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REVIEW

Recent Developments in Synthesis of Sulfur Heterocycles *via* Copper-Catalyzed C-S Bond Formation Reaction

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ABSTRACT

In a large number of biologically active natural products and pharmaceuticals, the important substructures are sulfur containing heterocycles. Thioethers and other sulphur-rich molecules commonly occur in chemical biology, organic synthesis and material chemistry. In case of the formation of carbon-heteroatom bonds, copper catalyzed cross-coupling reactions provide a powerful tool as its cost is low and here the readily accessible and stable ligands are used. It has been recognized that copper catalyzed C–S coupling reactions are an efficacious strategy for synthesizing sulfur-rich heterocyclic compounds and so the strategy has gained worldwide attention. This review sums up recent research developments in the field of synthesis of sulfur-containing heterocycles using copper-catalyst.

KEYWORDS

Copper, Sulfur, Heterocyclic compound, Sulfur-heterocyles, Cross-coupling, C-S coupling.

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INTRODUCTION

For the preparation of important compounds in biological, pharmaceutical and material sciences, transition-metal-catalyzed cross-coupling reactions [1-5] leading to the formation of carbon–heteroatom [6-11] has been adopted as a popular and powerful strategy. The copper-mediated C-S bond formation is an important transformation, which includes a wide range of substrates. It has evolved in course of time and gained much attention due to its applications in the synthesis of molecules having biological and pharmaceutical impact. Researchers also take interest in exploring new application of Cu-catalyzed coupling. The synthesis of natural products and biologically interesting molecules are typical examples and they have been comprehensively reviewed [12,13]. The following reasons have made copper catalysis popular and advantageous: (a) availability of copper in the earth and low cost; (b) high catalytic activity in carbon-heteroatom bond formation; (c) low toxicity and easy recyclability; (d) excellent tolerance to different functional groups as well as reaction conditions [14-16]. Although various research groups have referred to many attractive Cu-catalyzed coupling processes, the Cu-catalyzed synthesis of sulfur-containing heterocycle has not been reviewed yet. Sometimes discussion of C-S coupling and sulfur-containing heterocycle synthesis has been made in articles concerned with other carbon-heteroatom coupling reactions [17-21]. Here the developments in Cu-catalyzed coupling reactions in the synthesis of sulfur-heterocyclic compounds have been summed up systematically. It must be noted that for the first time an attempt has been made to produce a concise article on the synthesis of the sulfur-heterocycles promoted by copper catalyst. In this review, the current strategies and applications of Cu-catalyzed C-S cross coupling reactions to the synthesis of sulfur-heterocyclic compounds have been preented.

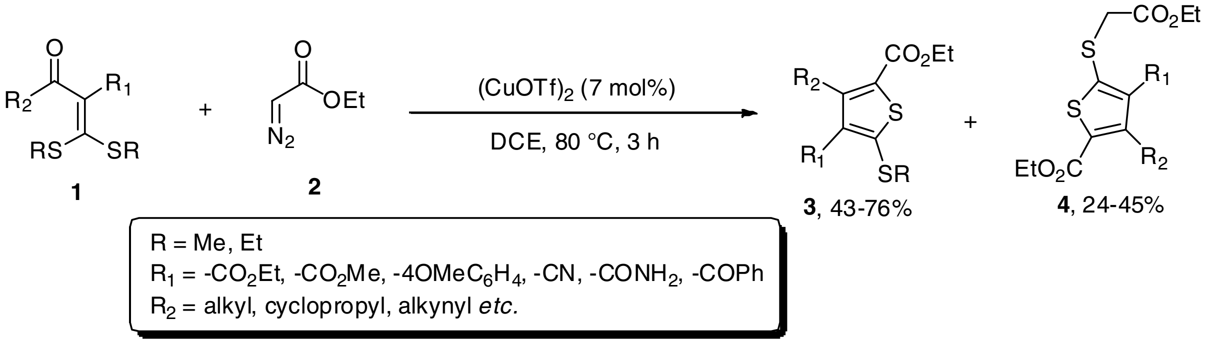
Substituted thiophenes and its analogues are valuable building blocks widely present in pharmaceutical and natural product chemistry [22-29], copper(II)-catalyzed C-S coupling reaction for the synthesis of substituted thiophenes have been reported by Wang and his group [30]. They have successfully utilized $Cu(OTf)_2$ in a domino reaction of the acyclic ketene-(*S*,*S*)-acetals (**1**) with diazo compounds **2** for the synthesis of poly-substituted thiophenes (**Scheme-I**). Investigation of copper catalysts revealed that $Cu(OTf)_2$ was found to be better than other Cu(II) salts and the reaction proceeded best in DCE and it was observed that DMF, THF and CH_3CN are not suitable for this reaction. It was found that when the R_1 group in **1** was CO_2Me, CO_2Et and 4-$OMeC_6H_4$, the poly-substituted thiophenes **3** and **4** were obtained as major and minor products, respectively. However, when R_1 group was changed for -CN, -COPh and –$CONH_2$, the tandem reaction yielded the exclusive poly-substituted thiophenes **3** in moderate to good yields.

It is interesting to note that when substitutions R_1 group was replaced by –COC_2H_5 and –$COCH_3$, the product **3** were isolated as the minor products and the fused-ring derivatives **5** obtained in 55-59% yields as the major products (**Scheme-II**). The reaction was carried out by **1** (0.2 mmol) and $Cu(OTf)_2$ (7 mol%) in DCE, followed by a solution of **2** (0.6 mmol) and DCE (1 mL) at 80 °C for 3 h. However, with increasing the amount of **2** the yields of the products **5** also increased. The overall reaction proceeds *via* consecutive formation of electrophilic copper carbenoid, sulfur ylide and then C-S bond formation and final cleavage to furnish the products **3** and **4**. When the R_1 substitutions were propionyl and acetyl, an additional intramolecular aldol cyclization afforded fused thiophene **5** in good yields.

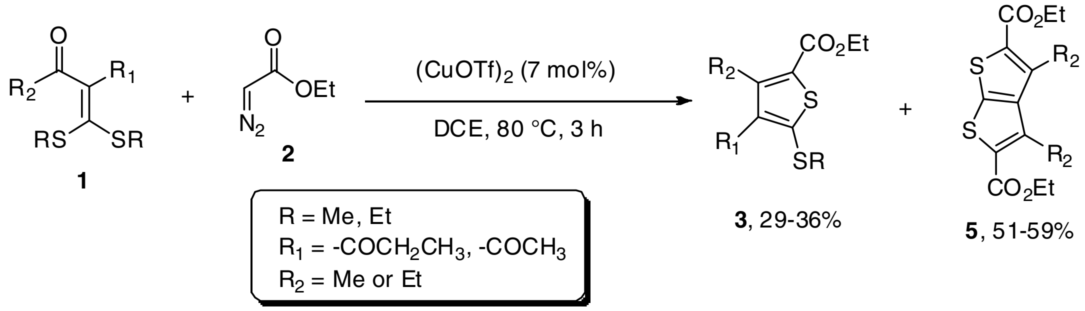
Recently, Liu and his co-workers [31] developed an unique copper-catalyzed three-component reactions of 2-iodobenzamides (**6**), elemental sulfur and CH_2Cl_2 for the synthesis of 2,3-dihydrobenzothiazinones (**7**) in moderate yields (**Scheme-III**). A variety of 2-iodobenzamides (**6**) were introduced to react with elemental sulfur and CH_2Cl_2 under the optimized reaction conditions. As outlined in **Scheme-IV**, the reaction and consequence synthesis of **6** exhibited functional group tolerance to the *N*-benzyl (**8-10** and **16-17 Scheme-III**), *N*-benzethyl (**15**, **Scheme-III**), *N*-alkyl (**11** and **19**, **Scheme-III**) as well as *N*-aryl (**12-14** and **18 Scheme-III**) substituents.

In the same article, authors also synthesized benzoisothiazolone derivatives **20** from *o*-iodobenzamides **6**. The reaction was carried out without using dichloromethane and *o*-iodobenzimide **6**, mixed with sulfur powder, $CuBr_2$, Et_3N in DMSO at 120 °C with microwave irradiation for 10 min in sealed tube under air. The MW irradiation turned out to be an efficient tool for rapid synthesis of **20**. This microwave-assisted copper-catalyzed domino synthesis of benzoisothiazolones is shown in **Scheme-V**. The benzamides **6** with different substitution, including benzyls, phenylethyl, alkyls as well as aryls reacted with elemental sulfur to give corresponding products **20** in good yields.

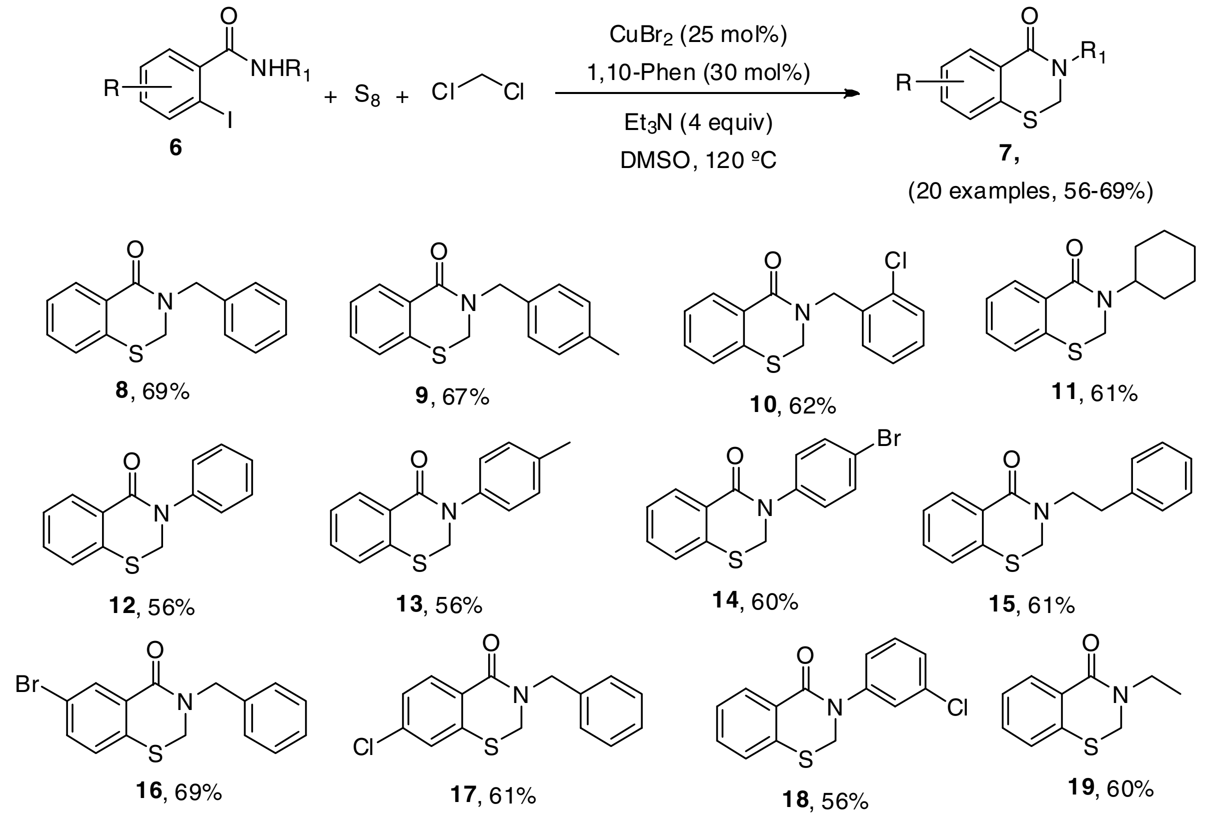
Zhao *et al.* [32] developed Cu-catalyzed C-H thioamination of maleimides with 2-aminoethanethiol hydrochloride. The reaction between maleimides **21** and 2-aminoethanethiol hydrochloride (**22**) in the presence of CuI (20 mol%) along with aerial oxygen smoothly produced the desired product in good



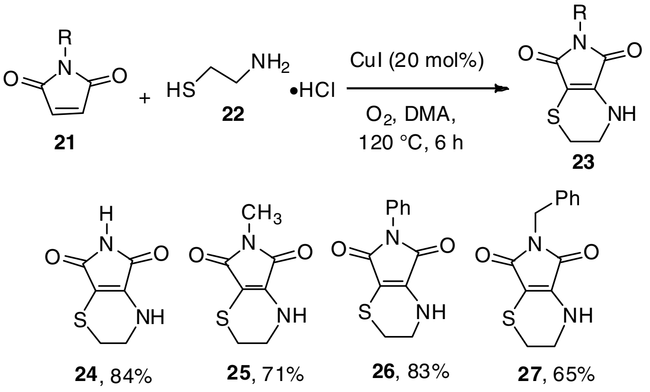
Scheme-I



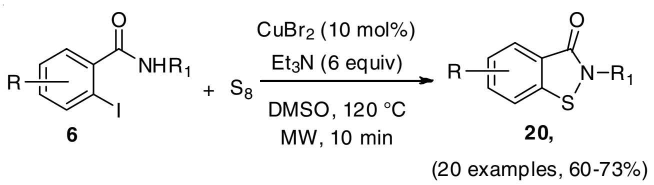
Scheme-II



Scheme-III



Scheme-IV



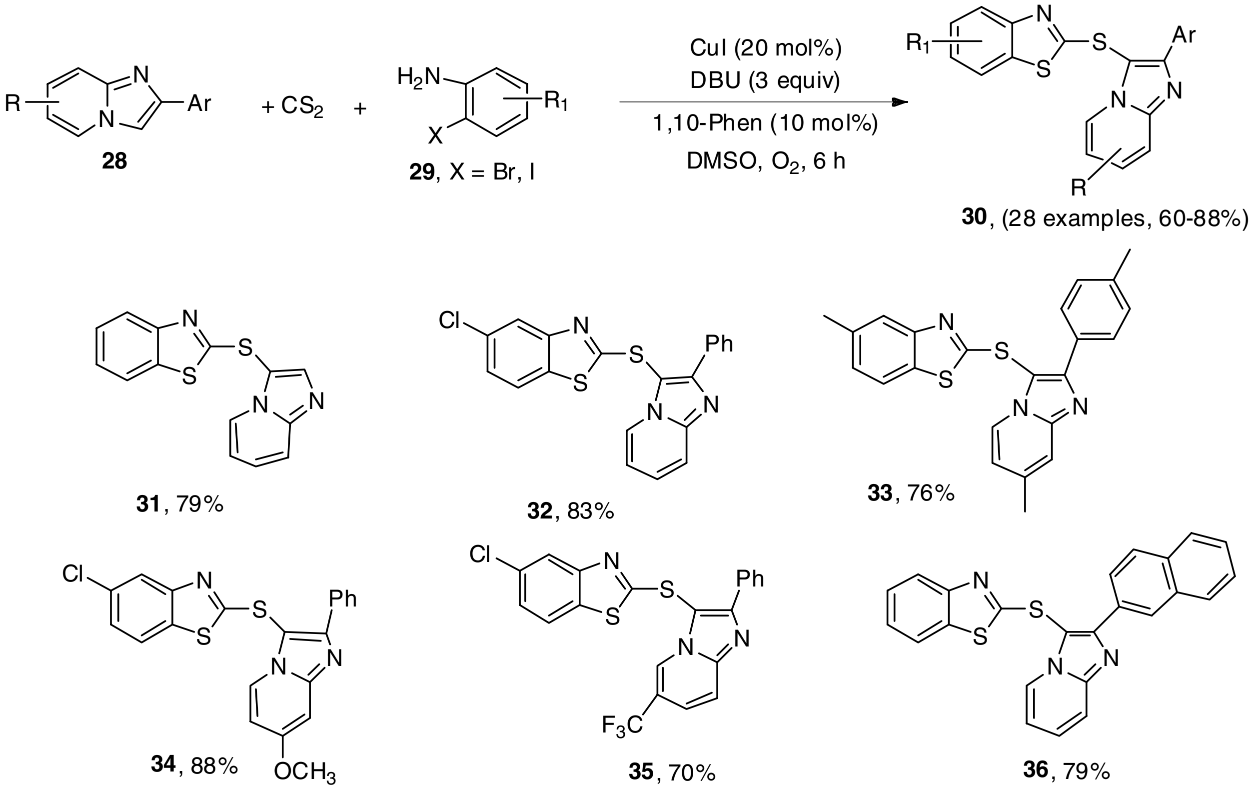
Scheme-V

yields (**Scheme-IV**). Similar reaction of maleimides with 2-aminothiophenol have also been carried out and the coupling product was obtained as yellow-white solid.

Carbon disulfide (CS_2) is a well known, cheap and readily accessible raw material widely used in the synthesis of sulfur-containing compounds. However, the use of CS_2 is very limited in transition-metal-mediated carbon-sulfur bond forming reactions. Recently, Yang *et al.* [33] developed an efficient domino method for the synthesis of C-3 sulfenylated imidazo[1,2-*a*]pyridine derivatives from the reactions between substituted imidazo[1,2-*a*]pyridines (**28**), CS_2 and 2-haloanilines (**29**) using CuI as the catalyst, 1,10-phenanthroline as the ligand, DBU as base in DMSO under atmospheric oxygen (**Scheme-VI**). They have prepared almost 28 different derivatives and highlighted only few to show the control of the reaction on different substitutions. The substrates bearing electron-attracting group such as chlorine (**32**, **34**) and trifluoromethyl (**35**) or electron-releasing group such as methyl (**33**) and methoxy (**34**) were found to be effective substrates for the formation of C-3 sulfenylated imidazo[1,2-*a*]pyridine derivatives (**Scheme-VI**). These experiments also showed that oxygen is necessary for this domino reaction and copper iodide is essential for the formation of three chemical bonds in an one-pot organic transformation.

2-Aminobenzothiazole derivatives are very important benzothiazole scaffold, have important anticancer activity and the moieties are proved to be effective pharmacophores as well as valuable reactive intermediates [34-40]. A ligand-free copper(I)-catalyzed one-pot cascade method for the formation of *N*-substituted-2-aminobenzothiazoles was developed by Bao *et al.* [41] where variety of isothiocyanates coupled with 2-iodoanilines to produce *N*-substituted-2-amino-benzothiazoles in good yields under mild conditions.

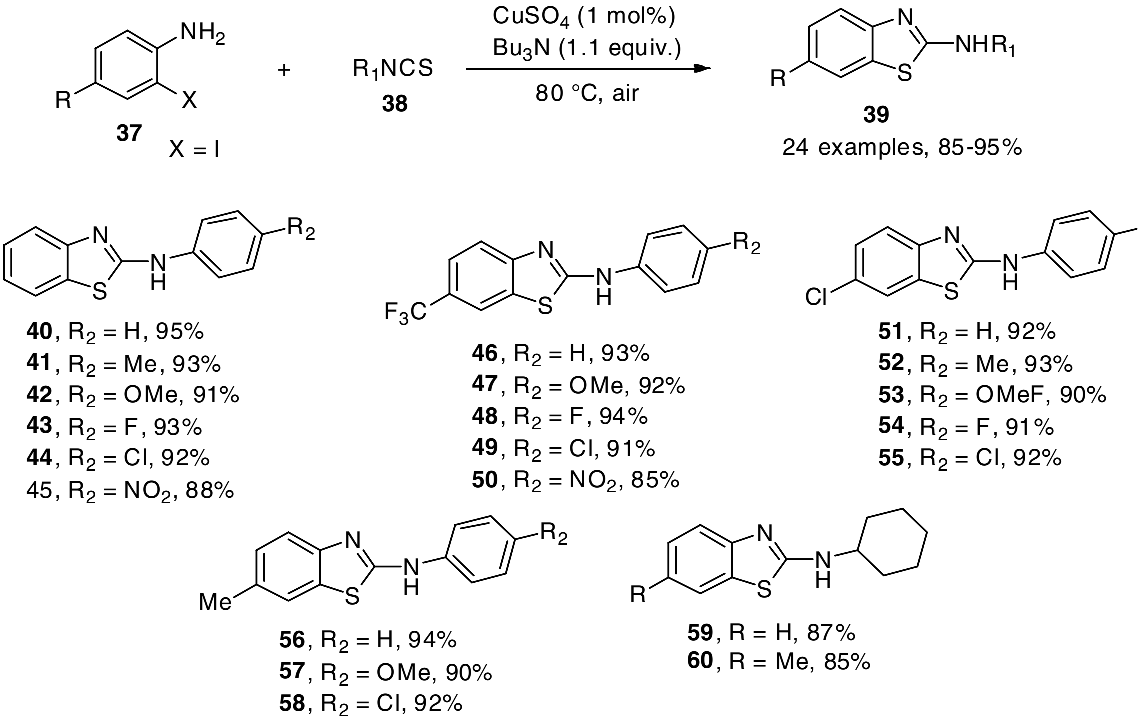
Cai *et al.* [42] recently reported another efficient and convenient method for the synthesis of 2-aminobenzothiazoles by a Cu(II)-catalyzed cascade reaction of isothiocyanates with 2-haloanilines under an unique ligand- and solvent-free conditions in air. The method for the synthesis of **39** by a Cu-catalyzed tandem reaction of substituted 2-iodoanilines **37** with a variety of isothiocyanates **38** using $CuSO_4$ (1 mol%) as catalyst and Bu_3N (1.1 equiv.) as a base under ligand- and solvent-free



Scheme-VI

conditions in air and the results are shown in **Scheme-VII**. Various functional groups, both electron-releasing and electron withdrawing groups, such as methyl, methoxy, fluoro, chloro and nitro groups, were well tolerated. Similarly, both the electron rich and electron poor aryl isothiocyanates underwent this tandem reaction successfully with a good yield (**Scheme-VII**). Products **39** were also successfully isolated starting from 2-bromoaniline derivatives in 90-93% yields under a very similar reaction condition.

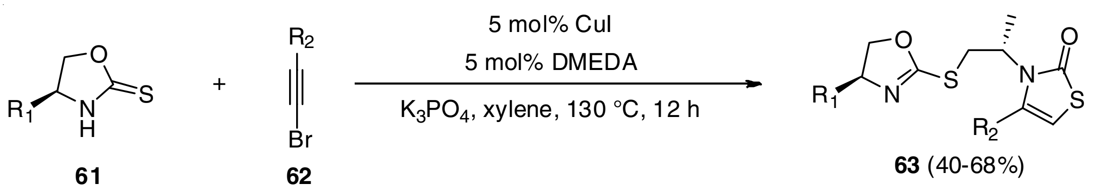
Copper-catalyzed domino reaction for the synthesis of thiazol-2-ones **63** has been reported recently by Zhang & Xie [43]. The reaction was carried out in presence of CuI



Scheme-VII

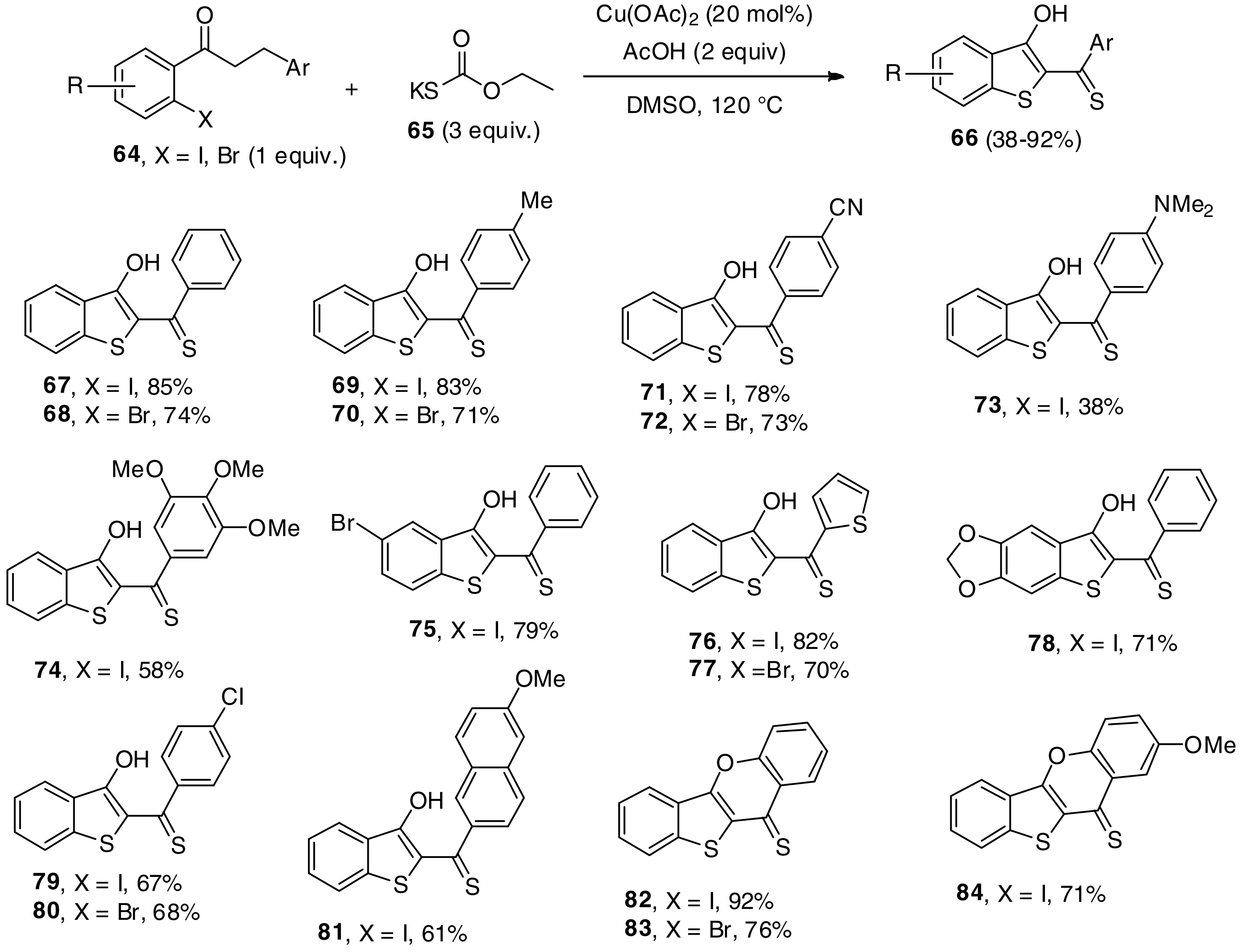
(5 mol%) and N,N′-dimethylethylenediamine (DMEDA) (5 mol%) along with K_3PO_4 between alkynyl bromides **62** and oxazolidine-2-thione derivatives **61** to furnish the cyclized products **63** in good to moderate yield (**Scheme-VIII**). One important aspect of this reaction is that the C-N and C-S bonds are formed simultaneously in a single operation.

Multi-substituted 3-hydroxybenzo[*b*]thiophene is a versatile precursor covering a vast area of research fields, including medicinal and material chemistry. 3-Hydroxybenzo[*b*]thiophene is also proved to be exhibited inhibitor activity against human monoamine oxidase (hMAO) [44]. It works good as an anti-inflammatory agent [45], a synthetic precursor for the synthesis of hemithioindigo (HTI), which has a chromophoric unit that denotes photoswitching properties under visible light irradiation [46]. Recently, Sekar *et al.* [47] reported the Cu-catalyzed tandem synthesis of poly-substituted benzo[*b*]thiophene **66** *via* radical cyclization of 2-halophenyl ketones **64** using xanthate **65** as a sulfur replacement in good yields. The scope of this tandem synthesis was explored with differently substituted 2-halophenyl ketones and the results are shown in **Scheme-IX**. The reaction worked well for both 2-iodo and 2-bromophenyl ketone with substituents (both electron-releasing and electron-withdrawing) on the arene attached to the aliphatic chain, ensuing the desired products in moderate to good yield

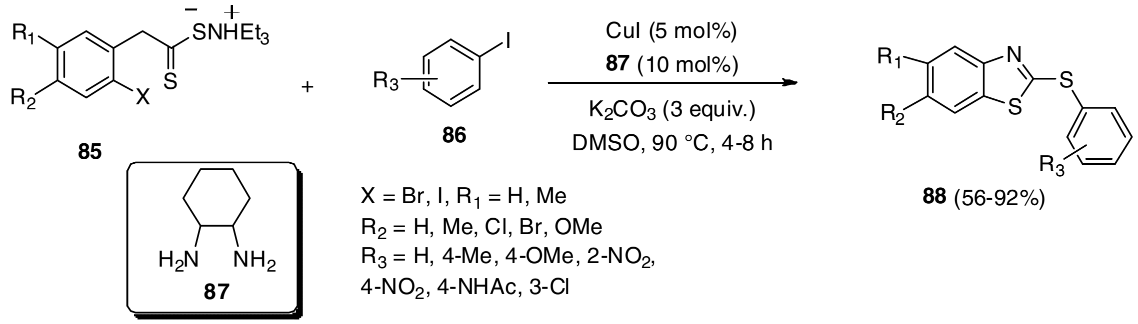


R_1 = Me, *i*-Pr, Ph *etc.*
R_2 = *n*-Bu, *n*-C_6H_{13}, 3-F-C_6H_4, Ph, 4-MeO-C_6H_4 *etc.*

Scheme-VIII: CuI-catalyzed synthesis of thiazol-2-ones



Scheme-IX

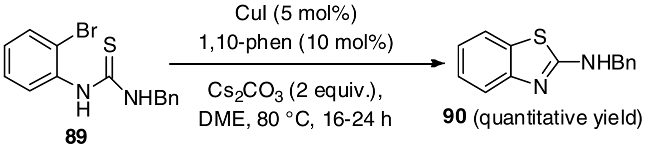


Scheme-X

(**Scheme-IX**). The reaction also developed in the formation of tetracyclic Lupinalbin analogues by introducing *ortho*-methoxy group in the iodophenyl ketones. 2-Thioaroyl-3-hydroxy-benzo-[*b*]thiophene was further derivatized to generate hemithioindigo, which is known to exhibit an efficient photo-switching property.

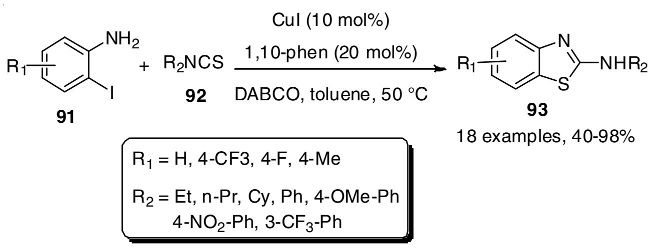
Patel and co-workers [48] developed one-pot reaction technique for the synthesis of 2-arylthiobenzothiazoles (**88**) starting from dithiocarbamates **85** using a ligand **87** and CuI as a catalyst *via* cross-coupling reaction methodology. The key step of this technique is a sequential intra- and intermolecular S-arylation (**Scheme-X**). The effects of various substituents and ligands were also studied, which evolved that the ligand **87** was found to be the best for such transformations. The dithiocarbamates (**85**) were prepared by the reaction of 2-bromoaniline derivatives with CS_2 and triethylamine.

Another interesting copper-catalyzed intramolecular C-S coupling reaction of **89** was developed to furnish 2-aminobenzothiazoles (**90**). It was found that Cu catalysis was more superior and cost effective than that of Pd catalysis (**Scheme-XI**) [38].



Scheme-XI

2-Aminobenzothiazole is present in many pharmaceuticals and agrochemicals as core moiety that exhibit exceptional biological activities [49-53] although the benzothiazole unit is bioactivatible [54]. Wu *et al.* [40] recently developed Cu(I) catalyzed tandem reaction between 2-iodobenzenamine **91** and isothiocyanate **92** under mild reaction conditions for an efficient and practical synthesis of 2-aminobenzothiazole (**93**) in good yield (**Scheme-XII**). The reaction condition was quite simple and usually finish within 2-48 h. The advantages of this method include high efficiency, good substrate tolerance and mild reaction conditions.



Scheme-XII

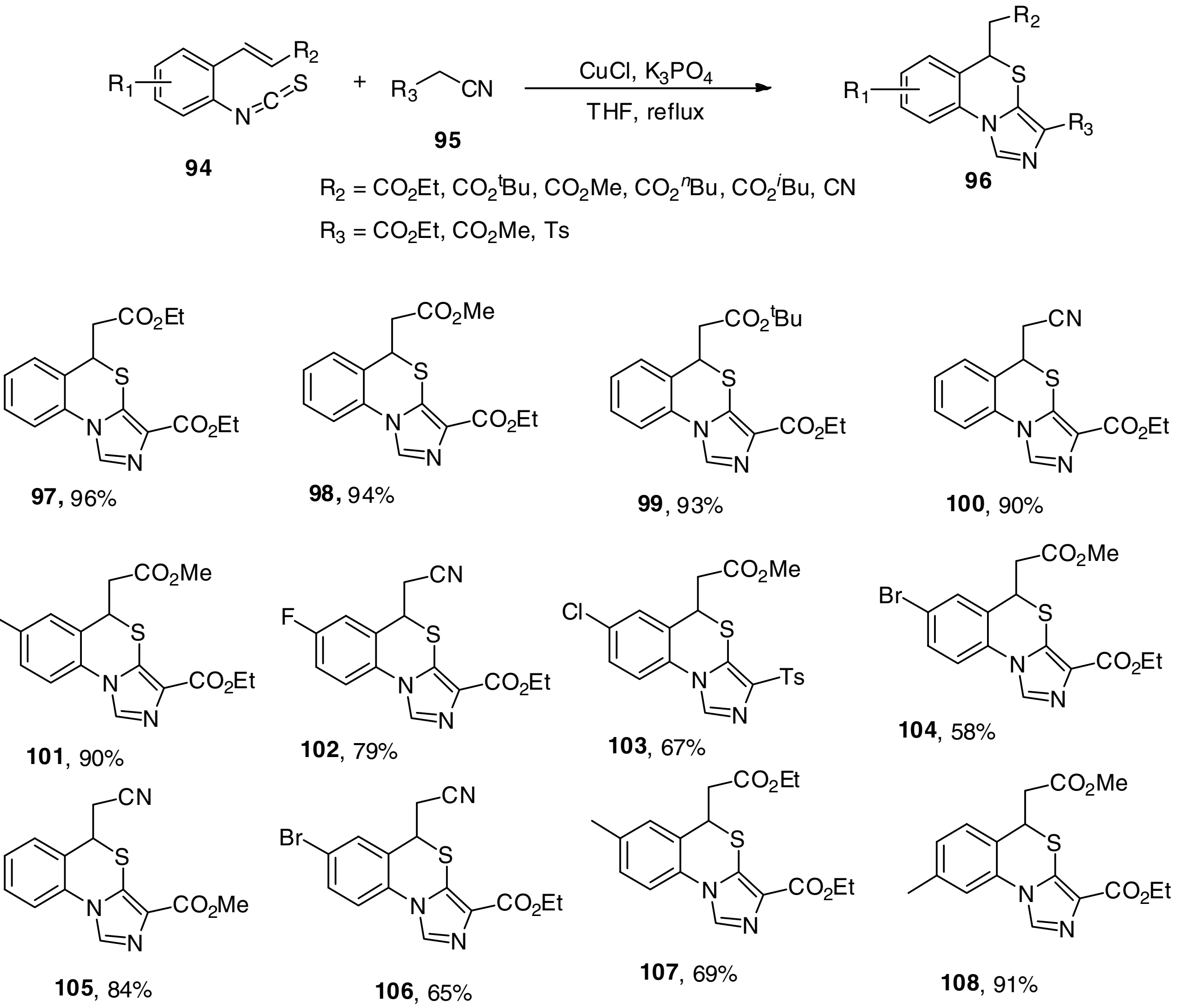
An efficient copper(I)-catalyzed cascade reaction of (*E*)-3-(2-isothiocyanatophenyl)acrylates and (*E*)-3-(2-isothiocyanatophenyl)acrylonitriles **94** with isocyanides **95** for the synthesis of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines **96** was explored by Cai and his co-workers [55]. In this methodology, a [3+2] cycloaddition reaction was involved and two new rings were formed. The tandem addition–cyclization reaction mechanism provides a facile route for making small N,S-heterocycles **96** in good yield (**Scheme-XIII**).

Xi *et al.* [56] recently developed an effecient approach to the synthesis of benzisothiazol-3(2*H*)-one **110** *via* copper-catalyzed reaction of 2-bromobenzamide **109** and potassium thiocyanate in water medium. The best results were obtained when they have used CuI as a precatalyst, 1,10-phenanthroline as ligand, DABCO as a base, Bu_4NI as an additive and H_2O as a solvent at a moderate temperature of 140 ºC (**Scheme-XIV**). The reaction proceeds *via* simultaneous formation of S–C bond and S–N bond.

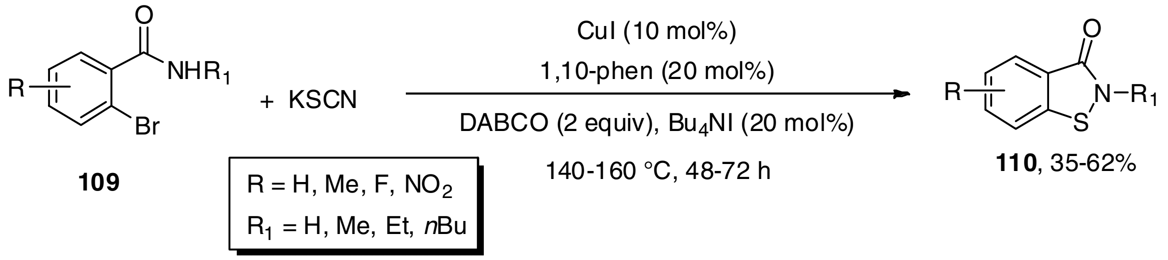
Zhang *et al.* [57] described an important method of copper-catalyzed aerobic oxidative sulfuration and annulation of propargylamines with elemental sulfur for the synthesis of 1,2-dithiole-3-thiones *via* C-N bond cleavage and the formation of multiple C-S bonds in good to excellent yields as shown in **Scheme-XV**. Various secondary and tertiary amines for example, *N*-phenylpropargyl aniline, *N*-methyl and *N*-ethyl anilines underwent the annulation smoothly to afford product **112** in good yield. Other amines such as aliphatic *N*,*N*-dimethyl, *N*,*N*-diethyl amines and cyclic piperidine, morpholine were also compatible under this reaction condition to give product **112** in good yield [58].

A versatile and efficient synthesis of benzo-fused thiacycles *via* Cu-catalyzed intermolecular C–S coupling/cyclization reaction was reported by Peñéñory *et al.* [58]. The reaction involves the synthesis of 2-methyl-4*H*-benzo[*e*][1,3]thiazine derivatives **115** by the reaction of 1-(azidomethyl)-2-iodobenzene **113** and **114** (eqn. 1, **Scheme-XVI**) and similarly 2-aminobenzo[*b*]thiophene derivatives **117** were also synthesized starting from 116 under similar reaction conditions in good yield (eq. 2, **Scheme-XVI**).

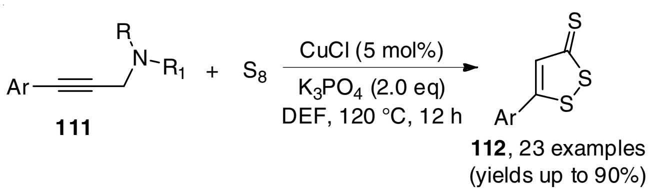
Liang *et al.* [59] developed a novel procedure for the synthesis of benzothiazoles from easily available *N*-benzyl-2-iodoaniline derivatives **118** and potassium sulfide [59]. The results suggested that the reaction proceeds *via* a traditional cross-coupling reaction followed by an oxidative cross-coupling



Scheme-XIII



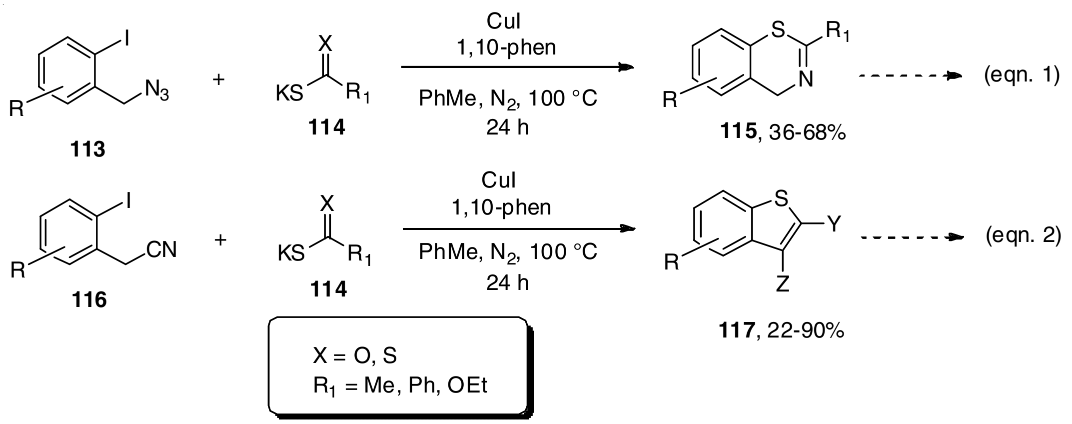
Scheme-XIV



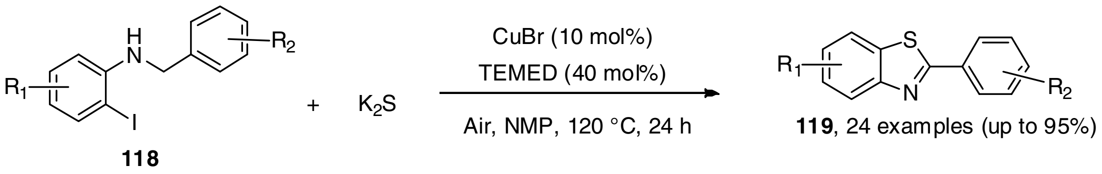
Scheme-XV

reaction. 2-Phenyl benzothiazole derivatives **119** were obtained in good to excellent yield starting from *N*-benzyl-2-iodoaniline **118** and potassium sulfide in one-pot Cu-catalyzed double sulfuration reaction (**Scheme-XVII**).

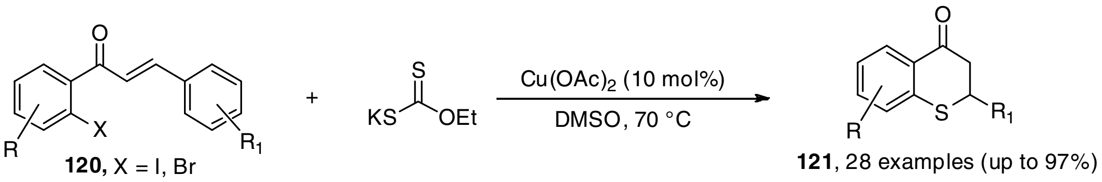
Sekar *et al.* [60] reported a copper-catalyzed domino process for the synthesis of 2-arylthiochroman-4-ones **121** without use of any external ligand. A variety of thioflavanones **121** have been synthesized from easily accessible 22-halochalcones **120** in excellent yield (**Scheme-XVIII**). The reactivity and yields were not at all affected by the steric hindrance of substituents. This method can be considered as a general approach for the synthesis of thioflavanones as it requires easily accessible starting materials and the unpleasant smell of thiol precursor can be avoided. This domino process proceeds *via* Cu-catalyzed C(aryl)–S bond formation by the coupling reaction between xanthate and 22-halochalcones followed by C–S bond cleavage



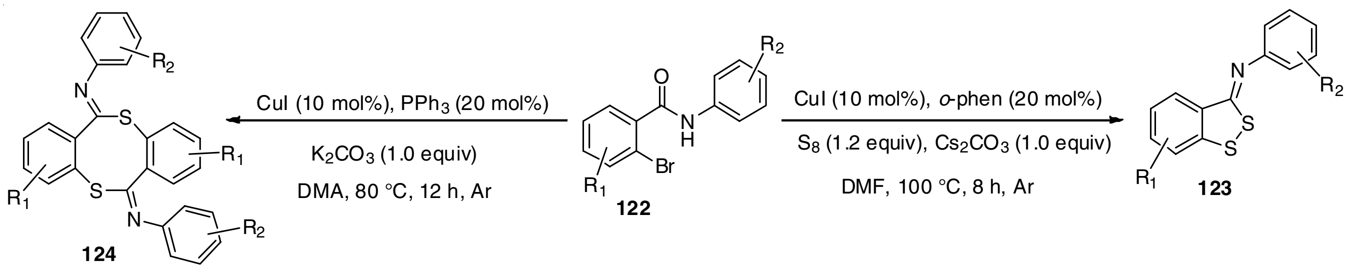
Scheme-XVI



Scheme-XVII



Scheme-XVIII

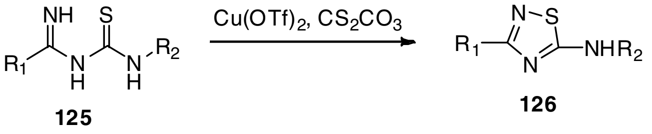


Scheme-XIX

of thioester and finally, S–C bond formation by intramolecular Michael addition.

Wang and co-workers [61] described the copper-catalyzed reaction between 2-bromo-benzothioamides **122** and elemental sulfur to furnish the benzodithioles **123** in presence of Cs_2CO_3. In absence of elemental sulfur the reaction afforded dibenzodithiocines **124** *via* two sequential C(sp^2)–S Ullmann coupling reactions (**Scheme-XIX**).

Another one-pot synthesis of substituted-5-amino-1,2,4-thiadiazoles **126** *via* intramolecular N-S bond formation of imidoyl thiourea **125** was also reported by Gong and his group as shown in **Scheme-XX** [62].



Scheme-XX

Conclusion

In brief, in the synthesis of a wide variety of compounds ranging from simple to complex molecular targets, the use of the copper-mediated C-S bond formation is very common. The recent developments in copper-catalyzed carbon-sulfur bond forming reactions, which is less toxic and inexpensive constitute the essential part of this review. The Cu-catalyzed C–S coupling reaction has ushered in a new era in organic synthesis due to the unique contribution of ligands. The presently available reports on Cu-catalyzed tandem reactions mainly centre round the synthesis of quite a large number of sulfur-containing heterocycles of different orientations. Still there is a vast scope of the Cu-catalyzed coupling reaction and one finds ample opportunity to explore new vista in this area.

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