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Copper-catalyzed/mediated synthesis of thiophenes and benzothiophenes: an updated review

Rajaghatta N. Suresh [a,b], Toreshettahally R. Swaroop [c,*], Kanchugarakoppal S. Rangappa [d,**]

[a] Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysuru, 570 006, Karnataka, India
[b] Department of Chemistry, Ben-Gurion University of the Negev, Beer-Sheva, 8410501, Israel
[c] Department of Studies in Organic Chemistry, University of Mysore, Manasagangotri, Mysuru, 570 006, Karnataka, India
[d] Institution of Excellence, University of Mysore, Manasagangotri, Mysuru, 570 006, Karnataka, India

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Dedicated to Prof. Goverdhan Mehta on the occasion of his 82nd birthday

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ABSTRACT

Copper-catalyzed/mediated synthesis of heterocycles plays a crucial role in the field of medicinal chemistry as well as synthetic organic chemistry. Notably, copper salts facilitate the C-S bond formation during the synthesis of heterocycles. On the other hand, they also serve as oxidizing agents, metal catalysts and Lewis acids. This review summarizes an updated collection of copper-catalyzed/mediated synthesis of thiophenes and benzothiophenes. Furthermore, optimal reaction conditions, reaction's scope/generality, pros and/or cons, discussion of control experiments and plausible mechanisms of the reactions are presented. In addition, this review article collects important strategies of copper-catalyzed/mediated synthesis of thiophenes and benzothiophenes reported from 2010 to 2024, which is advantageous for many chemists interested in transition metal-catalyzed reactions.

1. Introduction

Thiophenes and benzothiophenes represent a ubiquitous class of heterocycles due to their occurrence in nature and wide existence in pharmaceuticals, functional materials and agrochemical molecules [1–3]. Furthermore, they have numerous applications in the biological field. For instance, they exhibit antioxidant [4], antibacterial [5], antitumor [6] and antifungal activities [7]. Notably, these derivatives are useful building blocks for the synthesis of library of complex molecules in organic synthesis [8–10]. Tetra-substituted thiophene derivatives generally show good pharmacological activities. For example, tinoridine and strontium ranelate are inflammation and osteoporosis treatment agents respectively (Fig. 1a). It is noteworthy to mention that, the marketed accessible drugs such as zileuton, raloxifene and arzoxifene [11–13] (Fig. 1b) encompass benzothiophene skeleton and demonstrate selective inhibition of 5-lipoxygenase and estrogen receptor modulators. The synthesis of thiophene and its benzo-fused derivatives typically relies on cyclization reactions involving organosulfur compounds [14]. Many reviews have been reported on copper-catalyzed syntheses in different perspectives. To mention a few, Stanley and co-workers reviewed reactions of copper-catalyzed enantioselective 1,3-dipolar cycloaddition reactions [15]. Shibasaki and his colleagues reported a review on copper-catalyzed asymmetric synthesis of tertiary alcohols/-amines [16]. Liu and co-workers published a review on cross-coupling reactions facilitated by copper metal salts [17]. Jerphagnon et al. reported a review on enantioselective copper-catalyzed 1,4-addition tandem reactions [18]. In addition, many reviews are reported on transition metal-free synthesis of thiophenes and benzothiophenes [19–27]. Encouraged by these publications and our interest in organic synthesis [28–32], herein we present a review on copper-catalyzed/mediated synthesis of thiophenes and benzothiophenes, which are reported from 2010 to 2024, that includes several strategies including C-S bond construction, multi-component reactions, inter- and intramolecular bond constructions, poly-substitution and one-pot synthesis. To the best of our knowledge, a review on copper-catalyzed/mediated synthesis of these particular heterocycles has not been published so far.

* Corresponding author.
** Corresponding author.
E-mail addresses: swarooptr@gmail.com (T.R. Swaroop), rangappaks@gmail.com (K.S. Rangappa).

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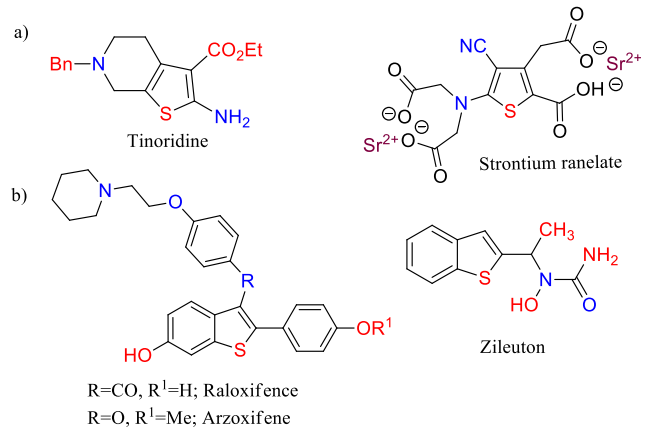


Fig. 1. a) Poly-substituted thiophene derivatives show pharmacological activities b) Examples of available drugs in market that contain benzothiophene moiety.

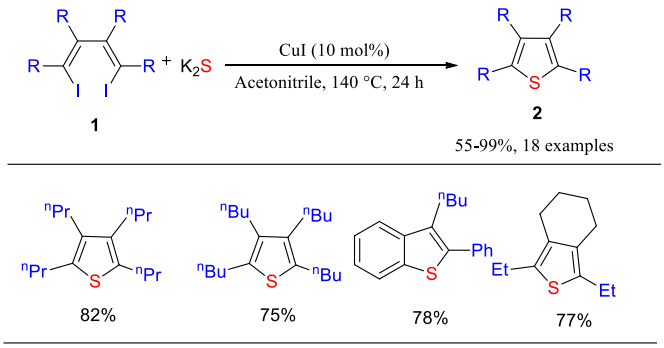
2. Copper-catalyzed synthesis of various substituted thiophene derivatives

2.1. Catalyzed by copper iodide (CuI)

Chanjuan Xi and co-workers [33] reported a C-S bond-forming copper-catalyzed synthesis of 2,3,4,5-tetrasubstituted-thiophenes **2** from 1,4-dihalo-1,3-dienes **1** (Scheme 1). Substrate (3*Z*,5*Z*)-4,5-diethyl-3,6-diiodoocta-3,5-diene (R = Et) **1** (1.0 mmol) underwent reaction with potassium sulfide (3.0 mmol) in the presence of copper iodide (10 mol%) and 1,10-phenanthroline (20 mol%) in acetonitrile at 140 °C for 24 h to give desired product **2** in 99 % yield. Interestingly, there was no change in the product yield when the reaction performed without using any ligand. The notable features of this protocol are excellent product yields, wide substrate scope and use of low-cost substrates.

Using the optimal reaction conditions, the generality of the reaction was examined. Thus, various electron-rich alkyl-substituted 1,4-dihalo-1,3-dienes (R = Et, *n*-Bu and *n*-Pr) **1** underwent smooth reaction with potassium sulfide and furnish products in good to high yields. Besides, the saturated cyclic ring fused with diiododiene underwent reaction similarly to afford bicyclic thiophenes in good yields. Gratifyingly, di-, tri- and tetra-substituted dienyl diiodides were well tolerated and did not affect product yields. The main limitation of the method is prolonged reaction time.

Thomas J. J. Müller et al. [34] developed a five-component one-pot copper-catalyzed synthesis of 2,5-di(het)arylthiophenes **3** by the reaction between iodobenzene, trimethylsilylacetylene (TMSA) and sodium sulfide (Scheme 2). Initially, iodobenzene (2.0 mmol) underwent a reaction in the presence of $PdCl_2(PPh_3)_2$ (0.04 mol%) and CuI (4 mol%) in



Scheme 1. Copper-catalyzed synthesis of 2,3,4,5-tetra-substituted thiophenes **2**.

DMF solvent under nitrogen atmosphere with trimethylsilylacetylene (3.0 mmol). Subsequently, KF in methanol was added and the entire reaction mixture was stirred under aerobic atmosphere overnight at room temperature. In the next step, a sequential addition of sodium sulfide nonahydrate and potassium hydroxide in methanol solvent under microwave (MW) irradiation at 120 °C for 1.5 h, afforded 2,5-bis(heteroaryl/aryl)thiophenes **3** in moderate yields. The main limitations of this approach are long reaction time, average product yields and the synthesis was not carried out in a single step. The authors also observed that temperature and reaction time did not affect the yield of the desired product. However, side products were observed in DMSO solvent.

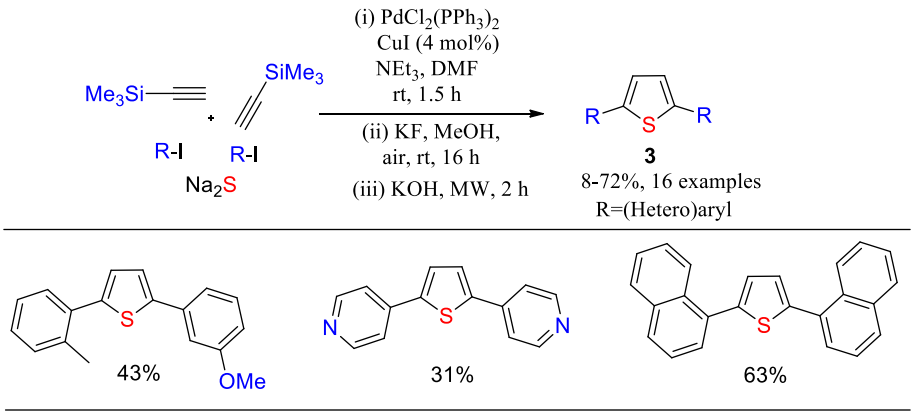
The substrate scope of this one-pot synthesis was examined by using the optimized reaction conditions. Substitutions on aryl benzene include electron-donating groups such as 2-methyl, 3-methoxy, 3-amino and 3-hydroxy, and electron-poor substituents such as 3-Br, 3-Cl, 4-Cl and 4-F, which were compatible in the reaction and corresponding substrates underwent smooth reaction under the optimized reaction conditions and produced anticipated products in moderate to good yields. Furthermore, heteroaryl substitutions such as pyridyl, thienyl, and bithienyl also provided corresponding products in moderate yields. Unfortunately, among all the derivatives, indole-substituted thiophene was formed in low yield. Later, electro-neutral substitutions namely, phenyl, biphenyl, naphthyl, and anthracenyl also furnished corresponding thiophene derivatives in good yields.

Jiang and co-workers [35] demonstrated a regioselective copper-catalyzed synthesis of 2,5-di-substituted thiophenes **5** and furans **6** from haloalkynes (Scheme 3). In the first example, phenylethynyl bromide **4** (R=Ph) (0.5 mmol) underwent reaction in the presence of CuI (15 mol%) and 1,10-phenanthroline (1,10-Phen) (20 mol%) in DMF solvent at 80 °C to afford desired product 2,5-diphenylfuran **6** in 65 % yield. The solvents such as 1,4-dioxane, toluene and DMSO were screened to find the best reaction conditions. Among all, moist DMSO with 5.0 equivalence of KOH at 80 °C and DMF with 2.5 mmol of $Na_2S\bullet 9H_2O$ at 70 °C are the best suitable reaction conditions for the synthesis of furan and thiophene derivatives respectively. The important feature of this approach is that the desired products bearing various aryl and heteroaryl groups obtained in excellent yields under mild reaction conditions by using simple starting materials.

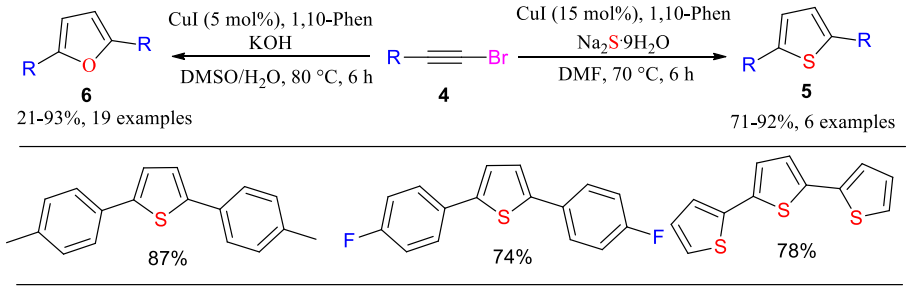
Substrate scope for the synthesis of copper-catalyzed di-substituted thiophenes involves electron-rich (4-methyl), electron-deficient (4-fluoro and 4-chloro) and heteroaryl (2-thienyl and 2-pyridyl) substitutions. It should be noted that, electro-neutral substituents on substrates enhanced thiophene products' yields. It is noteworthy to mention that 2,2':5′,2′-terthiophene exhibit anthelmintic and insecticidal activities and formed in good yield (78 %) in this manner.

Chanjuan Xi et al. [36] reported a copper-catalyzed synthesis of dihydrothiophenes **8** by one-pot reaction between 1,4-diiodobut-1-ene **7** and $Na_2S\cdot 9H_2O$. The reaction proceeded *via* *S*-alkylation and *S*-alkenylation (Scheme 4). When substrate **7** (R, R^1=Ph) (1.0 mmol) was treated with $Na_2S\cdot 9H_2O$ (3.0 mmol) in the presence of 20 mol% ethylene glycol in *N*-methylpyrrolidone (NMP) at 80 °C, the desired product **8** was obtained in 88 % yield. It is noteworthy to mention that, when an experiment was carried out using potassium sulfide (K_2S) instead of sodium sulfide (Na_2S), mixtures of products were observed. The formed products were 4,5-diphenyl-2,3-dihydrothiophene **8**, 2,3-diphenylthiophene **9** and 5,6-diphenyl-3,4-dihydro-1,2- dithiine **10** in the ratio of 8:6:1 and the structures were confirmed by analytical characterization (Scheme 5). Long reaction time is the main drawback of this method.

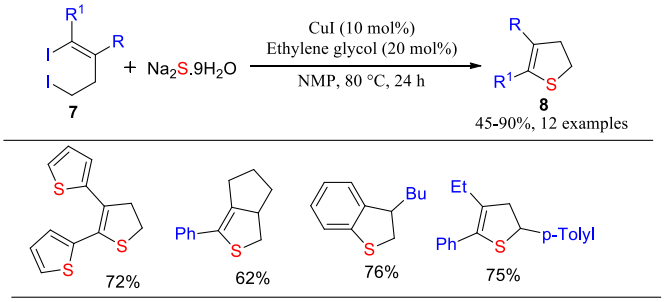
The substrate scope of this synthesis involves electron-rich, electro-neutral and heteroaryl substitutions. The main disadvantage of this protocol is that obtained dihydrothiophene products do not contain electron-poor substitutions. However, remaining dihydrothiophene products were formed in average to excellent yields. On the other hand, dihydrothiophenes **11** underwent dehydrogenative aromatization reaction to give substituted thiophenes **12** in good to excellent yields (Scheme 6). The *p*-benzoquinone was used as a dehydrogenating agent



Scheme 2. Copper-catalyzed synthesis of 2,5-bis(hetero/aryl)thiophenes **3**.



Scheme 3. One-pot copper-catalyzed synthesis of thiophene **5** and furan **6** derivatives.



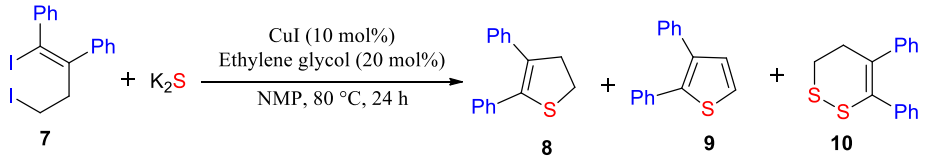
Scheme 4. Copper-catalyzed synthesis of 2,3-dihydrothiophenes **8**.

in the presence of *tert*-butyl peroxide at 100 °C, which afforded 2,3-diphenylthiophene (R^1, R^2=H, R^3, R^4=Ph) in 72 % yield from corresponding substrate. In addition to this, the reactions were screened to check the generality under the same experimental conditions. Interestingly, the branched terthiophene was formed in 55 % yield. Similarly, 2-phenylbenzothiophene and tri-substituted thiophene were afforded in 69 % and 57 % respectively.

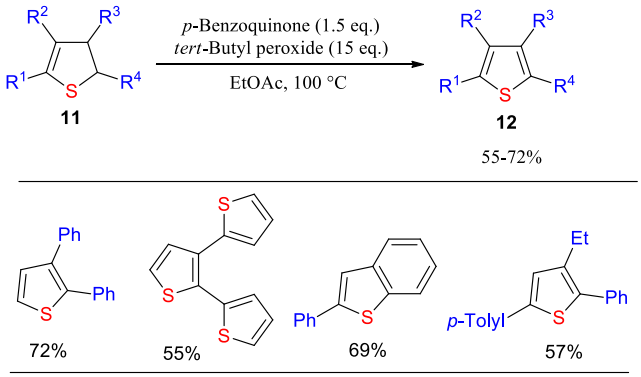
2.2. Catalyzed by copper acetate [$Cu(OAc)_2$]

Wei-Ping Deng and co-workers [37] reported a Cu-catalyzed formation of 2-aminothiophenes **15** from the reaction between thioamides **13** (R^1, R^2, and EWG = $COCH_3$) (0.2 mmol) and alkynoates **14** (R^3 = Me) (DMAD) (0.24 mmol) in the presence of copper acetate (10 mol%) at 80 °C in *N*,*N*-dimethylacetamide (DMA) solvent. The anticipated products **15** were formed *via* oxidative cyclization process (Scheme 7). The importance of this straightforward protocol involves mild reaction conditions, one-pot synthesis and a wide range of substrate scope in good to high yields. In addition, authors also revealed that the obtained desired products may also be helpful for biological studies. Notably, authors have not mentioned the exact reaction time in their article.

With this optimized reaction conditions, the substrate scope of the reaction was examined. Notably, methyl, ethyl, *tert*-butyl and benzyl 3-(dimethylamino)-3-thioxopropanoate substrates were screened, which afforded desired products in good to excellent yields (80–88 %). Furthermore, thioamides such as 3-(dimethylamino)-*N*,*N*-dimethyl-3-thioxopropanamide, dithioamide, and 2-cyano-*N*,*N*-dimethylethanethioamide underwent smooth reaction under the same experimental conditions to furnish anticipated products in moderate to good yields. In addition, various thioamides bearing different substitutions such as diethyl, morpholine and methylphenylamines also underwent reaction under optimal conditions and formed corresponding products in moderate to excellent yields (56–91 %). Moreover, the change in the ester group of **14** from methyl to ethyl group showed excellent reactivity and provided 2-aminothiophene in high yield.



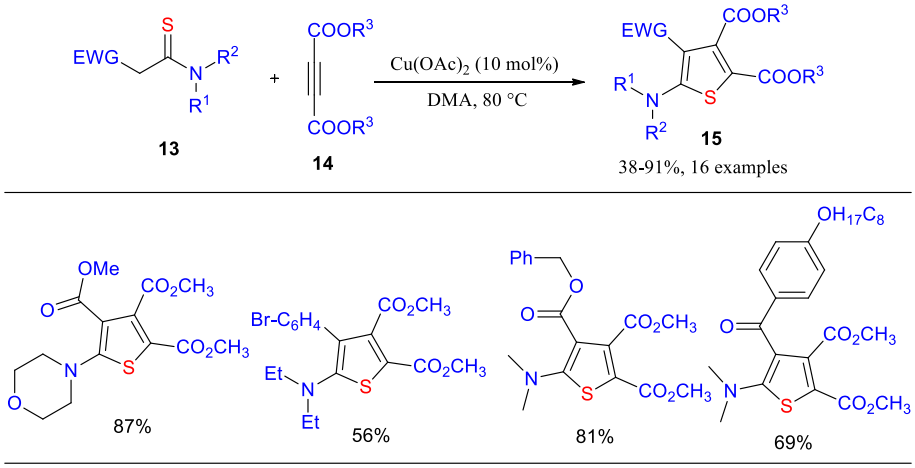
Scheme 5. Copper-catalyzed synthesis of dihydrothiophene **8**, diphenylthiophene **9**, and 3,4-dihydro-1,2- dithiine **10**.



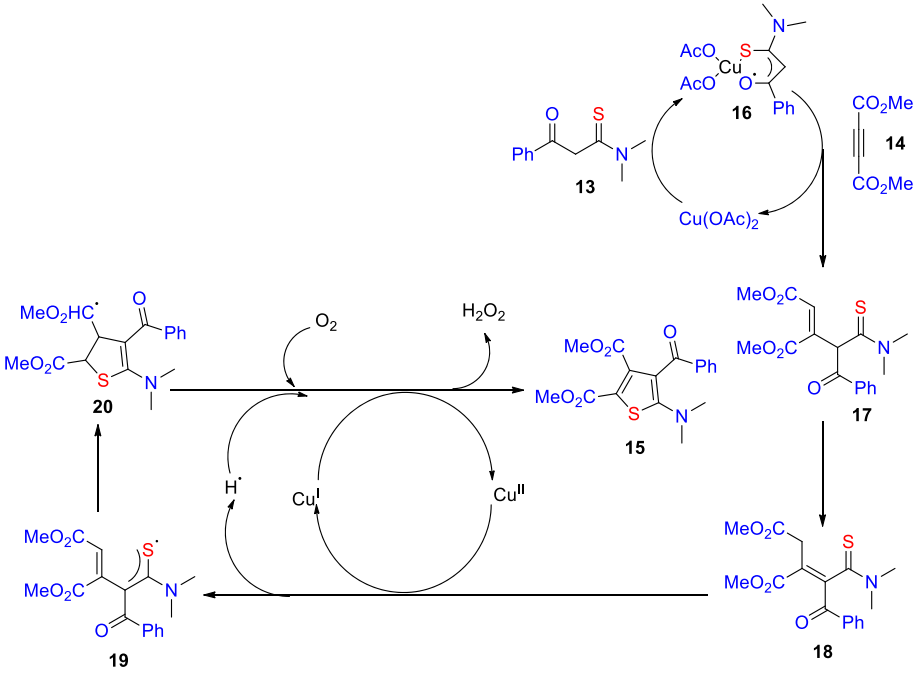
Scheme 6. An efficient synthesis of substituted thiophenes **12** from dihydrothiophenes **11**.

Based on the previous reports [38–40], the plausible mechanism for the formation of 2-aminothiophene is presented in Scheme 8. In the beginning, thioamide **13** is activated by Cu(II) to produce intermediate **16** which couples with alkynoates **14** to give intermediate **17** followed by the regeneration of the catalyst. Intermediate **17** furnishes **18** through double bond migration. Intermediate **18** undergoes to Cu (II)-catalyzed oxidation to form **19**, which cyclizes to furnish dihydrothiophene intermediate **20**. Subsequently, intermediate **20** is converted into 2-aminothiophene **15** *via* copper-catalyzed aerobic oxidative dehydrogenation.

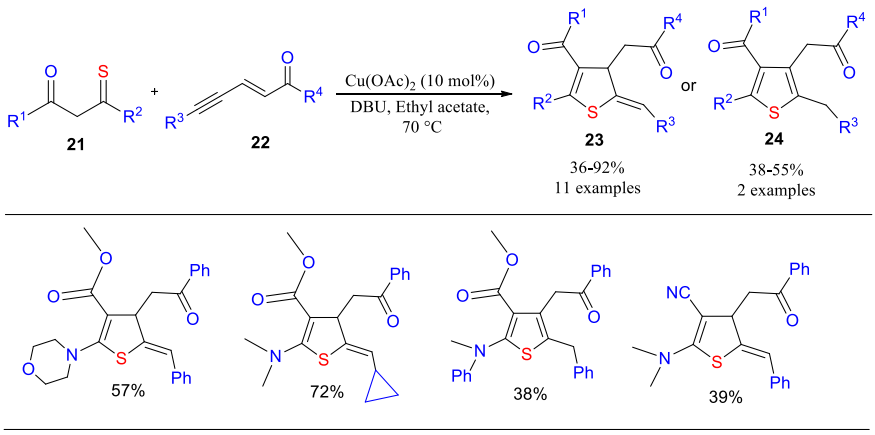
Min Wen et al. [41] demonstrated a facile synthesis of highly substituted dihydrothiophenes **23** and thiophenes **24**. Briefly, β-thiooxoketones **21** (0.2 mmol) were treated with enynones **22** (0.24 mmol) in the presence of copper acetate ($Cu(OAc)_2$) (10 mol%) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) base in ethyl acetate solvent at 70 °C to afford dihydrothiophenes **23** or thiophenes **24** in good to high yields (Scheme 9). The notable features of this facile approach involve the anticipated products afforded in one-pot synthesis and authors also explored that the obtained products might be useful for biological



Scheme 7. Synthesis of 2-aminothiophenes **15** from thioamides **13** and alkynoates **14**.



Scheme 8. The plausible mechanism for the synthesis of 2-aminothiophene **15**.



Scheme 9. Synthesis of dihydrothiophene **23** and thiophene derivatives **24** from β-thiooxoketone **21** and enynones **22**.

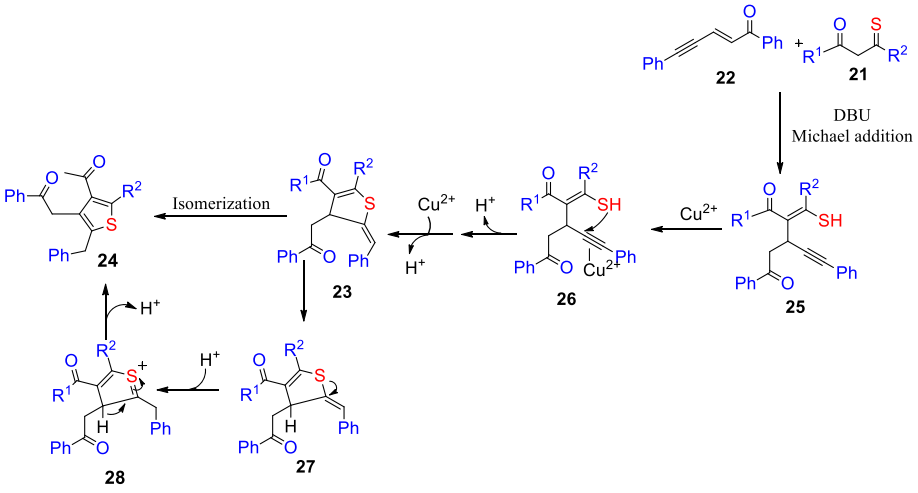
studies. The reaction times are not mentioned in the article. Finally, authors failed to obtain any product without catalyst, which indicate that copper catalyst is essential.

The substituents present on carbonyl group of β-thiooxoketone **21** made notable impact on yields. For instance, β-thiooxoketone **21** which contain methoxy group reacted with 1,5-diphenylpent-2-en-4-yn-1-one under the optimal reaction conditions to afford anticipated product in 92 % yield. Similarly, under the same experimental conditions, fully substituted dihydrothiophene derivatives containing wide range of substitutions on R^1, R^2, R^3 and R^4 (R^1=CO_2CH_3, CO_2CH_2Ph, $COCH_2CH_3$ and $COCH(CH_3)_2$; R^2=NMe_2, 4-morpholinyl; R^3 = phenyl, cyclopropyl, thienyl, 4-methoxy and 4-bromophenyl and R^4=CH_2COPh, $CH_2CO(4\text{-}OMe)C_6H_4$ and $CH_2CO(4\text{-}Cl)C_6H_4$) were obtained in moderate to high yields (36–80 %) from the reaction between corresponding substrates: β-thiooxoketone **21** and enynones **22**. On the other hand, fully substituted thiophenes were also formed in 38–55 % yield. Finally, electron-withdrawing substitution (cyano) containing dihydrothiophene was obtained in 39 % yield.

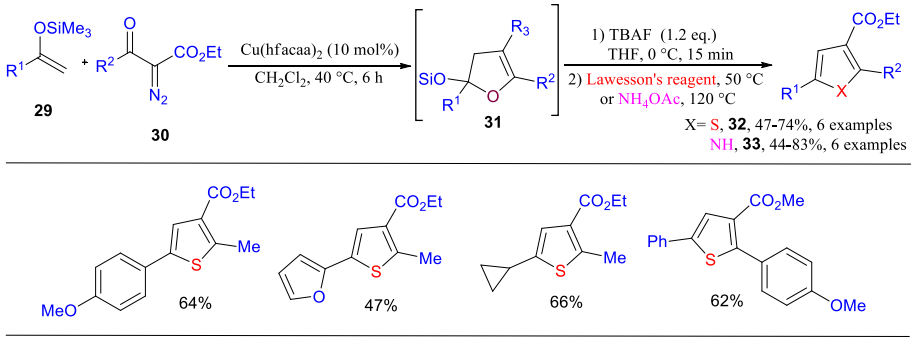
Based on earlier reported protocols [42–44], the possible reaction mechanism for this approach is shown in Scheme 10 β-Thiooxoketone **21** undergoes Michael addition with enynone **22** to generate intermediate **25**, which reacts with copper acetate to produce intermediate **26**. Later, intramolecular cyclization and deprotonation in **26** furnishes dihydrothiophene **23**. Consequently, few dihydrothiophenes **23** undergo isomerization of double bond to form thiophene products **24** *via* intermediates **27** and **28**.

2.3. Catalyzed by bis(hexafluoroacetylacetonato)copper(II) [Cu(hfacaa)$_2$]

Wei Wen Tan and Naohiko Yoshikai [45] reported a copper-catalyzed cyclization reaction for the synthesis of tri-substituted thiophenes. Silyl enol ethers **29** (0.2 mmol) which were derived from methyl ketones underwent reaction with α-diazo-β-ketoesters or α-diazoketones **30** (0.24 mmol) in the presence of catalyst bis(hexafluoroacetylacetonato)copper(II) (10 mol%) in dichloromethane to afford 2-siloxy-2,3-dihydrofuran derivatives or 2,3,5-tri-substituted furans **31**. The main importance of this efficient approach are that reagents are easy to handle and the intermediates formed can be directly transformed into corresponding 2,3,5-tri-substituted heterocycles. For instance, the substrate **31** could act as an excellent nucleophile in organic transformations. Interestingly, these dihydrofuran derivatives acted as 1,4-diketone surrogates for the synthesis of thiophenes **32** and pyrroles **33** (Scheme 11). Briefly, the fluoride-mediated desilylation of the crude coupling product **31** followed by treatment with Lawesson's reagent (0.48 mmol) in acetic acid under heating at 50 °C for 5–6 h afforded tri-substituted thiophenes **32** in average yields (47–74 %). In addition, tri-substituted pyrrole derivatives **33** were formed when ammonium acetate was used as a reagent under the same reaction conditions in average to good yields (44–83 %). The generality of the reaction was exemplified with six examples. Use of non eco-friendly halogenated solvent like dichloromethane is the main drawback of this method.



Scheme 10. The plausible mechanism for the synthesis of dihydrothiophenes **23** and thiophenes **24**.



Scheme 11. Synthesis of thiophenes **32** and pyrroles **33** from 2,3,5-tri-substituted furans **31**.

2.4. Catalyzed by copper bromide (CuBr)

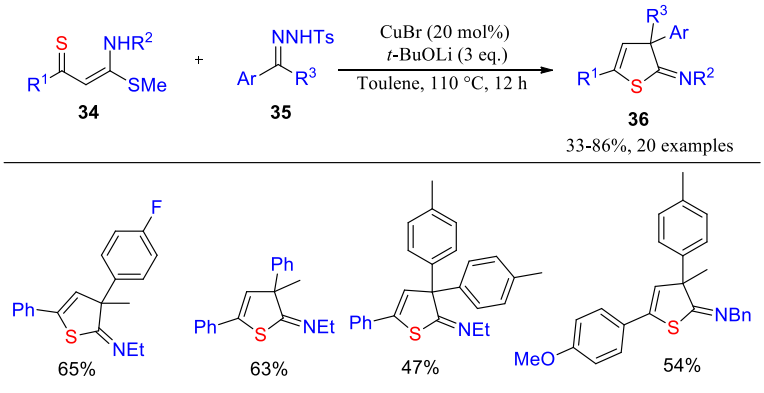
Zhengkun Yu and co-workers [46] reported an efficient synthesis of iminothiophene derivatives. They reacted α-thioxoketene-*N*,*S*-acetals **34** (0.5 mmol) with *N*-tosylhydrazones **35** (1.5 mmol) in the presence of copper bromide catalyst (20 mol%) and *t*-BuOLi base (1.5 mmol) in toluene at 110 °C to obtain iminothiophenes **36** in moderate to good yields (Scheme 12). The generality of the reaction was tested under this optimal reaction conditions. The substituents on iminothiophenes include electron-donating groups, electron-withdrawing groups, halogens and heteroaryl groups. The steric hindrance in both the starting materials **34** (R^1, R^2) and **35** (R^3) did not affect on the product yield or reaction speed. This work demonstrates copper-catalyzed synthesis of iminofurans and iminothiophenes from the reactions of α-oxo(thioxo) ketene-*N*,*S*-acetals with *N*-tosylhydrazones of ketones. This method requires high temperature to obtain desired products, which is the limitation of this protocol.

2.5. Catalyzed by copper chloride ($CuCl_2$)

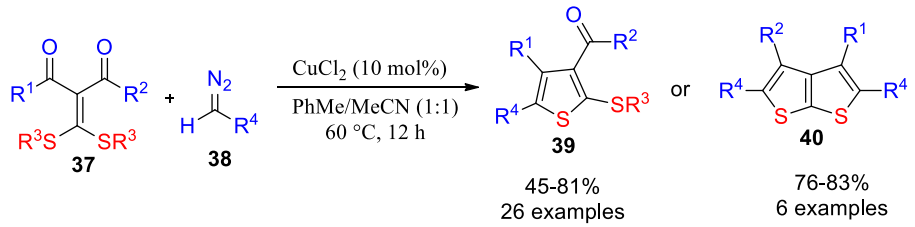
Zhengkun Yu et al. [47] synthesized thiophenes and thieno[2,3-*b*] thiophenes *via* copper catalysis. Briefly, *S*,*S*-di-substituted enones **37** (0.3 mmol) treated with diazo compounds **38** (0.6 mmol) in the presence of copper chloride ($CuCl_2$) catalyst (10 mol%) in a 1:1 ratio of toluene and acetonitrile solvent mixture at 60 °C to obtain desired products **39** only in good to excellent yields (Scheme 13). A notable key feature of this efficient protocol involves the construction of fully substituted thiophene moieties from easily accessible starting materials. This strategy shows good chemoselectivity and the reactions are performed under mild reaction conditions. The reaction failed in the absence of copper catalyst. In this method, mixture of products **39** (45 %) and **40** (27 %) (R^1=R^2 = R^3 = Me, R^4=CO_2Et) were obtained when 3 equivalence of diazo compound was used. Interestingly, further increase in the amount of diazo compound to 4 equivalence resulted in the formation of product **40** alone in 89 % yield.

The substrate scope of the reaction was explored using optimal reaction conditions. Some derivatives of tetra-substituted thiophenes and thieno[2,3-*b*]thiophenes with their yields are given in Scheme 14. A wide range of desired thiophene products bearing electron-donating groups, electron-withdrawing groups and heteroaryl groups were formed in low to high yields. Various substituents and electronic effects or steric hindrance did not affect on the yields of anticipated products. On the other hand, thieno[2,3-*b*]thiophenes **44** were formed by the reaction of *S*,*S*-di-substituted enones **41** with 4 equiv. of ethyl diazoacetate **42** under standard reaction conditions in good to high yields (Scheme 14). The formed desired products bear several substituents such as methyl, isopropyl, *n*-butyl, cyclopropyl and cyclobutyl.

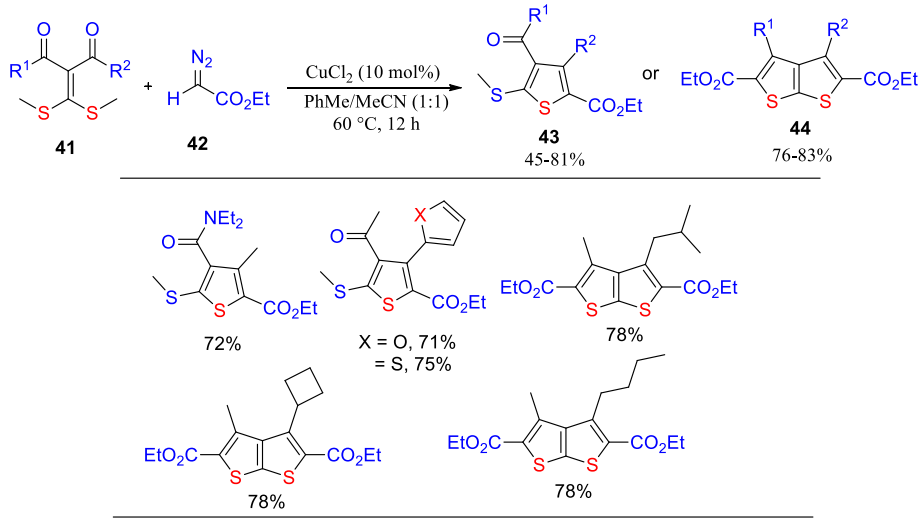
Notably, using this synthetic strategy, various types of *S*-substituted enones were treated with diazo compounds under optimal conditions for the synthesis of fully functionalized thiophenes (Schemes 15–17). Only trace amount of desired product **46** was observed when methylthio-mono-substituted enone **45** treated with ethyl diazoacetate **42** under standard conditions (Scheme 15). Surprisingly, a new enone product ethyl 4-acetyl-2,3-bis(methylthio)-5-oxo-2-phenylhex-3-enoate **49** was obtained in 80 % yield when ethyl diazophenylacetic acid ester **48** treated with 3-(bis(methylthio)methylene)pentane-2,4-dione **47** under standard conditions (Scheme 16). It is noteworthy to mention that a derivative of thiophene **50** showed several synthetic applications (Scheme 17a-c). For instance, the tetra-substituted derivative of thiophene **51** was obtained after cross-coupling with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and CuI in toluene at 80 °C under nitrogen atmosphere in 81 % yield (Scheme 17a). Similarly, **50** underwent reaction in the presence of *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichlromethane solvent at room temperature for 1 h to afford corresponding sulfone **52** in 90 % yield (Scheme 17b). More importantly, when fully substituted thiophene derivative **50** treated with ethyl



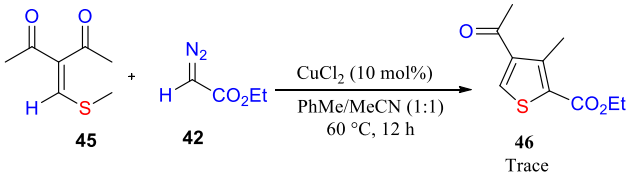
Scheme 12. Synthesis of iminothio *N*-tosyl hydrazones **36** from α-thioxoketene-*N*,*S*-acetals **34** and *N*-tosylhydrazones **35**.



Scheme 13. Synthesis of tetra-substituted thiophenes **39** and thieno[2,3-*b*]thiophenes **40**.



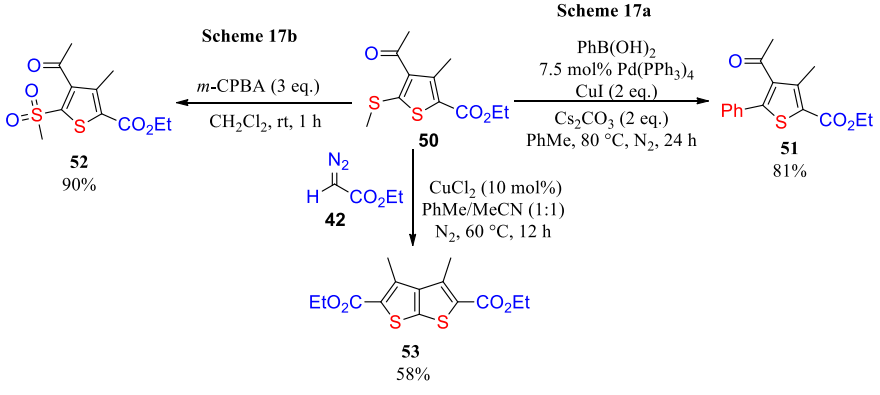
Scheme 14. Copper-catalyzed synthesis of thiophenes and thieno[2,3-*b*]thiophenes **43**.



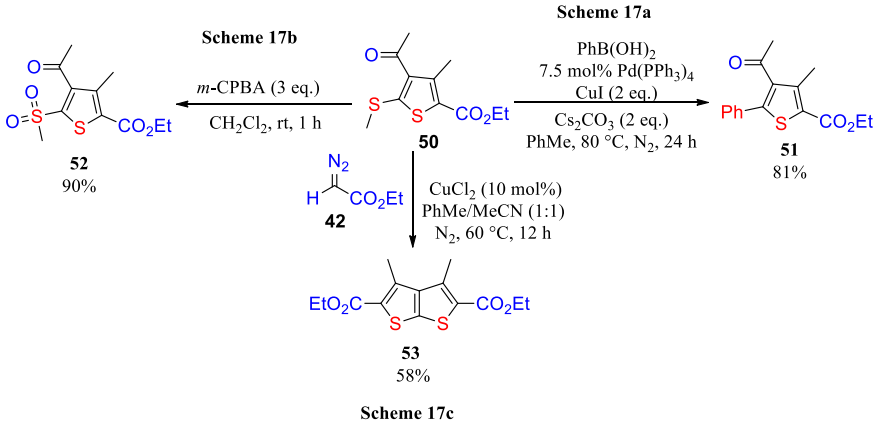
Scheme 15. Synthesis of ethyl 4-acetyl-3-methylthiophene-2-carboxylate **46**.

diazoacetate **42** and 10 mol% of $CuCl_2$ in toluene and acetonitrile mixture (1:1) at 60 °C under nitrogen atmosphere furnished thieno[2,3-*b*]thiophene **53** in 58 % yield (Scheme 17c).

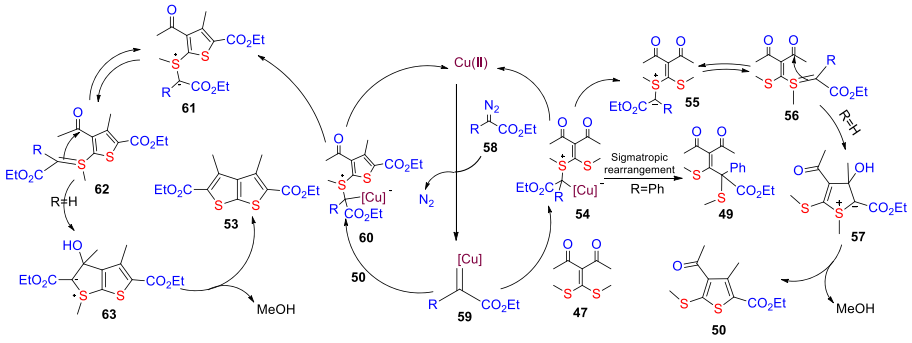
Reaction pathways for the synthesis of **50**, **53** and **49** are shown in Scheme 18. At the outset, Cu(II)−carbene species **59** are formed by the reaction of diazo compound **58** with copper catalyst, which on reaction with *S,S*-di-substituted enones **47** afford adducts **54**. Cu(II) species are regenerated and result in the formation of sulphur ylide **55**/**56**, which undergoes intramolecular annulation to furnish intermediate **57**. The ylide **57** is demethylated and dehydroxylated to afford thiophene product **50** *via* the elimination of methanol. Further, another Cu(II)−carbene species **59** react with **50** leading to the formation of intermediate **60**. The substoichiometric amount of Cu(II) catalyst is regenerated and affords sulphur ylide intermediates **61**, **62** and **63** sequentially. Finally, the anticipated product **53** is formed *via* the elimination of methanol. On the other hand, when R = Ph (in **58**/**59**/**54**), the intermediate **54** produces 4-acetyl-2,3-bis(methylthio)-5-oxo-2-phenylhex-3-enoate **49** *via* sigmatropic rearrangement.



Scheme 16. Synthesis of ethyl 4-acetyl-2,3-bis(methylthio)-5-oxo-2-phenylhex-3-enoate **49**.



Scheme 17. a–c. Synthesis of tetra-substituted thiophene **51**, sulphones **52** and thieno[2,3-*b*]thiophene **53**.

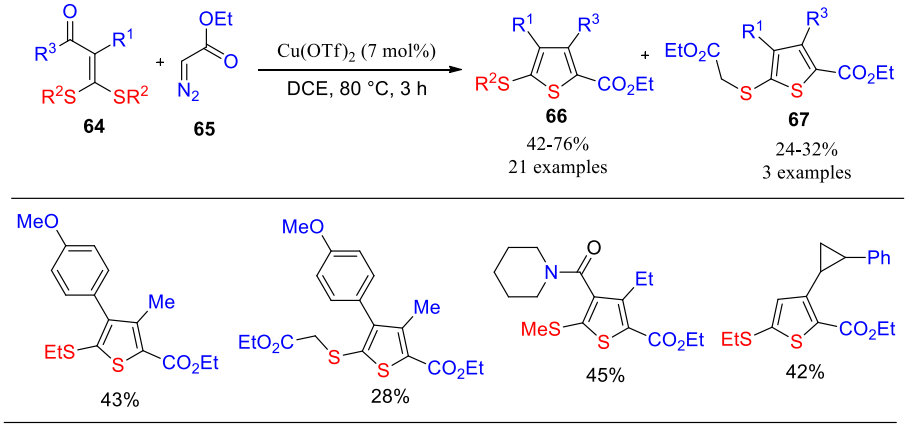


Scheme 18. The plausible mechanism for the synthesis of fully substituted thiophene **50**, thieno[2,3-*b*]thiophene **53** and a new enone product **49**.

2.6. *Catalyzed by copper triflate [Cu(OTf)$_2$]*

Yu-Long Zhao and co-workers [48] developed an efficient synthesis of highly substituted thiophenes. It include copper triflate-catalyzed reaction between the acyclic ketene-*S*,*S*-acetals **64** (0.2 mmol) and diazo compound **65** (0.6 mmol) in dichloroethane (DCE) at 80 °C, which afforded poly-substituted thiophenes **66** and **67** in moderate to good yields (Scheme 19). This tandem process provides a modular approach for synthesizing a wide range of highly substituted thiophene derivatives. In addition, the reactions also involve C-S bond formation, bond cleavage and the generation of sulphur ylide intermediates. Moreover, the process affords fully substituted thiophenes which might be converted into thieno[2,3-*b*]thiopyran-4-ones. In some cases, thiophenes **67** were formed as side products, which is the limitation of this method.

The generality of this reaction was examined by using the optimized reaction conditions. Various ketene dithioacetals **64** containing electron-withdrawing groups on treatment with ethyl 2-diazoacetate **65** in the presence of copper catalyst (Cu(OTf)$_2$) in dichloroethane solvent at 80 °C afforded multi-substituted thiophenes in 24–59 % yields. Similarly, methoxy-substituted thiophene was formed in moderate yield 43 % and piperidine substituent containing thiophene was formed in 45 % yield. Notably, ketene dithioacetals **64** without any substitution at the α-position (R^1=H) on reaction with ethyl 2-diazoacetate **65** under optimal reaction conditions furnished tri-substituted thiophene derivatives in moderate to good yields.



Scheme 19. Copper-catalyzed domino synthesis of poly-substituted thiophenes **66, 67**.

Interestingly, when substituent R^1 in **64** were propionyl and acetyl (**68**), under the same experimental conditions, desired tetra-substituted thiophenes **66a** were obtained as minor products. But, fused thienothiophene derivatives **69** were formed as major products. Importantly, on increasing the amount of **65** to 5 equiv. thienothiophene derivatives **69** were obtained in high yields (Scheme 20). Use of catalytic amount of copper catalyst is one of the key features of this approach. Again, formation of mixture of products is the limitation of this method.

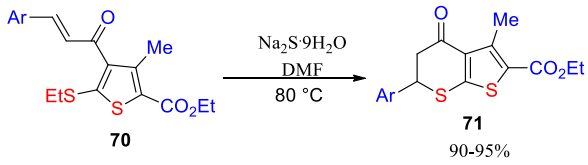
Furthermore, thiophenes **70**, which were Michael acceptors underwent smooth reaction *via* [5C+1S] annulation in the presence of $Na_2S\bullet 9H_2O$ in DMF solvent at 80 °C to give thieno[2,3-*b*]thiopyran-4-ones **71** in high yields (Scheme 21).

Based on some earlier reported protocols [49–51], a mechanism is postulated for the synthesis of fully substituted thiophenes **66** and fused thiophenes **69** as shown in Scheme 22. In the beginning, diazo compound **65** undergoes nucleophilic decomposition with $Cu(OTf)_2$ and furnishes copper carbenoid **72** *via* elimination of N_2. The intermediate **72** reacts with ketene-*S*,*S*-acetal **64** and produces sulphur ylide **73**, which affords intermediate **74** *via* the elimination of [CuLn]. The intermediate **74** undergoes intramolecular cyclization to produce a five-membered cyclic intermediate **75**. Later, elimination of hydroxide produces intermediate **76**, which is dealkylated to form desired product **66** through C-S bond cleavage. The obtained product **66** again reacts with copper carbenoid **72** and affords sulphur ylide intermediate **77**, which undergo C-S bond cleavage and subsequent elimination of [CuLn], leading to the formation of poly-substituted thiophene **67**. Furthermore, in intermediate **77** if R^1 is replaced by propionyl and acetyl groups, it further undergoes intramolecular aldol cyclization to afford fused ring alcohol intermediate **79** *via* **78**. Finally, the expected product **69** forms by the elimination of R^2OH.

2.7. Catalyzed by copper(I) thiophene-2-carboxylate (CuTc)

Chao Chen's group [52] developed a copper-catalyzed synthesis of 2,4-disubstitutedthiophenes **81**. Substrates aryl–vinyl iodonium salts **80** on treatment with elemental sulphur in the presence of copper salt and potassium triflate in DCE furnished substituted thiophenes **81** in moderate to high yields (Scheme 23). During optimization, various copper catalysts and ligands were tested. Among all, CuTc in the absence of ligand was found to be the best choice. Other sulphur sources such as Na_2S, KSAc and $Na_2S_2O_3$ were found to be ineffective. Once the optimal reaction conditions were identified, authors explored the substrate scope for the synthesis of thiophenes **81**. Various substrates **80** bearing different substituents such as electron-donating groups (Me, OMe, *t*-Bu, and OCF_3), electron-withdrawing groups (F, Cl, Br, and CF_3) and heteroaryl substituents underwent smooth reaction with elemental sulphur under standard optimal conditions to furnish respective anticipated products in moderate to good yields. Notably, based on these successful results of sulfuration, authors extended their work for selenization as well, which furnished 2,4-diaryl selenophenes from vinyl iodinium salts in the presence of same copper catalyst. Requirement of high temperature is the limitation of this protocol.

Authors explored the possible reaction mechanism for the synthesis of 2,4-disubstituted thiophenes **81** and it is shown in Scheme 24. Initially, aryl–vinyl iodonium salt **80** undergoes reaction with CuTc to afford vinyl–Cu(III) intermediate **82.** Then intermediate **82** coordinates



Scheme 21. Synthesis of thieno[2,3-*b*]thiopyran-4-ones **71** in excellent yield.

with trisulfur radical anion to furnish intermediate **83**, which further react with intermediate **82** leading to the formation of radical cation intermediate **84**. Deprotonation occurs in intermediate **84** to furnish **85**. Intramolecular cyclization occurs in intermediate **85** to produce intermediate **86**. Finally, desired product **81** forms from intermediate **86** *via* deprotonaton.

3. Copper-catalyzed synthesis of various substituted benzothiophenes

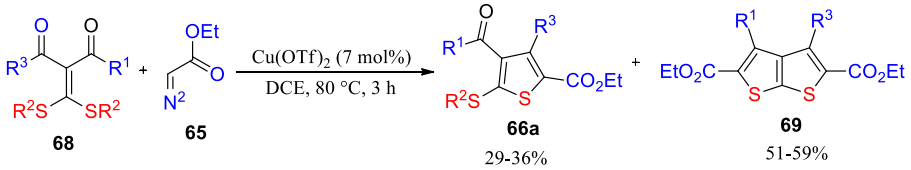
3.1. Catalyzed by copper iodide (CuI)

Jin-Heng Li et al. [53] reported a copper-catalyzed novel synthesis of 2-trifluoromethyl benzothiophenes **88**. In the reaction, 1,4-dihalides **87** (0.2 mmol) underwent thiolation annulation in the presence of sodium sulfide or sodium hydrosulfide (2 equiv.) and copper iodide (10 mol%) in DMF solvent at 80 °C to give benzothiophene derivatives **88** in good yields (Scheme 25). The importance of this one-pot protocol is that it allows the construction of two C-S bonds *via* thiolation annulation of various 1,4-dihalides **87**. Notably, desired benzothiophene products may show some interesting biological activities due to the presence of CF_3 functional group.

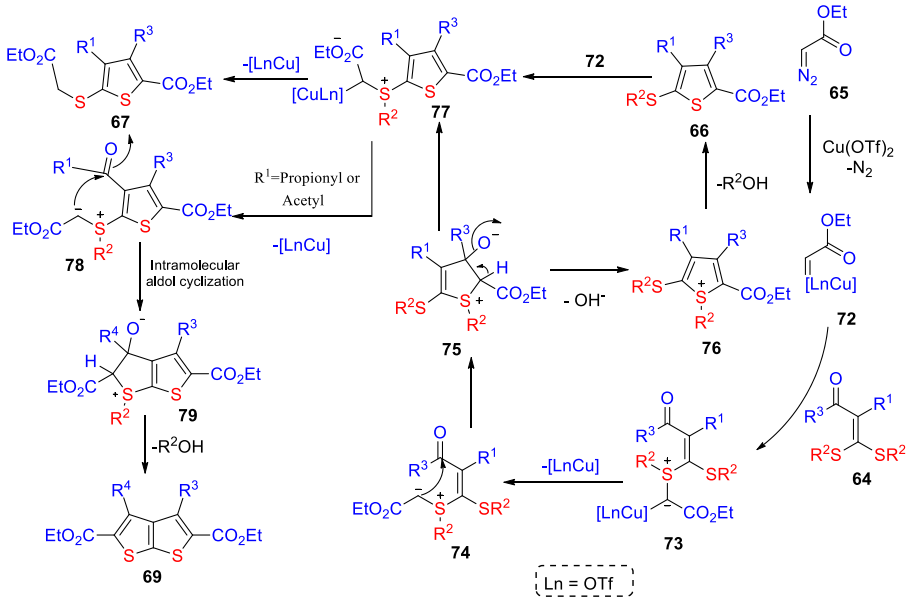
Using this optimized reaction conditions, the generality of the reaction was studied. Thus, various electron-donating and electron-withdrawing groups on fused benzene ring were tolerable. Notably, a substrate containing thienyl group underwent smooth reaction under standard reaction conditions to afford 2-(trifluoromethyl)thieno[2,3-*b*]thiophene in 64 % yield. It should be noted that the absence of trifluoromethyl group drastically reduced the yield of corresponding product.

Hui Yu and co-workers [54] reported an Ullmann-type C–S bond forming copper-catalyzed synthesis of benzo[*b*]thiophenes **91**. When (2-iodobenzyl)triphenylphosphonium bromide **89** (0.3 mmol) treated with thiocarboxylic acid **90** (0.33 mmol) in the presence of copper iodide, 1,10-phenonthroline and *n*-Pr_3N in dioxane solvent at 100 °C under nitrogen atmosphere furnished benzo[*b*]thiophene **91** in good yields (Scheme 26). Notably, it is one of the new alternative methods for the synthesis of benzo[*b*]thiophene derivatives **91**, which is useful in organic and medicinal chemistry. The synthesis of benzothiophenes from thiocarboxylic acids is reported for the first time by this group. The main drawbacks of this protocol are that the reactions take long time to complete and require high temperature.

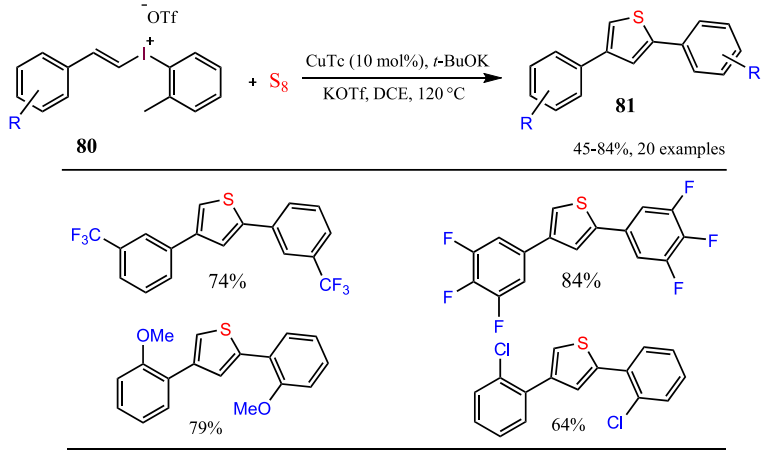
Later, the scope of the reaction was examined by using optimized reaction conditions. Thus, various substituted (2-iodobenzyl)triphenylphosphonium bromides bearing electron-donating groups and electron-withdrawing groups on the aromatic ring underwent smooth reaction with thiobenzoic acid under optimal reaction conditions to furnish



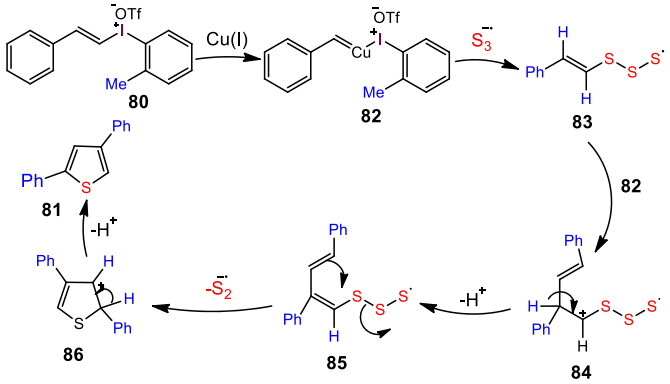
Scheme 20. Synthesis of thiophenes **66** and thienothiophenes **69**.



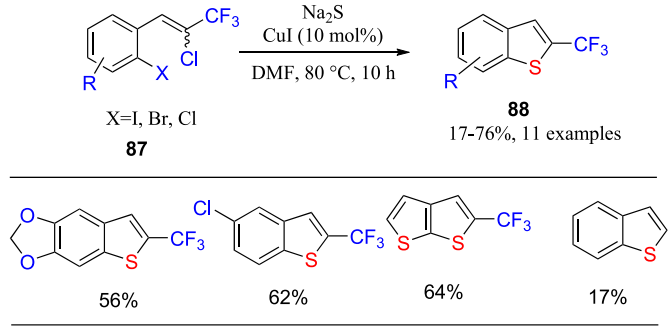
Scheme 22. The putative reaction mechanism for the synthesis of multi-substituted **66** and fused ring thiophenes **69**.



Scheme 23. Copper-catalyzed synthesis of 2,4-disubstituted thiophenes **81**.



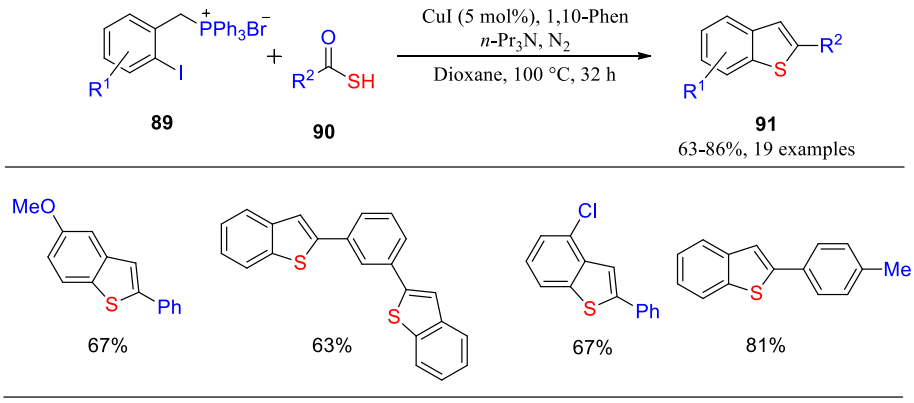
Scheme 24. The plausible reaction mechanism for the synthesis of 2,4-disubstituted thiophenes **81**.



Scheme 25. Copper-catalyzed synthesis of 2-trifluoromethyl benzothiophenes **88**.

corresponding benzothiophenes in moderate to good yields. The main drawback of this protocol is reaction failed when the substrate has methyl group at benzylic position. On the other hand, under optimal reaction conditions, thiobenzoic acid containing electron-donating groups showed better results than those with electron-withdrawing groups. Finally, when a reaction was performed with thioisophthalic acid, the desired product was obtained in 63 % yield.

The possible mechanism for the synthesis of benzothiophenes **91** is

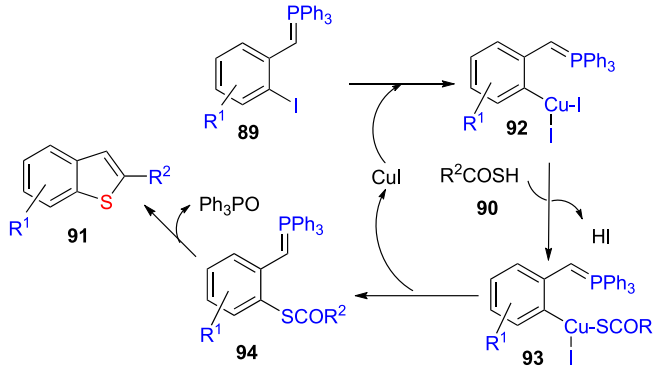


Scheme 26. Copper-catalyzed Ullmann-type C–S bond coupling synthesis of benzothiophenes **91**.

shown in Scheme 27. Substrate (2-iodobenzyl)triphenylphosphonium bromide **89** undergoes oxidative addition with copper iodide to afford intermediate **92**, which reacts with thiocarboxylic acid **90** to furnish intermediate **93**. Consequently, formation of intermediate **94** occurs along with regeneration of copper iodide. Finally, **94** undergoes an intramolecular Wittig condensation to furnish anticipated product **91**.

Jianbing, Liu and co-workers [55] developed a straightforward approach for the synthesis of benzo[*b*]thiophene-fused imidazopyridines **96** (Scheme 28). Moreover, the optical properties of wide range of benzo[*b*]thiophene-fused imidazopyridines were also studied. Furthermore, this protocol is useful for the preparation of benzo[*b*]thiophene-fused indoles. The authors also mentioned that both derivatives may show interesting biological activities. High reaction temperature and long reaction times are the limitations of this approach.

2-(2-Bromophenyl)imidazo[1,2-*a*]pyridine (R, R^1=H) **95** was selected as a model starting material and treated with K_2S in DMF solvent at 140 °C in the absence of any oxidant, which produced product in 40 % yield. When the same reaction was performed under nitrogen atmosphere, the product yield was obtained only in 21 % yield. Several oxidants such as $PhI(OAc)_2$, DDQ, 1,4-benzoquinone and molecular iodine were screened and identified that molecular iodine was the best oxidant and CuI was the suitable catalyst to synthesize further derivatives. The generality of this cyclization reaction were studied under standard optimal conditions. To begin with, the authors started the reaction by using different substituted imidazo[1,2-*a*]pyridines bearing various substituents on pyridine ring. The obtained results indicated that both electron-donating and withdrawing-groups were well tolerated, and substrates bearing them transformed into anticipated products in high yields. Also, the positions of methyl substitution in imidazo[1,2-*a*] pyridine have not affected the product yields. Notably, halo-substituted imidazo[1,2-*a*]pyridines underwent smooth reaction and afforded respective products in good to excellent yields. Regrettably, ester-substituted product was formed in only 27 % yield. Gratifyingly, 2-(2-bromophenyl)-6-(phenylethynyl)imidazo[1,2-*a*]pyridine reacted with K_2S under optimized experimental conditions to afford desired product in 63 % yield.



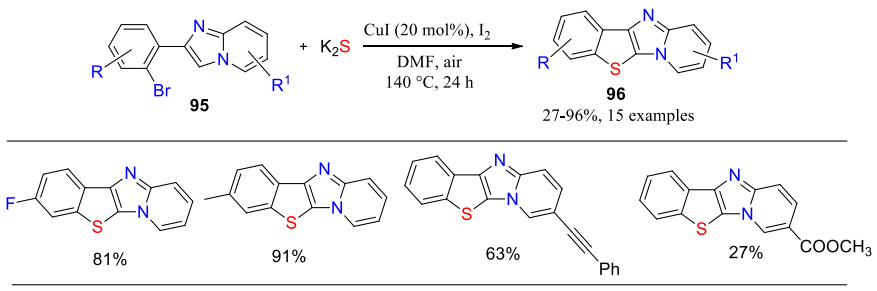
Scheme 27. The plausible mechanism for the synthesis of benzothiophenes **91**.

Two control experiments were performed to demonstrate the reaction pathway (Scheme 29). Firstly, **95** on treatment with molecular iodine in the presence of copper iodide in DMF solvent affords iodinated product **97** in 68 % yield (Scheme 29a). Consequently, its reaction with K_2S in the presence of CuI and in the absence of molecular iodine in DMF solvent furnishes expected product **96** in 57 % yield. In the meantime, deiodinated product **95** forms as a side product in 38 % yield (Scheme 29b).

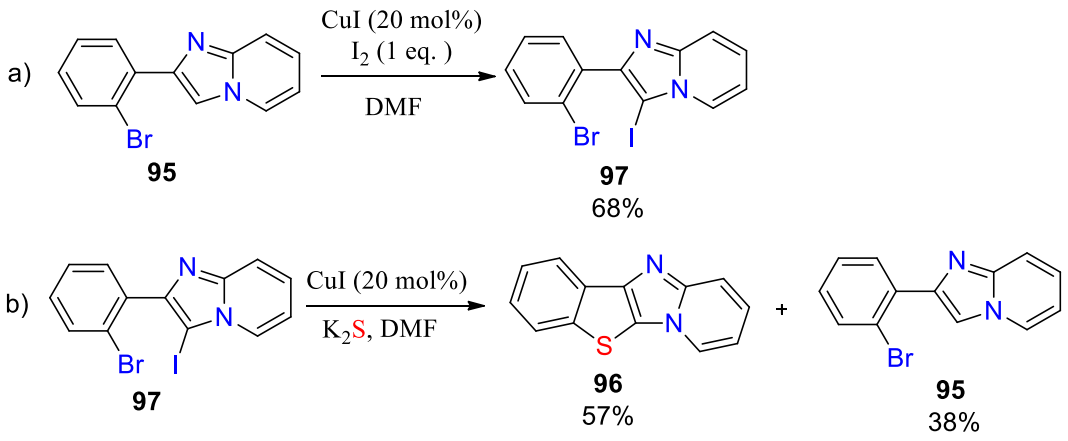
Based on previous reports [56–58], two reaction pathways are proposed for the synthesis of benzo[*b*]thiophene-fused imidazopyridines, and are shown in Scheme 30. In path 1, intermediate **98** forms by the reaction between 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine **95** and K_2S catalyzed by CuI. Then, **98** undergoes reaction with molecular iodine and furnish an electrophilic intermediate **99**, which upon intramolecular cyclization afford intermediate **100**. Finally, subsequent deprotonation occurs in **100** and leading to the formation of desired product **96**. In path 2, 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine **95** undergoes iodination and then subsequent copper-catalyzed formation of two C-S bonds through Ullmann-type *S*-arylation to give expected product **96**. Authors state that the reaction path 1 is more likely than path 2. However, the latter pathway cannot be ruled out.

Alicia B Peñéñory et al. [59] reported a copper-catalyzed C-S coupling reaction involving one-pot synthesis of benzothiophenes in good to excellent isolated yields (Scheme 31). In their reaction, when 2-(2-iodophenyl)acetonitrile **101** reacted with potassium salt of thioacetic acid (KSCOMe) **103** in the presence of CuI (10 mol%) and 1, 10-phenanthroline (10 mol%) at 100 °C in toluene under nitrogen atmosphere afforded *N*-(benzo[*b*]thiophen-2-yl)acetamide **104** in 65 % yield. Encouraged by this result, the substrate scope for this synthesis was examined. Thus, many reactions were performed by using different substituted (4-fluro, 4-bromo and 2-methyl) 2-(2-iodophenyl)acetonitriles **101** and KSCOMe **102** under the above optimal conditions, which furnished corresponding products in good yields. In addition, when 2-(2-iodophenyl)acetonitrile **101** treated with ethyl xanthate salt **102** under same experimental conditions, *S*-(2-(cyanomethyl)phenyl) *O*-ethyl carbonodithioate **105** was formed in 29 % yield instead of benzothiophene. When the substrate **101** reacted with thiobenzoic acid salt in the presence of K_2CO_3 base, benzothiophene **104** was obtained in 45 % yield. However, this protocol does not provide any heteroaryl-substituted products, which is the limitation of this synthesis. Further, requirement of high temperature and long reaction times restricts the application of this method.

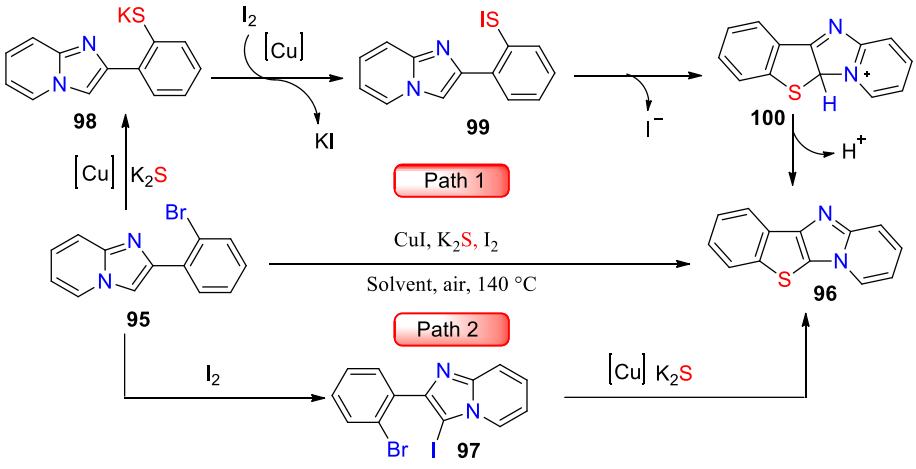
The possible mechanism of formation of benzothiophene **104** is presented in Scheme 32. Initially, oxidative addition takes place between the substrates **101** and **103**, which leads to the formation of intermediate **106**, which undergoes reductive elimination and further



Scheme 28. Copper-catalyzed synthesis of benzo[*b*]thiophene-fused imidazopyridines **96**.



Scheme 29. a) Synthesis of iodinated product **97** in the presence of iodine b) Synthesis of product **96** and side product **95**.

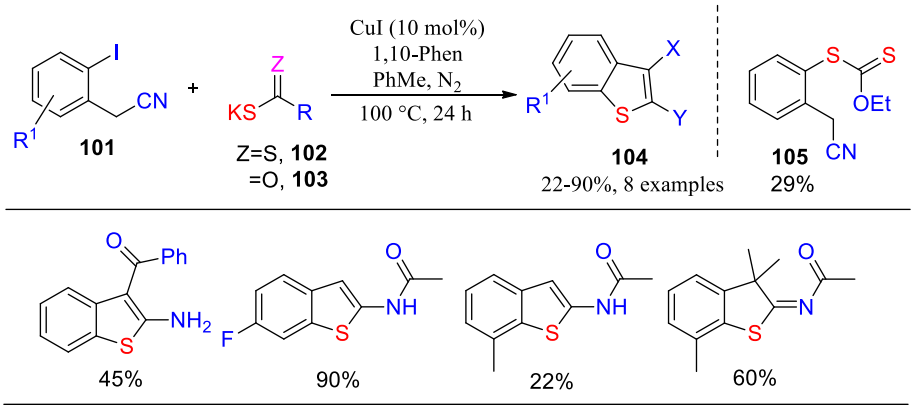


Scheme 30. Reaction mechanism for the synthesis of benzo[*b*]thiophene-fused imidazopyridines **96**.

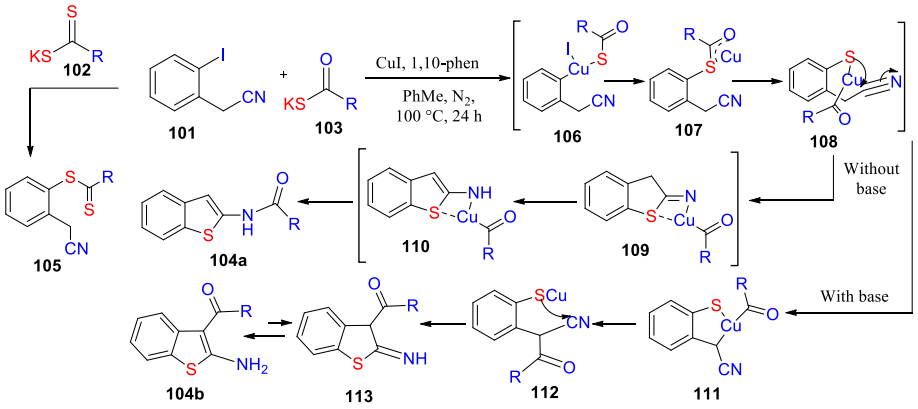
coordination with Cu(I) to deliver complex **107**. Further, rearrangement of **107** leads to Cu(II) intermediate **108**. The cyano group activates intermediate **108** and acts differently in the presence and absence of a base. In the presence of base, Cu(I) arenethiolate **111** forms, which rearranges to **112**. This undergoes intramolecular cyclization to afford 2-imino dihydrobenzo[*b*]thiophene **113**. Finally, it undergoes tautomerization to furnish 2-aminobenzo[*b*]thiophene derivatives **104b**. On the other hand, in the absence of base, acyl Cu(III)-imino intermediate **109** forms from intermediate **108** *via* thiolate addition to nitrile group. The intermediate **109** upon aromatization affords **110**, which undergoes reductive elimination to furnish 2-(*N*-acyl)-aminobenzo[*b*]thiophene product **104a**.

Ila and co-workers demonstrated [60] an intramolecular copper-catalyzed one-pot synthesis of functionalized benzothiophenes based on their previous studies on benzothiophenes [61,62]. In the beginning, they condensed 2-bromo-het(aryl)acetonitrile substrates **114** (1.0 mmol) with (het)aryl/alkyl dithioesters **115** (1.0 mmol) in the presence of sodium hydride (2.0 mmol) in DMF, which afforded enethiolate intermediates **116**. These underwent intramolecular copper-catalyzed arylthiolation and afford wide range of functionalized benzothiophene derivatives **117** in high yields (Scheme 33). This strategy is useful for the synthesis of many products.

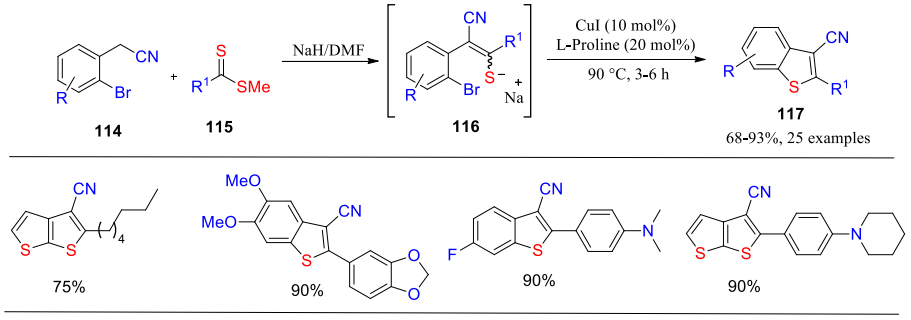
The scope of the protocol was explored by using optimal conditions. Various (het)aryl rings in **114** and different electron-withdrawing and electron-donating groups in **115** were compatible during the formation of benzo- or heterofused-thiophene products **117**. Sterically encumbering aryl or heteroaryl group-containing starting materials and also those bearing multiple-substitutions were well tolerated and afforded



Scheme 31. Copper-catalyzed synthesis of benzothiophenes **104** and *S*-(2-(cyanomethyl)phenyl) *O*-ethyl carbonodithioate **105**.



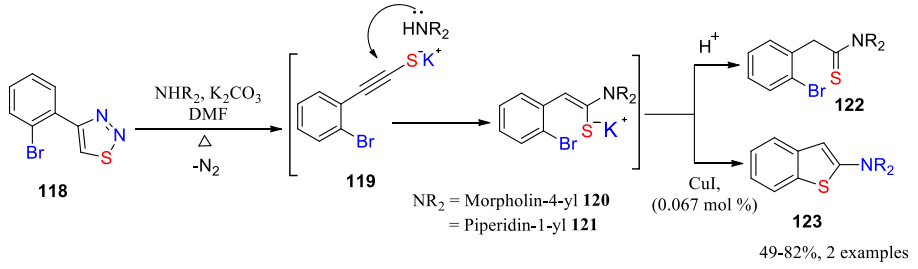
Scheme 32. Reaction pathway for the synthesis of benzothiophene **104** and *S*-(2-(cyanomethyl)phenyl) *O*-ethyl carbonodithioate **105**.



Scheme 33. Copper-catalyzed one-pot synthesis of functionalized benzothiophenes **117**.

corresponding products in good yields.

Petrov and co-workers [63] developed a copper iodide-catalyzed synthesis of 2-aminobenzothiophenes **123**. When 4-(2-bromo-phenyl)-1,2,3-thiadiazole **118** treated with secondary amines in the presence of catalytic amount of copper iodide and a base like potassium carbonate in DMF solvent furnished



Scheme 34. Synthesis of 2-(morpholin-4-yl)-1-benzothiophene and 2-(piperidin-1-yl)-1-benzothiophene **123**.

2-aminobenzothiophenes **123** (Scheme 34). In parallel, formation of thioamide **122** was also possible. Further, this thioamide (**124**) underwent intramolecular cyclization in the presence of CuI and potassium carbonate to furnish 2-aminobenzothiophene (**126**) *via* intermediate **125** (Scheme 35). The reaction pathways for the formation of **122** and **123** are shown in Scheme 34, which are formed by protonation and intramolecular cyclization respectively. Nowadays, only a few articles are reported for the synthesis of 2-aminobenzothiophene scaffolds [64–67]. Notably, Petrov's group has demonstrated a simple and unique strategy for the synthesis of aminobenzothiophenes from 4-(2-bromophenyl)-1,2,3-thiadiazoles, which is noteworthy. However, lack of substrate scope is the main limitation of this method since only two secondary amines (morpholine and piperidine) are used.

Sannaiah Ananda and co-workers [68] reported an intramolecular copper-catalyzed one-pot synthesis of substituted benzothiophenes. Substrates phenylacetonitriles **114** (1.0 mmol) reacted with dithioesters **115** (1.0 mmol) in DMF solvent in the presence of K_3PO_4 (2.0 mmol), pivalic acid (1.5 mmol), and cuprous iodide (20 mol%) at 80 °C to afford benzothiophenes **117** in good yields (Scheme 36). This efficient protocol does not need strong base and toxic tin reagents for cyclization and hence overcomes the limitations of earlier reported methods [61,62]. This approach is an important alternative for the synthesis of raloxifene analogues. Furthermore, this strategy has not used any hazardous reagents and takes less reaction time and gives good product yields.

Using the well-established reaction conditions, the generality of the reaction was examined. Thus, dithioesters **115** bearing electron-donating groups, electron-withdrawing groups on the phenyl ring and heteroaryl dithioesters underwent smooth reaction with *o*-halophenyl acetonitriles under standard experimental conditions to furnish corresponding benzothiophenes in good yields.

The pathway for the formation of benzothiophenes is shown in Scheme 37. In the first step, abstraction of a proton from active methylene group of **114** by the base and subsequent reaction with **115** affords intermediate **127**. In the next step, **127** reacts with K_3PO_4 and furnish potassium thioenolate **128a** which undergoes intramolecular *S*-arylation with aryl halogen *via* copper catalysis. Thus, oxidative addition of **128a** with CuI leads to the formation of intermediate **128b**. The intermediate **128c** forms *via* exchange of a pivalate with chlorine atom. Finally, **117** is formed from intermediate **128d** through reductive elimination with the regeneration of catalyst.

Daoshan Yang et al. [69] reported a copper-catalyzed double C-S bond formation for the synthesis of benzo[*b*]thiophene fused imidazo[1,2-*a*]pyridine derivatives **96** *via* Ullmann-type coupling. Treatment of bromophenyl imidazopyridine **95** (0.3 mmol) with K_2S (0.6 mmol) in the presence of copper catalyst (10 mol%) and 1,10-phenanthroline ligand (0.03 mmol) in DMF solvent furnished anticipated product in good to high yields. The notable features of this efficient one-pot protocol include use of inexpensive CuI as a catalyst and 1,10-phenanthroline as a ligand, and readily available various substituted 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines (Scheme 38).

The generality of the reaction was examined, which showed that no obvious change in the transformation when the benzene ring in the substrate **95** attached by electron-donating groups. The reaction failed in the presence of nitro group in **95**. Other functional groups such as ether, halogens, methyl and trifluoromethyl were well tolerated. The main drawback of this approach is, it failed when other *N*-heterocycles such as **129** and **130** are used as substrates (Scheme 39).

The postulated reaction pathway is presented based on previous literature [70–74] in Scheme 40. At the outset, the chelated Cu(I) complex forms by the reaction between CuX and ligand. Next, **95** undergoes oxidative addition with chelated Cu(I) complex leading to the formation of intermediate **131**, which reacts with K_2S and forms intermediate **131a**. The reductive elimination of LCuX occurs in **131a** and forms thionated intermediate **132**. The complex **133** is formed by the reaction between **132** and LCuX. Then, **133** produces **134** in atmospheric air. Finally, anticipated product **96** is formed *via* reductive elimination along with regeneration of catalytic intermediate LCuX.

3.2. Catalyzed by cuprous and cupric acetates [CuOAc and $Cu(OAc)_2$]

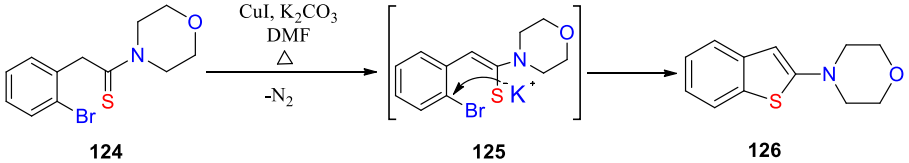
Jie Wu's group [75] demonstrated a copper-catalyzed synthesis of benzo[*b*]thiophene 1,1-dioxides **137** from (2-alkynylaryl)boronic acids **135** (0.2 mmol) by treating with DABSO (DABCO-bis(sulphur dioxide)) **136** (0.2 mmol). This approach proceeds in high efficiency when the reaction is carried out in the presence of 10 mol% copper(II) acetate in DMF solvent at 100 °C (Scheme 41). It is noteworthy to mention that the metal catalyst involved in this protocol plays a dual role. Briefly, it involved in coupling reaction of aryl boronic acid, sulphur dioxide and alkyne moieties.

Using the optimized reaction conditions, the substrate scope of the reaction was examined. The phenyl ring of (2-alkynyl-aryl)boronic acids **135** bearing electron-donating and electron-withdrawing groups showed good efficiency and furnished corresponding products in high yields. In addition, substrate **135** bearing alkyl, aryl and heteroaryl substitutions underwent smooth reaction with DABSO under standard reaction conditions to give products in good yields. Gratifyingly, fluoro-substituted benzo[*b*]thiophene 1,1-dioxide was produced in 95 % yield.

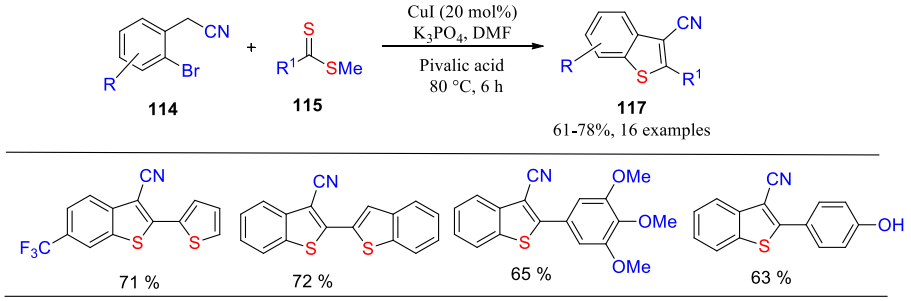
The reaction pathway for the formation of benzo[*b*]thiophene 1,1-dioxides is shown in Scheme 42. Intermediate **138** forms by the reaction between (2-alkynylaryl)boronic acid **135** and the copper catalyst. Next, SO_2 is inserted into **138**, which leads to the formation of intermediate **139**. Consequently, the triple bond of intermediate **139** is activated by the copper catalyst followed by 5-*endo* cyclization furnishes benzo[*b*]thiophene 1,1-dioxide **137**.

Prasad and Sekar [76] reported a domino synthesis of substituted benzothiophenes **142** *via* copper-catalyzed reaction between *o*-haloalkynes and dithiolates. Thus, reaction between *o*-haloalkynyl benzenes **140** (0.5 mmol) and xanthate **141** (1.5 mmol) in the presence of copper acetate ($Cu(OAc)_2$) catalyst (10 mol%) and 1,1′-binaphthyl-2,2′-diamine (BINAM) ligand (0.05 mmol) in DMF solvent at 80 °C furnished expected 2-substituted-benzothiophenes **142** in good to excellent yields (Scheme 43). Notably, authors identified that during the screening of catalysts, different copper catalysts has affected neither product yield nor reaction time. The reaction takes more time to complete, which is the drawback of this protocol.

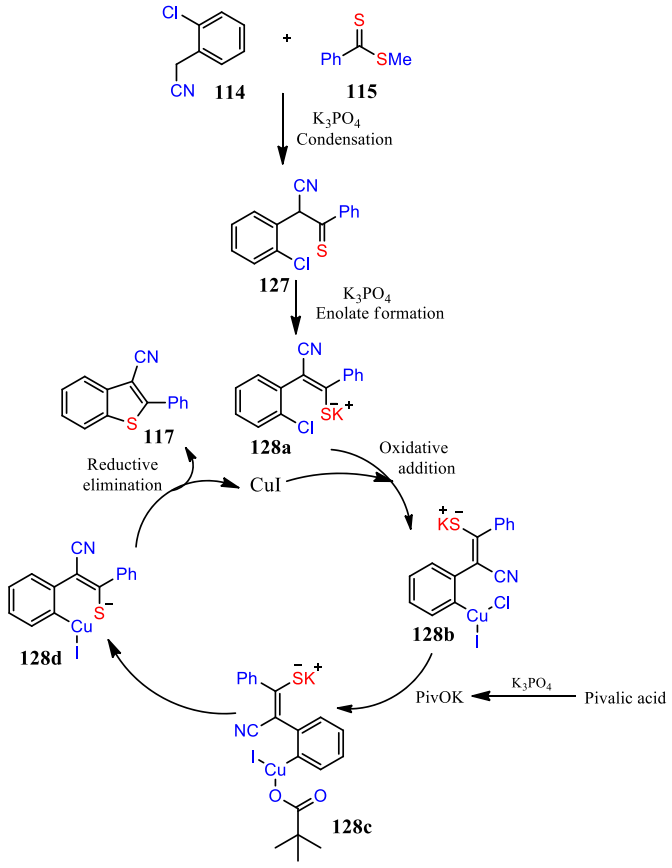
The generality of the reaction was examined using standard reaction conditions. Various substituted 2-iodoalkynylbenzenes **140** containing electron-rich and electron-poor groups underwent smooth reaction with xanthate **141** to furnish corresponding benzothiophenes **142** in excellent yields. Interestingly, sterically hindered benzothiophene was obtained in 97 % yield under the same optimal reaction conditions. Similarly, when 2-((2-iodophenyl)ethynyl)pyridine treated with



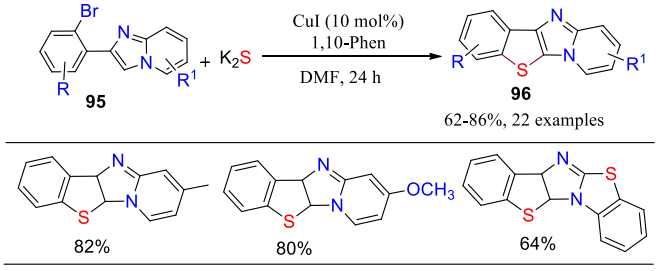
Scheme 35. Reaction pathway for the synthesis of benzothiophene **126** *via* intramolecular cyclization.



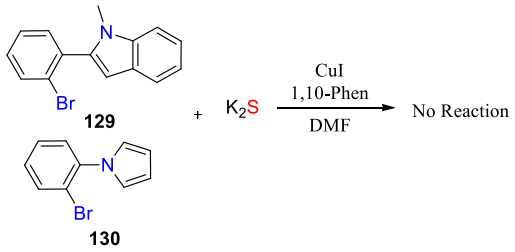
Scheme 36. Copper-catalyzed one-pot synthesis of benzothiophenes **117**.



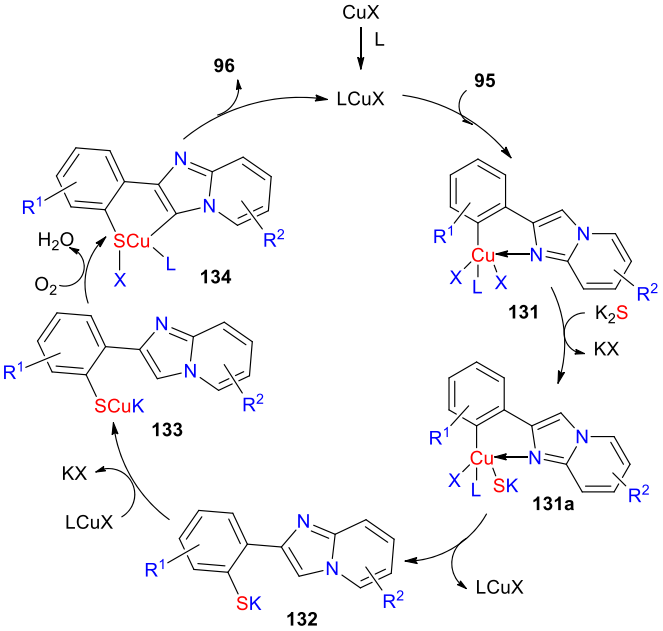
Scheme 37. The plausible reaction mechanism for the synthesis of benzothiophene **117**.



Scheme 38. Copper-catalyzed synthesis of benzo[*b*]thiophene fused imidazo [1,2-*a*] pyridines **96**.



Scheme 39. Failed reactions when *N*-heterocycles **129, 130** were used as starting materials.

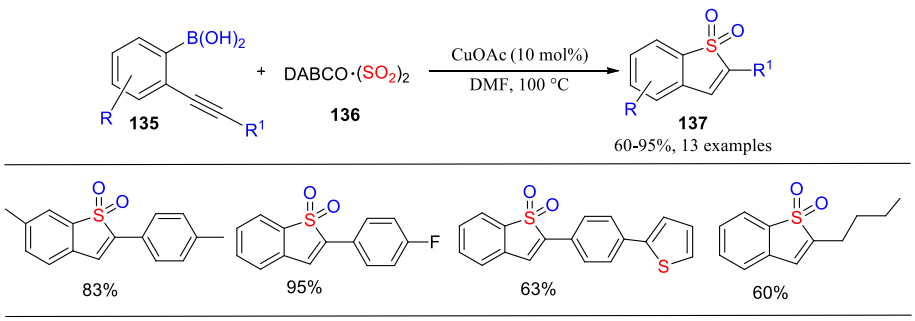


Scheme 40. The possible reaction mechanism for the formation of benzothiophenes **96**.

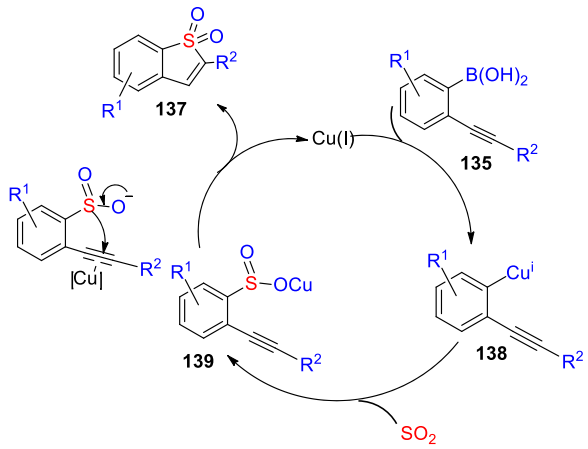
xanthate **141**, corresponding benzothiophene **142** was formed in 93 % yield.

The possible reaction mechanism for the domino synthesis of substituted benzothiophenes is as shown in Scheme 44. In the beginning, *o*-iodoalkynylbenzene **140** couples with xanthate substrate **141** leading to the formation of intermediate **143** through the C-S bond coupling. The intermediate aryl thiolate **144** forms from the intermediate **143** *via in situ* hydrolysis. Finally, 5-*endo-dig*-intramolecular cyclization occurs in aryl thiolates **144** to furnish benzothiophene **142**.

Govindasamy Sekar and co-workers [77] reported an efficient approach for the copper-catalyzed synthesis of 2-acylbenzo[*b*]



Scheme 41. Copper-catalyzed synthesis of benzo[*b*]thiophene 1,1-dioxides **137** *via* insertion of sulphur dioxide.



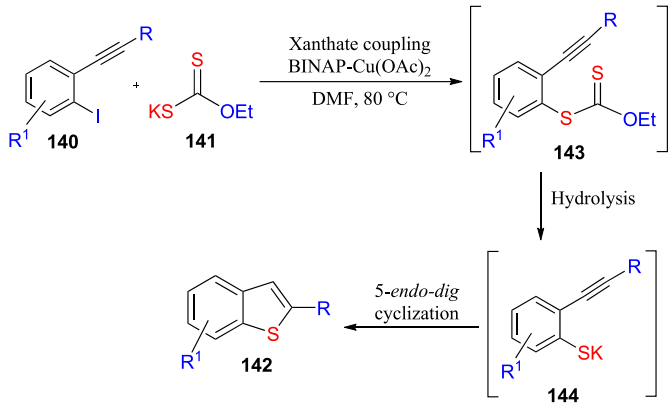
Scheme 42. The plausible mechanism for the synthesis of benzo[*b*]thiophene 1,1-dioxides **137**.

thiophenes. The easily accessible 2-iodochalcones **145** (0.5 mmol) were treated with odourless xanthate **141** (2 equiv.) in the presence of copper acetate (10 mol%) in DMSO solvent at 100 °C to obtain 2-acylbenzothiophenes in high yields (Scheme 45). A notable feature of this approach is synthesis of pre-mRNA splicing modulator, which has 1-(5-hydroxybenzothiophene-2-yl)ethanone moiety. It is noteworthy to mention that the desired products bear various substituents such as electron-donating, electron-withdrawing and heteroaryl groups. The control experiments of this protocol were also successful with solid analytical characterizations. The reaction requires high temperature to obtain anticipated products, which is the drawback of this protocol.

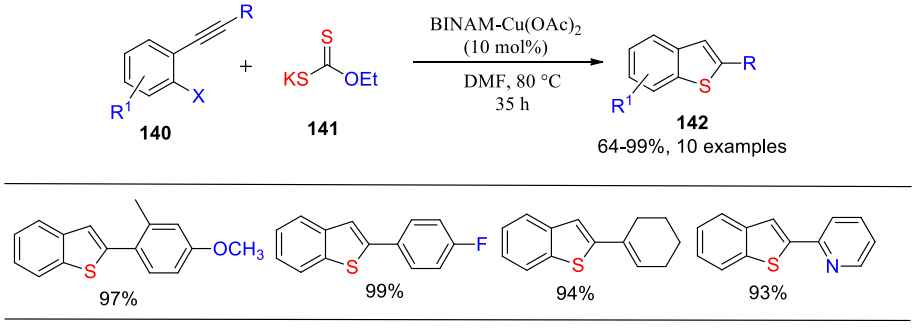
The substrate scope of the reaction using above optimized reaction conditions was examined. Notably, desired products bearing mono-, di-, and tri-substitutions with various groups such as electron-donating (methoxy), electron-withdrawing (halogens) and hetero aryl groups (1,3-dioxolane and thienyl) were obtained in high yields. The authors also conducted two control experiments to shed light on reaction mechanism. Firstly, when substrate **147** treated with xanthate (2 equiv.) **141** in the presence of copper acetate catalyst (10 mol%) in ethyl acetate solvent, the desired product was obtained in only 23 % yield. In addition, **148** was obtained as a major side product in 7 % yield, which was confirmed by single-crystal X-ray diffraction (XRD) studies (Scheme 46a). Secondly, the substrate **149** underwent smooth reaction with xanthate **141** under standard reaction conditions affording expected product **146** in 23 % yield along with **150** as a side product which was also confirmed by single-crystal XRD analysis (Scheme 46b).

Based on previous data [78], the reaction pathway is demonstrated in Scheme 47. Initially, substrate **145** reacts with copper acetate to afford intermediate **151** *via* oxidative addition. Then, this intermediate undergoes reaction with xanthate **141** and furnishes intermediate **152**, which provides intermediate **153** through reductive elimination process. Finally, excess of xanthate **141** reacts with intermediate **153** yielding the expected product **146**.

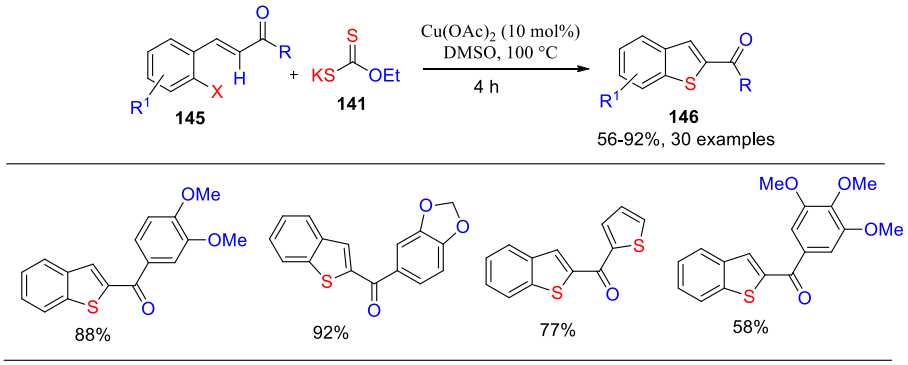
The same group [79] developed the synthesis of 2-acyldihydrobenzo[*b*]thiophenes **155** and 2-acylbenzo[*b*]thiophenes **156** *via*



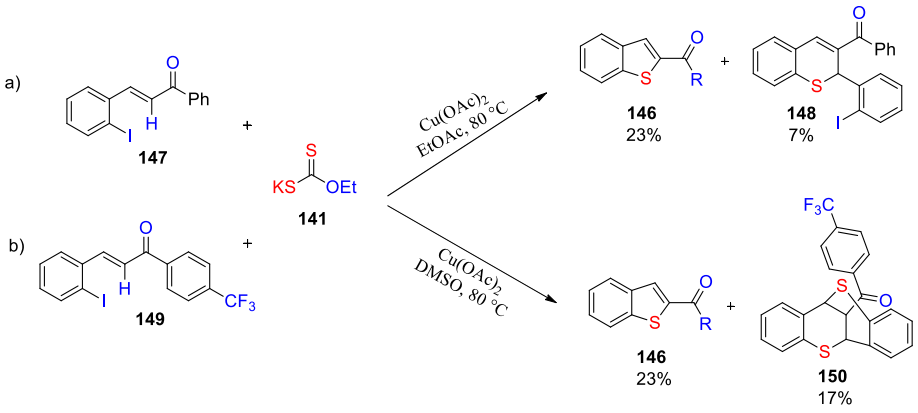
Scheme 44. The possible reaction mechanism for the synthesis of benzothiophenes **142**.



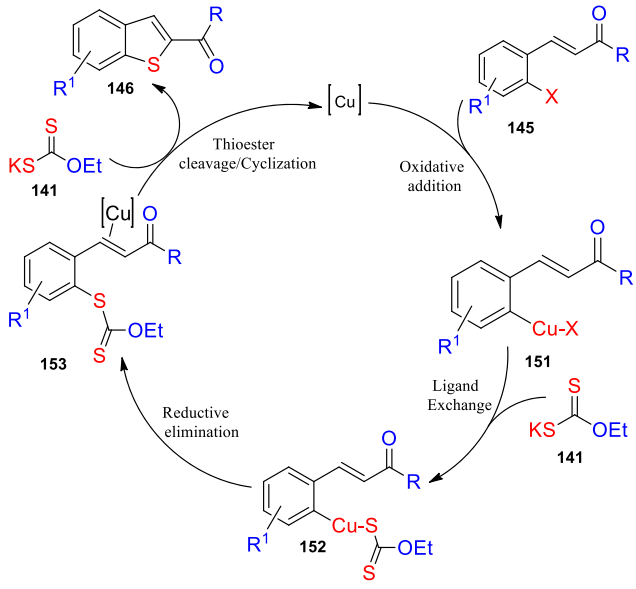
Scheme 43. Copper-catalyzed synthesis of benzothiophenes **142**.



Scheme 45. Copper-catalyzed synthesis of 2-acylbenzothiophenes **146** from 2-iodochalcones **145** and xanthate **141**.



Scheme 46. Control experiments for the synthesis of **146, 148** and **150**.

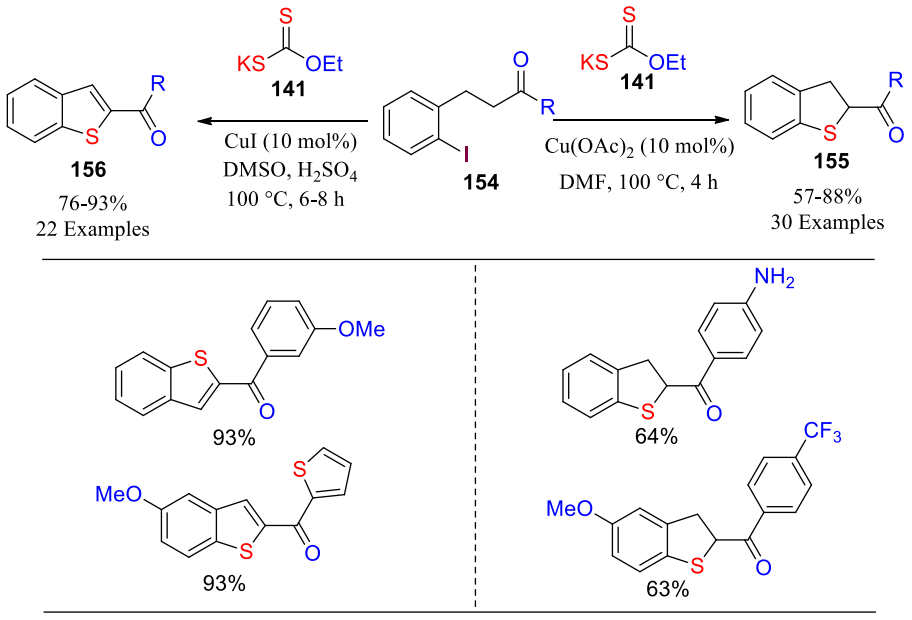


Scheme 47. The plausible mechanism for the synthesis of 2-acylbenzothiophenes **146**.

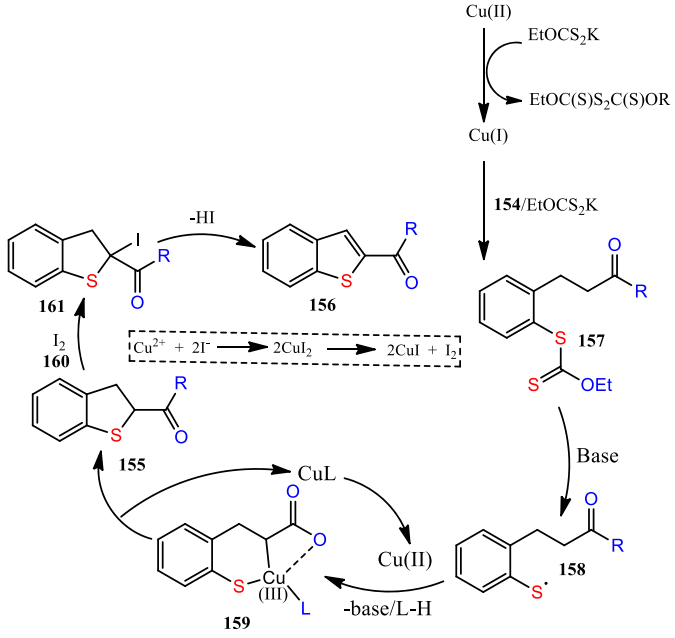
copper-catalyzed two C–S bond formation. During the treatment of 2-iodoketones **154** with xanthate **141** (2 equiv.) in the presence of copper acetate (10 mol%) in DMF, 2-acyldihydrobenzo[*b*]thiophenes **155** were formed. On the other hand, the same starting materials **154** and **141** underwent smooth reaction in the presence of copper iodide (10 mol%) and sulphuric acid (1 equiv.) in DMSO to furnish 2-acylbenzo[*b*]thiophenes **156** (Scheme 48). Under these conditions, authors explored the substrate scope for the synthesis of **155** and **156**. Thus, various substrates bearing electron-donating groups (Me, OMe and amine) substituted on carbonyl phenyl ring underwent reaction to give respective products in good yields. Authors also identified that sterically crowded substrates **154** did not affect the reaction. The substrates **154** containing electron-withdrawing groups also underwent reaction with xanthate **141** and produced products in fewer yields and took more time to complete. Notably, replacement of carbonyl phenyl group in substrate **154** by heteroaryl/aliphatic substitutions was also successful. On the other hand, authors investigated the substrate scope for the one-pot synthesis of **156** as well. A wide range of substrate scope, easily available starting materials and simultaneous formation of two C-S bonds are the notable key features of this approach. These syntheses require high temperature to complete, which is the limitation of these strategies.

The possible reaction mechanisms for the synthesis of **155** and **156** are shown in Scheme 49. In the beginning, substrate 2-haloketone **154** forms C-S bond with xanthate **141** catalyzed by Cu(I) to afford intermediate **157**. Later, intermediate **158** forms from **157** through homolysis of C-S bond. Then, intermediate **158** undergoes oxidation/metalation with copper catalyst to furnish intermediate **159**. The desired product **155** forms from **159** and along with subsequent elimination of Cu(I) catalyst. On the other hand, Cu(I) catalyst further oxidizes into Cu(II) by air/O_2. The copper(II) iodide undergoes autoreduction to give copper(I)iodide and iodine **160**. This liberated iodine, iodinates **155** to produce intermediate **161**. Finally, the anticipated product **156** forms from **161** after the elimination of hydrogen iodide.

Govindasamy Sekar and co-workers [80] demonstrated a copper catalyzed domino synthesis of benzo[*b*]thiophene derivatives **163** from the reaction between 2-iodophenyl ketones **162** and xanthate **141** in the presence of copper acetate *via* radical cyclization (Scheme 50).



Scheme 48. Copper catalyzed synthesis of 2-acyldihydrobenzo[*b*]thiophenes **155** and 2-acylbenzo[*b*]thiophenes **156**.



Scheme 49. The plausible reaction mechanisms for the synthesis of 2-acyldihydrobenzo[*b*]thiophenes **155** and 2-acylbenzo[*b*]thiophenes **156**.

Optimization of reaction conditions indicated that 20 mol% of copper acetate, 2 equivalence of acetic acid in DMSO solvent at 120 °C was the best condition. Using this optimized reaction conditions, generality or substrate scope of the reaction was explored. The substituents on the substrate **162** include electron-donating group, electron-withdrawing group and heteroaryl, which helped for the completion of reaction and furnished respective products in moderate to good yields. The final products were confirmed by analytical characterizations including single crystal X-ray analysis. Use of easily available odourless substrates and broad substrate scope are the main key features of this protocol. Further, 2-thioaroyl-3-hydroxybenzo[*b*]thiophene can be converted into hemithioindigo (which functions as a photoswitch and dethionated Lupinalbin analogue).

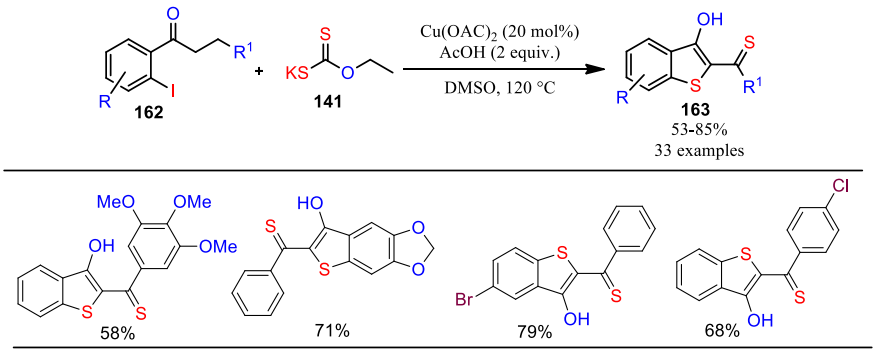
The plausible reaction mechanism for the synthesis of benzo[*b*]thiophene is shown in Scheme 51. At the outset, substrate 1-(2-iodophenyl)-3-phenylpropan-1-one **162** furnishes intermediate **164** through oxidative addition with Cu(I) catalyst. Intermediate **164** produces intermediate **165** *via* ligand exchange with potassium ethyl xanthate. Intermediate **166** forms from **165** *via* reductive elimination. Later, intermediate **166** on further reaction with copper acetate affords **167**. Intermediate **167** undergoes keto-enol tautomerism and produces intermediate **168**. Consequently, intermediate **168** undergoes homolytic cleavage to give radical intermediate **169**. Radical cyclization occurs in intermediate **169** and furnishes cyclized product **170**. The stable intermediate **171** forms from **170** through keto–enol tautomerism. Finally, methylene group in **171** is converted into thiocarbonyl *via* reaction with xanthate radical **172** and leads to the formation of desired product **163**.

Petrov and co-workers [81] developed a copper-catalyzed cyclization reaction for the synthesis of 2-(morpholin-4-yl)-1-benzothiophene **175** (R^2=$(CH_2CH_2)_2O$). In this approach, the authors identified that both copper(I) and Copper(II) salts can be used as catalysts for the synthesis of 2-(morpholin-4-yl)-1-benzothiophene **175**. The same reaction was also carried out under microwave irradiation and it was successful without affecting the product yield. The authors also performed detailed mechanistic studies for the synthesis of **175** (Scheme 52).

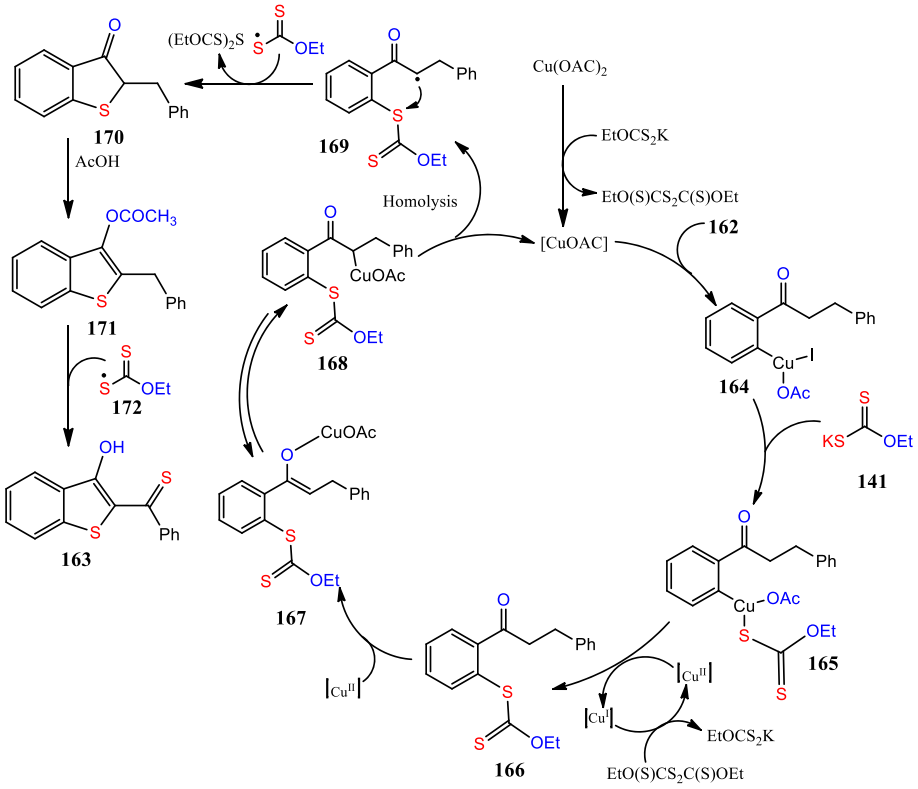
In addition, when the reaction was conducted under microwave irradiation, reaction times were reduced, which is one of the main advantages of this protocol.

The plausible mechanism for the synthesis of 2-(morpholin-4-yl)-1-benzothiophene **175** is presented in Scheme 53. The 1,2,3-thiadiazole **173** undergoes reaction with NHR_2 (R_2=$(CH_2CH_2)_2O$, $(CH_2)_5$) **174** and K_2CO_3 in DMF solvent, which leads to the formation of intermediate **176** *via* the elimination of N_2. The intermediate **177** forms from **176** and further undergoes intramolecular cyclization in the presence of catalytic amount of copper catalyst to afford anticipated product **175**.

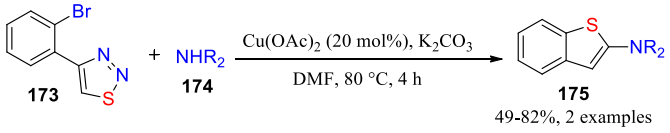
Meili Feng and co-workers [82] developed a novel, green and copper-catalyzed domino synthesis of substituted benzothiophenes **179** from the reaction between 2-iodoalkynylbenzenes **178** (0.5 mmol) and xanthate **141** (1.5 mmol) (Scheme 54). Notably, the catalyst Fe_3O_4@-SiO_2-(Imine-Thiazole)-Cu$(OAc)_2$ (5 mol%) used in this approach was characterized by FT-IR, SEM, EDX, XRD, AAS, TEM, TGA, VSM, and ICP-OES techniques. Importantly, this catalyst can be easily recovered from the reaction without change in its catalytic activity. All desired



Scheme 50. Copper catalyzed synthesis of benzo[*b*]thiophene derivatives **163**.



Scheme 51. The plausible reaction mechanism for the synthesis of benzo[*b*]thiophene **163**.

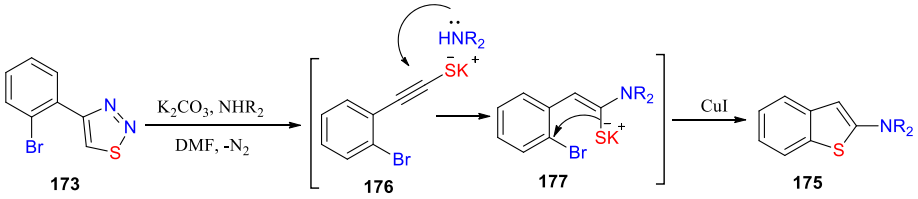


Scheme 52. Copper-catalyzed synthesis of 2-(morpholin-4-yl)-1-benzothiophene **175**.

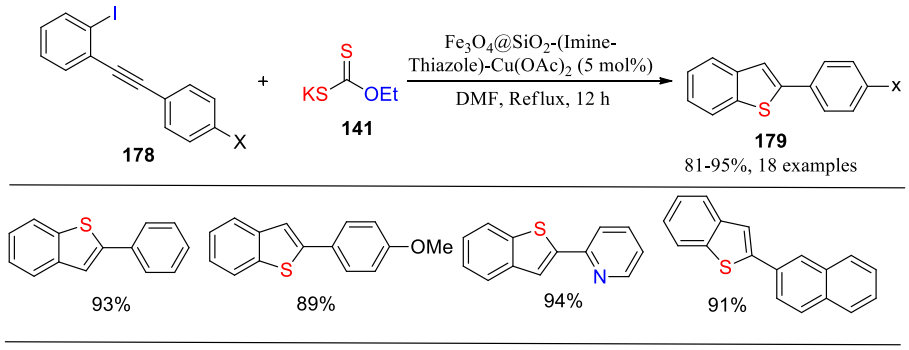
products were obtained in good to excellent yield.

Authors performed experiments to obtain the best reaction conditions, then the substrate scope of the reaction was examined using standard optimal conditions. The obtained anticipated products bearing electro-neutral, electron-donating, and electron-withdrawing substituents were afforded in high yields. Interestingly, the desired product which bears heteroaryl substitution was well tolerated and furnished corresponding product.

The reaction pathway for the formation of desired benzothiophene



Scheme 53. The plausible mechanism for the synthesis of 2-(morpholin-4-yl)-1-benzothiophene **175**.



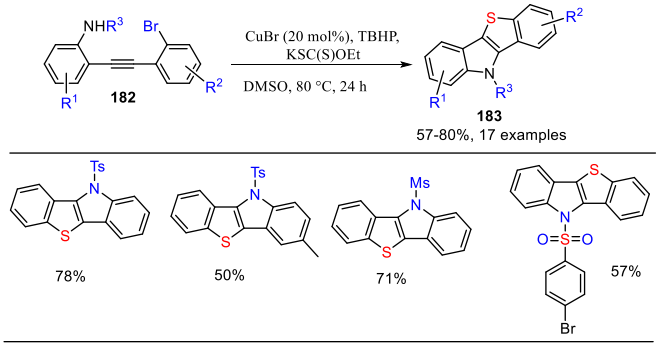
Scheme 54. Copper-catalyzed synthesis of benzothiophenes **179**.

product **179** which was catalyzed by Fe_3O_4@SiO_2-(Imine-Thiazole)-Cu$(OAc)_2$ nanocomposite is demonstrated in Scheme 55. In the beginning, C-S bond formation occurs between *o*-iodoalkynylbenzene **178** and xanthate **141** affording intermediate **180**, which undergoes hydrolysis and leads to the formation of intermediate **181**. Finally, desired benzothiophene **179** forms from intermediate **181** *via* 5-*endo dig* cyclization process.

3.3. Catalyzed by copper bromide (CuBr)

Yunfei Du et al. [83] described a copper-catalyzed cascade synthesis of benzothieno[3,2-*b*]indoles **183**. Substrates *N*-protected 2-((2-bromophenyl)ethynyl)anilines **182** (1.0 mmol) reacted with potassium ethylxanthate (2 equiv.) in the presence of TBHP and copper bromide (20 mol%) at 80 °C to afford benzothieno[3,2-*b*]indoles **183** in good yields (Scheme 56). Wide substrate scope and high product yields are the notable features of this protocol.

The substrate scope was studied using standard reaction conditions. The starting material **182** bearing various substituents transformed into corresponding desired product in good to high yields. Obtained products contain electron-donating (methyl and methoxy) and electron-withdrawing groups (fluro, chloro, and bromo), which were tolerable during the course of the reaction. Furthermore, authors also performed mechanistic studies for the synthesis of benzothieno[3,2-*b*]indoles (Scheme 57). When diarylalkyne **184** reacted with **141** under the optimized reaction conditions, no product formation was observed, which indicate that reaction was initiated by nitrogen moiety instead of sulphur substrate (Scheme 57a). Then, the second experiment revealed that a new product was formed by the reaction of substrate **186** with CuBr in DMSO solvent affording new intermediate **187** in 98 % yield (Scheme 57b). Furthermore, in the reaction of substrate **188** with **141** under optimal conditions, no product was observed (Scheme 57c), which encouraged the formation of the pyrrole ring instead of benzothiophene ring. In addition, they failed to obtain any product when intermediate **190** treated with **141** under the same experimental conditions (Scheme 57d). This suggests that the intermediate **190** is not involved in the formation of anticipated product **189**. Finally, when TEMPO was used in the reaction, it did not affect the formation of



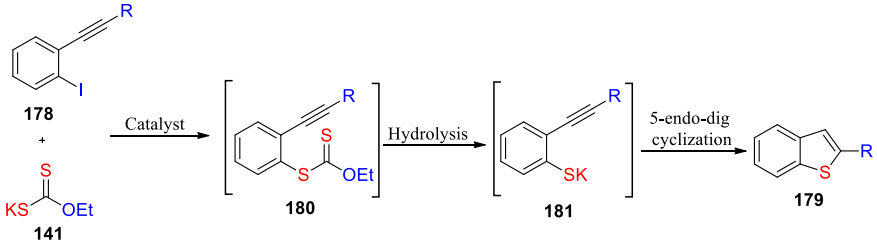
Scheme 56. Copper-catalyzed synthesis of benzothieno[3,2-*b*]indoles **183**.

desired product, which ruled out the radical mechanism (Scheme 57e).

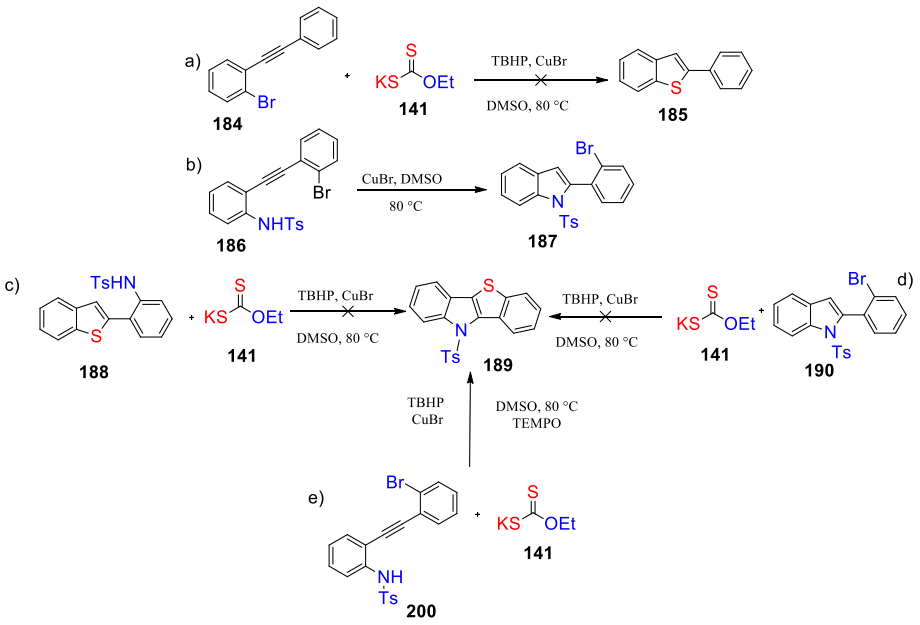
Based on the present and previously reported methods [84,85], the reaction mechanism was predicted and presented in Scheme 58. When substrate **182** reacted with **141** in the presence of copper catalyst produced intermediate **201** *via* an intramolecular, 5-*endo-dig* nucleophilic addition with alkyne. Intermediate **202** was formed from **201** in the presence of TBHP and potassium ethyl xanthate. Intermediate **202** underwent reductive elimination to generate CuBr and intermediate **203**, which reacted with ethyl xanthate anion to produce intermediate **205**. Intermediate **206** was formed by the reaction between **205** and copper bromide through oxidative addition. Finally, the anticipated product **183** was formed from intermediate **206** *via* C-S bond formation along with the regeneration of copper bromide.

3.4. Catalyzed/mediated by copper chloride ($CuCl_2$)

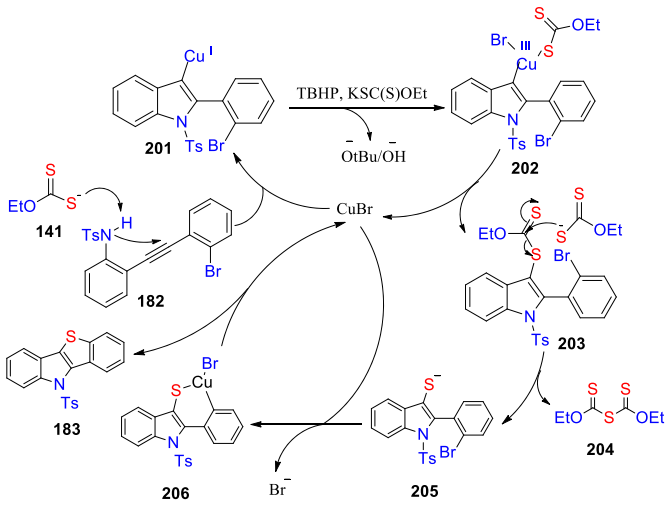
Masaki Shimizu's group [86] developed a copper-catalyzed facile synthesis of unsymmetrical dibenzothiophenes **208** by the reaction between potassium thioacetate (1.5–5.0 equiv) and dibenziodolium triflates **207** (0.5 mmol) (Scheme 59). A notable feature of this protocol is that symmetrical and unsymmetrical products are obtained in high yields. Long reaction times and requirement of high temperature are the



Scheme 55. The mechanism for the copper-catalyzed synthesis of benzothiophenes **179**.



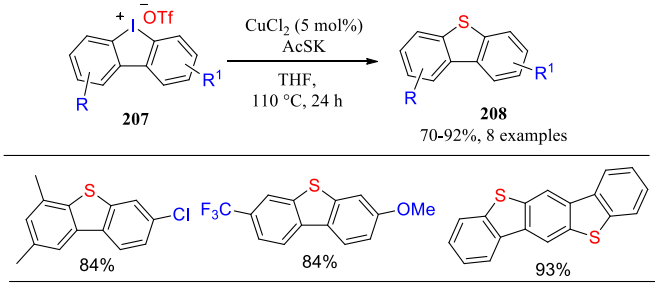
Scheme 57. Control experiments.



Scheme 58. The plausible mechanism for the synthesis of benzothieno[3,2-*b*] indoles **183**.

limitations of this method.

Using standard reaction conditions, the generality of this cross-coupling reaction was examined. Chloro-substituted desired products are formed in good to excellent yields. The substrates bearing electron-donating groups (such as methyl and methoxy), electron-withdrawing groups (such as cyano, trifluoro and chloro) did not affect the reaction efficiency and furnished products in high yields.



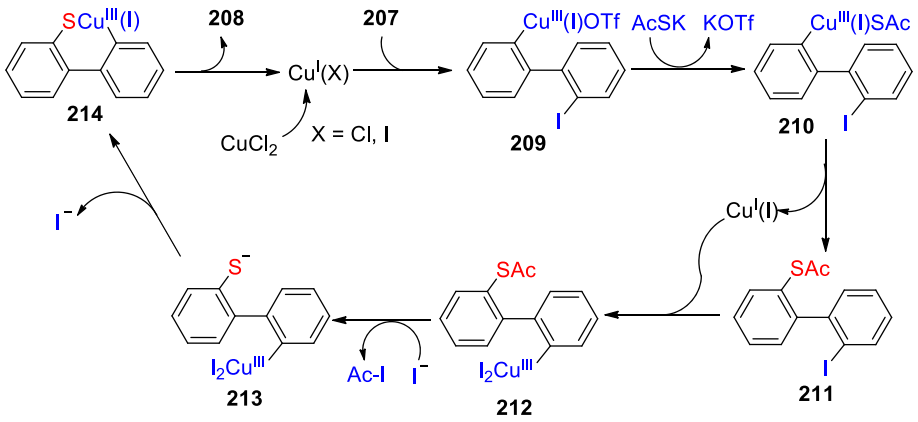
Scheme 59. Copper-catalyzed synthesis of dibenzothiophenes **208**.

Based on a previous report [87], the possible reaction mechanism for the synthesis of dibenzothiophenes is shown in Scheme 60. In the beginning, aryl–Cu^{III} complex **209** forms by the reaction between Cu^{I} and **207** *via* oxidative addition. Then, **209** undergoes ligand exchange with AcSK leading to the formation of intermediate **210**. Further, it affords 2-acetylthio-2′-iodobiphenyl **211** through the regeneration of CuI catalyst. Subsequently, aryl–Cu^{III} complex **212** forms by the oxidative addition that occurs at the C–I bond in **211**. The intermediate **213** forms by the nucleophilic attack of iodide to SAc complex **212** and then undergoes ligand exchange to afford aryl–Cu^{III}–S complex **214**. Ultimately, the anticipated product **208** is produced from **214** *via* reductive elimination process.

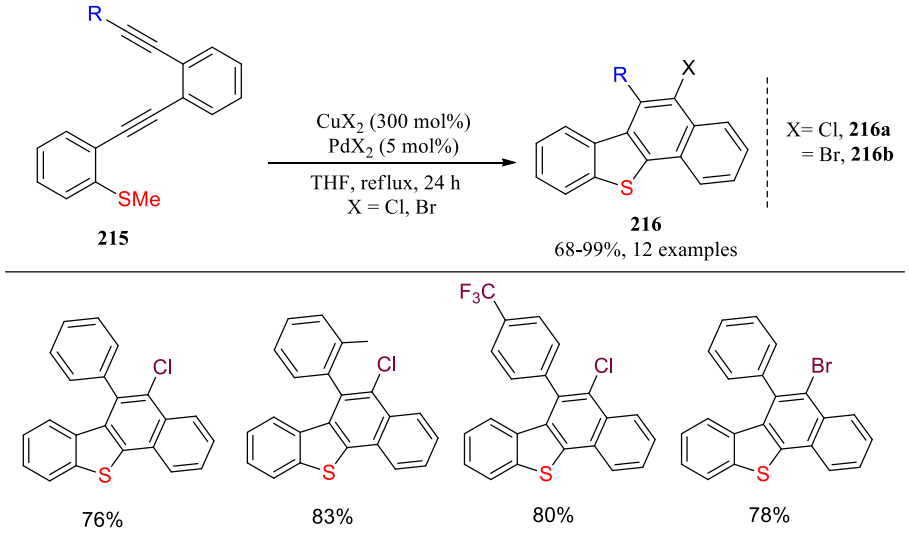
Ming-Jung Wu's group [88] developed a copper-mediated synthesis of benzo[*b*]naphtho[2,1-*d*]thiophene derivatives **216** from the cyclization reaction of aryldiynes **215**. Substrate **215** underwent chlorination reaction with 3 equivalents of copper chloride and 5 mol% of palladium chloride under reflux conditions in THF solvent to afford **216a** in good yields. On the other hand, cyclization of **215** using palladium bromide under same reaction conditions furnished **216b** in good yields (Scheme 61). Authors investigated substituents and catalysts effects on the cyclization reaction. The generality of the reaction is exemplified with good number of examples. Compounds benzo[*b*]naphtho[2,1-*d*]thiophenes are important in material science, which is one of the applications of this method. Authors have not proposed the plausible mechanism in their report.

3.5. Catalyzed/mediated by copper sulphate ($CuSO_4$)

Tanay and co-workers [89] synthesized 2,3-disubstituted benzo[*b*] thiophenes **218** *via* electrophilic cyclization. Substrates 2-phenylethynylthioanisoles **217** underwent reaction with excess of $CuSO_4$ (5 equiv.) and sodium halide (5 equiv.) in ethanol solvent at room temperature to form 3-halo substituted benzo[*b*]thiophenes in good yields. Different sodium halide salts (X = Cl, Br, I) were successfully used in the reactions (Scheme 62). These reaction conditions worked well for alkyl substituted thioanisoles as well. Besides, thioanisole containing propargyl alcohol or propargyl ether also underwent smooth reaction under the same experimental conditions to furnish corresponding products in 90 % and 97 % yield respectively. The key features of this protocol



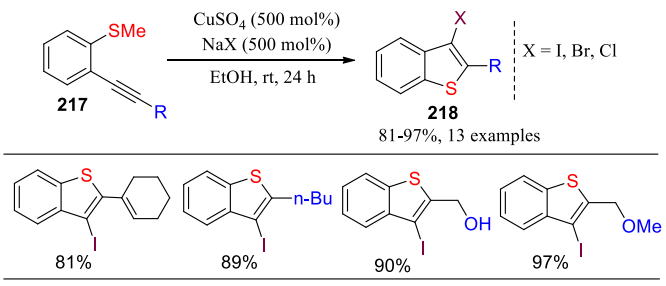
Scheme 60. The reaction mechanism for the synthesis of dibenzothiophenes **208**.



Scheme 61. Copper-mediated synthesis of benzo[*b*]naphtho[2,1-*d*]thiophene derivatives **216**.

include mild reaction conditions, high product yields without purification, use of inexpensive inorganic salts, green approach and broad substrate scope. The only limitation is that the reactions took long time to complete.

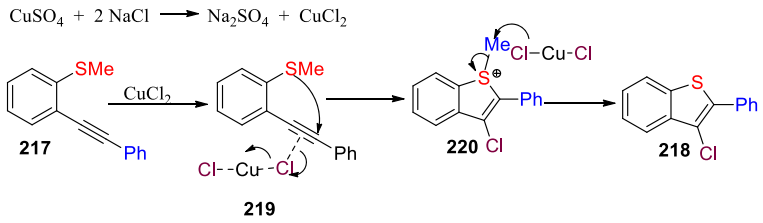
The reaction mechanism for the synthesis of 3-halo substituted benzo[*b*]thiophenes is as shown in Scheme 63. At the outset, intermediate **219** is generated from the reaction between the substrate **217** with cupric chloride. Cyclization occurs in intermediate **219** through anti attack from sulphur leading to the formation of cationic intermediate **220**. With the help of copper chloride, methyl group is removed *via* S_N2 displacement and affords anticipated product **218**.



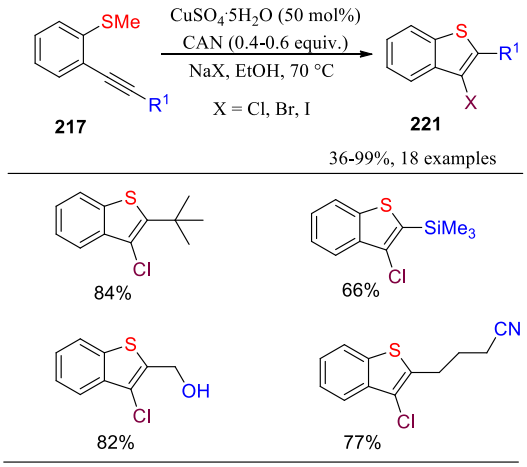
Scheme 62. Copper-mediated synthesis of 3-halo substituted benzo[*b*]thiophenes **218**.

Tanay and co-workers [90] developed a copper-catalyzed synthesis of benzothiophenes *via* electrophilic cyclization in the presence of sodium chloride as a source of electrophilic chlorine. Previously, Stahl and co-workers [91] investigated the use of an external oxidant to sustain a catalytic copper cycle in the Wacker oxidation. However, Tanay's group explored a similar copper catalytic cycle and minimized the amount of copper sulphate required by introducing an external oxidant (Scheme 64). Substrates 2-alkynyl thioanisoles **217** were cyclized in the presence of sodium chloride (5 equiv.), copper sulphate (50 mol%) and ceric ammonium nitrate (CAN) (0.6 equiv.) in ethanol solvent under air atmosphere at 70 °C to furnish benzothiophene products **221** in excellent yields (up to 99 %). This synthesis shows a broad substrate scope across diverse 2-alkynyl thioanisoles **217**. Thus, electron-rich (4-methoxyphenyl) and electron-deficient (4-cyanophenyl) aryl substituents on the substrate **217** gave high yields, showing that the electronic effects had little impact on the reaction outcome. Consequently, the substrate **217** bearing alkyl substituents such as *n*-butyl and *t*-butyl were also well tolerated. The methodology was successfully extended to chlorocyclization, bromocyclization and iodocyclization to afford the respective 3-halo-benzo[*b*]thiophenes **221** in excellent yields. The key features of this method include greener, low cost reagents, broad substrate scope and versatile halogenation. The reaction requires long reaction time (48 h) for maximum yields which is the main limitation of this protocol.

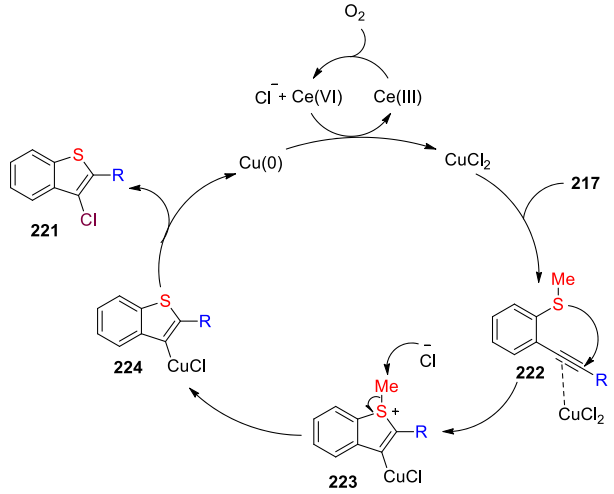
The reaction mechanism for the synthesis of benzothiophenes **221** is as shown in Scheme 65. Initially, the reaction proceeds through *in situ*



Scheme 63. The possible reaction mechanism for the synthesis of 3-halo substituted benzo[*b*]thiophenes **218**.



Scheme 64. Copper-catalyzed synthesis of benzothiophenes **221**.



Scheme 65. The plausible mechanism for the synthesis of benzothiophenes **221**.

generation of copper chloride from copper sulphate and sodium chloride. The copper chloride coordinates with 2-alkynyl thioanisole **217** to afford intermediate **222**. Nucleophilic attack by the nearby sulphur atom in intermediate **222** furnishes cyclic cationic intermediate **223**. Chloride assisted demethylation in **223** leads another intermediate **224**. Finally, 3-chlorobenzothiophene product **221** is obtained from the intermediate **224** along with the regeneration of copper catalyst *via* oxidation by CAN.

4. Conclusion

The sulphur-containing heterocyclic compounds such as thiophenes and benzothiophenes play a vital role and continue to be a cornerstone of synthetic organic chemistry. The main advantages of copper-catalyzed/mediated synthesis of these compounds over processes without copper catalysts/salts are high efficiency and milder reaction conditions. In this review, we summarized an in-depth exploration of novel methodologies, pros and/or cons, shed light on substrate scope, mechanistic insights (if reported), optimization of reaction conditions and discussion of control experiments (if given) for these privileged scaffolds. The involvement of catalytic/sub-stoichiometric/stoichiometric amount of copper salts in the synthesis of thiophenes and benzothiophenes is noteworthy. Furthermore, this review article contains several synthetic strategies such as multicomponent reactions, one-pot syntheses, regioselective, inter-/intramolecular cyclizations and C-S bond constructions. We have collected research articles which contain various synthetic designs of copper-catalyzed/mediated thiophene and benzothiophene synthesis from 2010 to 2024. Readers can see only few articles between 2020 and 2022. To the best of our knowledge, few articles are reported after 2022 in this area, which reflects that the field may be approaching saturation. Thus, this review highlights the need to develop new substrates for the copper-catalyzed synthesis of thiophenes and benzothiophenes. Additionally, the organosulfur substrates discussed in this review are limited, highlighting the importance of exploring novel substrates and methods for the synthesis of these heterocycles. Besides, novel sulphur-containing substrates or thionating agents are in demand in the future for the construction of these classes of heterocycles. Further, mechanistic studies are required, where mechanisms are not reported. Moreover, the current trend needs development of new nano-copper catalysts and green reaction conditions. The review may be useful to medicinal chemists for the preparation of biologically interesting thiophenes and benzothiophenes.

CRediT authorship contribution statement

Rajaghatta N. Suresh: Writing – original draft. **Toreshettahally R. Swaroop:** Writing – review & editing, Supervision. **Kanchugarakoppal S. Rangappa:** Supervision.

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Declaration of competing interest

We have no conflicts of interests to disclose.

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Data availability

No data was used for the research described in the article.

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Dr. R. N. Suresh is an accomplished academic specializing in organic chemistry as well as in medicinal chemistry. He completed his Master's degree in Organic Chemistry at the University of Mysore, India in 2016 and also his doctoral studies completed at the same esteemed University in 2024. Through his PhD journey, he contributed significantly to organic chemistry field. Currently, he is working as a postdoctoral fellow at the Department of Chemistry, Ben-Gurion University of the Negev, Israel.

Dr. T. R. Swaroop is an Assistant Professor at the Department of Studies in Organic Chemistry, University of Mysore, India. He received Ph. D from the University of Mysore. He has worked as a postdoctoral fellow at the Memorial University of Newfoundland, Canada and the Guangxi Normal University, China. He visited Yildiz Technical University, Turkey, the Utrecht University, the Netherlands and the Hokkaido University, Japan as a visiting scientist. He has received eleven gold medals and eight cash prizes in B.Sc. and M.Sc. degrees. He is a young faculty in the University of Mysore and published more than 95 research articles. He is currently working on developments of new synthetic methods for heterocyclic compounds and their biological applications, green chemistry and material chemistry in conjunction with computational chemistry and history of chemical science. He is also involved in academic writings like reviews and textbooks.

Dr. K. S. Rangappa is currently a Distinguished Professor at the University of Mysore, India. He served as a Vice-Chancellor of the University of Mysore, Mysore and the Karnataka State Open University, Mysore. His research areas include chemical biology, drug discovery and medicinal chemistry. His most important contributions have been towards the probing of synthetic small molecules towards cellular therapeutic targets in cancer. Prof. Rangappa has published more than 650 papers and holds 14 patents with h-index 66 and citations 16100. He is the fellow of the Royal Society of Chemistry, London; Fellow of National Academy of Sciences, India and the World Academy of Sciences. He has been among the top 2 % of World Scientists released by Stanford University, USA in 2024.