SYNTHESIS OF BENZO[*b*]THIOPHENES USING ALKYNES AS PRECURSORS UNDER METAL-FREE CONDITIONS

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Abstract. *Benzo[b]thiophenes consist of a synthetically valuable class of compounds that found several applications in different areas, such as synthetic organic chemistry, medicinal chemistry, and new materials sciences as building blocks to construct organic semiconductors. Over the past decade, many advances have been achieved to synthesize these compounds, especially on using alkynes as easy-to-prepare synthetic precursors. In addition, organic synthesis under environmentally friendly and sustainable conditions has been highly demanding in recent years. This review aims to cover a literature survey of the synthesis of benzo[b]thiophenes through intra- and intermolecular cyclization reactions under metal-free conditions. Among the outstanding features of these new protocols, the use of electrophilic species that directly install into the newly formed heterocycle, and radical-mediated cyclization reactions have been highlighted. Moreover, methodologies employing electrochemical and photochemical conditions have been addressed.*

Contents

1. Introduction

Benzo[*b*]thiophene is an important heterocyclic scaffold found in several bioactive compounds.[1] As typical representatives, raloxifene is a drug used for the treatment of osteoporosis in postmenopausal women,[2] benocyclidine is a well-known psychoactive molecule,[3] zileuton is an inhibitor of leukotrienes employed for the treatment of asthma,[4] and sertaconazole,[5] is a topical antifungal agent with broad activity for the treatment of skin mycoses (Figure 1). Moreover, new drugs based on benzo[*b*]thiophene precursors have been designed and synthesized for achieving pharmacological activities such as antimicrobial, anticancer, antiproliferative, anti-inflammatory, antioxidant, anti-tubercular, anti-diabetic, and anticonvulsant.[6-8] In the field of crop protection, benzo[*b*]thiophenes also found application as fungicidal and pesticidal candidates.[9,10] Additionally, benzo[*b*]thiophenes have attracted growing interest in the manufacturing of dye-sensitized solar cells (DSSCs),[11] and to design and prepare functional organic semiconductors for other technical applications on organic electronics, including organic field-effect transistors (OFETs) and organic light-emitting diodes (OLEDs).[12,13]

In the past few years, a variety of reliable synthetic methods have been developed to access highly substituted benzo[*b*]thiophenes, highlighting electrophilic cyclization,[14-17] base-mediated condensation,[18,19] and transition-metal catalyzed annulation reactions.[20,21] This privileged structure allows several patterns of substitution which may provide different properties to the heterocyclic molecule. So, in view of the synthetic, biological, and industrial value of benzo[*b*]thiophene derivatives, the development of methods for the preparation and application of this heterocycle is in constant progress.[22-24] Therefore, we present in this review some of the most recent advances to access benzo[*b*]thiophene derivatives from alkynes, through intra- and

intermolecular cyclization pathways, under several reaction conditions. Mostly, easy access to 2-alkynylthioanisoles attached to a diversity of substituents including alkyl, alkoxy, halogen, and carbonyl groups make them the most convenient substrate. Furthermore, examples of using electron-deficient alkynes reacting with many sulfur sources are discussed. To mitigate the potentially toxic and polluting nature, as well as high cost of some metal-based salts to be employed as catalyst, approaches under eco-friendly and sustainable conditions have been adopted.[25] In this scenario, only metal-free cyclization protocols are reviewed here, employing electrochemical oxidative conditions and light-induced photoredox catalysis, in the presence of a wide diversity of electrophilic or radical species, covering the period from 2014 until the first quarter of 2024.

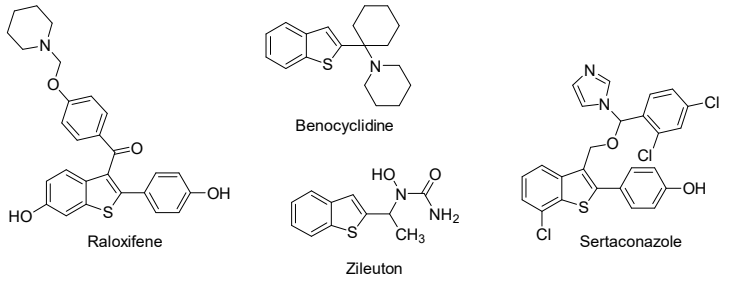


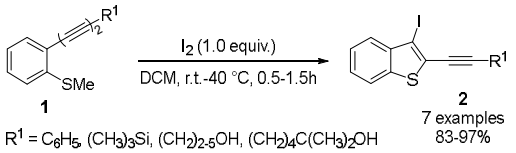
Figure 1. Benzo[*b*]thiophene-based drugs.

2. Benzo[*b*]thiophenes obtained through electrophilic cyclization reactions

The electrophilic cyclization reaction of alkynes neighboring nucleophilic sulfur atoms at an appropriate position (in general *ortho*-position) has been proving to be an effective approach to prepare benzo[*b*]thiophene derivatives. These reactions are also viewed as an opportunity to the direct incorporation of new functionalities in the new heterocycle formed. In this sense, electrophilic reagents have gained attention due to their capacity to activate the carbon-carbon triple bond, making it susceptible to an intramolecular cyclization process followed by a dealkylation reaction.[26,27] The analysis of these methods revealed the success of employing diverse 2-alkynylthioanisoles and electrophilic species based on halogen, chalcogen, and boron, as the prominent substrates used in recent years. This strategy was first reported by Flynn[14] and Larock[15] in 2001, and since then this approach has advanced under various reaction conditions and applications.

2.1. Halogen-based electrophiles

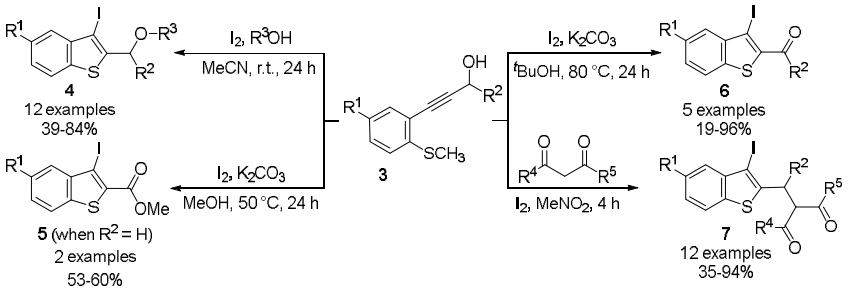
Iodine promoting electrophilic cyclization of *ortho*-functionalized aryldiacetylenes **1** for the synthesis of alkynes bonded benzo[*b*]thiophenes **2** has been reported (Scheme 1).[28] The developed reaction condition has demonstrated a good substrate compatibility, allowing the application of several diynes bearing aryl, trimethylsilyl, and alcohols as substituents. Moreover, reactions conducted in dicloromethane (DCM) were faster than that in MeCN, and according to the authors, the last S_N2 dealkylation step should be the limiting step of the overall process. Furthermore, several modifications were proposed in compounds **2** to obtain asymmetrically substituted enediyne systems fused to a benzo[*b*]thiophene unit based on Sonogashira-type coupling reactions.



Scheme 1. Synthesis of 2-alkynyl-3-iodobenzo[*b*]thiophenes **2**.

A novel iodine-mediated one-pot electrophilic cyclization / functionalization reaction of propargylic alcohols **3** to synthesize diverse 3-iodo-2-substituted-benzo[*b*]thiophene derivatives **4**-**7** was reported (Scheme

2).[29] This strategy had a wide range of substrate scopes, whether the nucleophile was alcohol derivatives, including alkylic, allylic, propargylic, or benzylic ones, the ether product **4** is formed. Meanwhile, when a non-substituted propargylic alcohol (R^1=H) is used and methanol is the solvent, the ester **5** group is obtained. If *tert*-BuOH is the solvent at 80 °C, ketones or aldehydes bearing 3-iodobenzo[*b*]thiophene **6** are isolated, while using 1,3-dicarbonyl compounds as alkylating agents, products **7** are obtained. It has been proposed that molecular iodine acts both as an electrophile promoting the cyclization reaction forming the intermediate 3-iodobenzo[*b*]thiophene and as a Lewis acid catalyzing the subsequent transformations.

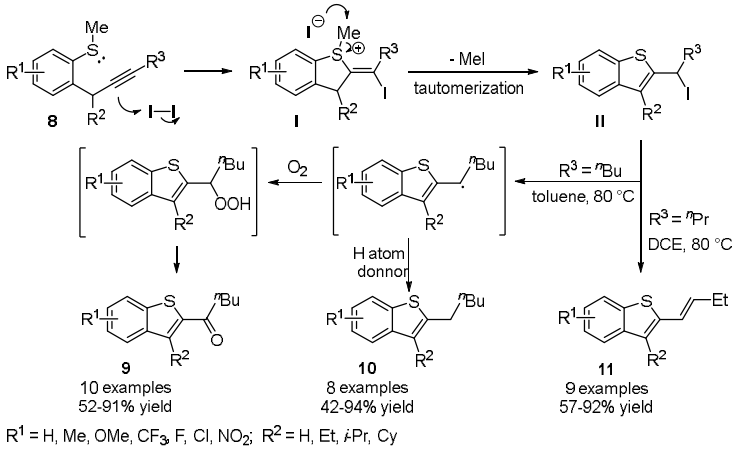


Scheme 2. Synthesis of 2,3-disubstituted benzo[*b*]thiophenes **4**-**7** *via* successive iodocyclization/functionalization reaction.

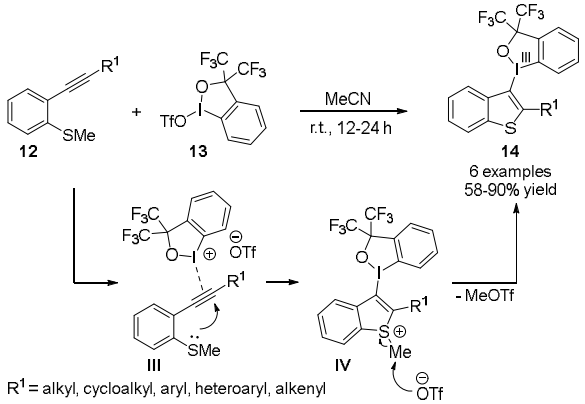
In a study conducted by Procter and co-workers, a series of benzo[*b*]thiophene-based structures were produced from *ortho*-alkynyl thioethers **8**.[30] This work envisioned the use of iodine-mediated heterocyclization and carbocyclative dimerization reactions. The starting materials synthesis were prepared in an earlier work.[31] From these readily available substrates it was possible to obtain a series of twenty-seven benzo[*b*]thiophene **9**-**11** scaffolds (Scheme 3). According to the authors, iodine interacts with the triple bond of the alkynyl thioether allowing an intra-heterocyclization reaction by a nucleophilic attack from the nonbonding electron pair of the neighboring sulfur atom furnishing cationic intermediate **I**. Subsequently, a demethylation restores the sulfur electron pair and follows towards aromatization of thiophene to give intermediate **II**. Upon heating in toluene, followed by quenching with O_2, ketone products **9** are formed. If 1,4-cyclohexadiene is present in the reaction media, alkyl substituted product **10** is obtained. Under 80 °C in 1,2-dichloroethane (DCE), elimination gives alkene **11**. Furthermore, it was also demonstrated that multiple reactions can take place in a controlled fashion, to produce symmetrical and unsymmetrical bis-benzo[*b*]thiophene products.

The efficiency of benziodoxole triflate **13** as substrate in iodo(III)-mediated cyclization reaction was explored.[32] In order to test the limitations of this novel iodine(III) source, a series of heterocyclizations were performed using 2-alkynylthioanisoles **12** as starting materials. Based on this protocol, six benzo[*b*]thiophenes **14** along with benzo[*b*]furans (17 examples), and isocoumarins (4 examples) were synthesized (Scheme 4). The authors reported that diverse substituents were well tolerated by benziodoxole triflate resulting in easy workup and good to excellent yields. Based on the reaction outcome, a reaction mechanism was proposed. Initially, the triple bond interacts with the hypervalent iodine reagent forming **III**, followed by an intramolecular attack of the sulfur atom to form a five-membered ring **IV**, which undergoes methyl group displacement by the triflate anion restoring the heteroatom electron pair.

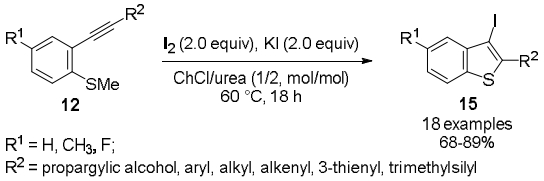
Avoiding the use of volatile organic compounds (VOCs) including methylene chloride and 1,2-dichloroethane as solvents in organic reactions, has become an urgent requirement for safety and environmental protection.[33] Addressing this issue, Mancuso, Gabriele and co-workers reported the iodocyclization of 2-alkynylthioanisoles **12** using a recyclable and biodegradable deep eutectic solvent (DES) system to obtain diverse 3-iodobenzo[*b*]thiophenes **15** (Scheme 5).[34] The substrate scope covered triple bond substituted with diverse alcohol, alkyl, trimethylsilyl, 1-cyclohexenyl, aryl, and heteroaryl groups. In addition, the solvent system has been recycled up to six times without loss of efficiency.



Scheme 3. General pathway for the synthesis of **9**-**11**.



Scheme 4. Benziodoxole triflate promoted synthesis of benzo[*b*]thiophenes **14**.

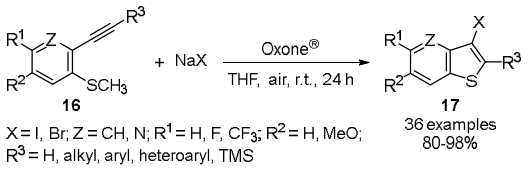


Scheme 5. Iodocyclization under choline chloride (ChCl)-based DES media.

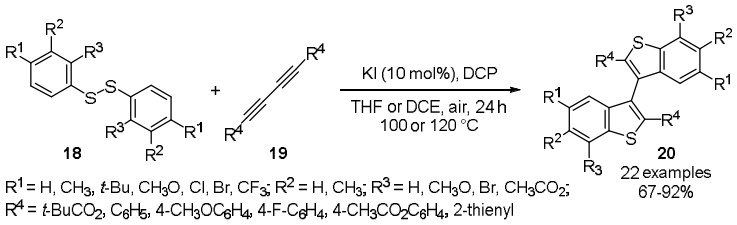
The direct cyclization/halogenation of 2-alkynylthioanisoles **16** to synthesize 3-halobenzo[*b*]thiophenes **17** has been achieved *via* Oxone®-mediated reaction with sodium halides as halogen source (Scheme 6).[35] The reaction features readily available reagents, commercially available and cheap oxidizing agent, as well as good compatibility with several functional groups, affording products **17** in good to excellent yields. In addition, while the method was successfully applied to prepare 3-iodobenzo[*b*]selenophene and 3-iodoindole derivatives, attempts to access 3-iodobenzo[*b*]furans or 3-chlorobenzo[*b*]thiophenes failed under the standard conditions.

The oxidative C-H annulation reaction of diaryl disulfides **18** with 1,3-diynes **19**, catalyzed by potassium iodide (10 mol%), using dichlorophenol (DCP) as oxidizing agent, proceeds to form symmetrical

3,3'-bisbenzo[*b*]thiophenes **20** (Scheme 7).[36] The reaction occurs *via* ArSI intermediate that adds selectively to 1,3-diyne generating a thiolated vinyl cation intermediate, which undergoes an intramolecular cyclization followed by deprotonation to give the target product **20**. The preparation of nonsymmetrical bisbenzo[*b*]thiophenes has also been demonstrated by two consecutive monoannulations catalyzed by CuCl and KI, respectively.



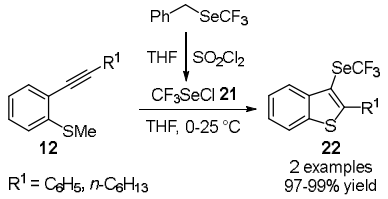
Scheme 6. Oxone®-mediated synthesis of 3-halobenzo[*b*]thiophenes **17**.



Scheme 7. Synthesis of 3,3'-dibenzo[*b*]thiophenes **20**.

2.2. Chalcogen-based electrophiles

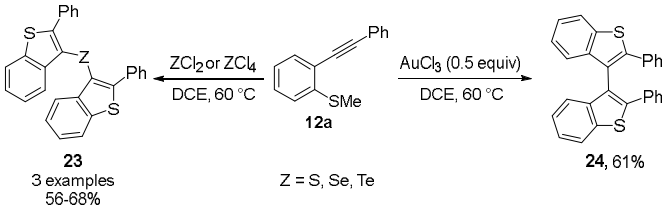
Chalcogens play a pivotal role in the electrophilic cyclization of alkynes with direct chalcogen-containing group installation, allowing the formation of *N*, *O*, *S*, and other heterocyclic units.[37] In 2018, Billard and co-workers developed a method to successfully synthesize five- and six-membered heterocyclic compounds bearing fluoroalkylselanyl groups.[38] This work also explored the synthetic potential of 2-alkynylthioanisoles **12** in an intramolecular ring closure reaction with fluoroalkylselanyl chloride **21**, generated *in situ*, as electrophile. This elegant reaction pathway proved to be especially successful for the synthesis of benzo[*b*]thiophenes **22**, when compared to benzo[*b*]furans, which was rationalized by the larger C–S bond that kinetically favors 5-*endo*-dig cyclization reaction. Although not many examples were produced, they showed a near quantitative yield (Scheme 8).



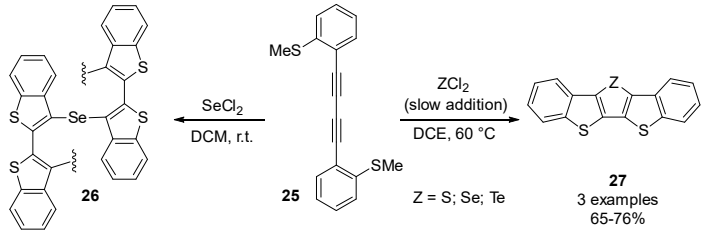
Scheme 8. General synthetic pathway of 3-(trifluoromethylselanyl)benzo[*b*]thiophenes **22**.

The synthesis of bis- and poly-benzo[*b*]thiophenes was explored (Scheme 9).[39] The reaction strategy employed 2-alkynylthioanisole **12a** in presence of a dielectrophilic chalcogen source, such as sulfur dichloride, selenium dichloride or tellurium tetrachloride, DCE as solvent at 60 °C. Through this protocol bis-benzo[*b*]thiophenes **23** bridged by the correspondent chalcogen atom were obtained in 56-68% yield. Alternatively, when $AuCl_3$ as a Lewis acid was used, a dibenzo[*b*]thiophene **24** was obtained in 61% yield.

By using a buta-1,3-diyne **25** as starting material, the authors have further explored the synthesis of a polymeric chain **26** and heteroacenes **27**. It was demonstrated that, when a slow addition of the dielectrophile occurs, heteroacenes are produced in good yields (Scheme 10).

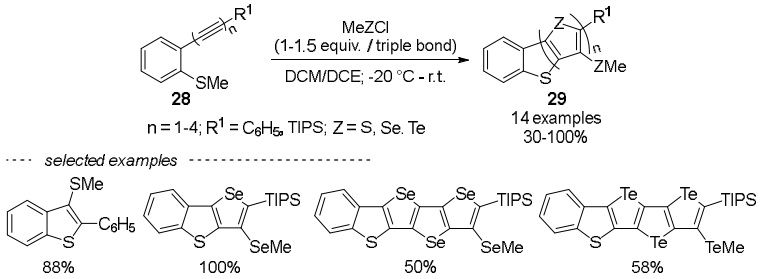


Scheme 9. General reaction for the synthesis of bisbenzo[*b*]thiophenes **23** and dibenzo[*b*]thiophene **24**.



Scheme 10. Synthetic pathway for polybenzo[*b*]thiophene **26** and heteroacenes **27**.

The use of polyynes **28** bearing an *ortho* nucleophilic group reacting with ambiphilic chalcogenated reagents to furnish polyheterocyclic compounds was further described (Scheme 11).[40] To obtain linearly fused chalcogenophenes **29**, the authors proposed an intramolecular (poly)electrophilic cyclization reaction of alkynes and polyynes with pre-formed electrophilic chalcogen species (MeZCl where Z=S, Se, Te). MeZCl reagents were obtained by the reaction of the corresponding dimethyl dichalcogenide with SO_2Cl_2 in dichloromethane (DCM). Along with the synthesis of several π-conjugated molecules obtained by mono- and bidirectional cyclization reactions, the authors also reported the occurrence of addition reactions, especially those using MeSCl as the electrophile, which formed complex mixture of products that arose from multiple additions of MeS species.

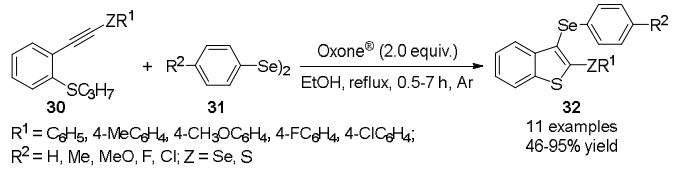


Scheme 11. Polyelectrophilic cyclization of alkynes to synthesize chalcogenophenes **31**.

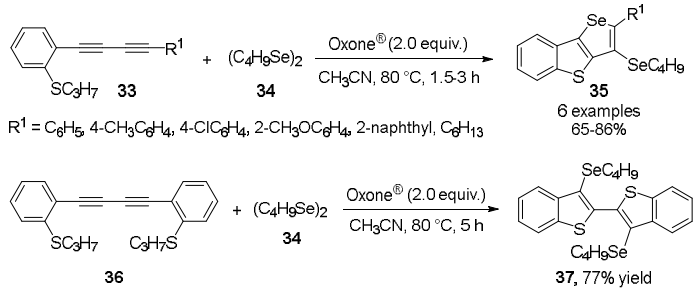
A series of selenium-containing benzo[*b*]thiophenes were synthesized by Perin, Lenardão, and co-workers through Oxone®-mediated electrophilic selenocyclization of chalcogenoalkynes **30** (Scheme 12).[41] Using Oxone® as the oxidizing agent and diaryl diselenides **31** as the organochalcogen source, eleven 2,3-bis(chalcogenyl)benzo[*b*]thiophenes **32** were prepared in moderate to excellent yields (46-95%). This key reaction still covered the synthesis of highly functionalized benzo[*b*]furans and benzo[*b*]selenophenes.

Later, the synthesis of benzo[*b*]thiophenes fused to selenophenes **35** *via* intramolecular bis-cyclization of 1,3-diynes **33** with dibutyl diselenide **34** and potassium peroxymonosulfate (Oxone®) as oxidizing agent was reported (Scheme 13).[42] It was demonstrated that the electrophilic selenium species triggers intramolecular domino cyclization reactions forming one new C–S bond and two C–Se bonds in moderate to good yields. In this elegant approach to accessing benzo[*b*]thiophenes, it was also observed that the

nucleophilic substituent in the *ortho*-position of the alkyne plays an important role directing the formation of the polycyclic system. When 1,3-diyne **36**, produced by the homocoupling of an 2-alkynylthioanisole, is used, a dibenzo[*b*]thiophene ring system **37** is obtained in 77% yield.

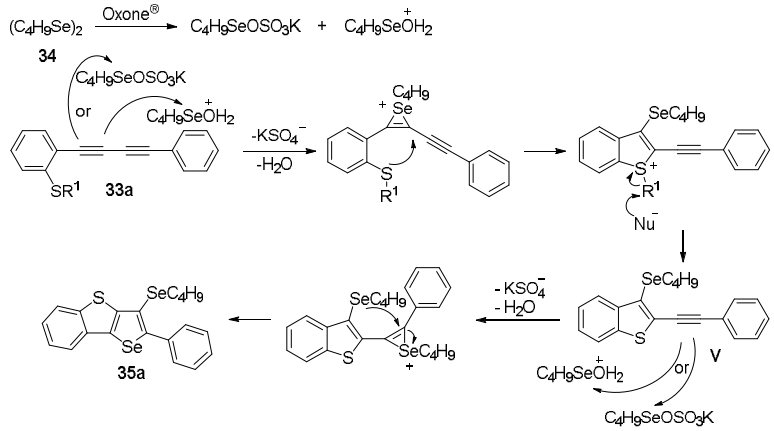


Scheme 12. Oxone®-mediated synthesis of 2,3-bis(chalcogenyl)benzo[*b*]thiophenes **32**.



Scheme 13. Synthesis of benzo[*b*]chalcogenophenes promoted by Oxone®.

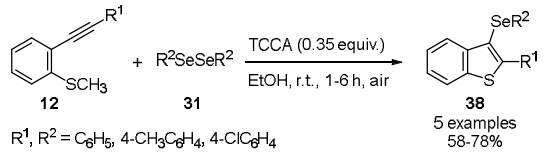
According to the authors, the synthesis of **35** is based on the proposed reaction mechanism shown in Scheme 14. Initially, electrophilic selenium species are generated *in situ* by the reaction of dibutyl diselenide **34** with Oxone®. After the interaction of these species with the alkyne **33a**, followed by intramolecular cyclization and dealkylation, affords intermediate **V** bearing a Se–butyl moiety neighboring a triple bond. Then, a second electrophilic cyclization occurs through the C−Se bond formation followed by butyl group displacement, synthesizing product **35a**.



Scheme 14. Proposed reaction mechanism for Oxone®-mediated synthesis of **35**.

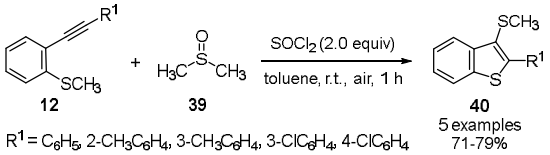
A concise methodology for the electrophilic selenocyclization of 2-alkynylthioanisoles **12** was also developed using trichloroisocyanuric acid (TCCA) (0.35 equiv.) as oxidizing agent and diaryl diselenides **31** as selenium source (Scheme 15).[43] Under optimal reaction conditions, which includes ethanol as solvent at

room temperature, a series of 3-selanylbenzo[*b*]thiophenes **38** was prepared in yields ranging from 58% to 78%. In addition, this methodology was also satisfactorily applied to produce selenylated benzo[*b*]furans, benzo[*b*]selenophenes, and indoles in moderate to excellent yields. The highlights of this methodology are the broad substrate scope and the use of ethanol as a green and renewable solvent. To obtain more information about the reaction mechanism, ^{77}Se NMR experiments were conducted, which revealed that PhSeCl species, formed *in situ* by the reaction of diphenyl diselenide with TCCA, is the key precursor in this electrophilic cyclization reaction.



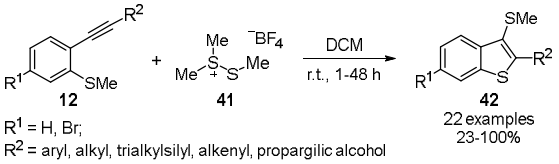
Scheme 15. TCCA-mediated synthesis of 3-selanylbenzo[*b*]thiophenes **38**.

A method employing dimethyl sulfoxide (DMSO) **39** as sulfur source to synthesize 3-(methylthio)benzo[*b*]thiophenes **40** was developed (Scheme 16).[44] It was proposed that reactive CH_3SCl was obtained, *in situ*, *via* a reaction of DMSO with $SOCl_2$ followed by electrophilic addition of this species to alkyne **12**, forming a cyclic sulfonium cation, which subsequently undergoes cyclization and methyl group removal to furnish the target product **40**. It should be mentioned that this protocol was mainly developed to synthesize 3-(methylthio)benzo[*b*]furans and that DMSO can be satisfactorily replaced by DMSO-d_6 to directly install a SCD_3 portion at position 3 of the formed heterocycles.



Scheme 16. Synthesis of 3-(methylthio)benzo[*b*]thiophene **40** employing DMSO and $SOCl_2$.

An improved protocol for synthesizing 3-(methylthio)benzo[*b*]thiophenes **42** using stable and commercially available dimethyl(thiodimethyl)sulfonium tetrafluoroborate salt **41** as an electrophilic sulfur source reacting with alkyne **12** was explored (Scheme 17).[45] This methodology requires milder reaction conditions, non-toxic reagents, and the products are obtained in moderate to excellent yields. To evaluate this protocol, reactions were conducted with alkynes bearing substituents such as alkyl and aryl containing methoxy, halogen, cyano, and alcohol groups. Although primary propargylic alcohol gave the desired product in good yield under modified conditions, secondary and tertiary alcohols were ineffective in this cyclization reaction. It is worth mentioning that the protocol was satisfactorily expanded to a gram-scale, without significant loss of efficiency.

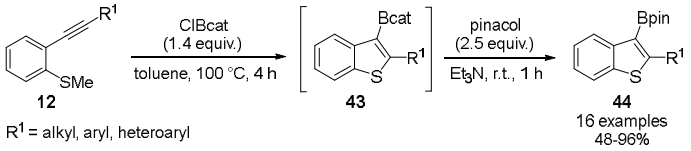


Scheme 17. Dimethyl(thiodimethyl)sulfonium tetrafluoroborate-mediated cyclization reaction.

2.3. Boron and silicon-based electrophiles

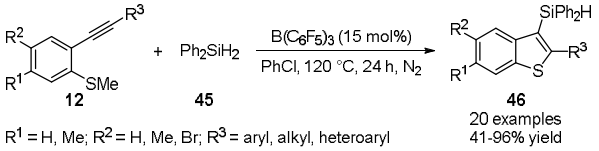
In recent years, Blum and co-workers envisioned the use of *β*-chlorocatechol borane (ClBcat) as an effective electrophile for intramolecular cyclization reaction under a metal free protocol (Scheme 18).[46]

According to the authors this is the first example of a thioborylation reaction across C≡C π-bonds. This study developed an efficient protocol where 2-alkynylthioanisoles **12** reacted with ClBcat (1.4 equiv.), to form organo-boron benzo[*b*]thiophenes **43** which were submitted to a transesterification transformation, employing pinacol to obtain more stable organoboron compounds **44**. In this way, sixteen novel compounds were synthesized bearing alkyl, alkenyl, aryl, and heteroaryl substituents, providing a broad scope of tolerated functional groups. Additionally, having **44** in hand, diverse work up conditions were conducted to further demonstrate the versatility of these compounds successfully subjecting it to oxidative, conjugate addition, Suzuki cross-coupling, and trifluoromethylation conditions.



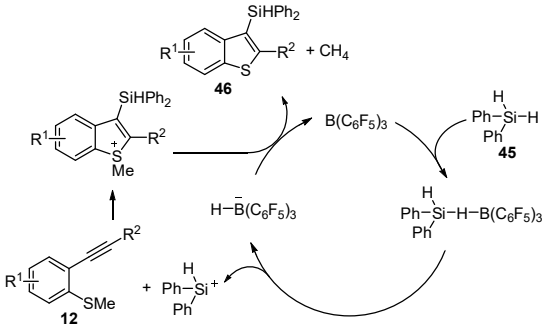
Scheme 18. Synthesis of 3-boronbenzo[*b*]thiophenes **44** by ClBcat-activating alkyne.

A convenient $B(C_6F_5)_3$-catalyzed cyclization of 2-alkynylthioanisoles **12** with diphenylsilane **45** was described (Scheme 19).[47] In this manner, twenty 3-silylbenzo[*b*]thiophenes **46** were successfully synthesized with yields ranging from 41% to 96%.



Scheme 19. General synthesis of 3-silylbenzo[*b*]thiophenes **46**.

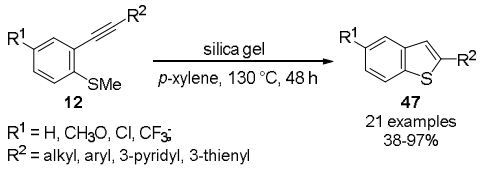
The authors envisioned the use of $B(C_6F_5)_3$ as a powerful metal-free catalyst to activate the hydrosilane (Ph_2SiH_2) through a B-H interaction that results in the formation of cationic Ph_2SiH^+ species, which are selectively attacked by the triple bond furnishing target products **46** by an electrophilic cyclization reaction (Scheme 20).



Scheme 20. Proposed reaction mechanism for $B(C_6F_5)_3$-catalyzed reaction.

A simplified strategy based on silica gel-assisted cyclization reaction of 2-alkynylthioanisoles **12** for the preparation of 2-substituted-benzo[*b*]thiophenes **47** has been reported (Scheme 21).[48] Although tertiary alkyl groups directly bonded to the sulfur atom (*tert*-butyl, 1-adamanthyl, *tert*-dodecyl) showed to be more suitable for this transformation under mild conditions, 1-ethynyl-2-(methylsulfanyl)benzenes were chosen as ideal substrates due to their easy access and solubility. The cyclization reactions were conducted in *p*-xylene as a

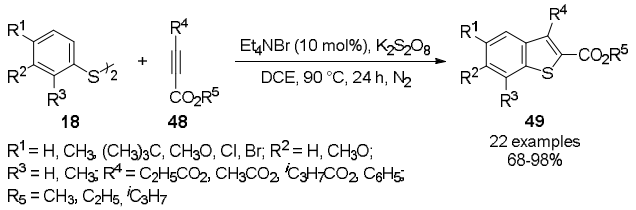
non-polar solvent in the presence of silica gel 60 under nitrogen atmosphere at 130 °C for 48 h. Under these conditions diverse groups were tolerated, including ester, amine, amide, nitrile, nitro, and aldehyde directly attached to the aryl group (R^2), giving twenty-one benzo[*b*]thiophenes in moderate to excellent yields.



Scheme 21. Silica gel-assisted synthesis of 2-substituted-benzo[*b*]thiophenes **47**.

3. Benzo[*b*]thiophene obtained through radical cyclization reactions

An efficient synthetic approach on Et_4NBr-catalyzed radical cyclization reaction between several diaryl disulfides **18** and symmetric or unsymmetric alkynyl esters **48** to give highly functionalized benzo[*b*]thiophenes **49** has been reported (Scheme 22).[49] The standard condition employs 10 mol% of Et_4NBr as catalyst, $K_2S_2O_8$ as oxidizing agent, and DCE as solvent, at 90 °C for 24 h. Initially, a diversity of *ortho* and *para* substituents on diaryl dilsulfide were employed including alkyl, alkoxy, and halogen groups, giving the target products in good yields. Moreover, when *meta*-substituted disulfides were employed, two regiosiomeric benzo[*b*]thiophenes were obtained. Then, several alkynes underwent radical sulfenylation/cyclization reaction, producing the corresponding products **49** in good to excellent yields. The terminal alkynes, 1,2-diarylethyne, and 1,2-dialkylethyne were inefficient forming the target products under these reaction conditions.

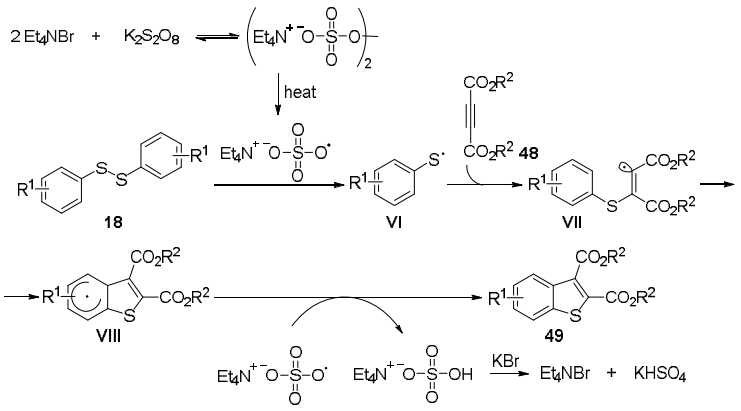


Scheme 22. Metal-free Et_4NBr-catalyzed radical cyclization reaction.

The proposed mechanism describes the initial reaction between Et_4NBr and $K_2S_2O_8$ producing sulfate radical anion, which reacts with diaryl disulfide **18**, thus affording the thyil radical species **VI**. Then, the addition of the radical **VI** to the alkyne **48** generates the corresponding alkenyl radical intermediate **VII**, which further undergoes intramolecular radical substitution reaction to give **VIII**. Finally, radical hydrogen abstraction furnishes benzo[*b*]thiophene **49** (Scheme 23).

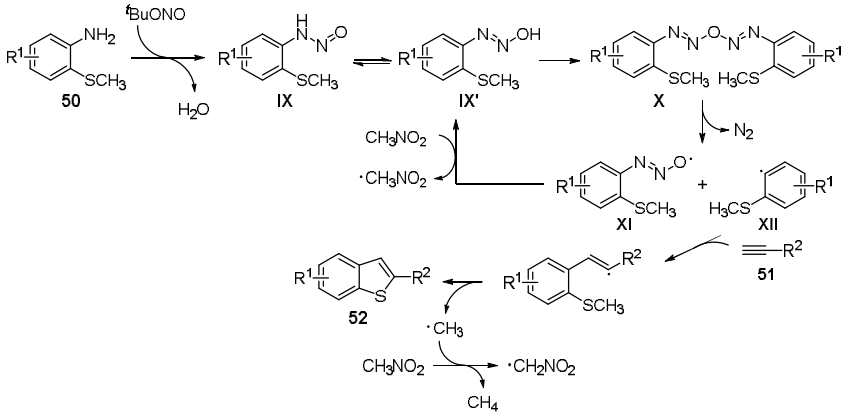
An improved protocol from readily available 2-(methylthio)-arylamines **50** and terminal alkynes **51** for the synthesis of 2-substituted-benzo[*b*]thiophenes **52** was proposed (Scheme 24).[50] Reactions were conducted using *tert*-BuONO as a nitrosating agent in CH_3NO_2 as solvent at 80 °C under N_2 atmosphere. Notably, the target products were obtained in yields ranging from 30% to 75% bearing groups such aryl, heteroaryl, alkyl, ester, and trimethylsilane, bonded on position 2 of benzo[*b*]thiophene. Moreover, this metal-free reaction has been proved to be an efficient strategy for the preparation of a key synthetic intermediate for the synthesis of raloxifene. In addition, the present protocol was extended to the synthesis of eleven benzo[*b*]selenophenes, in which many 2-(methylselanyl)arylamines were smoothly employed as substrates.

Validated by several control experiments and literature surveys, the radical reaction mechanism outlined in Scheme 25 was proposed. In this, nitrosamine intermediate **IX** and **IX'** is initially formed from the reaction between arylamine **50** and the nitrosating agent. Then, its self-condensation produces **X**, which after N–O homolysis provides one equivalent amount of azoxy radical **XI** and aryl radical species **XII**. Thus, the intermediate **XI** is interconverted into **IX** and **IX'**, which additionally provides **X**. A tandem regioselective addition of **XII** to the terminal alkyne **51**, followed by radical cyclization, leads to the desired product **52**.



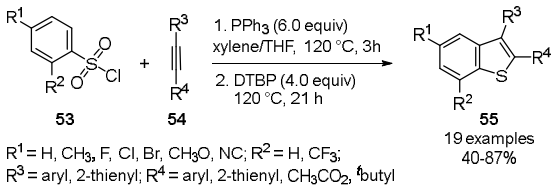
Scheme 23. Proposed mechanism for Et_4NBr-catalyzed synthesis of **49**.

Scheme 24. Synthesis of **52** from 2(thio)arylamines and terminal alkynes.

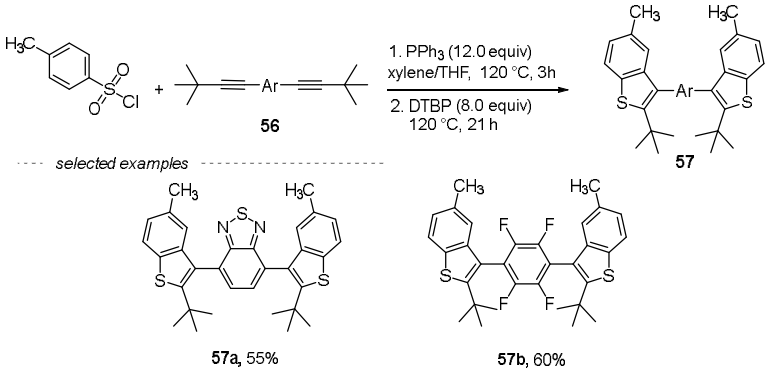


Scheme 25. Proposed reaction mechanism.

2,3-Diarylbenzo[*b*]thiophenes **55** were efficiently synthesized through thiyl radical addition followed by an intramolecular cyclization reaction of arylsulfonyl chlorides **53**, in the presence of internal alkynes **54** (Scheme 26).[51] The protocol reports the initial use of PPh_3 (6 equiv), which was demonstrated to reduce the sulfonyl chloride to a disulfide derivative, followed by the addition of DTBP as an oxidizing agent, in a mixture of xylene:THF (1:1) as solvent at 120 °C. These conditions were tolerated by several functional groups including ether, halogen, nitrile, ketone, and ester on both arylsulfonyl chloride and alkyne reaction partners, resulting in the expected benzo[*b*]thiophenes **55** in moderate to good yields. Additionally, unsymmetrical alkynes reacted selectively under optimal conditions. Remarkably, when dialkynyl compounds **56** were used, the π-extended polyheterocycles **57** were synthesized, providing the donor-acceptor-donor (D-A-D) structures shown in Scheme 27.

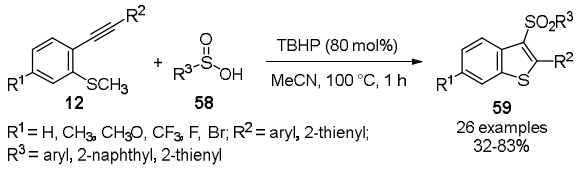


Scheme 26. Radical cyclization of arylsulfonyl chlorides and alkynes.



Scheme 27. π-Extended polyheterocycles synthesized **57a** and **57b**.

A series of arylsulfonylated benzo[*b*]thiophenes **59** was depicted *via* TBHP-initiated radical cyclization of 2-alkynylthioanisoles **12** with sulfinic acids **58** (Scheme 28).[52] The best reaction condition was achieved by employing *tert*-butyl hydroperoxide (TBHP) (80 mol%) as a radical initiator, in MeCN as solvent, being the resulting mixture stirred for 1 hour at 100 °C. The reaction scope demonstrated a good functional group tolerance, being compatible with strong and mild electron-donating or electron withdrawing groups attached to the aryl sulfinic acid, and on different positions of 2-alkynylthioanisole. In addition, the naphthyl- and thienyl-sulfinic acids also formed the desired products, but aliphatic sulfinic acids and aliphatic alkynes were not suitable under the optimized conditions. The same standard reaction conditions enabled the preparation of a series of six 3-sulfonylbenzo[*b*]selenophenes in good yields.

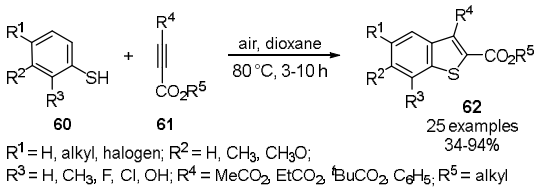


Scheme 28. Synthesis of 3-sulfonylbenzo[*b*]thiophenes *via* TBHP-initiated radical cyclization.

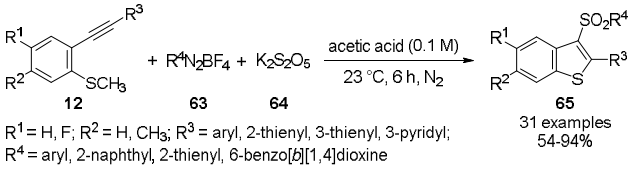
Another notable example comes from the chemo- and regioselective synthesis of benzo[*b*]thiophenes **62** *via* air promoted annulation of thiophenols **60** with electron-deficient alkynes **61** (Scheme 29).[53] This strategy does not apply any catalyst, chemical oxidant or additive, being the reactions conducted only in dioxane as solvent at 80 °C in open air vials. The reaction scope demonstrated a good functional group tolerance for both *ortho*, *meta*, and *para*-substituted thiophenols, and could be carried out even on a gram scale. Notably, under argon atmosphere or in the presence of TEMPO, the benzo[*b*]thiophene is not formed, instead only a Michael adduct is obtained. These results indicate that the radical annulation pathway is dominant under aerobic conditions and proceed through the formation of an alkenyl radical intermediate.

A very convenient and efficient multicomponent synthetic route was developed for the construction of benzo[*b*]thiophenes **65** bearing an arylsulfonyl group attached on the position 3 of the heterocyclic unit

(Scheme 30).[54] In this alternative approach, 2-alkynylthioansisole **12**, aryl diazonium tetrafluoroborate **63**, and potassium metabisulfite **64**, as a SO_2 source, were used as reagents in acetic acid as solvent at room temperature. In addition, by using 2-alkynylselenoanisoles under standard conditions, a range of 3-sulfonylbenzo[*b*]selenophenes were obtained in 85-90% yield. Easy availability of substrates, catalyst and additive-free conditions, and the potential for the preparation of bioactive compounds can be highlighted as some outstanding features of the present protocol.

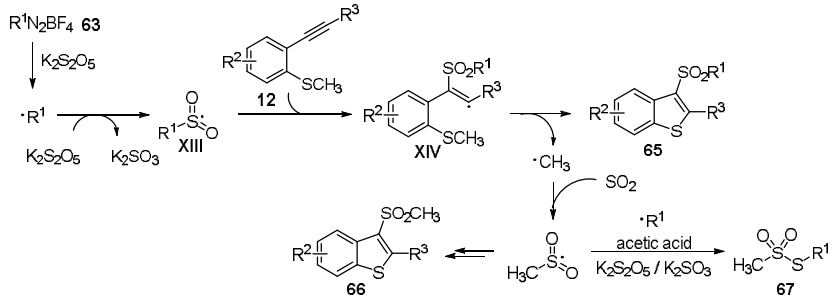


Scheme 29. Air-promoted annulation of thiophenols with alkynes.



Scheme 30. Multicomponent synthesis of 3-(arylsulfonyl)benzo[*b*]thiophenes **65**.

According to the authors, the mechanism of this transformation involves a radical pathway (Scheme 31). Thus, the reaction of aryldiazonium salt **63** with $K_2S_2O_5$ *via* a single electron transfer forms an aryl radical, which further reacts with sulfur dioxide generating sulfonyl radical **XIII**. Species **XIII** reacts with alkyne **12** leading to the intermediate **XIV**, which undergoes an intramolecular radical cyclization to provide **65**. Interestingly, it is mentioned that other solvents than acetic acid gave compound **66** as a by-product in considerable yields. In acidic media its formation is suppressed by the formation of thiosulfonate **67** by quickly removal of methyl radical that reacts with excess of diazonium salt, $K_2S_2O_5$ and K_2SO_3 present in the reaction media, which was characterized by NMR and GCMS analysis.

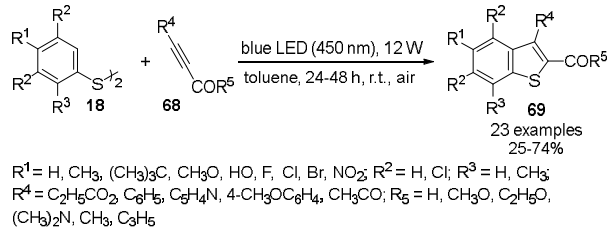


Scheme 31. Proposed mechanism for the multicomponent reaction.

4. Benzo[*b*]thiophenes obtained through photochemical reactions

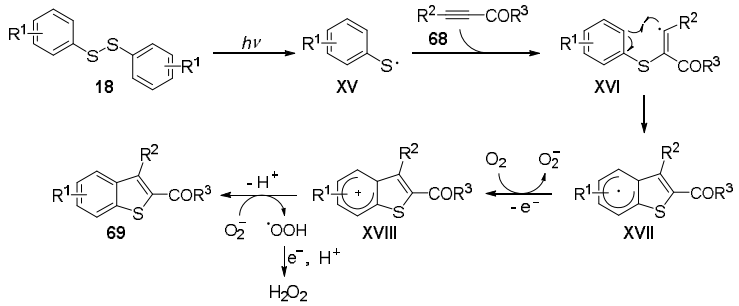
Considering the interest of accessing highly functionalized benzo[*b*]thiophenes, as well as the need to minimize the environmental impact of pollutants from classical organic synthesis, the development of light-mediated strategies becomes an ideal candidate for eco-friendly protocols to prepare these compounds. Visible light represents a clean and abundant energy source that has been satisfactorily used to break and form chemical bonds selectively.[55] In this sense, the visible-light-induced tandem addition/cyclization reaction of

diaryl disulfides **18** with electron-deficient alkynes **68** to produce regioselectively 2,3-disubstituted-benzo[*b*]thiophenes **69** has been reported (Scheme 32).[56] The substrate scope covered several diaryl disulfides bearing electron-donating or electron-withdrawing groups and diverse substituents attached to alkyne, including ester, ketone, aldehyde, alkyl, and aryl functions. Despite the broad scope and functional group compatibility, limitations to provide benzo[*b*]thiophenes were observed for terminal alkynes and those with amide or sulfonyl moieties.



Scheme 32. Synthesis of 2,3-disubstituted benzo[*b*]thiophenes **69** from disulfides.

Based on radical trapping and "ON/OFF" light experiments, the following reaction mechanism was proposed (Scheme 33). Firstly, a photo-induced homolytic cleavage of the diaryl disulfide **18** provides arylthiyl radical species **XV**. Then, the addition of **XV** to internal alkyne **68** furnishes vinyl radical species **XVI**, which undergoes intramolecular cyclization affording benzo[*b*]thiophene radical species **XVII**. Subsequently, a single electron transfer to molecular oxygen from air generates cationic intermediate **XVIII** and a superoxide radical. Finally, a hydrogen abstraction forms the target product **69** and hydrogen peroxide.

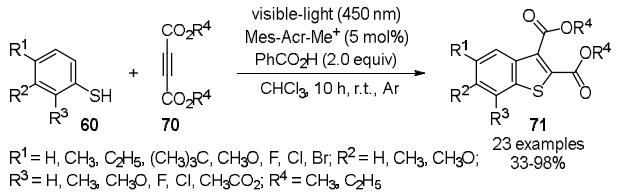


Scheme 33. Proposed reaction mechanism for the preparation of **69**.

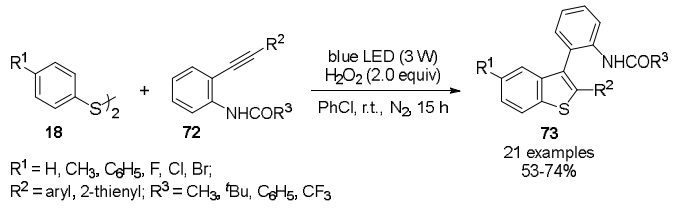
The photoannulation reaction of thiophenols **60** with dicarbonylated alkynes **70** for the synthesis of benzo[*b*]thiophenes bearing 2,3-dialkyldicarboxilates **71** has also been achieved (Scheme 34).[57] The optimal conditions include the use of organic dye, Mes-Acr-Me$^+$ (5 mol%) as catalyst, benzoic acid (2.0 equiv) as additive under argon atmosphere and in $CHCl_3$ as solvent at room temperature for 10 h. The substrate scope covered a wide range of thiophenols containing alkyl, alkoxy, halogen, ester, and hydroxyl as substituents, providing the benzo[*b*]thiophenes in yields ranging from 33% to 98%. Interestingly, the use of diphenyl diselenide, under the same standard conditions, gave the benzo[*b*]selenophenes in moderate yields. However, poor selectivity for *meta*-substituted thiophenols was observed, and pyridine-2-thiol was not a suitable substrate for this synthetic protocol.

An improved visible-light-assisted tandem sulfenilative cyclization reaction was carried out using diaryl disulfides **18** and *N*-protected-2-alkynylanilines **72** under 3 W blue LED irradiation in the presence of hydrogen peroxide as oxidizing agent (Scheme 35).[58] Noteworthy, this method could lead to diverse benzo[*b*]thiophenes **73** bearing amide groups, including acetamide, pivalamide, benzamide, and trifluoroacetamide in moderate to good yields. Mechanistic studies have shown that a thiyl radical, generated

by blue light irradiation, selectively adds to the alkyne to produce an alkenyl radical, which then undergoes intramolecular cyclization to form the target products **73**.

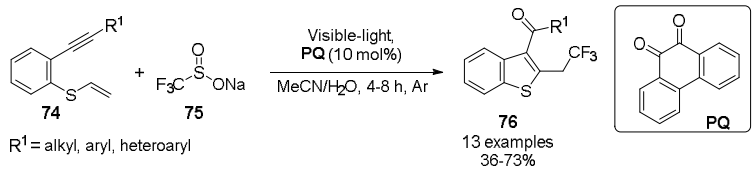


Scheme 34. Synthesis of 2,3-disubstituted benzo[*b*]thiophenes **71** from thiophenols.



Scheme 35. Visible-light-mediated synthesis of benzo[*b*]thiophenes **73**.

The synthesis of trifluoromethylated C3-aryloyl-benzo[*b*]thiophenes **76** was briefly reported as part of a broad study that also describes the preparation of benzo[*b*]furan and indole derivatives through a visible-light-induced oxy-trifluoromethylation of 1,6-enynes **74** with sodium trifluoromethanesulfinate **75** (Langlois' reagent) and H_2O as an oxygen source (Scheme 36).[59] The reactions were conducted in the presence of MeCN as solvent, and phenanthrene-9,10-dione (PQ) as a photoredox catalyst, which has demonstrated having two-electron redox property, crucial for this transformation. Under sun-light irradiation a range of highly substituted 3-acylbenzo[*b*]thiophenes **76** were selectively obtained from thio-linked 1,6-enynes in moderate to good yields (36-73%).

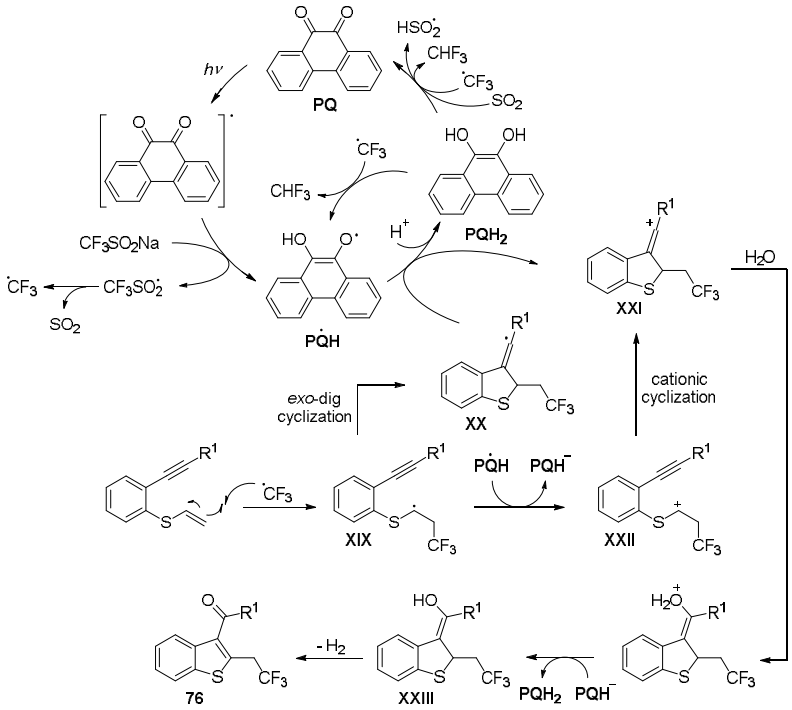


Scheme 36. Visible-light-induced synthesis of trifluoromethylated 3-acylbenzo[*b*]thiophenes **76**.

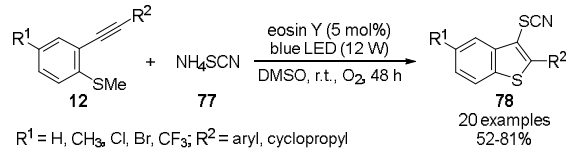
To propose a plausible mechanism, the authors performed several control and spectroscopic experiments, including monitoring the reaction by NMR and EPR analysis, UV-visible studies, as well as cyclic voltammetry, and DFT calculations. Firstly, the **PQ** photoredox catalyst is excited by visible light irradiation, transferring a single electron to Langlois' reagent and generating carbon-centered CF_3 radical species. Then, these species react with 1,6-enyne to form the radical intermediate **XIX**, which undergoes intramolecular 5-*exo*-*dig* cyclization to generate **XX**. An electron transfer from **XX** to **PQ** would form cationic species **XXI** and **PQH₂** (Path A). Alternatively, path B proposes that radical species **XIX** may transfer one electron to radical **PQ·H** intermolecularly, achieving **XXII** *via* cationic cyclization. Following, cationic species **XXI** can react with water, leading to enol intermediate **XXIII**, whose hydrogen release gives rise to C3-aryloyl heteroarene **76** (Scheme 37).

The thiocyanation of 2-alkynylthioanisoles **12** under photoredox-catalyzed cascade radical annulation reaction has been reported (Scheme 38).[60] The target 3-thiocyanatobenzo[*b*]thiophenes **78** were prepared using ammonium thiocyanate **77** in the presence of eosin Y (EY) as a catalyst and visible-light (blue light) as a green energy source, employing DMSO as a solvent and oxygen as a terminal oxidant. The photoredox catalysis

tolerated a diversity of groups attached on both alkyne and thioanisole moieties, providing the desired products in yields ranging from 52% to 81%. Mechanistic investigations revealed that a single electron transfer (SET) process might be involved in a reductive quenching of the eosin Y activated state **EY***, in the presence of thiocyanate anion ($^{-}$SCN), generating thiocyanate radical species ($^{\bullet}$SCN) and eosin Y radical anion species **EY**$^{\bullet-}$. Additionally, oxygen might be responsible for both EY ground state regeneration and oxidation of benzo[*b*]thiophene radical species to a cationic intermediate.



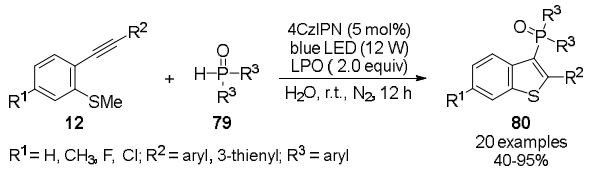
Scheme 37. Proposed mechanism for the synthesis **76**.



Scheme 38. Synthesis of 3-thiocyanatobenzo[*b*]thiophenes **78** under photocatalyzed reaction.

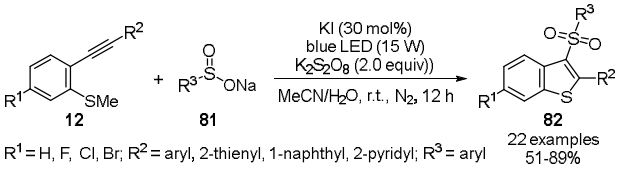
In 2020, Yu and co-workers proposed a metal-free visible-light-promoted tandem phosphorylation/cyclization reaction of 2-alkynylthioanisoles **12** with diarylphosphine oxides **79** in H_2O as sustainable solvent (Scheme 39).[61] The synthesis of 3-phosphorylayed benzo[*b*]thiophenes **80** was achieved using 4CzIPN (5 mol%) as a photocatalyst and dilauroyl peroxide (LPO) as an oxidizing agent under blue light irradiation (460 nm) for 12 h in a N_2 atmosphere. This photochemical phosphorylation tolerated a series of different substituents attached on the thioanisole providing the desired products **80** in moderate to excellent yields. To broaden the substrate scope, diarylphosphine oxides with 4-methyl or 4-fluoro substituents on the benzene ring and 2-alkynylselenoanisole were explored, giving the desired products in 75%, 66%, and 95%, respectively. According to the authors, limitations were observed for alkynes derived from anisole and aniline that failed to give the corresponding phosphorylated benzo[*b*]furan and indole as products under the standard

conditions. It is worth mentioning that this photocatalytic protocol was satisfactorily scaled up to a gram-scale using H_2O/DCM mixture as solvent without significant lack of efficiency.



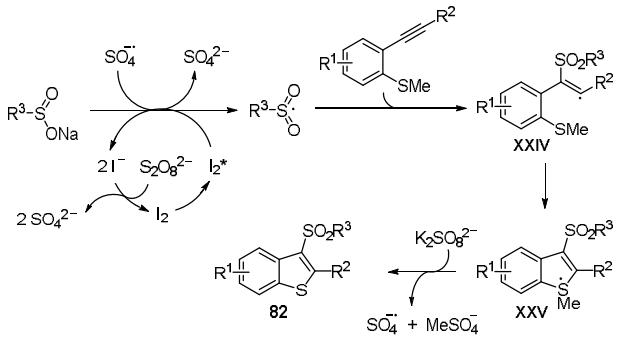
Scheme 39. Blue-light-mediated synthesis of 3-phosphorylated benzo[*b*]thiophenes **80**.

A radical cascade sulfonylative / cyclization of 2-alkynylthioanisoles **12** with sodium sulfinates **81** under blue light irradiation for the synthesis of 3-sulfonylated benzo[*b*]thiophenes **82** has been disclosed. The reactions were conducted in the presence of KI as an additive and $K_2S_2O_8$ as an oxidant in a mixture of MeCN:H_2O (3:1) as solvent under nitrogen atmosphere (Scheme 40).[62] This protocol seems not to be affected by such electronic or steric effects from substituents on both substrates, allowing to afford a library of benzo[*b*]thiophene derivatives from 51% to 89% yield. In addition, the presence of heteroaromatic derivatives as substituents, including pyridine and thiophene, directly attached to the alkyne does not affect negatively the transformation towards the formation of the products **82**. Meanwhile, the optimal reaction conditions were also employed to the annulation of aryl ynones, producing thioflavones in good yields.



Scheme 40. Visible-light-mediated synthesis of 3-sulfonylbenzo[*b*]thiophenes **82**.

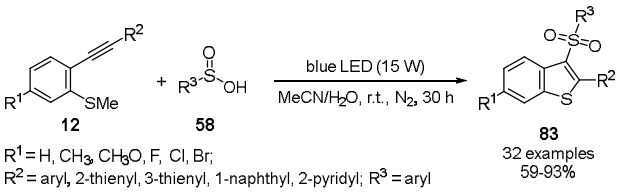
Mechanistic studies indicated that the transformation should proceed through the initial formation of a sulfonyl radical, followed by the addition to the C≡C triple bond of the alkyne to form a vinyl radical intermediate **XXIV**, which subsequently produces the benzo[*b*]thiophene radical **XXV**. Finally, an oxidation promoted by the persulfate anion, followed by demethylation event, furnishes the desired product **82** (Scheme 41).



Scheme 41. Proposed mechanism for the synthesis of **82** under blue light irradiation.

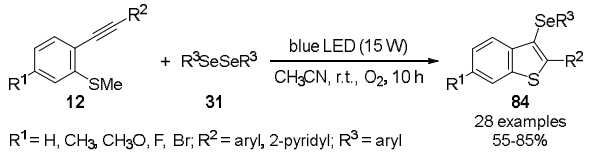
An improved protocol for the preparation of 3-sulfonylated benzo[*b*]thiophenes **83** has been established by the reaction of 2-alkynylthioanisoles **12** with sulfinic acids **58** (Scheme 42).[63] According to the authors, the UV-Vis analysis indicated the formation of an electron-donor-acceptor (EDA) complex by observing a red

shifting spectra behavior when substrates were mixed in solution, in comparison to the spectra acquired separately. This new photoactive EDA complex allowed the formation of thirty-two target products in yields ranging from 59% to 93%. In addition, sulfone-substituted thiochromenones were synthesized from the selective 6-*endo*-dig cyclization reaction of alkynones with arylsulfinic acids.



Scheme 42. Synthesis of sulfonylated benzo[*b*]thiophenes **83** using sulfinic acids.

The photoinduced cascade installation of organoselenium groups and cyclization of 2-alkynylthioanisoles **12** using organoselenyl radical, generated *in situ*, was reported by Yang and co-workers (Scheme 43).[64] The best reaction condition was obtained by using 15 W blue LEDs and MeCN as solvent at room temperature under O_2 atmosphere. Under the visible-light-promoting reaction twenty-eight 3-selanylbenzo[*b*]thiophenes **84** were obtained in 55% to 85% yield. In order to evaluate the scope and limitations, the authors explored a range of substituted 2-alkynylthioanisoles **12,** including electron-donating and electron-withdrawing substituents attached to the benzene ring (R^1) and to the terminal position of the alkyne (R^2), and several diaryl diselenides (R^3) **31**. The reaction proceeded smoothly and afforded the desired products **84** in moderate to good yields. Limitation was observed when 2-alkynylanisole was explored, which failed in giving the desired 3-selanylbenzo[*b*]furan. Aiming to propose a plausible mechanism for the transformation, authors have performed several control experiments using different radical-scavenging substrates, which supported that selenium-centered radical species might be involved in this reaction.



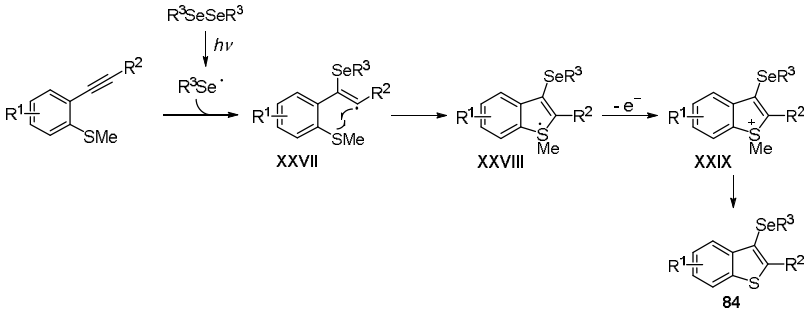
Scheme 43. Photoinduced synthesis of 3-selanylbenzo[*b*]thiophenes **84**.

Thus, a plausible mechanism is shown in Scheme 44. Firstly, the photoirradiated diaryl diselenide generates selenium-centered radical species, which adds to the alkyne rendering vinyl radical intermediate **XXVII**. A subsequent intramolecular radical cyclization produces the radical intermediate **XXVIII**, which is converted to cationic species **XXIX** *via* SET with oxygen, followed by demethylation to provide the benzo[*b*]thiophene derivative **84**.

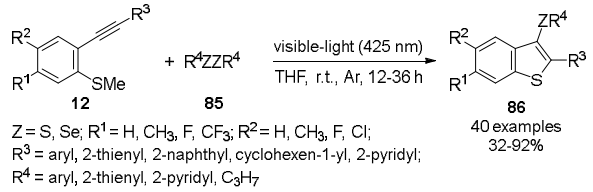
In the same year, Wang, Li, and co-workers reported their results on the preparation of 3-chalcogenyl-benzo[*b*]thiophenes **86** by applying tandem chalcogenative cyclization reaction under visible-light irradiation (Scheme 45).[65] This strategy was smoothly applied to a wide range of substrate scopes, including thioanisoles **12** bearing substituents such as halogen, methoxy, trifluoromethyl, naphthyl, thienyl, and cyclohexen-1-yl, and alkylic and (hetero)arylic disulfides and diselenides **85**. Meanwhile, diverse 2-alkynylselenoanisoles were also compatible with these reaction conditions. Noteworthy, a gram-scale reaction was demonstrated without significant loss in yield. Although for most of the starting materials the reaction proceeded smoothly, some limitations were observed when alkynes bearing aliphatic or ester groups bonded to the terminal position, 2-alkynylanisole, and diphenyl ditelluride were employed as substrates.

A photo-driven halocyclization of 2-alkynylthioanisoles **12** with alkyl halides **87** for the preparation of C-3 halogenated benzo[*b*]thiophenes **88** was reported (Scheme 46).[66] The substrate scope covered the synthesis of highly functionalized 3-bromo and 3-iodobenzo[*b*]thiophenes with good functional groups tolerance, along with the obtention of benzo[*b*]selenophene, benzo[*b*]furan and indole derivatives. In addition,

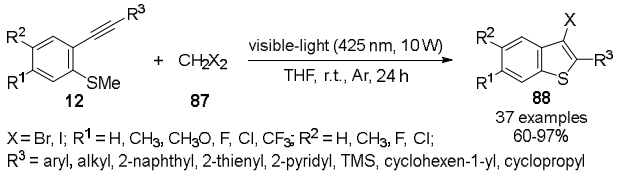
several bromo and iodo-substituted alkanes were effectively used as halogen sources such CH_2I_2, $(CH_2)_2I_2$, CH_2Br_2, $BrCH_2CH_2Br$, CBr_4, and *tert*-BuBr, while di-, tri-, and tetrachloro alkanes, CH_3I or C_6H_5Br were not suitable under these reaction conditions. Furthermore, some important features can be highlighted including scalability, and the absence of photocatalytic species. Finally, the authors have demonstrated the efficient use of these benzo[*b*]thiophenes as key building motifs for the synthesis of fine chemicals *via* transition-metal catalyzed cross-coupling reactions.



Scheme 44. Proposed mechanism for photochemical reaction.



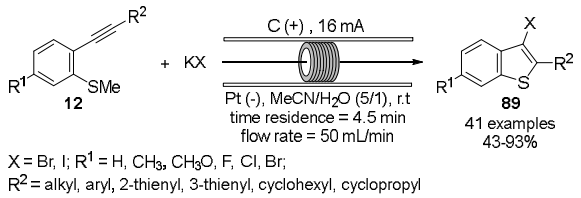
Scheme 45. Photoinduced synthesis of 3-chalcogenylbenzo[*b*]thiophenes **86**.



Scheme 46. Photo-driven synthesis of 3-halobenzo[*b*]thiophenes **88**.

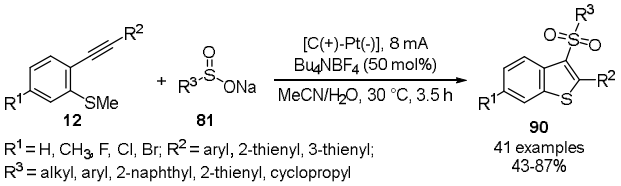
5. Benzo[*b*]thiophenes obtained through electrochemical reactions

Annulation reactions under electrochemical conditions have been becoming a powerful tool in organic synthesis due to their environmental sustainability and simple-to-operate apparatus.[67] The electrochemistry associated with the use of alkynes bearing a nucleophilic sulfur atom in proximity to the triple bond is a field that represents an efficient and direct way to prepare benzo[*b*]thiophenes decorated with several functional groups, such as halogen, sulphone, and chalcogenocyanate. In 2020, Guo and co-workers disclosed a strategy for the synthesis of halogen substituted benzo[*b*]thiophenes **89** under electrochemical conditions assembled in a continuous flow system (Scheme 47).[68] Carbon and platinum plates were employed as the anode and cathode, respectively; using KI or KBr as halogen source and electrolyte, reacting with 2-alkynylthioanisole **12**. This method simultaneously constructed the C–S bond and C–halogen bond in moderate to good yields, tolerating a wide range of functional groups. According to the authors, controlling the reaction system current and the flow rate is crucial for achieving higher yields and good selectivity. For example, C3 iodinated benzo[*b*]thiophenes were best obtained by conducting the reaction under 16 mA constant current and operating with a flow rate of 50 μL/min. Meanwhile, C3 dehalogenated products could also be obtained by adjusting the flow rate to 10 μL/min and the current to 20 mA.



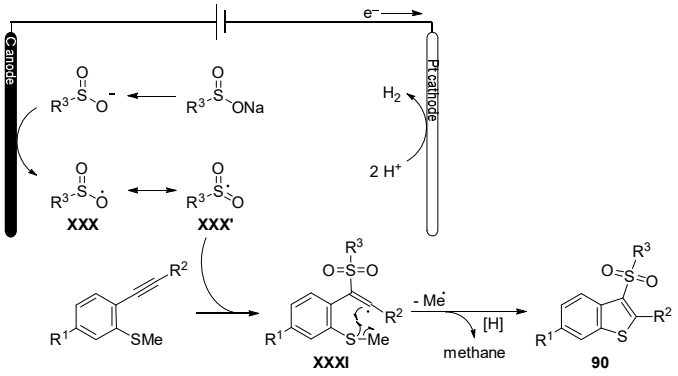
Scheme 47. Electrochemical synthesis of 3-halobenzo[*b*]thiophenes **89**.

In 2021, Zhang and co-workers reported the synthesis of 3-sulfonylbenzo[*b*]thiophenes **90** based on reactions between 2-alkynylthioanisoles **12** and sodium sulfinates **81** *via* a tandem addition of sulfonyl radicals-cyclization reaction (Scheme 48).[69] Through this approach, forty-one C3-sulfonylated benzo[*b*]thiophenes were selectively produced in moderate to good yields. For achieving good reaction efficiency, Pt plate cathode and carbon rod anode were placed in an undivided cell using *n*-Bu_4NBF_4 as supporting electrolyte under 8 mA constant current in a mixture of acetonitrile and water (v/v=2/1) as solvent. This methodology has tolerated the presence of alkyl, alkoxy, halogen, and ester substituents attached to the alkyne, and the reaction conditions could be applied to both aryl- and alkyl-substituted sulfinates **81**. The gram-scale synthesis was demonstrated under standard reaction conditions, affording 2-phenyl-3-tosyl-benzo[*b*]thiophene in 68% yield. According to the authors, the benefits described are the avoidance of external catalysts and chemical oxidants under an environmentally friendly platform, which is easily scalable.



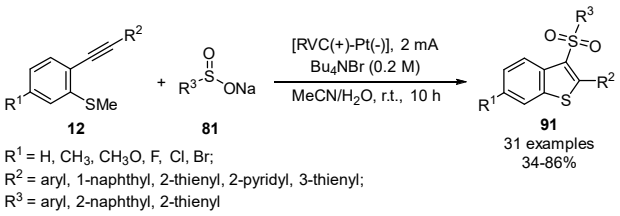
Scheme 48. Synthesis of C3-sulfonylated benzo[*b*]thiophenes under electrochemical conditions.

A plausible reaction mechanism for the transformation was proposed (Scheme 49). Initially, sodium sulfinate loses one electron at the carbon rod anode giving the oxygen-centered radical species **XXX**, which can be quickly converted into the sulfur-centered radical **XXX'**. Then, an intermolecular addition of sulfonyl radical species to the C≡C triple bond of 2-alkynylthioanisole furnishes vinyl radical intermediate **XXXI**, which undergoes intramolecular cyclization along with the displacement of a methyl radical to form 3-sulfonylbenzo[*b*]thiophene **90**.



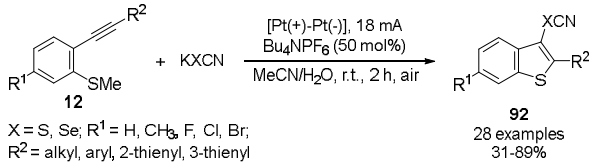
Scheme 49. Mechanism proposed.

3-Sulfonylbenzo[*b*]thiophenes **91** were also obtained directly by electrochemical radical addition/annulation reactions of internal alkynes **12** with sodium sulfinates **81** established in an undivided cell outfitted with reticulated vitreous carbon (RVC) and platinum electrodes under 2.0 mA constant current (Scheme 50).[70]



Scheme 50. Electrochemical synthesis of **91**.

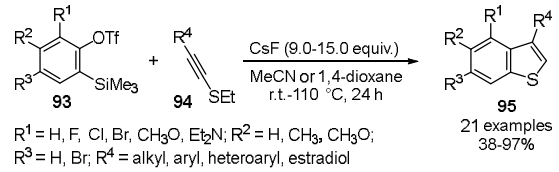
In 2023, Zhang and co-workers reported an efficient approach for the synthesis of 3-thiocyanato- and 3-selenocyanatobenzo[*b*]thiophenes **92** through a reaction between 2-alkynylthioanisoles **12** and potassium chalcogenocyanates under electrolytic conditions (Scheme 51).[71] Twenty-eight products **92** were obtained in moderate to good yields using an undivided cell equipped with Pt plates as cathode and anode under 18 mA constant current, in the presence of *n*-Bu_4NPF_4 as an electrolyte. The electrochemical radical addition/cyclization exhibited excellent compatibility with a variety of electron-donating and electron-withdrawing substituents, but lower yields were observed when octyne was attached to thioanisole and potassium selenocyanate was used. On the other hand, to scale up this reaction, the authors demonstrated that a continuous flow electrochemical system can be used to improve the reaction efficiency when compared to batch conditions.



Scheme 51. Synthesis of 3-(chalcogenocyanato)benzo[*b*]thiophenes under electrochemical conditions.

6. Benzo[*b*]thiophenes obtained through aryne intermediate

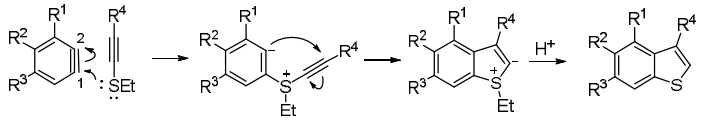
Considering the diversity of alkynes that can be used to prepare benzo[*b*]thiophenes, the synthetic application of *o*-silylaryl triflates **93** and alkynyl sulfides **94** has been demonstrated (Scheme 52).[72] In this work, highly substituted benzo[*b*]thiophenes **95** were obtained *via* nucleophilic attack by the sulfur atom of alkynyl sulfide to the benzyne, generated *in situ*, followed by the new C–C bond formation, protonation and dealkylation.



Scheme 52. Synthesis of benzo[*b*]thiophenes **95** by aryne reaction with alkynyl sulfides.

According to the authors, no regioisomers were detected when R^1 is a hydrogen atom, and nucleophilic attack of sulfur atom occurs selectively at C1. However, when 4-methyl- and 4-methoxybenzyne intermediates ($R^2 \neq H$) are present, sulfur reacts equally with both C1 and C2, giving a 1:1 mixture of regioisomers. In addition

to the tolerance to a wide range of functional groups, the synthesis of benzo[*b*]thiophenes having π-extended aromatics and heteroaromatics was demonstrated. Furthermore, the multifaced characteristic of **95** was further demonstrated by various functionalization reactions, including sulfenylation, iodination, ethoxycarbonylation, Suzuki-Miyaura cross-coupling reaction, and the preparation of polycyclic aromatic compounds (Scheme 53).



Scheme 53. Reaction mechanism for the synthesis of **95**.

7. Conclusions

Benzo[*b*]thiophenes play important roles in the development of biologically active and organic semiconductors molecules. In this chapter we summarized the advances and current uses of different protocols that employ triple bonds and sulfur containing reagents to promote the synthesis of structurally diverse benzo[*b*]thiophenes under metal-free conditions. The results related in this review demonstrate the versatility of alkynes as starting materials to construct libraries of new molecules for fine applications. Mostly, these new methods include reactions of 2-alkynylthioanisoles with both electrophilic and radical species. In addition, thiols, diaryl disulfides, sulfonyl chlorides, and thioethers have been successfully employed as a sulfur source to synthesize the benzo[*b*]thiophene moiety. To minimize the environmental impact of classical organic synthesis on using transition-metals and oil bath heating, alternative protocols have been introduced to demonstrate the outstanding potential of photocatalysis and electrochemistry. From this point, future perspectives on heterocyclization reactions should be increasingly supported by environmentally friendly platforms that include the use of sustainable solvents, abundant sources of sulfur, use of alternative energy sources, and avoidance of the use of expensive, toxic and polluting reagents, catalysts and additives.

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