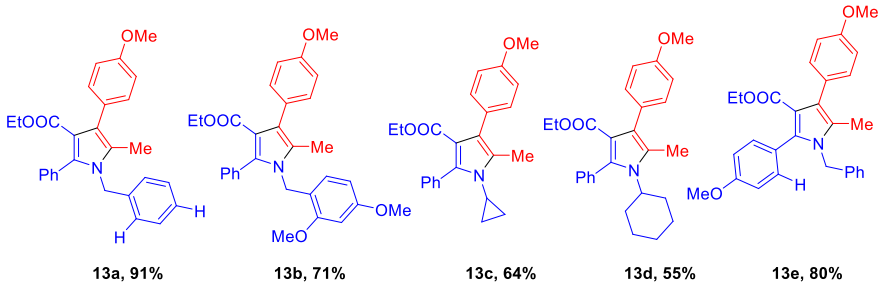

substituents (**15a, 15b, 15c, 15d**) yielded well to generate the appropriate isoindolinones in comparison of electron withdrawing group (**15e, 15f, 15g**).

Mechanistically, first, benzamide **14** was activated by $Cu(OR)_2$ to result an *N*,*N*-bidentately coordinated Cu species **A**. Next, the cyclo-metalated complex **B** is produced at the proximal benzylic site by the irreversible and rate-limiting C−H cleavage. Finally, the intermediate **C** underwent disproportionation and reductive elimination to generate the isoindolinone **15** (Figure 4).[11]

Subsequently, in 2017, our group established a very effective and environment-friendly technique for the synthesis of 5-substituted 1*H*-tetrazole derivatives using Cu(I) catalyst. As depicted in Scheme 6, substituted nitriles **16** and sodium azide

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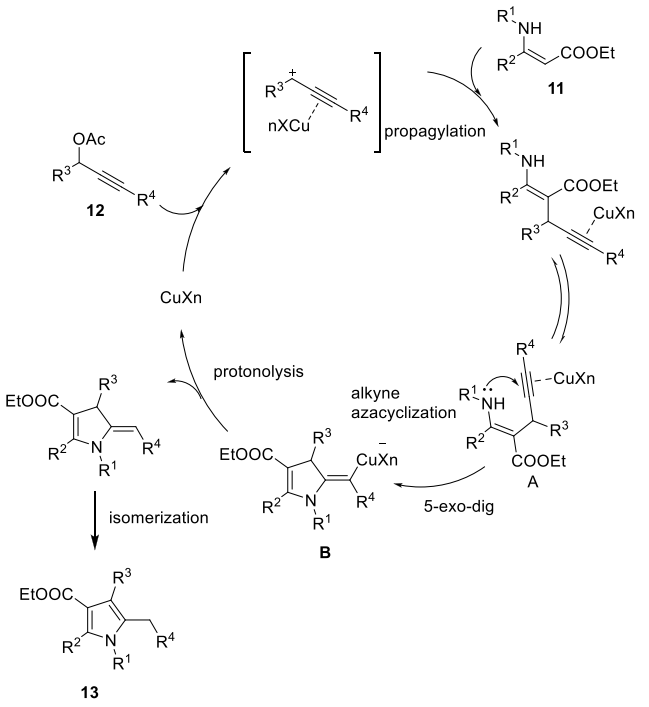
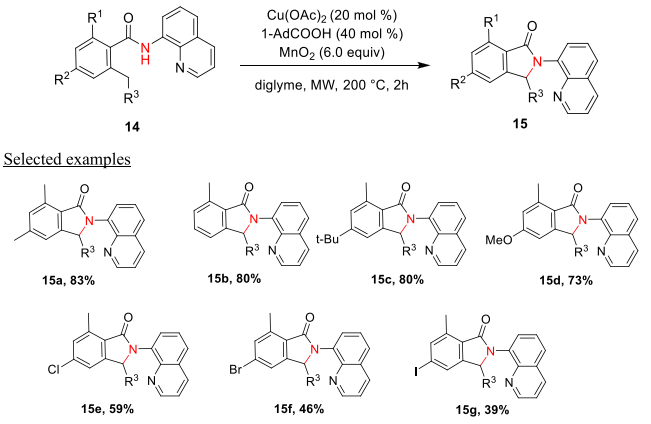


Figure 3. Plausible mechanism for the synthesis of pyrroles under microwaves.

Scheme 5. Cu(II) Catalyzed Synthesis of Isoindolinones under Microwaves



underwent (3 + 2) cycloaddition reaction to form 5-substituted 1*H*-tetrazole **17** in the presence of 10 mol % [Cu(phen)-$(PPh_3)_2$]NO_3 catalyst in green media under microwaves at 65 °C for 15 min. Outstanding yields of the corresponding 1*H*-tetrazole derivatives were obtained from the reaction of aromatic nitriles having unsubstituted or electron-withdrawing groups as opposed to the lower yields obtained from aromatic nitriles containing electron-donating substituents.[12a] In the same year, we have utilized CuO nanoparticles for the synthesis of 5-substituted 1*H*-tetrazoles under microwave irradiation.[12b]

In 2018, Murthy and his group synthesized benzofuran linked aminothiazoles derivatives **25** via microwave irradiation. Initially, two equivalents of benzaldehyde were reacted with starting material **18** to generate the intermediate **19** under basic conditions. Subsequent hydrogenation of compound **19** using 10% Pd/C in ethyl acetate generated the intermediate **20** which upon reacting with chloroacetone generated furan derivatives

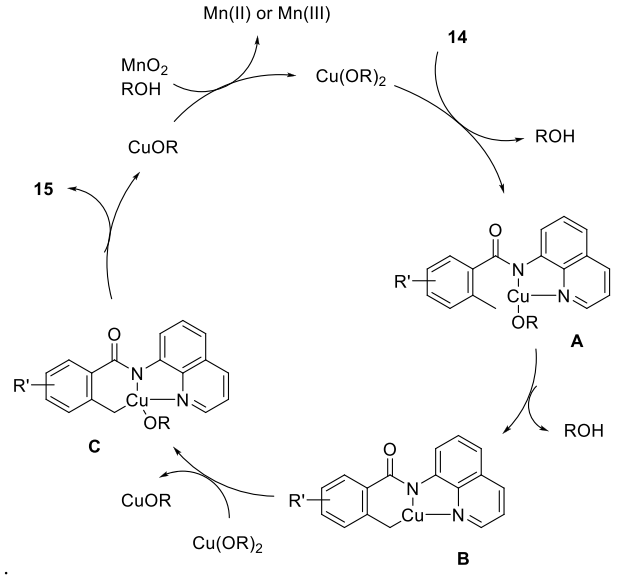
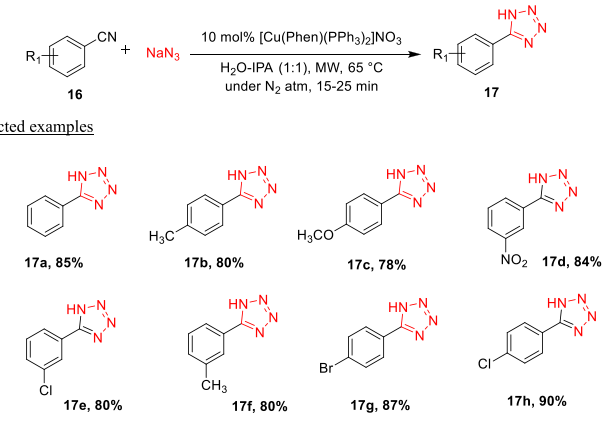


Figure 4. Plausible mechanism of synthesis of isoindolinones under microwaves.

Scheme 6. Synthesis of 5-Substituted 1*H*-Tetrazole under Microwaves in Green Media



21. Further the intermediate **21** reacted with $NH_2OH{\cdot}HCl$ in EtOH medium under microwaves from dioxime **22** in the presence of K_2CO_3. Under microwave (MW) irradiation, compound **21** was utilized to react with $NH_2OH{\cdot}HCl$ in EtOH to form dioxime **22**. The compound **22** was then subjected to acetylation in EtOH medium under microwaves generating compound **23**. Further the acetylated derivative **23** underwent Cu(I) catalyzed heterocyclization with substituted isothicynates using Cs_2CO_3 as base resulting in benzodifuran linked aminothiazoles derivatives **25** under microwaves for 15−25 min with excellent yields (Scheme 7). Ironically the same reaction took 12−18 h under refluxing dioxane solution to generate benzodifuran linked aminothiazoles derivatives **25**. Antibacterial and antimycobacterial testing was performed *in vitro* on the synthesized products. The derivatives **25b**, **25c**, and **25d** demonstrated superior growth inhibition against a Gram-positive *B. subtilis* strain. Antibacterial activity of the studied compounds against *B. subtilis* and *M. bovis* strains was enhanced by the presence of Br and F atoms in the ortho position of aromatic rings.[13]

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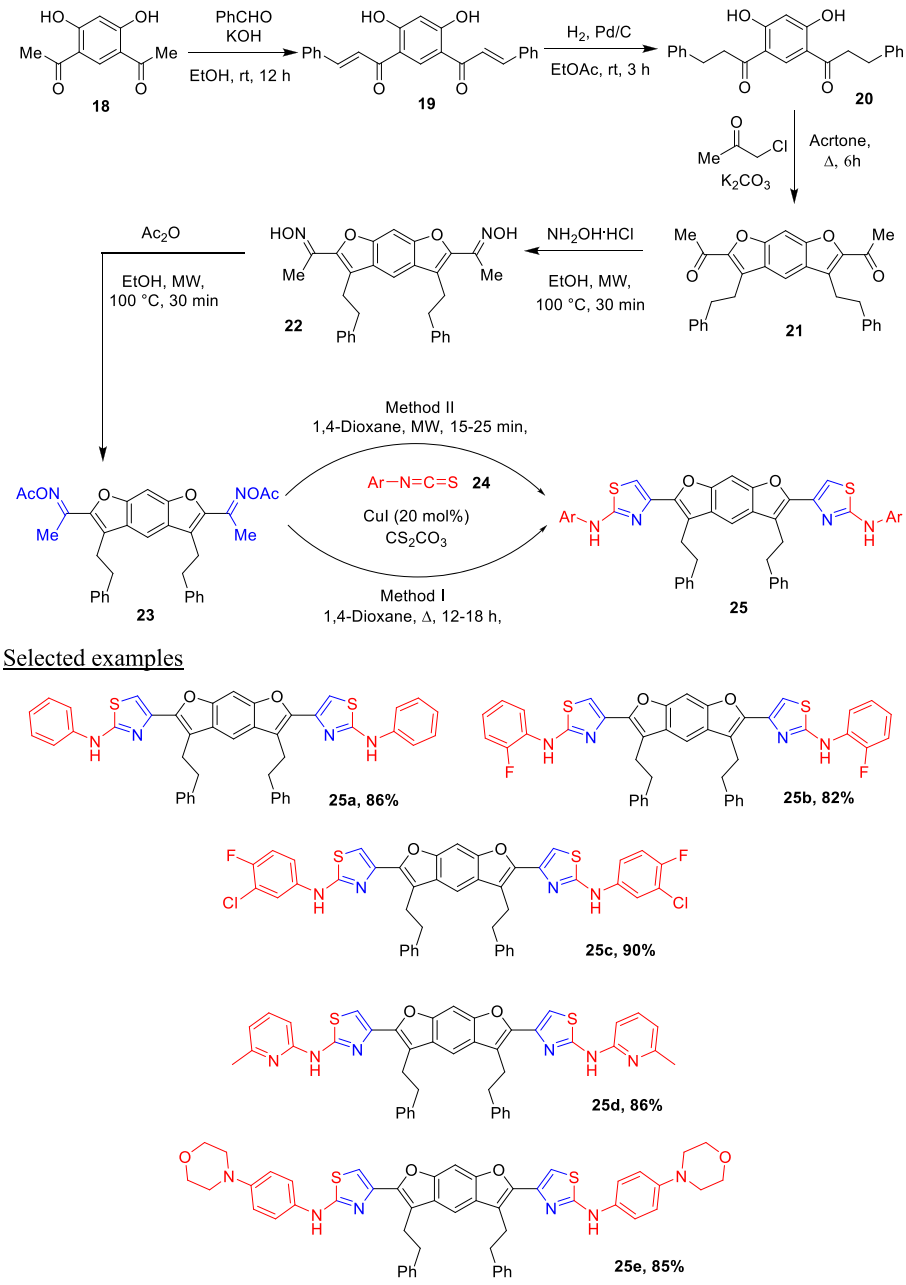
Scheme 7. Microwave Assisted Synthesis of Functionalized Benzodifuran Linked Aminothiazoles Derivatives



Further, in 2018, Choudhury et al. reported the synthesis of pyrimidine fused quinolines **28** via copper-catalyzed domino reactions. Pyrimidine fused quinoline derivatives **28** were achieved in 30 min under microwaves by reacting substituted 2-bromo benzaldehyde **26** with enaminone **27** using K_2CO_3 as base and 10 mol % of cupric chloride as Cu(II) source in DMF solvent at 150 °C (Scheme 8). Excellent results were obtained when the reaction is carried out in DMF as solvent without the use of any additive or ligand because DMF has both reducing and coordinating properties. Using various substituted 2-bromo benzaldehyde having electron-donating and pulling substituents at various positions on the phenyl ring, moderate to good yields of target compounds were obtained.[14]

Subsequently, in the same year, Cho and his group reported the Cu-catalyzed coupling and cyclization reaction to synthesize quinazoline derivatives **32**. Primary amides **31** were reacted with different benzimidazole derivatives **29** or **30** at 130 °C for 1 h in the presence of CuI, L-proline, and Cs_2CO_3 in DMF under microwave irradiation (100 W) to produce quinazoline derivatives **32a−p** with modest to good yields (66−83%) (Scheme 9).[15]

In 2018, Fang et al. reported the synthesis of quinazolinone derivatives **36** in water via a microwave-assisted copper-catalyzed cascade reaction. To generate quinazolinone derivatives **36**, Cu-catalyzed cascade reaction of amidines **35** with functionalized 2-halobenzoic acids **34** in water as solvent under microwaves is described here (Scheme 10). Consequently, the best catalytic conditions were achieved by heating $CuCl_2$ (10 mol %), ligand **33** (10 mol %), and sodium hydroxide in H_2O at ambient condition for 20 min under microwaves. A wide range of substrates with functional groups such as methoxy, methyl, nitro, and bromo were successfully subjected to the catalytic

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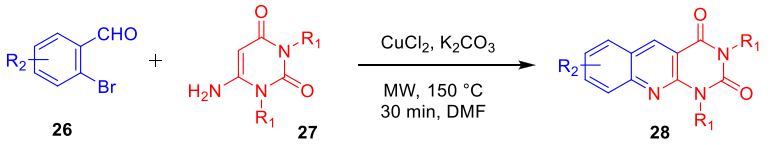
Scheme 8. Synthesis of Pyrimidine Fused Quinolones under Microwaves Using Cu(II) Catalyst



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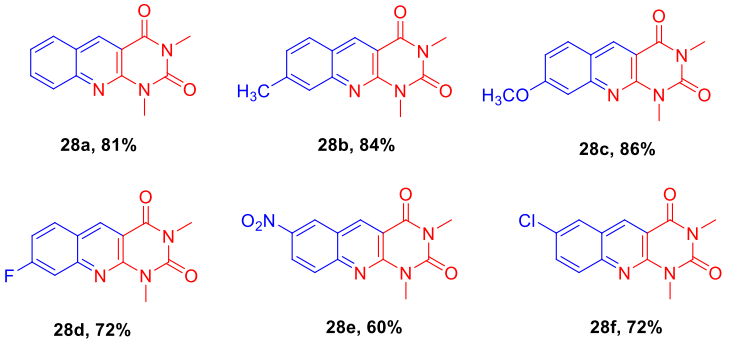
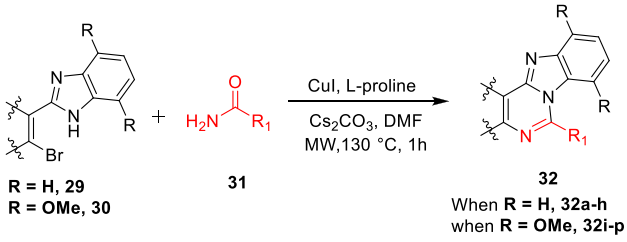


Scheme 9. Synthesis of Pyrimidine Fused Quinolones under Microwaves



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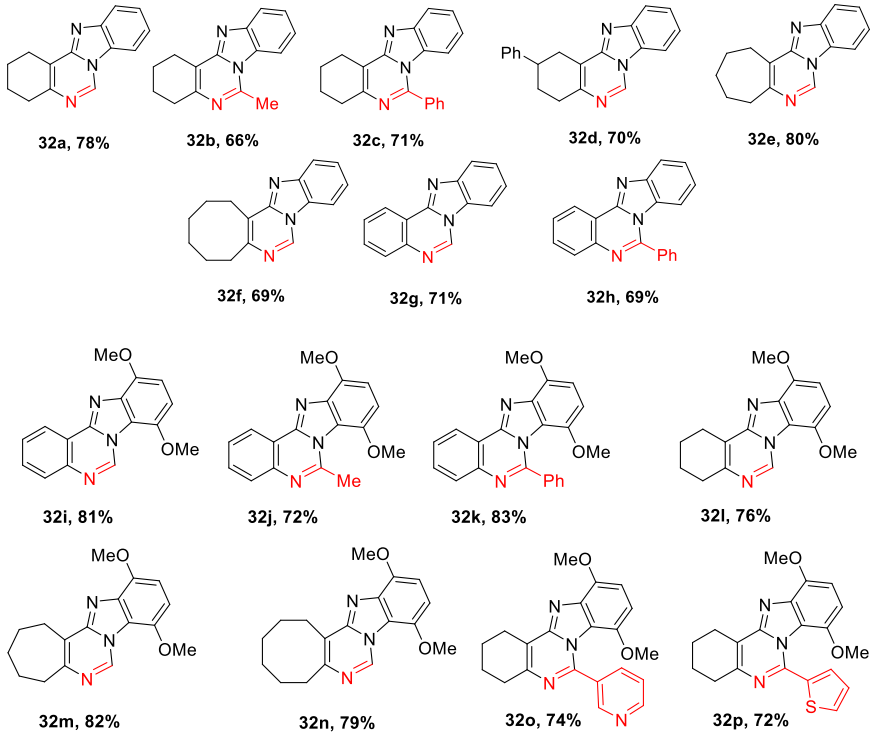

processes with good to excellent yields of 55% to 94%. When compared to aryl bromide and aryl chloride, aryl iodide reacted

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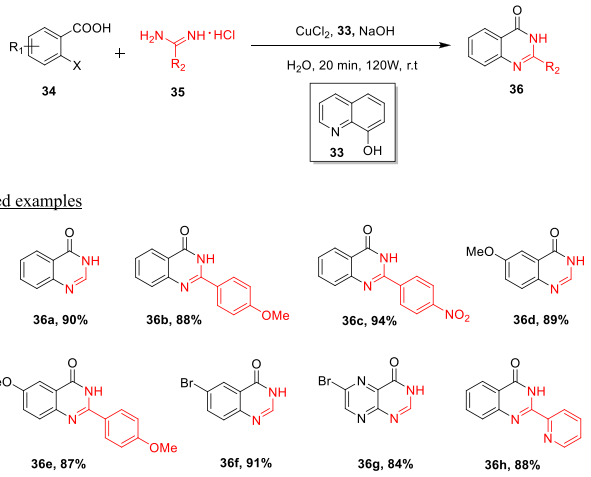
Scheme 10. Cu(II) Catalyzed Synthesis of Quinazolinones under Microwaves



more strongly. The substituted 2-halobenzoic acids **34** and amidines **35** with electron-withdrawing groups were somewhat more reactive than those with electron-donating groups.[16]

The intermediate amide **A** synthesized from 2-halobenzoic acid **34a** and amidine **35a**, underwent Cu(II) catalyzed intramolecular C−N bond forming reaction to provide the desired product **36a** (Figure 5).

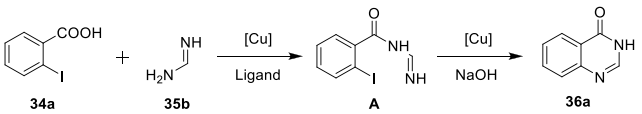
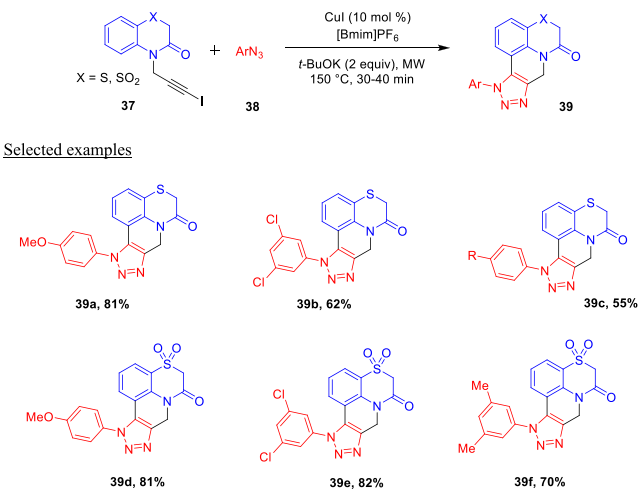


Figure 5. Plausible mechanism of synthesis of quinazolinone.

In 2018, Nagavelli and his co-worker synthesized quinolinone derivatives **39** by using copper catalyst via one-pot synthesis. The synthetic scheme initiated from the reaction of iodoalkynes **37** and aryl azides **38** using CuI as catalyst (10 mol %) with *t*-BuOK (2 equiv) in [Bmim]PF_6 under microwaves for 0.5 h (Scheme 11). High yields, a simple workup, and rapid reactions are just a few of the benefits of this one-pot approach. *In vitro* cytotoxic assays were performed on the A549, MCF-7, IMR-32, and HeLa human cancer cell lines to determine the efficacy of each compound. Among them, high activity was observed for both **39b** and **39c** against the MCF-7 and A-549 cell lines.[17]

Scheme 11. Synthesis of Benzothiazino[1,2,3]triazolo[4,5-*c*]quinolinone in Microwaves



The [3 + 2] cycloaddition of an aryl azide and the Cu(I)-acetylide intermediate of iodoalkyne **37** yielded the 5-iodo-1,2,3-triazole intermediate **A**. The mechanism involved the activation of iodoalkyne **37** by Cu(I) catalyst to form the Cu(I)-acetylide intermediate. Further C−H activation of triazole-iodide bond by Cu(I) catalyst led to the generation of intermediate **B** which upon intramolecular electrophilic aromatic substitution/direct arylation generated the intermediate **C**. The seven-membered intermediate **D** was created by the removal of proton from intermediate **C** using *t*-BuOK. Finally, the reductive elimination of intermediate **D** obtained benzothiazino[1,2,3-triazolo[4,5-*c*]quinolinone **39**. (Figure 6).[17]

In the year 2020, our group demonstrated the synthesis of 1,4-disubstituted 1,2,3-triazoles **43** using ionic liquid supported Cu(II) catalyst **42** under microwaves. The synthetic scheme commenced by reacting various benzyl bromide **40** with sodium azide followed by the addition of alkynes derivatives **41** and ionic liquid supported Cu(II) catalyst **42** in MeOH solvent (Scheme 12). Here the solvent MeOH acts as a reducing agent. The reaction was accomplished at 65 °C for 8 min under microwave irradiation. Substituted benzyl bromide bearing an electron-donating group interacted favorably, resulting in high yields of the corresponding triazoles. Likewise, slow reaction rates were seen when similar triazoles were prepared from benzyl bromides or substituted benzyl bromides bearing electron withdrawing groups.[18] This methodology was further extended to the synthesis of rufinamide, an antiepileptic drug.

This synthetic process began with the *in situ* formation of azides from the interaction of organic halides and NaN_3 in methanol. A five-membered copper metallacycle was generated with the addition of a Cu(I) catalyst, which was reduced from Cu(II) species through methanol. The triazole derivative **43** was synthesized by a further protonolysis of intermediate **A**, and the catalytic cycle is closed via arial oxidation to the Cu(II) species (Figure 7). In 2021, Nanduri and his group designed a unique microwave-assisted tandem process for the synthesis of fused quinazoline derivatives, which involved the production of new C−N bonds. 2-Bromoquinazolinone/2-bromobenzimidazole **44** reacted with substituted aldehyde **45** using Cu_2O (10 mol %) as catalyst with NH_4OAc in isopropanol medium for 30 min at 120 °C under microwaves to form fused quinazoline derivatives **46** (Scheme 13). Results showed that various substituted heterocyclic aldehydes and benzaldehydes were well tolerated and yielded the expected products in moderate to excellent proportions (73−85%). Better yields were obtained from benzaldehydes that had electron-donating substituents rather than those that included electron-withdrawing groups.[19]

Mechanistically the final compound fused quinazoline could be produced in two different pathways. In route A, the activation of compound **44** by Cu(I) catalyst followed by reacting with NH_3 generated from NH_4OAc which upon reacting with aldehydes obtained imine intermediate **D**. Finally, the intermediate **D** underwent intramolecular nucleophilic addition reaction resulting in the formation target compound **46**. In Path B, the reaction of aldehyde **45** with NH_3 followed by the reduction generated the intermediate **F**. Subsequently, the reaction of compound **44** with the intermediate **F** under Cu(I) catalyzed conditions followed by *in situ* generated benzyl amines

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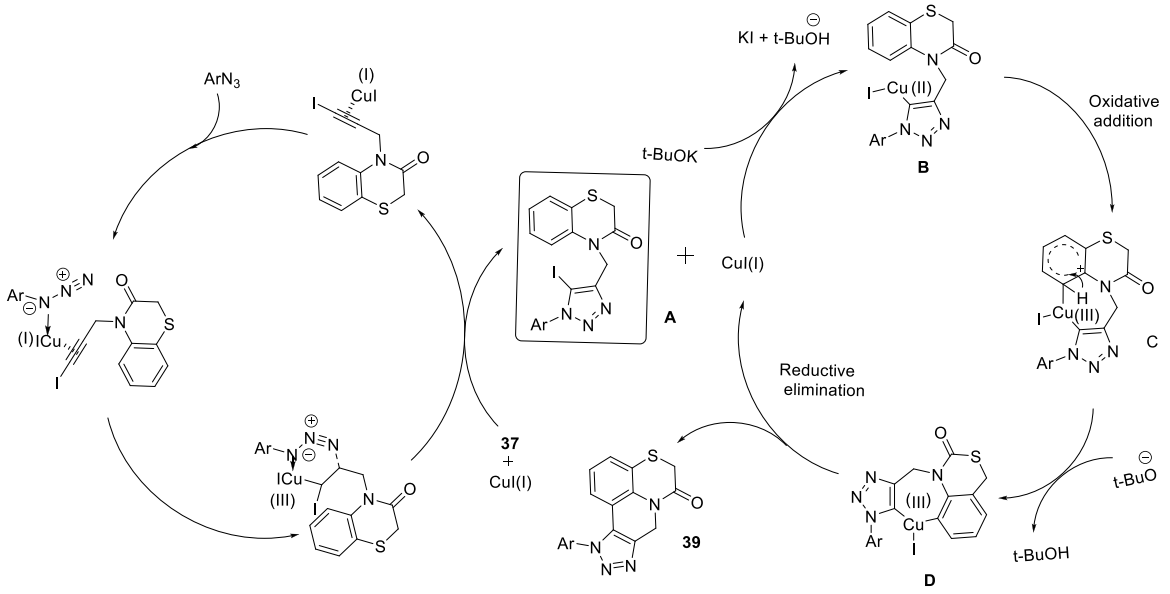
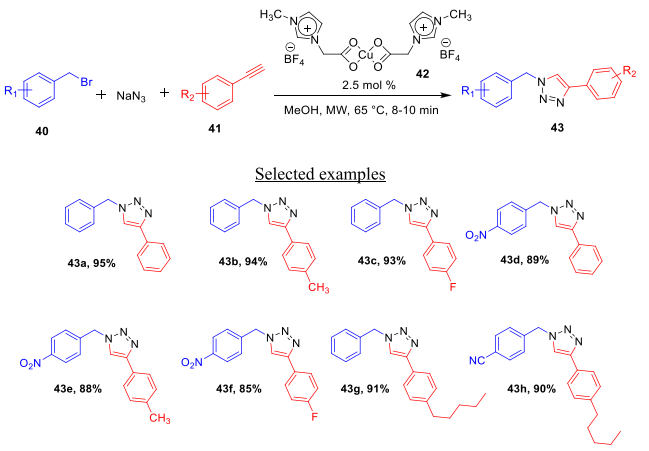


Figure 6. Plausible mechanism for the synthesis of benzothiazino[1,2,3]triazolo[4,5-*c*]quinolinone.

Scheme 12. Synthesis of 1,4-Disubstituted 1,2,3-Triazoles by Cu(II) Catalyst



resulted the intermediate **G** which on rearrangement resulted in intermediate **H**. The intermediate **G** upon oxidation followed by intramolecular nucleophilic addition resulted in the target moiety in good to excellent yields (Figure 8).

In 2021, Kumbar and his group developed a rapid and selective synthesis of quinoline-linked triazoles in microwave condition (Scheme 14). The synthesis of quinolin-3-yl-methyl-1,2,3-triazolyl-1,2,4-triazol-3(4*H*)-ones **51** was achieved via Click chemistry, representing the pinnacle of the approach where [3 + 2] cycloaddition of azides with terminal alkynes was established. The reported protocol was environmentally friendly for the rapid and efficient regioselective synthesis of quinolinyl-1,2,3-triazolyl-1,2,4-triazol-3 (4*H*)-one **51** with high yields and excellent purity. The compound **48** synthesized using the Vilsmeier−Haack reaction was reduced with $NaBH_4$ to the corresponding alcohol followed by treatment with PBr_3 in DCM to obtain the bromo-substituted quinoline. After reacting 3-(bromomethyl)-2-chloro-6/7/8-substituted quinoline with NaN_3 in aqueous acetone at ambient conditions, the corresponding azide **49** was produced. The compound **49** subsequently underwent (3 + 2) cycloaddition with acetylenic

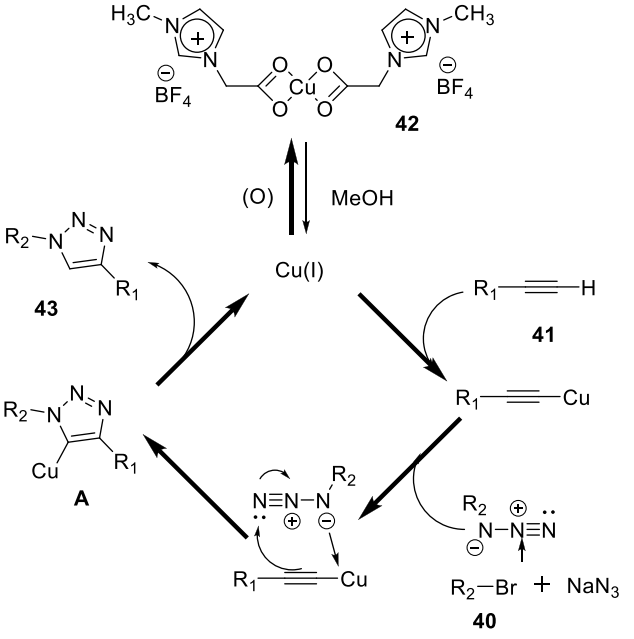


Figure 7. Plausible mechanism for the synthesis of 1,4-disubstituted 1,2,3-triazoles by Cu(II) catalyst.

dipolarophiles **50** under click conditions using microwaves to synthesize quinoline-linked triazoles **51** (Scheme 14).[20]

In 2022, Cho et al. developed the synthesis of indole-fused quinazolinones by using copper-catalyzed nucleophilic addition followed by a C−N coupling reaction. Irradiating the mixture of 2-(2-bromoaryl)indoles **52** with aryl isocyanates **53** under microwaves in the presence of CuI and Cs_2CO_3 using DMF as solvent at 130 °C for 2 h yielded 5-arylindolo[1,2-*c*]quinazolin-6(5*H*)-ones **54** (Scheme 15). The synthetic manipulation was also possible with straight and branched alkyl chains at position 3 of the indole moiety in 2-(2-bromoaryl)indoles. Similarly, both electron-withdrawing and electron-donating substituents on bromophenyl and indole moieties were resulted in good yield.[21]

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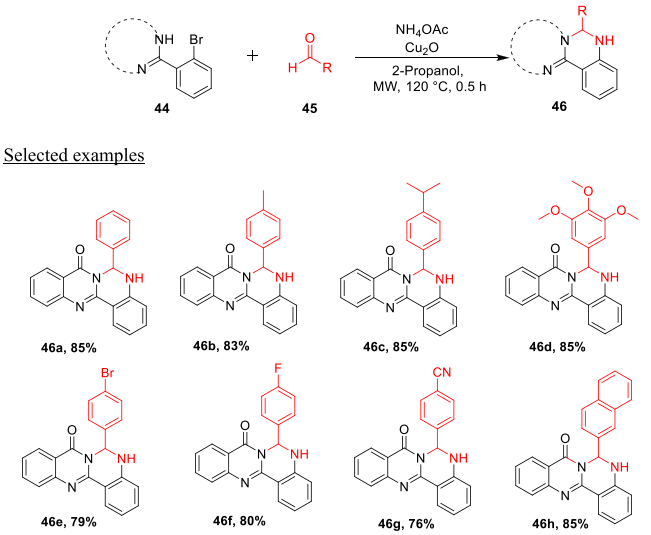
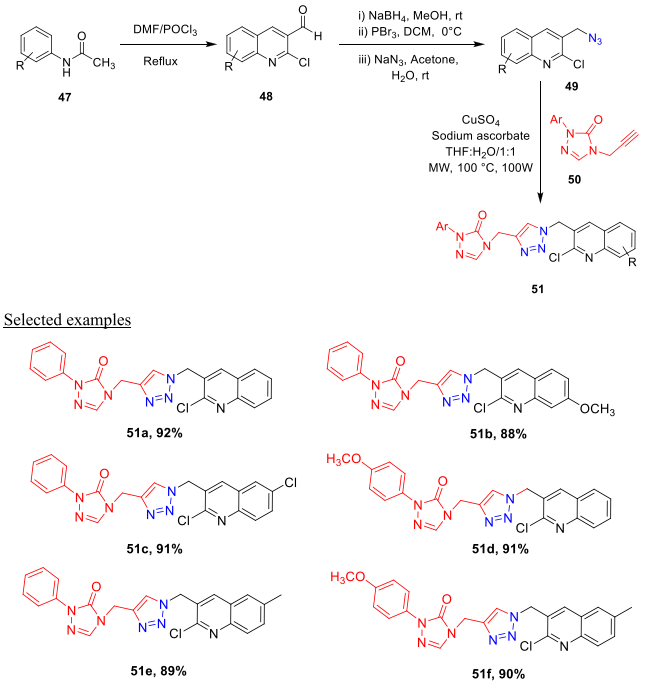
Scheme 13. Synthesis of Fused Quinazoline Using Cu(I) Catalyst under Microwaves



Scheme 14. Synthesis of Quinoline-Linked Triazoles under Microwaves



Mechanistically the nucleophilic addition of compound **52a** with compound **53a** led to the formation of the intermediate **A**. The intermediate **A** then underwent an intramolecular C−N bond formation by an addition−elimination nucleophilic aromatic substitution via Meisenheimer complexes **B, C, D, E** and a copper-catalyzed Ullmann-type coupling to obtain the compound **54a** (Figure 9).

In 2022, Sridharan et al. reported the microwave-assisted Cu(II) catalyzed cascade cyclization reaction to synthesize oxazepines derivatives **60** and diazepines derivatives **61**. The corresponding oxazepane/diazepines derivatives **60/61** were synthesized by a cascade reaction of various O/N-propargylated 2-hydroxybenzaldehydes **55/56** and o-phenylenediamines **57** in the presence of 10 mol % of $Cu(OTf)_2$ and K_2CO_3 as base in DMF under microwave irradiation at 100 °C for 15 min (Scheme 16). Both electron withdrawing and electron donating groups showed good to excellent yield.[22]

The intermediate imine **A** produced from the reaction between aldehyde **55/56** and o-phenylenediamine **57** underwent Cu(II) catalyzed intramolecular 5-endo-trig cyclization, followed by aerial oxidation/aromatization, to provide the imidazole intermediate **58/59** through species **B**. The internal alkyne of **58/59** is activated by the copper(II) catalyst in the presence of a base, resulting in the production of desired products **60/61** followed by 7-exo-dig cyclization (Figure 10).

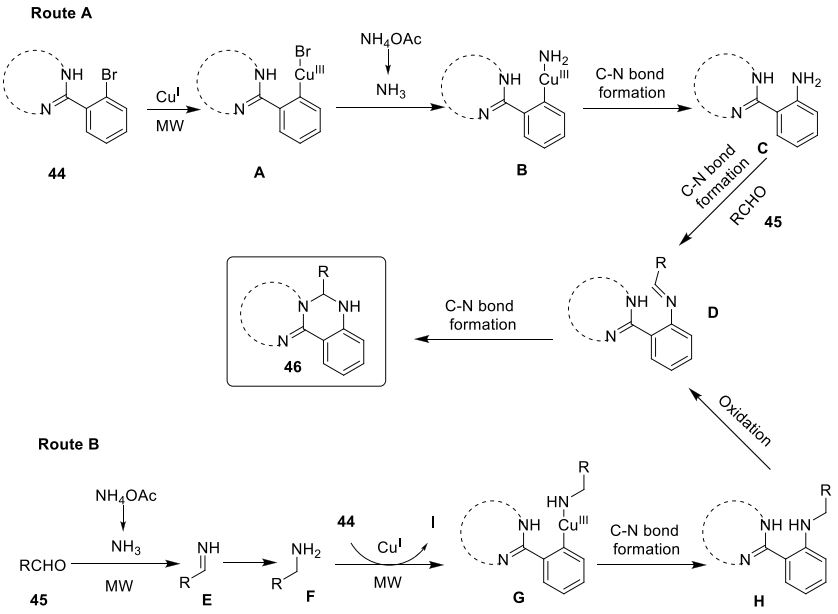


Figure 8. Plausible mechanism of synthesis of fused quinazoline using microwaves.

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Scheme 15. Microwave-Assisted Synthesis of Indole-Fused Quinazolinones

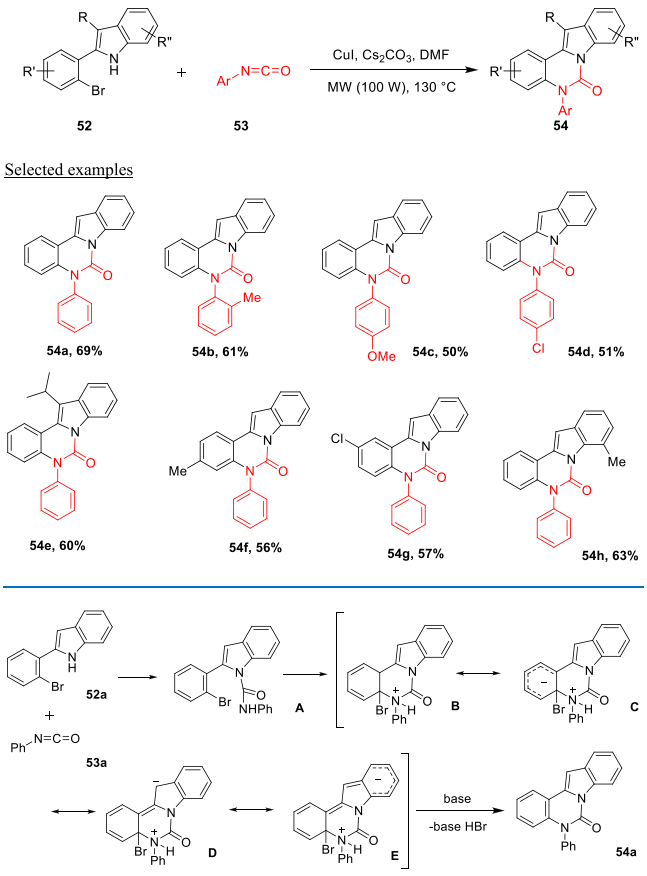

Figure 9. Plausible mechanism for the synthesis of indole-fused quinazolinones in microwaves.

Further in the same year, Sushmita and her group reported the synthesis of a novel series of N-substituted indole derivatives **66** using both conventional and microwave heating techniques. It was observed that microwave irradiation yielded a higher percentages of yields (72−96%) and shorter reaction times compared to the conventional approach (64−94%). The indole derivatives **66** were obtained by a three-step synthetic route beginning with the N-alkylation of tetrahydro-1*H*-carbazoles, followed by copper-catalyzed Huisgen [3 + 2] cycloaddition reaction with aromatic azides **65** in the presence of $CuSO_4$ and sodium ascorbate in DMF-H_2O (2:1) for 6 min under microwave irradiation (Scheme 17). Among the synthesized compounds, **66b**, **66d**, and **66e** were found to exhibit good antioxidant, anticancer, and antimicrobial activities.[23]

3. SYNTHESIS OF CU-CATALYZED HETEROCYCLIC MOIETIES VIA MICROWAVE ASSISTED C−O BOND FORMATION REACTION

The preference of copper (in the form of oxides, salts, and complexes) over palladium in C−O cross coupling reaction could be due to the low cost, ease of handling, and nontoxicity. In many cases, it has been observed that particularly in the formation of C−O bond via substitution reactions copper catalysis demonstrated excellent results. Cu-catalyzed cross-coupling reactions are sometimes more selective than Pd-catalyzed reactions as these reactions can produce the desired products with a smaller amount of undesirable side products. In terms of compatibility, Cu-catalyzed cross-coupling reactions are compatible with a greater variety of functional groups compared to those of Pd-catalyzed reactions.

In the year 2015, Lopez et al. established a fast and effective protocol for the regio- and diastereoselective cycloisomerization of compound **67**. The cycloisomerization of compound **67** catalyzed by CuBr (5 mol %) in water under microwave irradiation at 100 °C for 8 min was presented a diastereo and regioselective approach for gaining access to a wide range of highly functionalized lactones **68** in excellent yields (Scheme 18). For a wide range of highly functionalized compound **68**, this approach allows for high yields under moderate reaction conditions.[24]

In the same year, Punniyamurthy and his group reported a Cu(I) catalyzed multicomponent tandem synthesis of coumarins derivative **73** using microwaves. In order to synthesize 3-*N*-sulfonylamidine coumarin, a four-component tandem synthesis was planned using salicylaldehydes **69**, propiolates **70**, sulfonyl azides **71**, and secondary amines **72**. The multicomponent reaction was carried out in the presence of CuI (10 mol %), K_2CO_3 as base in 1,4-dioxane medium at 130 °C under microwave irradiation for 1 h (Scheme 19). Aldehydes with substitution at the 3/5-position resulted products in good yield compared to the substitution at the 4-position. Using electron-withdrawing groups such as CHO and NO_2 at 5-position produced final products in lower yields. Similarly, both aliphatic and aromatic sulfonyl asides were useful in the process with satisfactory yields, and the coupling process is very selective to the propiolate and secondary amine species.[25]

Mechanistically, the Cu(I) catalyzed (3 + 2) cycloaddition reaction between alkyne **70** and azides **71** resulted in the generation of ketenimine **B** via **A** which underwent nucleophilic addition with amine resulting in the intermediate **C**. The intermediate **C** further reacted with aldehyde **69** to obtain intermediate **D** which underwent transesterification leading to the formation of 3-*N*-sulfonylamidine coumarin **73** (Figure 11).

In 2015, Ahmed and his co-worker synthesized napthofuranones **78** via microwave irradiation with or without the metal salt. In path I, 2-oxoaldehydes **75**, pyrrolidine **76**, and *β*-naphthol **74** in toluene (1 mL) underwent microwave irradiation (50 W) at 100 °C for 10 min to form tetrahydrofuro-[3,2-*d*]oxazoles **77**. Subsequently, tetrahydrofuro[3,2-*d*]-oxazoles **77** converted to napthofuranones using Cu(II) catalyst under microwave irradiation at 100 °C in toluene solvent for 20 min. In path II, napthofuranones **78** were synthesized straightforwardly from 2-oxoaldehydes **75**, pyrrolidine **76**, and *β*- naphthol **74** in the presence of Cu(II) catalyst at 100 °C for 15 min via microwave irradiation (50 W) with excellent yields (81−92%) (Scheme 20).[26]

Synthesis of compound **78** began with the formation of 2-oxoiminium ion (intermediate **A**) through the interaction of 2-oxoaldehyde **75** and pyrrolidne **76**. The behavior of this intermediate **A** changes between metallic pathway (path A), and nonmetallic pathway (path B). In path-A, the 2-oxoiminium ion **A** underwent ene reaction and O- cyclization to form intermediate **C**. Later intermediate **C** underwent aerial oxidation followed by Cu(II) catalyzed reaction resulting in the target compound **78**. Likewise in path B, ammoniumyl radical cation (intermediated **D**) derived via single electron transfer (SET) from intermediate-**A** and compound **74**. In the end, Cu(II) mediated cyclization and hydrolysis of the iminium intermediate yielded the target compound **78** (Figure 12).

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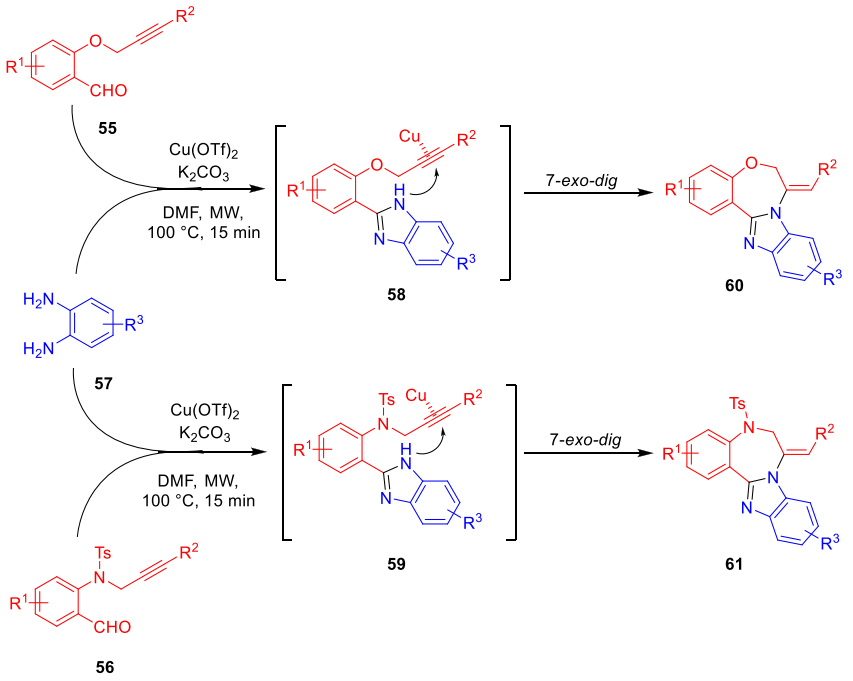
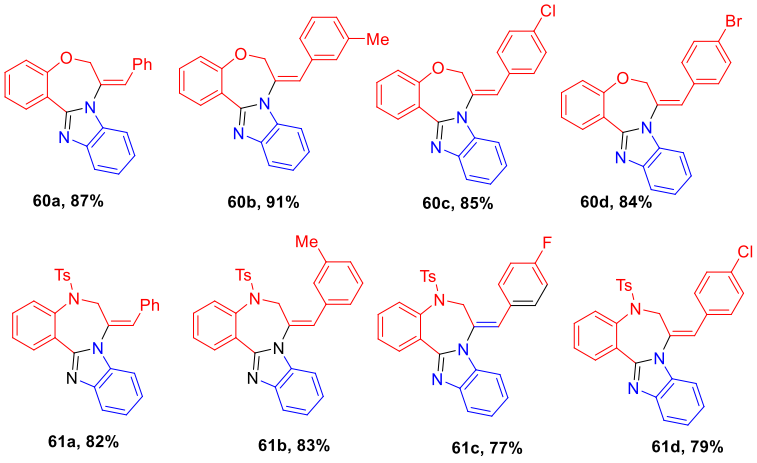
Scheme 16. Synthesis of Benzo[f]imidazo[1,2-*d*][1,4]oxazepines and Benzo[f]imidazo[1,2-*d*][1,4]diazepines under Microwaves



Selected examples



In 2016, our group established a microwave assisted telescopic synthetic protocol to develop 3,5-disubstituted isoxazoles **82** from *N*-hydroxyl imidoyl chlorides **80** with substituted alkynes **81** in water medium with 2 mol % of $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst. *N*-hydroxybenzimidoyl chloride **80** was obtained by condensing benzaldehyde **79** with hydroxylamine hydrochloride using NaOH as base in aqueous medium under microwaves for 7 min at 65 °C followed by subsequent reaction with N-chlorosuccinimide. Further, *N*-hydroxybenzimidoyl chloride **80** underwent Cu(I) catalyzed 1,3-dipolar cycloaddition with alkyne **81** at 65 °C for 5 min under microwaves resulting into 3,5-diphenylisoxazole **82** with excellent yield. Aromatic aldehydes having electron-donating substituents could not react efficiently to obtain corresponding isoxazoles as compared to electron-withdrawing substituents. Similarly, this reaction was unaffected by the presence of electron-withdrawing groups or electron-donating substituents at the aromatic terminal alkyne. Microwave irradiation utilizing a green solvent such as water, significantly speeds the reaction with less time and provides excellent yields (Scheme 21).[27]

In 2018, Zhang and his group reported a comparison study to synthesize a new 1,2,3-triazoles linked with an isoxazole ring by conventional heating and microwave irradiation. The reaction improves with microwave irradiation compared to conventional heating methods. Click chemistry was used to synthesize 1,2,3-triazoles with isoxazole ethers **85**/**87** from substituted isoxazolyl alkyne **84** and substituted benzyl azide **83** or neopentylglycol diazide **86** using $Cu(OAc)_2$/sodium ascorbate as the catalyst in aqueous THF at 50 °C for 10 min in microwaves. The higher yields were observed for electron donating groups owing to the electron-rich property as compared to that of the electron withdrawing substituents in the 1,3-dipolar cycloaddition reaction (Schemes 22 and 23).[28]

Further, in 2021, Hajji et al. synthesized benzimidazolone linked isoxazoles which were known for their antioxidant and antimicrobial activities. The desired benzimidazolone tethered

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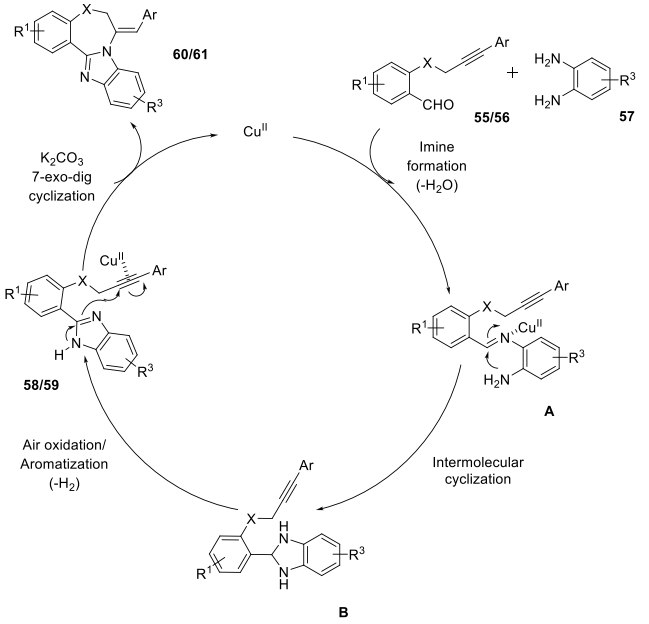
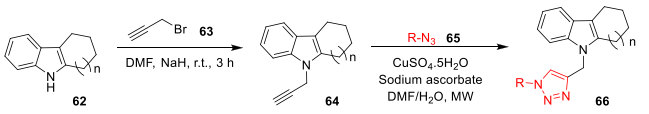


Figure 10. Plausible mechanism for the synthesis of benzo[f]imidazo-[1,2-*d*][1,4]oxazepines and benzo[f]imidazo[1,2-*d*][1,4]diazepines.

Scheme 17. Synthesis of 1,2,3-Triazolylmethyl Indole Using Microwaves



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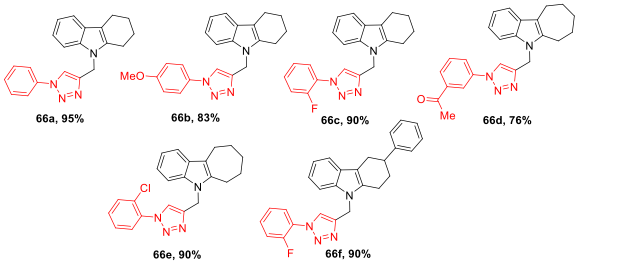
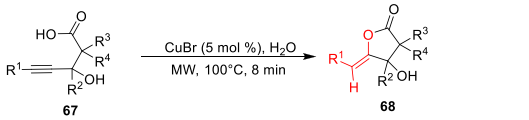


Scheme 18. Microwave-Assisted Synthesis of Functionalized-Lactones via Cu Catalyst



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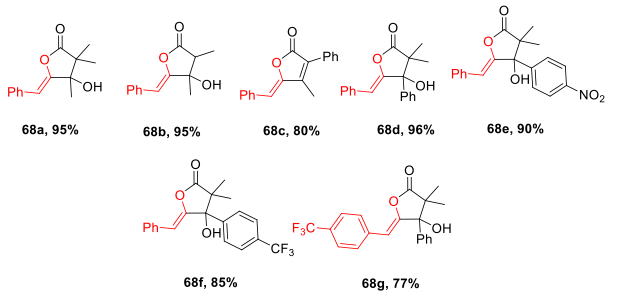
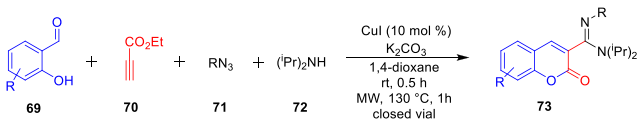


Scheme 19. Microwave-Assisted Synthesis of 3-*N*-Sulfonylamidine Coumarins via Cu(I) Catalyst



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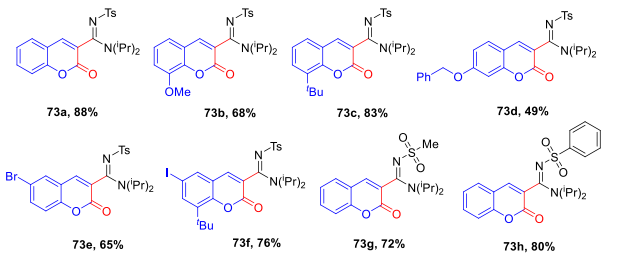


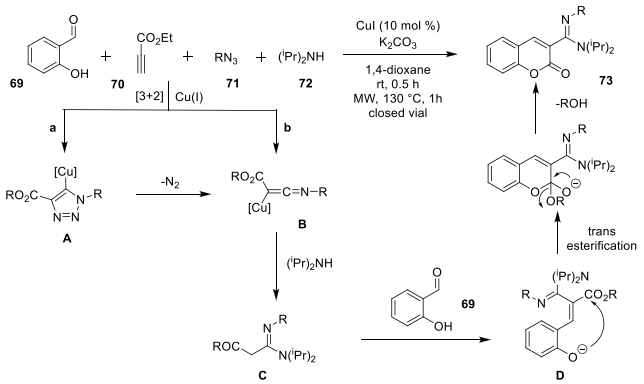
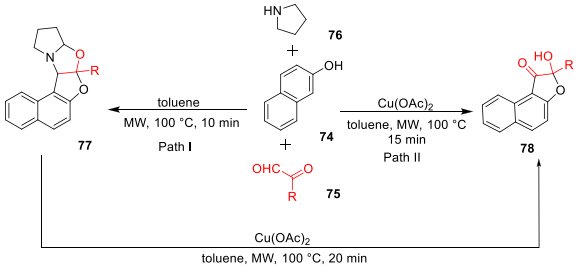


Figure 11. Plausible mechanism for the synthesis of 3-*N*-sulfonylamidine coumarins.

Scheme 20. Microwave-Assisted Synthesis of Napthofuranones via Cu(II) Catalyst



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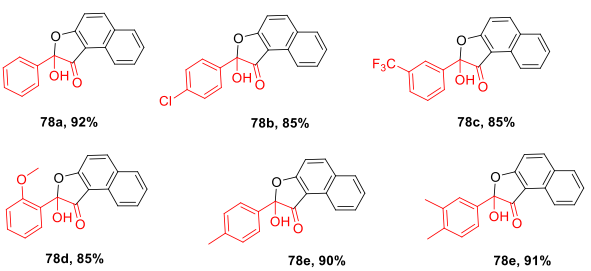

benzimidazolone **90** was synthesized from benzimidazol-2-one-alkyne **88** and various aryl nitrile oxides **89** in the presence of Cu(I) catalyst using Et_3N as base in DMF solvent under

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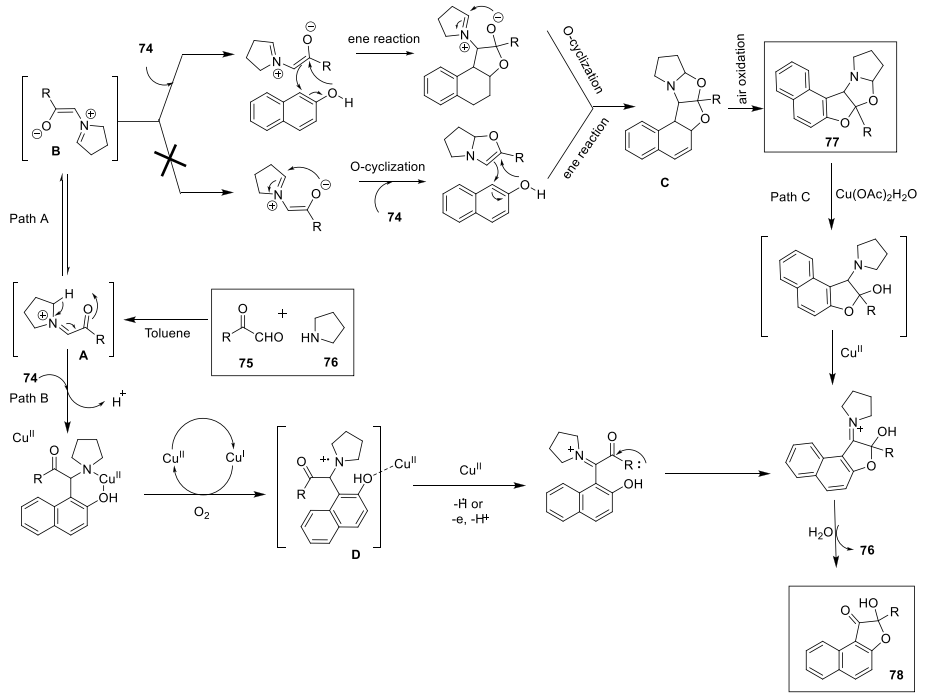
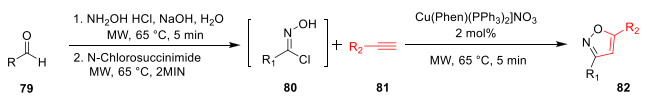


Figure 12. Plausible mechanism of synthesis of napthofuranones.

Scheme 21. Microwave-Assisted Synthesis of 3,5-Disubstituted Isoxazoles in Green Media



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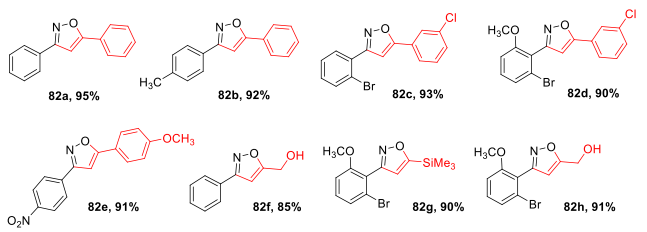
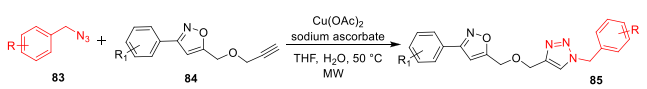
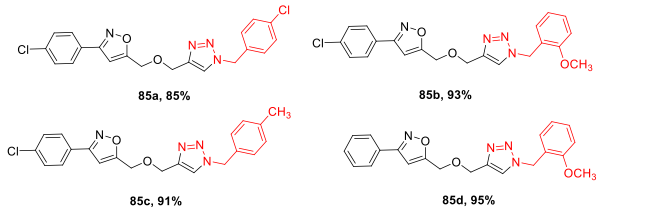


Scheme 22. Synthesis of 1,2,3-Triazoles Fused Isoxazoles



Selected examples



microwaves for 4−7 min. This procedure is attractive for the synthesis of putative active biological compounds because of the simple procedure, quick reaction time, and excellent yield of biheterocyclic products. The *in vitro* antibacterial and antioxidant properties of each of the freshly produced species **90** have been examined. Compounds **90d** and **90e** showed best antibacterial activity specifically against *E. coli*, *P. aeruginosa*, and *S. aureus* and showed the highest antifungal activity against *C. albicans*, *A. fumigatus*, and *A. brasiliensis* (Scheme 24).[29]

In 2022, Shanmugam et al. developed 2-iminopyrans **94** through microwave-assisted tandem Cu(I) catalyzed multicomponent reaction. 2-Iminopyrans **94** were synthesized by coupling the reaction of enaminones **91**, phenyl acetylenes **92**, and tosyl azide **93** in the presence of Cu(I) as catalyst and Et_3N as base in dichloroethane solvent under microwave conditions at 60 °C for 10 min. Good to modest yields of the corresponding 2-iminopyran were obtained from electron-donating and electron-withdrawing group substituted phenyl enaminones, respectively. Under the reported optimal conditions, several distinct styryl enaminones were tested, and all of them effectively formed the corresponding 2-iminopyran **94** (Scheme 25).[30]

Mechanistically, tosyl azide **93** and phenyl acetylene **92a** produced metalated ketenimine intermediate via Cu(I) catalyst. Afterward, intermediate **A** was formed via addition of enaminone to ketenimine intermediate. Then the final compound 2-iminopyran **94a** was formed via metal−carbon bond dissociation followed by 6π-electron cycloaddition reaction (Figure 13). Finally we have observed that the ligands have tremendous effect on the Cu-catalyzed reactions discussed in this review. The catalytic complexes have a wide range, excellent stability, and reactivity owing to the presence of electron-rich and highly adjustable ligands. The electron-rich ligands could greatly enhance the reducing capability of the copper catalyst, whereas coordination with copper enhances the good stability and solubility in organic solvents.

CONCLUSION

Copper-catalyzed coupling processes have come a long way in the previous decade, and significant progress has been made in this area. A number of copper precursors, both metallic and salt-based, have been used effectively, with the latter having a

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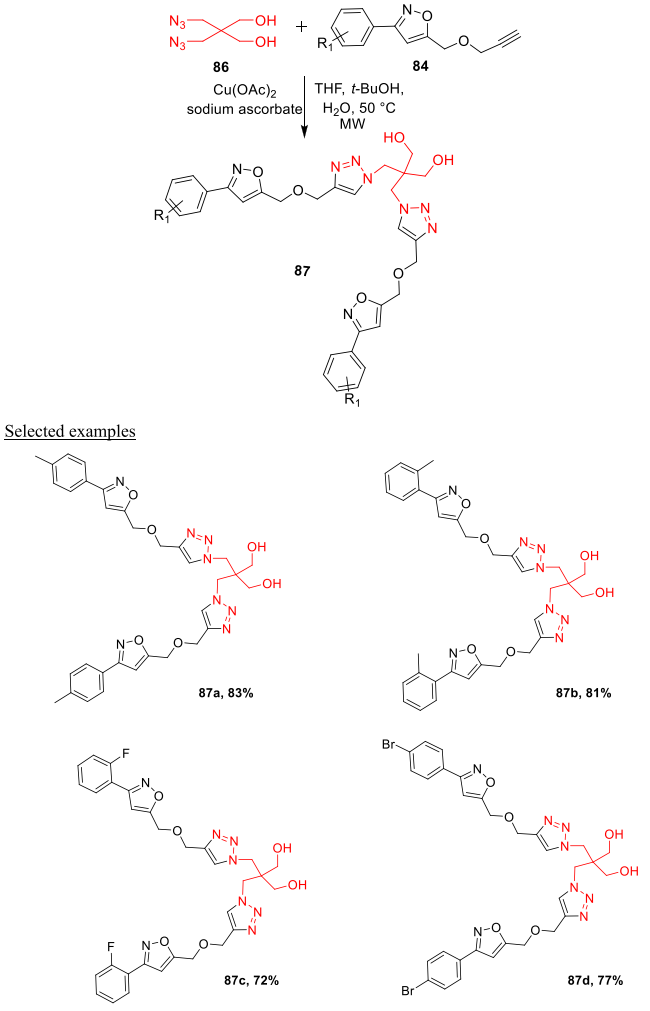
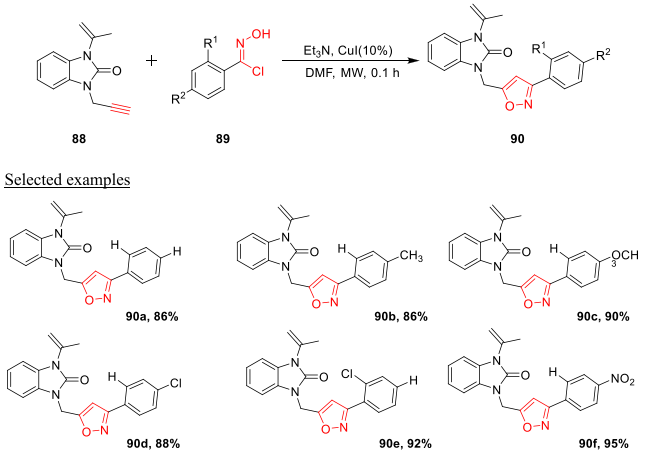
Scheme 23. Synthesis of Dimeric 1,2,3-Triazoles Fused Isoxazoles under Microwaves



Scheme 24. Microwave-Assisted Synthesis of Isoxazole Linked Benzimidazolones



noticeable impact on the transformation in the presence of microwaves heating. Microwave assisted organic reactions have clear advantages over conventional reaction conditions in terms of cleaner reaction profile, lower energy consumption, and higher yields. In this review, there are several metal species that

Scheme 25. Cu(I) Catalyzed Microwave Assisted Synthesis of 2-Iminopyrans

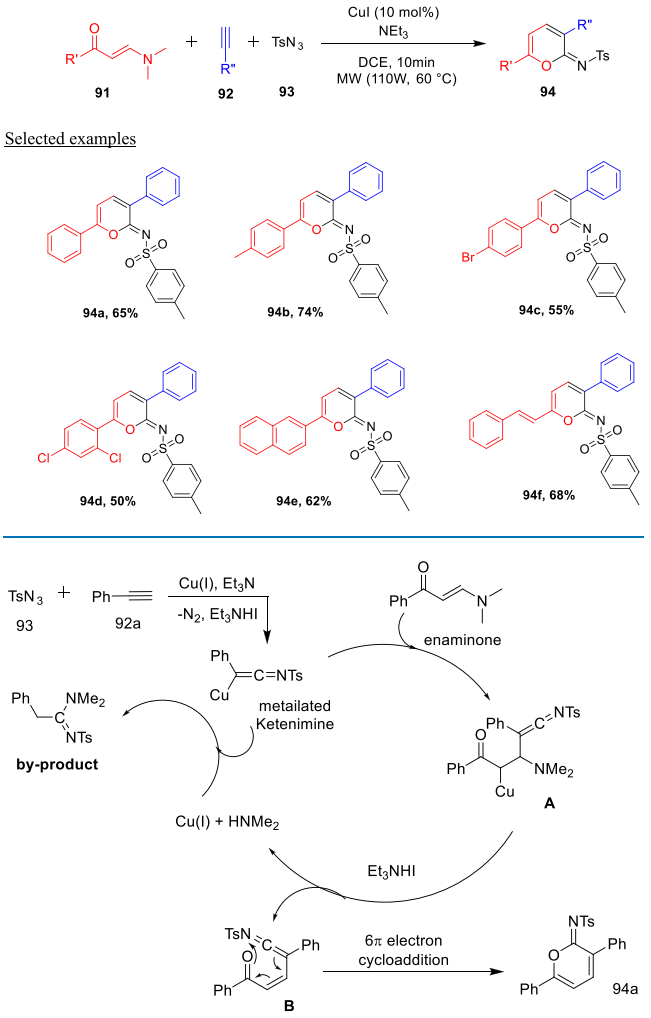


Figure 13. Plausible mechanism of the synthesis of 2-iminopyrans.

have been shown to provide the greatest conversion of starting materials, and copper(I) is one of them. Further work is needed to produce environmentally friendly and sustainable procedures with a high degree of atom economy, such as by designing new ligands, synthesizing novel copper complexes, and using environmentally friendly solvents under microwave irradiation.

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Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acsomega.3c02041
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■ ACKNOWLEDGMENTS

The authors thank the Chancellor and Vice Chancellor of Vellore Institute of Technology for providing opportunity to carry out this study. Further the authors wish to thank the management of this institute for providing seed money as research grant.

■ REFERENCES

(1) (a) Huang, J.; Ding, F.; Rojsitthisak, P.; He, F. S.; Wu, J. Recent Advances in Nitro-Involved Radical Reactions. *Org. Chem. Front.* **2020**, *7* (18), 2873−2898. (b) Louillat, M. L.; Patureau, F. W. Oxidative C-H Amination Reactions. *Chem. Soc. Rev.* **2014**, *43* (3), 901−910. (c) Zhou, K.; Yu, Y.; Lin, Y. M.; Li, Y.; Gong, L. Copper-Catalyzed Aerobic Asymmetric Cross-Dehydrogenative Coupling of C(Sp^3)-H Bonds Driven by Visible Light. *Green Chem.* **2020**, *22* (14), 4597−4603.

(2) (a) Ullmann, F. Ueber Eine Neue Bildungsweise von Diphenylaminderivaten. *Berichte der Dtsch. Chem. Gesellschaft* **1903**, *36* (2), 2382−2384. (b) Goldberg, I. Über Phenylierung von primären aromatischen Amine. *Dtsch. Chem. Ges.* **1907**, *40*, 4541−4546. (c) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angew. Chem., Int. Ed. Engl.* **1995**, *34* (12), 1348−1350. (d) Hartwig, J. F. Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. *Angew. Chemie Int. Ed.* **1998**, *37* (15), 2046−2067. (e) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-Arylations with Phenylboronic Acids and Cupric Acetate. *Tetrahedron Lett.* **1998**, *39* (19), 2933−2936. (f) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New Aryl/Heteroaryl C-N Bond Cross-Coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation. *Tetrahedron Lett.* **1998**, *39* (19), 2941−2944.

(3) Shilpa, T.; Neetha, M.; Anilkumar, G. Recent Trends and Prospects in the Copper-Catalysed "on Water" Reactions. *Adv. Synth. Catal.* **2021**, *363* (6), 1559−1582.

(4) Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y. Copper(I)-Catalyzed Asymmetric Reactions Involving Radicals. *Acc. Chem. Res.* **2020**, *53* (1), 170−181.

(5) (a) Nishanth Rao, R.; Jena, S.; Mukherjee, M.; Maiti, B.; Chanda, K. Green Synthesis of Biologically Active Heterocycles of Medicinal Importance: A Review. *Environ. Chem. Lett.* **2021**, *19* (4), 3315−3358. (b) Martina, K.; Cravotto, G.; Varma, R. S. Impact of Microwaves on Organic Synthesis and Strategies toward Flow Processes and Scaling Up. *J. Org. Chem.* **2021**, *86*, 13857−13872. (c) Shalaby, M. A.; Fahim, A. M.; Rizk, S. A. Microwave-assisted synthesis, antioxidant activity, docking simulation, and DFT analysis of different heterocyclic compounds. *Sci. Rep.* **2023**, *13*, 4999.

(6) (a) Urbina, K.; Tresp, D.; Sipps, K.; Szostak, M. Recent Advances in Metal-Catalyzed Functionalization of Indoles. *Adv. Synth. Catal.* **2021**, *363*, 2723−2739. (b) Liu, F.; Anand, L.; Szostak, M. Diversification of Indoles and Pyrroles by Molecular Editing: New Frontiers in Heterocycle-to-Heterocycle Transmutation. *Chem.—Eur. J.* **2023**, *29*, No. e202300096.

(7) Kuang, J.; Chen, B.; Ma, S. Copper-Mediated Efficient Three-Component Synthesis of 1,2,4-Triazoles from Amines and Nitriles. *Org. Chem. Front.* **2014**, *1* (2), 186−189.

(8) Naresh, G.; Kant, R.; Narender, T. Copper(II) Catalyzed Expeditious Synthesis of Furoquinoxalines through a One-Pot Three-Component Coupling Strategy. *Org. Lett.* **2014**, *16* (17), 4528−4531.

(9) Kumar, Y.; Matta, A.; Kumar, P.; Parmar, V. S.; Van Der Eycken, E. V.; Singh, B. K. Cu(i)-Catalyzed Microwave-Assisted Synthesis of 1,2,3-Triazole Linked with 4-Thiazolidinones: A One-Pot Sequential Approach. *RSC Adv.* **2015**, *5* (2), 1628−1639.

(10) Zhang, X. Y.; Yang, Z. W.; Chen, Z.; Wang, J.; Yang, D. L.; Shen, Z.; Hu, L. L.; Xie, J. W.; Zhang, J.; Cui, H. L. Tandem Copper-Catalyzed Propargylation/Alkyne Azacyclization/Isomerization Reaction under Microwave Irradiation: Synthesis of Fully Substituted Pyrroles. *J. Org. Chem.* **2016**, *81* (5), 1778−1785.

(11) Yamamoto, C.; Takamatsu, K.; Hirano, K.; Miura, M. Copper-Catalyzed Intramolecular Benzylic C-H Amination for the Synthesis of Isoindolinones. *J. Org. Chem.* **2016**, *81* (17), 7675−7684.

(12) (a) Padmaja, R. D.; Meena, D. R.; Maiti, B.; Chanda, K. $[Cu(Phen)(PPh_3)_2]NO_3$-Catalyzed Microwave-Assisted Green Synthesis of 5-Substituted 1*H*-Tetrazoles. *Res. Chem. Intermed.* **2017**, *43* (12), 7365−7374. (b) Padmaja, R. D.; Rej, S.; Chanda, K. Environmentally friendly, microwave-assisted synthesis of 5-substituted

https://doi.org/10.1021/acsomega.3c02041
ACS Omega 2023, 8, 23240−23256

1*H*-tetrazoles by recyclable CuO nanoparticles via (3 + 2) cycloaddition of nitriles and NaN_3. *Chin. J. Catal.* **2017**, *38*, 1918−1924.
(13) Kumar Baba, N. H.; Ashok, D.; Rao, B. A.; Sarasija, M.; Murthy, N. Y. S. Microwave-Assisted Synthesis of Novel Benzodifuran-Based Bis(N-(Het)Arylthiazol-2-Amine) Derivatives and Their Antibacterial and Antimycobacterial Activities. *Chem. Heterocycl. Compd.* **2018**, *54* (6), 658−663.
(14) Panday, A. K.; Mishra, R.; Jana, A.; Parvin, T.; Choudhury, L. H. Synthesis of Pyrimidine Fused Quinolines by Ligand-Free Copper-Catalyzed Domino Reactions. *J. Org. Chem.* **2018**, *83* (7), 3624−3632.
(15) Dao, P. D. Q.; Ho, S. L.; Cho, C. S. Synthesis of N-Fused Benzimidazole-4,7-Diones via Sequential Copper-Catalyzed C-N Coupling/Cyclization and Oxidation. *ACS Omega* **2018**, *3* (5), 5643−5653.
(16) Ke, F.; Liu, C.; Zhang, P.; Xu, J.; Chen, X. Efficient and Selective Microwave-Assisted Copper-Catalyzed Synthesis of Quinazolinone Derivatives in Aqueous. *Synth. Commun.* **2018**, *48* (24), 3089−3098.
(17) Narsimha, S.; Battula, K. S.; Reddy, Y. N.; Nagavelli, V. R. Microwave-Assisted Cu-Catalyzed C-C Bond Formation: One-Pot Synthesis of Fully Substituted 1,2,3-Triazoles Using Nonsymmetrical Iodoalkynes and Their Biological Evaluation. *Chem. Heterocycl. Compd.* **2018**, *54* (12), 1161−1167.
(18) Saikia, A. A.; Nishanth Rao, R.; Das, S.; Jena, S.; Rej, S.; Maiti, B.; Chanda, K. Sequencing [3 + 2]-Cycloaddition and Multicomponent Reactions: A Regioselective Microwave-Assisted Synthesis of 1,4-Disubstituted 1,2,3-Triazoles Using Ionic Liquid Supported Cu(II) Precatalysts in Methanol. *Tetrahedron Lett.* **2020**, *61* (36), 152273.
(19) Malasala, S.; Polomoni, A.; Chelli, S. M.; Kar, S.; Madhavi, Y. V.; Nanduri, S. A Microwave-Assisted Copper-Mediated Tandem Approach for Fused Quinazoline Derivatives. *Org. Biomol. Chem.* **2021**, *19* (8), 1854−1859.
(20) Nesaragi, A. R.; Kamble, R. R.; Bayannavar, P. K.; Shaikh, S. K. J.; Hoolageri, S. R.; Kodasi, B.; Joshi, S. D.; Kumbar, V. M. Microwave Assisted Regioselective Synthesis of Quinoline Appended Triazoles as Potent Anti-Tubercular and Antifungal Agents via Copper (I) Catalyzed Cycloaddition. *Bioorg. Med. Chem. Lett.* **2021**, *41*, 127984.
(21) Dao, P. D. Q.; Cho, C. S. Copper-Catalyzed Synthesis of 5-Arylindolo[1,2-c]Quinazolin-6(5H)-Ones from 2-(2-Bromoaryl)-Indoles and Aryl Isocyanates under Microwave Irradiation. *Eur. J. Org. Chem.* **2022**, *2022* (22), No. e202200479.
(22) Rajput, D.; Kumar, A.; Jandial, T.; Karuppasamy, M.; Bhuvanesh, N.; Kumar, R. S.; Almansour, A. I.; Sridharan, V. Microwave-Assisted Copper(II)-Catalyzed Cascade Cyclization of 2-Propargylamino/Oxy-Arylaldehydes and O-Phenylenediamines: Access to Densely Functionalized Benzo[f]Imidazo[1,2-d][1,4]Oxazepines and Benzo[f]Imidazo-[1,2-d][1,4]Diazepines. *J. Org. Chem.* **2022**, *87* (14), 8956−8969.
(23) Ashok, D.; Thara, G.; Kumar, B. K.; Srinivas, G.; Ravinder, D.; Vishnu, T.; Sarasija, M.; Sushmitha, B. Microwave-Assisted Synthesis, Molecular Docking Studies of 1,2,3-Triazole-Based Carbazole Derivatives as Antimicrobial, Antioxidant and Anticancer Agents. *RSC Adv.* **2022**, *13* (1), 25−40.
(24) López-Reyes, M. E.; Toscano, R. A.; López-Cortés, J. G.; Alvarez-Toledano, C. Fast and Efficient Synthesis of Z-Enol-γ-Lactones through a Cycloisomerization Reaction of β-Hydroxy-γ-Alkynoic Acids Catalyzed by Copper(I) under Microwave Heating in Water. *Asian J. Org. Chem.* **2015**, *4* (6), 545−551.
(25) Murugavel, G.; Punniyamurthy, T. Microwave-Assisted Copper-Catalyzed Four-Component Tandem Synthesis of 3- N -Sulfonylamidine Coumarins. *J. Org. Chem.* **2015**, *80* (12), 6291−6299.
(26) Battini, N.; Battula, S.; Kumar, R. R.; Ahmed, Q. N. 2-Oxo Driven Unconventional Reactions: Microwave Assisted Approaches to Tetrahydrofuro[3,2- d]Oxazoles and Furanones. *Org. Lett.* **2015**, *17* (12), 2992−2995.
(27) Meena, D. R.; Maiti, B.; Chanda, K. Cu(I) Catalyzed Microwave Assisted Telescopic Synthesis of 3,5-Disubstituted Isoxazoles in Green Media. *Tetrahedron Lett.* **2016**, *57* (49), 5514−5517.
(28) Li, J.; Liu, H.; Meng, F.; Yan, L.; Shi, Y.; Zhang, Y.; Gu, Q. Microwave-Assisted Synthesis of New 1,2,3-Triazoles Bearing an Isoxazole Ring by the Azide-Alkyne Cycloaddition Click Chemistry. *Chem. Res. Chinese Univ.* **2018**, *34* (2), 197−202.
(29) Ibrahim, S.; Ghabi, A.; Amiri, N.; Mtiraoui, H.; Hajji, M.; Bel-Hadj-Tahar, R.; Msaddek, M. Microwave-Assisted Synthesis of (3,5-Disubstituted Isoxazole)-Linked Benzimidazolone Derivatives: DFT Calculations and Biological Activities. *Monatshefte fur Chemie* **2021**, *152* (5), 523−535.
(30) Pasumpon, K.; Mahendran, V.; Shanmugam, S. Microwave-Assisted Tandem Copper-Catalyzed Three-Component Reaction for Synthesis of 2-Iminopyrans. *ChemistrySelect* **2022**, *7* (46), No. e202203659.

https://doi.org/10.1021/acsomega.3c02041
ACS Omega 2023, 8, 23240−23256