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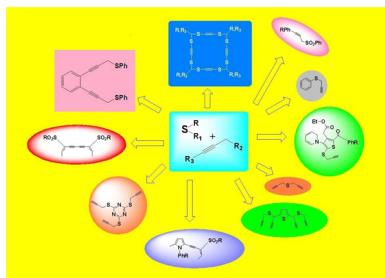
Propargylic Sulfides: Synthesis, Properties, and Application

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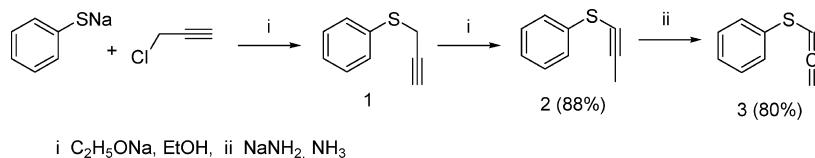
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1. INTRODUCTION

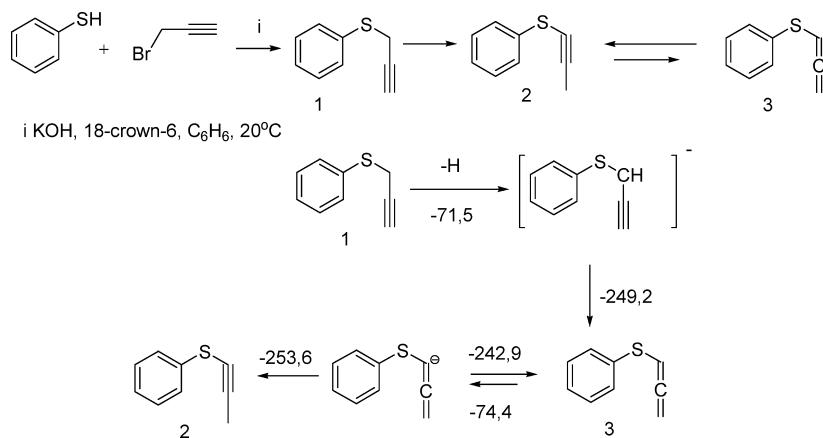
Investigation of acetylene chemistry¹ and sulfur chemistry^{2,3} combined provides a wide range of opportunities for development and applications of new monomers, intermediates for fine organic synthesis,^{1a,2d,3} selective extracting agents for precious metals,⁴ additives for lubricating oils,⁵ compounds with anticorrosive activity,⁶ and biologically active compounds,⁷ including antidotes for heavy metal poisoning,⁸ radiation protection materials,⁹ and blood anticoagulants.¹⁰ Dipropargyl sulfides are also of special interest because of their electrical conductivity.¹¹ Mono- and dialkynyl sulfides are successfully used as precursors for producing optically active natural compounds¹² and synthetic analogues of various natural compounds¹³ and for synthesis of various types of chiral sulfur derivatives.¹⁴

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Scheme 1



Scheme 2



The synthetic methods and properties of mono- and dipropargyl sulfides are essentially described in this review, which is considered a pioneering work devoted to propargyl sulfides.

At the beginning of the second section, we shed light on our research interest, which is the synthesis and reactions of aromatic propargyl sulfides. Initially, the synthesis of propargyl phenyl sulfides was achieved through C–S bond formation by addition of propargyl halides to sodium benzenethiolate in ethanol, which was usually accompanied by prototropic rearrangements. Accordingly, obtaining propargyl sulfides in high yields was quite difficult since a mixture of allyl and 1-propynyl sulfides is produced. In addition, related reactions are discussed.

Then the synthesis of a variety of aromatic propargyl sulfides in sufficiently high yields with little or no isomerization of propargyl substituents is presented.

After the development of catalytic methods for carbon–carbon and carbon–heteroatom bond formation using transition-metal complexes, the synthesis of propargyl-type sulfides was highly studied under conditions that enabled the formation of the desired products in quantitative yield as shown in section 2.3.

Besides, sulfenylation of propargyl alcohols catalyzed by Lewis acid allowed C–S bond formation to give α -substituted propargyl sulfides in quantitative yield (section 2.4).

Phenyl propargyl sulfides with various substituents at the α -position to the sulfur atom were also obtained by reaction of $[\gamma$ -(phenylthio)allenyl]stannanes with acetals under Lewis acid catalysis (section 2.5).

In addition, the reactivity, transformations, and rearrangements of aryl propargyl sulfides to produce organosulfur compounds are broadly described.

In the third section, we illustrate the synthesis and chemical properties of alkynyl, propargyl, bispropargyl, and bisalkynyl sulfides with emphasis on the original work of L. Brandsma,^{15a,b} who reported direct synthesis of dialkynyl sulfides, to see the

distinctive features of the direct synthesis of dialkynyl sulfides from synthesis of dipropargyl sulfides given in section 3.3.

In the fourth section of this review, we highlight the cyclization reactions of propargyl sulfides and their derivatives, such as propargyl sulfoxides and propargyl sulfones. Various heterocyclic compounds were produced utilizing thermal Claisen reactions as well as catalytic reactions. Various compounds with multicyclic structures were formed under acidic and basic conditions in the presence of catalytic transition-metal complexes.

In the fifth section, we focus on the wide practical applications of the propargyl sulfides, including industry (section 5.1), agriculture (section 5.2), and medicine (section 5.3). Natural sulfides with propargyl and thiarubrine structures are also illustrated.

2. SYNTHESIS AND TRANSFORMATIONS OF AROMATIC PROPARGYL SULFIDES

2.1. Synthesis and Prototropic Rearrangement of Aromatic Propargyl Sulfides Using Strong Bases

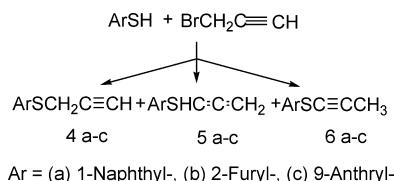
In their monographs, Brandsma and Verkruisze summarized various methods of synthesis of various alkynyl sulfides, sulfoxides, and sulfones.^{15a,b} They described a facile synthetic method for phenyl propargyl sulfide (**1**) by addition of propargyl chloride to sodium benzenethiolate in ethanol. In the presence of a strong basic medium such as sodium alkyl oxides in alcohol or sodium amide in liquid ammonia, the product **1** was transformed to prop-1-ynyl phenyl sulfide (**2**) and with further isomerization to allenyl phenyl sulfide (**3**) (Scheme 1).

Propargyl sulfide **1** was obtained by reacting benzenethiol with propargyl bromide under phase transfer catalysis conditions (KOH, 18-crown-6, benzene, 20°C). Filippova et al.^{16a,b} showed effective isomerization of **1** into (phenylthio)-allene (**3**) (80% yield) using sodium ethanolate. When potassium *tert*-butoxide was used, **1** rearranged to (prop-1-ynylthio)benzene (**2**) and did not undergo further trans-

formation (Scheme 2).^{16c} The authors observed that when potassium hydroxide was replaced by potassium carbonate, prop-2-ynyl phenyl sulfide (**1**) was obtained in 86% yield with only 5% prop-1-ynyl phenyl sulfide (**2**). The rearrangement mechanism was investigated using the semiempirical quantum chemical method AM1 with MOPAC 6 software based on the heat of formation of the isomerization products and the intermediates (the values (kcal/mol) are next to the arrows).

In a separate study, the synthesis and thermal properties of a new series of aryl propargyl and aryl allenyl sulfides **4a–c–6a–c** were studied by Himbert and coauthors¹⁷ (Scheme 3).

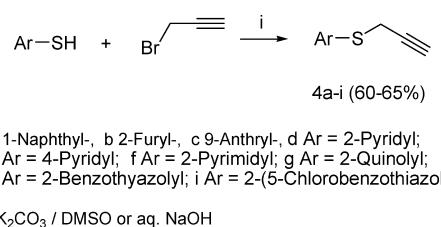
Scheme 3



2.2. Synthesis and Isolation of Aromatic Propargyl Sulfides

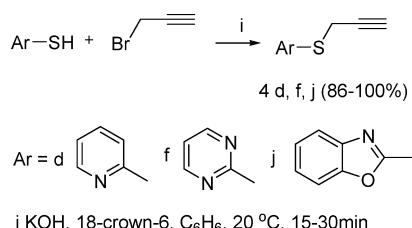
Riyadh et al.¹⁸ prepared and isolated various heterocyclic aromatic propargyl sulfides **4a–f** in good yields without further isomerization using potassium carbonate in DMSO or aqueous sodium hydroxide as shown in Scheme 4.

Scheme 4



Also, Rubina et al.^{16b} reported a selective synthesis of heteroaromatic propargyl derivatives of 2-pyridinethiol (**4d**), 2-pyrimidinethiol (**4f**), and 1,3-benzoxazol-2-thiol (**4j**) under similar phase transfer catalysis conditions (Scheme 5).

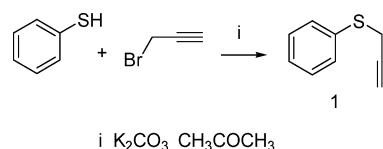
Scheme 5



Samyratov found a unique method for the preparation of phenyl propargyl sulfide (**1**) without further isomerization to prop-1-ynyl phenyl sulfide (**2**) in 92% yield by reacting benzenethiol and propargyl bromide in boiling acetone in the presence of potassium carbonate as a base (Scheme 6).¹⁹

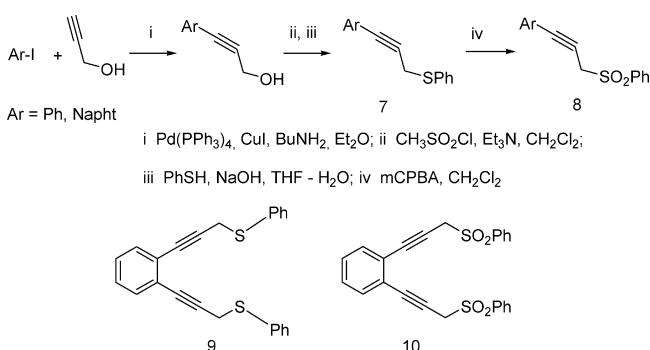
Wu et al.²⁰ proposed a multistep synthetic route for arylpropargyl derivatives of phenyl sulfide (**7**) by reacting propargyl alcohol and aryl iodide in the presence of Cu and palladium catalyst. The obtained intermediate was reacted with methanesulfonyl chloride to give the corresponding mesylate

Scheme 6



followed by treatment with thiophenol under alkaline conditions. Oxidation of aryl sulfide **7** by *m*-chloroperoxybenzoic acid gave phenyl sulfone **8**. Similarly, dipropargyl derivatives **9** and **10** were obtained from 1,2-diiodobenzene (Scheme 7).

Scheme 7



The tricyclic derivatives of (propargylthio)thieno[3,4-*b*]-indolizine (**11**) were generated by alkylation of pyridinium betaines using propargyl bromide and NaI in acetone followed by the reaction of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with chloranil in chloroform (Scheme 8).²¹ Also, no isomerization products were observed under these reaction conditions.

Reddy and Varma²² demonstrated the versatility of cerium-exchanged NaY zeolite as an effective catalyst for the synthesis of unsymmetrical sulfides, including phenyl propargyl sulfide **12**, in good yield (Scheme 9).

2.3. Catalytic Synthesis of Propargyl Sulfides in the Presence of a Transition-Metal Complex

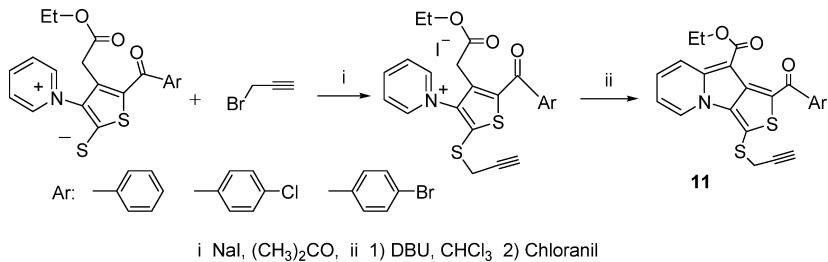
The cross-coupling of tributyl(phenylethynyl)tin (**13**) with chloromethyl phenyl sulfide was mediated by Pd(0) to furnish a propargylic sulfide (**14**) in good yield (Scheme 10).²³

Kondo et al.²⁴ found a rapid synthesis of aryl propargyl sulfides **15** in quantitative yields using ruthenium complex $CpRuCl(cod)$ [Cp = cyclopentadienyl, cod = 1,5-cyclooctadiene], which catalyzed the S-propargylation of aromatic thiols with internal propargylic carbonates in tertiary amine (Scheme 11).

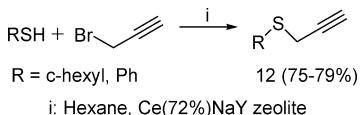
Uemura et al.²⁵ found a highly selective and effective propargylic substitution reaction of propargylic alcohols with thiols catalyzed by the cationic diruthenium complex **16**. This catalytic reaction provided a general and environmentally friendly synthetic method for propargylic sulfides **17** in high yield directly from thiols and propargylic alcohols with either a terminal or an internal alkyne group (Scheme 12).

Tsutsumi and coauthors²⁶ reported that propargylic bromide **18** reacted with an equivalent amount of benzenethiol at 60 °C in DMF to afford alkynyl phenyl sulfide **19** in excellent yield (99%). The reaction was carried out in the presence of a catalytic amount of Pd^0 -dppe complex [dppe = 1,2-bis-

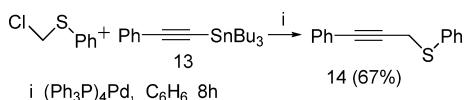
Scheme 8



Scheme 9



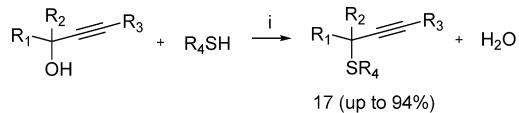
Scheme 10



Scheme 11

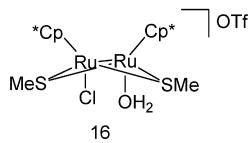


Scheme 12



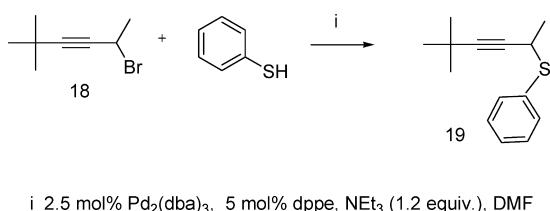
R₁ = Ph, Ph₂C=CH, p-MeC₆H₄, p-FC₆H₄, 2-naphthyl, c-C₆H₁₁,
 R₂ = H, Me, Ph,
 R₃ = H, Ph, n-Bu, n-hexyl, t-Bu,
 R₄ = Ph, n-Bu, n-octyl, (CH₂)CHMe₂, (CH₂)₂CO₂Me, CH₂Ph,
 (CH₂)₃Cl, (CH₂)₂OH, c-C₆H₁₁

i 5 mol% 16, CICH₂CH₂Cl, 60°C, 1 h



(diphenylphosphanyl)ethane], which was generated in situ from [Pd₂(dba)₃·CHCl₃] and dppe (Scheme 13).

Scheme 13



Müller and Netz^{27,28} used the S_N1 reaction of sulfuric nucleophiles with planar chiral *ortho*-substituted (arene)Cr(CO)₃-stabilized propargylic cations **20** for a regioselective formation of the corresponding propargyl derivatives **21** in high yields and excellent diastereoselectivities (Scheme 14).

2.4. Propargyl Sulfides by Nucleophilic Substitution of Propargyl Alcohols or Their Derivatives Catalyzed by a Lewis Acid

Yoshimatsu et al.²⁹ used scandium triflate as a catalyst for sulfonylation of substituted propargyl alcohols using trimethyl-(phenylthio)silane to produce the corresponding propargyl sulfides **22** in quantitative yield (Scheme 15).

Then Yoshimatsu and co-workers³⁰ applied this method for sulfonylation of propargyl alcohols by Lewis acid-catalyzed C–S bond formation in which the desired propargyl sulfides **23** were obtained in good to high yields (Scheme 16).

2.5. Various Derivatives of Phenyl Propargyl Sulfide via [γ -(Phenylthio)allenyl]stannanes

A series of phenyl propargyl sulfide derivatives **24** were obtained by the reaction of [γ -(phenylthio)allenyl]stannanes with acetals in the presence of TiCl₄.³¹ The intermediates [γ -(phenylthio)allenyl]stannanes were gained by treatment of (tributylstanny) copper(I) reagent with 1,1-bis(phenylthio)-2-alkyne in tetrahydrofuran at –78 °C (Scheme 17).

2.6. Phenyl Propargyl Sulfones by Reactions of Propargyl Chloride with Thiophenol and Excess Hydrogen Peroxide

Van Zanten et al.³² showed that sequential reactions of propargyl chloride with thiophenol in the presence of NaOH and 2 mol % TiCl₃ in methanol using excess hydrogen peroxide resulted in the formation of phenyl propargyl sulfone (**25**) in 81% yield. Then 2,3-dibromo-1-(phenylsulfonyl)-1-propene isomers **26** and **27** were generated in 93% yield (*E*:*Z* = 20:1) by bromination of **25** under a catalytic amount of aluminum oxide (Scheme 18).

2.7. Hydrostannylation of Propargyl Aryl Sulfide

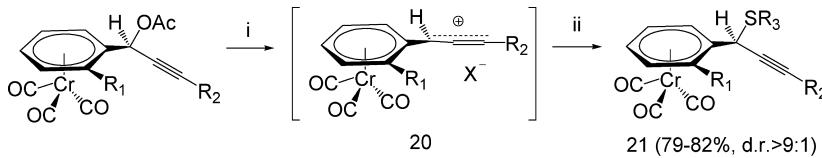
Hydrostannylation of propargyl *p*-tolyl sulfide which was carried out by Lambert et al.³³ led to the production of (*Z*)-1,2-bis(organylstannylolefin **28** (Scheme 19).

2.8. Transformations of Phenyl Propargyl Sulfide Utilizing Acetylenic Hydrogen

Armstrong et al.³⁴ described a facile anionic method for the transformations of phenyl propargyl sulfide. For instance, the respective iodo and carboxylic derivatives **29** and **30** were obtained by lithiation of the acetylenic moiety followed by either an iodination process or CO₂ addition (Scheme 20).

Another utilization of acetylenic hydrogen includes implementation of Mannich conditions in amination of phenyl propargyl sulfide (**1**) using diethylamine and formaldehyde. The reaction was carried out in dioxane in the presence of

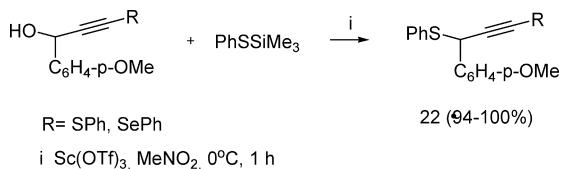
Scheme 14



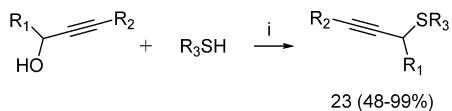
$R_1 = \text{Me, OMe}$; $R_2 = \text{Ph, } p\text{-C}_6\text{H}_4\text{OCH}_3, n\text{-Bu}$; $R_3 = i\text{Pr, } (\text{CH}_2)_2\text{CO}_2\text{CH}_3$

i TMSOTf or TiCl_4 , -78°C , CH_2Cl_2 ; ii HSR_3

Scheme 15



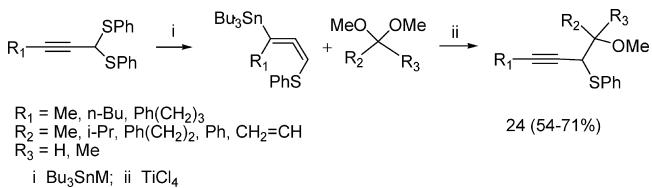
Scheme 16



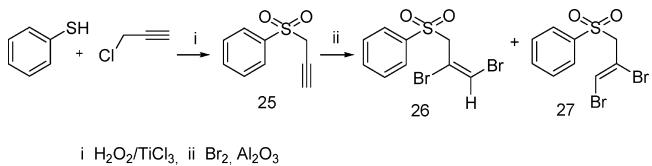
$R_1 = p\text{-MeOC}_6\text{H}_4, 2\text{-Thenyl, 1-Naphthyl, Benzodioxol-5-yl, Ph, }$
 $R_2 = \text{SPh, Ph, } n\text{-Bu, }$
 $R_3 = \text{Me}(\text{CH}_2)_9, 2\text{-Naphthyl, 2-Thienyl, } p\text{-ClC}_6\text{H}_4, \text{ Cyclohexyl}$

i $\text{Sc}(\text{OTf})_3$ (10 mol%), Bu_4NHSO_4 (0.1 equiv), $\text{MeNO}_2\text{-H}_2\text{O}$ (10:1), 30°C

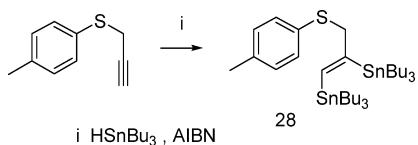
Scheme 17



Scheme 18



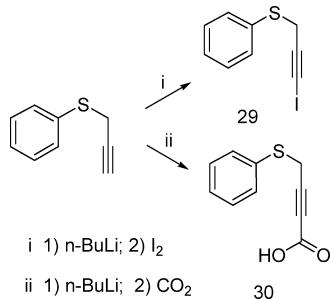
Scheme 19



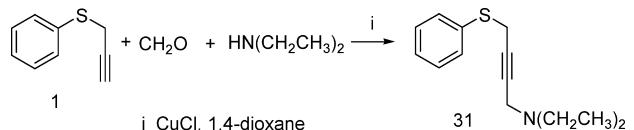
copper(I) chloride to produce 1-(phenylthio)-4-(diethylamino)but-2-yne (**31**) in almost quantitative yield (Scheme 21).³⁵

The compound 2,5-dimethylphenyl propargyl sulfide was obtained in good yield by condensation of propargyl bromide with 2,5-dimethylbenzenethiol in methanol in the presence of KOH. Its lithiation at -78°C followed by condensation with benzaldehyde produced a propargyl alcohol moiety which was

Scheme 20

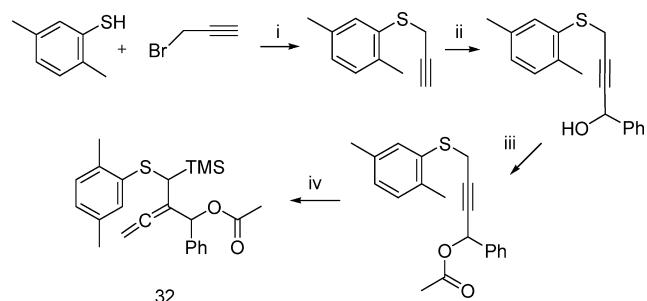


Scheme 21



isomerized to the allene derivative **32** by silylation with trimethylsilane in the presence of an iron complex (Scheme 22).³⁶

Scheme 22

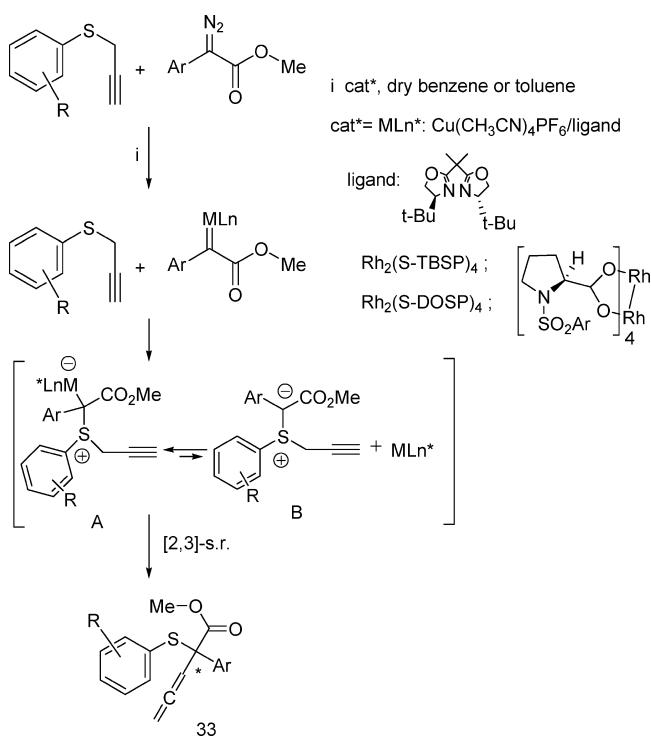


2.9. Asymmetric Catalytic Synthesis of Chiral Propargyl (Allenyl) Sulfides

In the past decade, Wang et al. advanced an interesting catalytic method of asymmetric synthesis of chiral propargyl (allenyl) sulfides by catalytic [2,3]-sigmatropic rearrangement of sulfur ylides derived from metal carbenes. For instance, several highly optically active allenes **33** were obtained (up to 81% ee) by catalytic [2,3]-sigmatropic rearrangement of sulfur ylides **B** which were generated from aryl diazoacetates and aryl propargyl sulfide in the presence of chiral Cu(I) and Rh(II) catalysts in dry benzene or toluene (Scheme 23).³⁷ It is proposed that the metal catalyst is incorporated with ylides **A** and **B**, which are

present in equilibrium that strongly favors the metal catalyst combining with ylide A.³⁸

Scheme 23

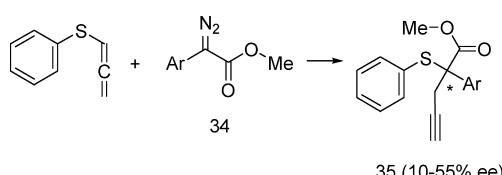


Ultimately, Wang and Liao³⁹ demonstrated that [2,3]-sigmatropic rearrangement of sulfur ylide derived from rhodium(II) carbene and propargyl phenyl sulfide was efficiently done in water to afford allene derivatives in up to 96% chemical yields. Generally, these types of reactions are carried out in anhydrous organic solvent in an inert atmosphere to avoid side reactions. However, it is worthwhile to note that in aqueous solvent the reaction of methyl (*p*-methoxyphenyl)-diazoacetate and 2-chlorophenyl propargyl sulfide was done under other conditions but in lower enantioselectivity relative to that in an organic medium.

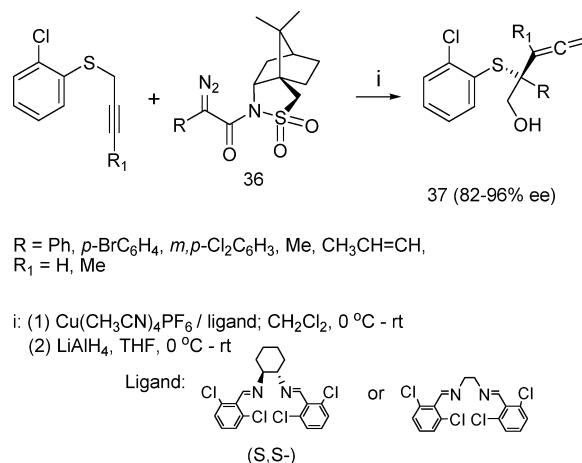
In a separate study, Wang and co-workers⁴⁰ carried out asymmetric [2,3]-sigmatropic rearrangement of sulfonium ylides which were obtained from allenic sulfide and methyl aryl diazoacetates 34 to yield the acetylenic derivatives 35. However, despite carrying out the reaction under similar conditions and applying the same chiral catalytic system as in the reaction of propargyl sulfide (Scheme 23), the enantioselectivity of this reaction was much lower (Scheme 24).

In addition, the scope of the reaction of 2-chlorophenyl propargyl sulfide and diazo compounds 36 bearing a chiral auxiliary group catalyzed by Cu(I) with achiral or chiral ligands was investigated⁴¹ (Scheme 25). High enantioselectivity of

Scheme 24



Scheme 25

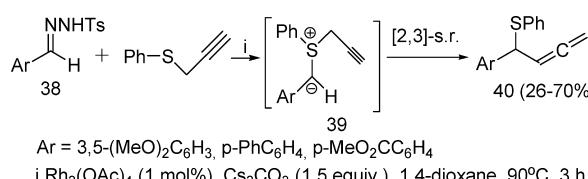


allenyl sulfides 37 up to 96% ee was gained. The authors indicated that the chiral auxiliary group of the diazo compound determined the absolute configuration in the asymmetric induction instead of the chiral ligand.

Other transition-metal (ruthenium, iron, gold, samarium) complexes were also recently explored as catalysts in [2,3]-sigmatropic rearrangement of sulfur ylide derived from metal carbene.³⁸

In a recent paper, Wang et al.⁴² reported an effective Rh₂(OAc)₄-catalyzed reaction between *N*-tosylhydrazones 38 and propargyl phenyl sulfide. For various substituted *N*-tosylhydrazones, the reaction smoothly afforded the corresponding allenyl sulfides 40 in moderate yields on the basis of the GC/MS analytical method. However, only three examples of this reaction were demonstrated due to the difficulties in product isolation (Scheme 26). Nevertheless, it is evident that this kind of [2,3]-sigmatropic rearrangement of sulfur ylides 39 is highly applicable to propargyl sulfide.

Scheme 26

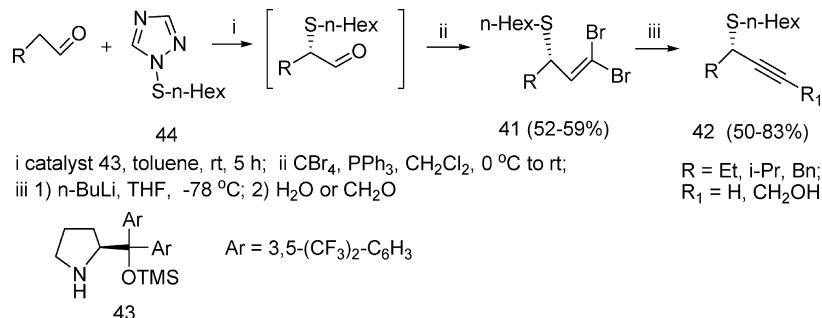


Amstrong and Emmerson⁴³ developed a multistep method for asymmetric synthesis of chiral propargyl sulfides 42 by α -sulfenylation of aldehydes using the sulfur electrophile 44 under a catalytic amount of prolinol 43. Then Corey–Fuchs reaction conditions were utilized to give the desired chiral propargyl sulfides 42 in good yield through the dibromoolefin 41, which was debrominated using *n*-BuLi followed by hydrolysis (Scheme 27).

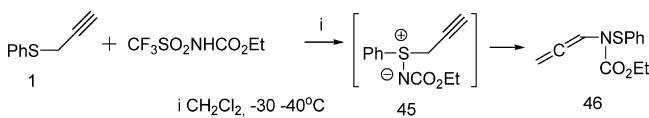
2.10. Sulfimidation of Phenyl Propargyl Sulfide

Sulfimidation of phenyl propargyl sulfide (1) followed by [2,3]-sigmatropic rearrangement of propargylic sulfimide 45 afforded sulfenamide 46 in 84% yield. It is worth noting that this reaction in which *N*-[((trifluoromethyl)sulfonyl)oxy]carbamate was used as an amidating agent was initially reported by Tamura and co-workers (Scheme 28).⁴⁴

Scheme 27

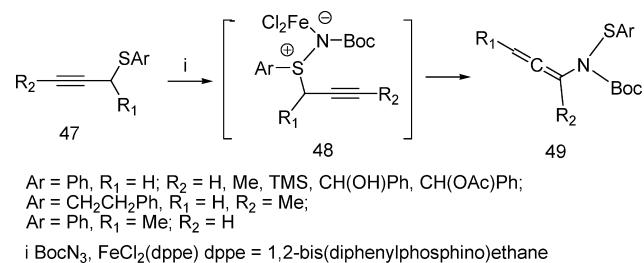


Scheme 28



Iron(II)-catalyzed sulfimidation followed by [2,3]-sigmatropic rearrangement of aryl propargyl sulfides **47** was then studied.^{45,46} For instance, aryl propargyl sulfides **47** were reacted with *tert*-butoxycarbonyl azide (BocN_3) in the presence of 10 mol % (dppe)- FeCl_2 in 1,2-dichloroethane at 0 $^\circ\text{C}$ to yield *N*-allenylsulfenamides **49** in 31–73% yield. It was suggested that the stable $\text{Cl}_2\text{Fe}-\text{NBoc}$ complex was initially formed. Then this complex reacted with the propargylic sulfides **47** to produce sulfimides **48**, which rearranged to the desired *N*-sulfonyl allenamides **49** (Scheme 29). Further transformation of allenamide **49** to propenyl carbamate ($\text{Ar} = \text{Ph}$; $\text{R}^1 = \text{R}^2 = \text{H}$) was detected by Pd/C-catalyzed hydrogenation.⁴⁵

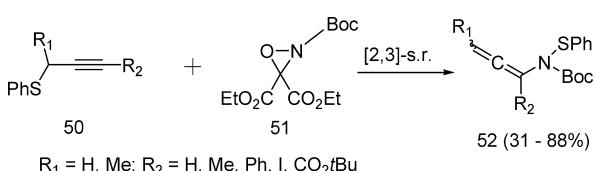
Scheme 29



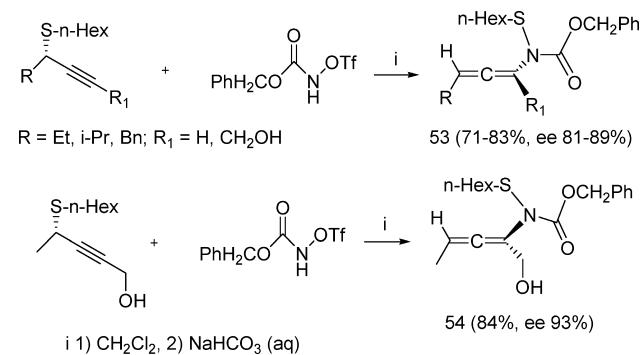
A metal-free process which involved amination of propargylic sulfides **50** with the novel oxaziridine **51** to form *N*-allenylsulfimides **52** via [2,3]-sigmatropic rearrangement was reported by Armstrong (Scheme 30).³⁴

Armstrong and Emmerson⁴³ were pioneers in demonstrating that chiral propargylic sulfides can undergo amidation accompanied by [2,3]-sigmatropic rearrangement with a high level of chirality, affording allenamide enantiomers **53** and **54** (Scheme 31).

Scheme 30



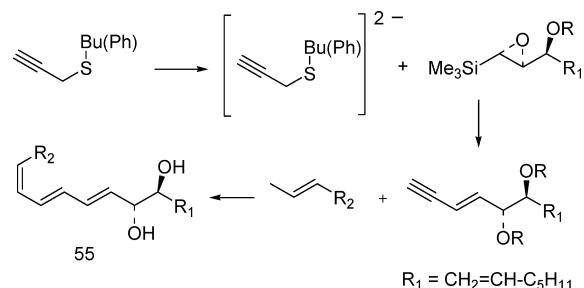
Scheme 31



2.11. Utilization of Aryl Propargyl Sulfide as a Synthetic Intermediate for the Synthesis of Various Compounds

Kobayashi et al.⁴⁷ described a full synthesis of dihydroxyicosatetraenoic acid **55**. The most significant step of this reaction is the epoxide cleavage by prop-2-ynyl sulfide anion, which was

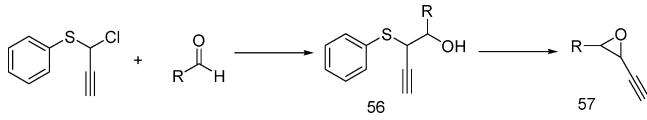
Scheme 32



obtained from alkyl (aryl) propargyl sulfide and BuLi at -15 $^\circ\text{C}$ (Scheme 32).

Mitzel et al.⁴⁸ detected a mixture of *syn* and *anti* secondary alcohol products **56** as a result of the reaction between α -chloropropargyl phenyl sulfide and benzaldehyde (or *p*-chlorobenzaldehyde) in water or aqueous DMF solutions. Propargyl alcohols **56** were obtained in 70–85% yield. The *syn* to *anti* ratio was dependent on the catalytic system. For instance, when InCl_3 was used under the same optimized conditions, a change in the ratio from 77:23 to 88:12 was observed. This ratio variation can be attributed to a steric difference in the transition state in which a chelation between the PhS group and InL_2 takes place. Moreover, alcohol

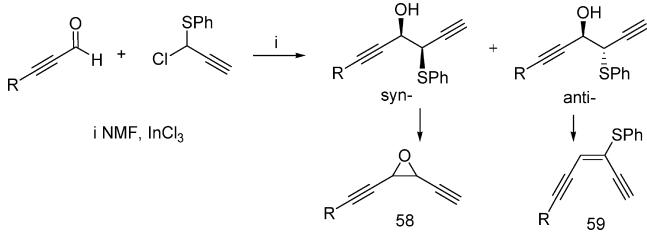
Scheme 33



cyclization was achieved in CH_2Cl_2 using $\text{Me}_3\text{O}^+\text{BF}_4^-$ to afford acetylene epoxide 57 (Scheme 33).

Recently, Frimpong and co-workers⁴⁹ found that indium-promoted Barbier-style coupling reaction between α -chloropropargyl phenyl sulfide and alkynyl aldehydes was enhanced when it was carried out in *N*-methylformamide (NMF) compared to water. The authors were the first to study this reaction in NMF and reported excellent regioselectivities and

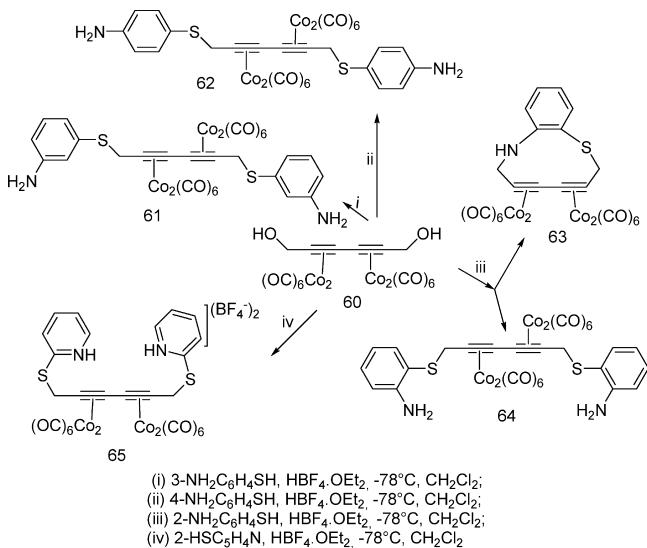
Scheme 34



good stereoselectivities in forming epoxy diyne 58 and enediyne 59 structures (Scheme 34).

Golovko et al.^{50a} implemented the principles of Nicholas-type reaction^{50b} to promote the formation of ring systems containing both alkynes and S,N -substituted aromatics. They showed that the acid-mediated reactions of biscoordinated diyne-diol cobalt complex 60 with the *m*- and *p*-aminothiophenols afforded the linear chain products 61 and 62, respectively. However, the reaction of complex 60 with *o*-aminothiophenol furnished the 10-membered ring macrocyclic compound 63 together with the linear chain complex 64. Moreover, treatment of cobalt complex 60 with *ortho*-substituted mercaptopyridine in the presence of HBF_4 gave the neutral complex salt 65 in good yield after workup with a

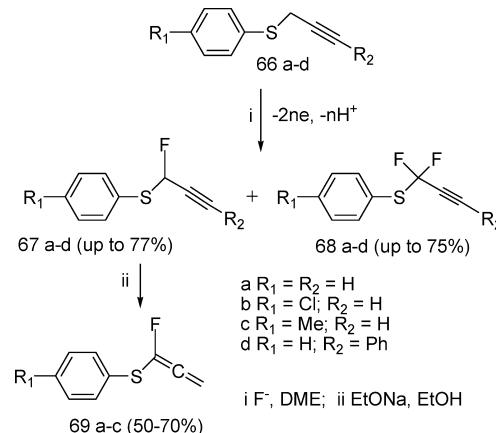
Scheme 35



base (Scheme 35). Structures 62–65 were confirmed by X-ray diffraction analysis.

When aryl propargyl sulfides 66 were subjected to electrochemical fluorination in dimethoxyethane (DME) using various fluoride supporting electrolytes in undivided cells, they selectively provided the corresponding α -monofluorinated 67 or α,α -difluorinated sulfides 68 in good yields. Unlike the α,α -difluorinated sulfides 68, which were stable enough to be isolated, α -monofluorinated compounds 67 were very unstable

Scheme 36



and readily converted to the corresponding stable α -monofluoroallenyl sulfides 69 (Scheme 36).⁵¹

The scope and reactivity of propargyl sulfides were explored in iron-catalyzed Doyle–Ando–Kirmse reaction with (trimethylsilyl)diazomethane (TMSD).^{36,52} Yields of the α -silyllallenyl sulfides were in the range of 70–90%. Thus, interaction of $\text{MeC}\equiv\text{CCH}_2-\text{S}-\text{C}_6\text{H}_4-4\text{-OMe}$ with $\text{Me}_3\text{SiCHN}_2/\text{CICH}_2\text{CH}_2\text{Cl}/(\text{dppe})\text{FeCl}_2$ gave allenyl compound $\text{H}_2\text{C}=\text{C}=\text{CHCH}(\text{SiMe}_3)-\text{S}-\text{C}_6\text{H}_4-4\text{-OMe}$ in 73% yield. Longer alkyne chains gave allene products in higher yields, presumably because they disfavor a second addition rearrangement. Also, it has been observed that addition of TMSD after the catalyst was premixed with the sulfide substrate gave significantly higher yields in a lower reaction time. This is apparently due to the fact that the sulfide may serve as an iron ligand. One possible mechanism for the iron-catalyzed Doyle–Ando–Kirmse reaction is that the diazo compound attacks the iron catalyst with a sulfide ligand migration to displace N_2 . Then α -silyllallenyl sulfide products are efficiently oxidized to give sulfones that have potential synthetic utility.

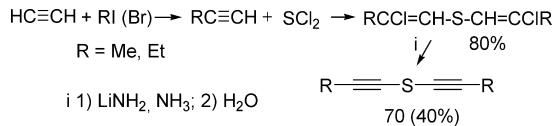
3. SYNTHESIS AND CHEMICAL PROPERTIES OF BISPROPARGYL, ALKYNYL PROPARGYL, AND BISALKYNYL SULFIDES

3.1. Synthesis of Dialkynyl Sulfides by the Reactions of Sulfur-Containing Reagents with Acetylenes

One of the perspective methods for the synthesis of organosulfur compounds is the interaction of sulfur or sulfur-containing reagents with acetylenes. Trofimov and Amosova⁵³ described a new method for sulfonation of acetylenes using sulfonation reagents (sulfur, hydrogen sulfide, sulfides and hydrosulfides of alkaline-earth metals, di- and polysulfides, carbon bisulfide, different thio systems, ethers/esters, and various thioacid salts) under extreme basic conditions.

Almost six decades ago, Brandsma and Arens successfully synthesized dialkyn-1-yl sulfides in liquid ammonia in the presence of lithium amide,^{54a} but due to the multistep route,

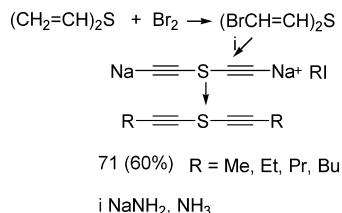
Scheme 37



the corresponding sulfides **70** were gained in relatively low yields ($\sim 40\%$) (Scheme 37).

Then the same authors^{54b} provided an additional synthetic method for the preparation of dialk-1-ynyl thioethers **71** in

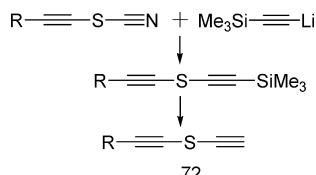
Scheme 38



higher yields through bromination of divinyl sulfide followed by dehydrobromination (Scheme 38).

Generally, the synthesis of alk-1-ynyl ethynyl sulfide analogues **72**, which are efficient precursors for heterocycle

Scheme 39



construction, was performed by the reaction of alk-1-ynyl cyano sulfides with lithiated acetylenic compounds (Scheme 39).⁵⁵

3.2. Synthesis of Dialkynyl Sulfides by Carbothiolation Reaction

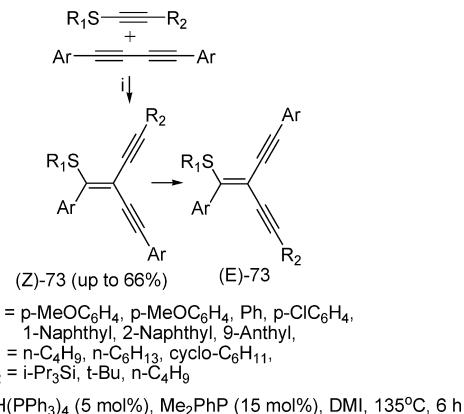
Arisawa et al.⁵⁶ obtained (*Z*)-4-(alkylthio)-4-aryl-3-(arylethynyl)-3-butene-1-yne **73** by carbothiolation reaction of 1-(alkylthio)-1-alkynes and 1,4-diaryl-1,3-butadiynes catalyzed by a rhodium complex derived from $\text{RhH}(\text{PPh}_3)_4$ and Me_2PhP . However, (*Z*)-isomers **73** slowly isomerized to (*E*)-**73** if maintained at room temperature (Scheme 40).

3.3. Dipropargyl Sulfide from Propargyl Bromide and Elemental Sulfur

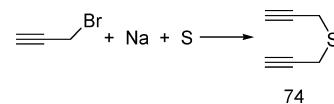
Also, a long time ago, Brandsma and Wijens⁵⁷ observed that when propargyl bromide and a mixture of sulfur and sodium in liquid ammonia are mixed, a rapid reaction occurs with the possibility of an explosion. Accordingly, portions of sodium and sulfur were gradually added to propargyl bromide, and the product dipropargyl sulfide (**74**) was immediately extracted in 60% yield (Scheme 41).

Later, they studied the reaction of propargyl bromide with elemental sulfur under various conditions, including a strong basic medium, phase transfer catalysis, hydrazine hydrate in the

Scheme 40

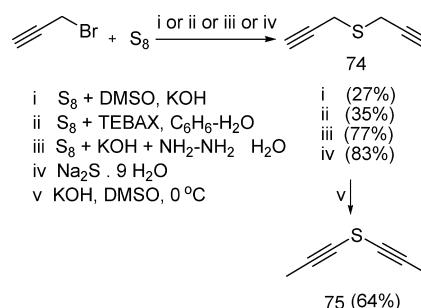


Scheme 41



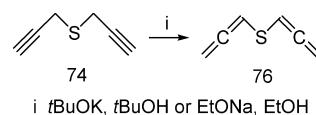
presence of potassium hydroxide, and sodium sulfide, which gave **74**.^{58a,b} A higher yield was obtained when propargyl bromide was reacted with sodium sulfide. Also, it was observed

Scheme 42



that **74** was easily isomerized to diprop-1-ynyl sulfide (**75**) in a strong base medium (KOH–DMSO) at 0°C (Scheme 42).

Scheme 43



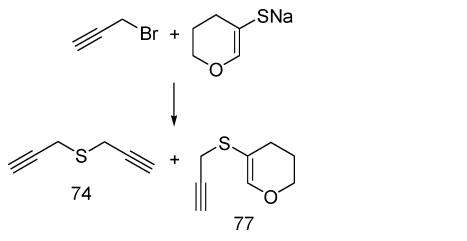
Isomerization of dipropargyl sulfide in a strong base medium produced diallenyl sulfide (**76**) (Scheme 43), which was also observed previously by Braverman et al.⁵⁹

74 was formed as a byproduct during the synthesis of 3-(propargylthio)tetrahydropyran (**77**) from propargyl bromide and sodium thiolate (Scheme 44).⁶⁰

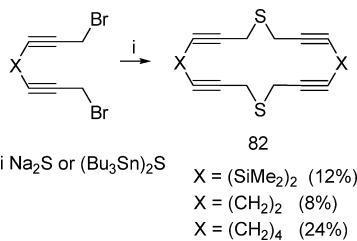
3.4. Synthesis of Propargyl Types' Cyclic Thioalkynes

Ensley et al.⁶¹ synthesized 4,17,30-trithia[73](1,3,5)cyclophane **79** by palladium-catalyzed coupling of tetrahydropyranyl ether with propargyl alcohol using 1,3,5-tribromobenzene followed by sulfide ring closure. Then the acetylenic sulfide intermediate

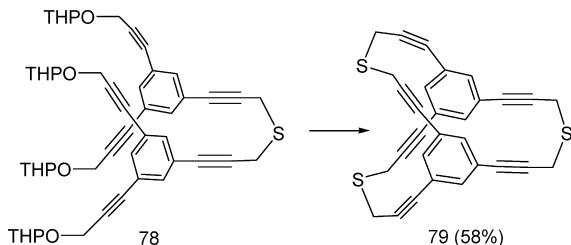
Scheme 44



Scheme 47



Scheme 45



78 was deprotected and reacted with sodium sulfide to afford 79 in good yield (Scheme 45).

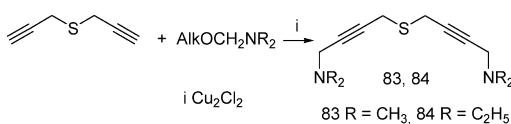
Braverman and coauthors⁶² synthesized various sulfur-bridged 13–30-membered cyclic dialkynes **80a–d** and tetraalkynes **81a–d** derived from 1,2-, 1,3-, and 1,4-dihydroxybenzene and 1,2-bis(bromomethyl)benzene as shown in Scheme 46. They confirmed their structures by X-ray crystallography.

Rausch et al.⁶³ employed another method for the synthesis of a series of macrocyclic tetraynes **82** with sulfur atoms in the propargylic positions of the triple bonds. This was accomplished either by reacting an α,ω -bis(propargyl bromide) with sodium sulfide under phase transfer conditions or by the reaction of the dibromide with (Bu₃Sn)₂S (Scheme 47).

3.5. Reactivity of the Acetylenic Hydrogens, Carbon–Carbon Triple Bonds, and Sulfur Atom in Dipropargyl Sulfide

Aminomethyl derivatives of dipropargyl sulfide were produced by reacting the latter with (alkoxymethyl)amines.⁶⁴ Thus, the synthesis of (dimethylamino)- and (diethylamino)methylated derivatives of sulfides **83** and **84** was described as well as some manipulations of the Mannich reaction which increased the

Scheme 48

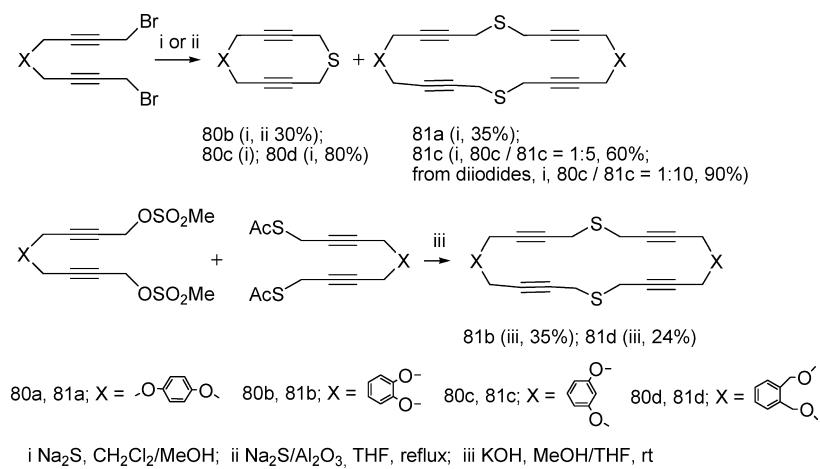


reaction yield of aminomethylated products (up to 74%) (Scheme 48).

In the same context, various chemical reactions of dipropargyl sulfide (**74**) (Scheme 49) were investigated utilizing the reactivity of the carbon–carbon triple bonds, acetylenic hydrogens, and sulfur atom.^{65–71} The reactivity of the acetylenic hydrogens of diprop-2-ynyl sulfide (**74**) under Mannich reaction conditions afforded the novel bis(aminobutynyl) sulfides **85a–e** by the interaction of **74** with the various amines (diethylamine, diisopropylamine, N-methylaniline, piperidine, morpholine) in dry 1,4-dioxane at 60 °C with a catalytic amount of copper(I) chloride.⁶⁶ Additional sulfur-containing compounds were also obtained by oxidation of **74** to sulfoxide **86** (95%) and sulfone **87** (90%) using hydrogen peroxide in acetic acid and acetone.⁶⁷ In addition, hydrogenation of **74** under Kucherov reaction conditions in diluted sulfuric acid and the presence of mercury sulfate gave 4-thiaheptane-2,6-dione (**88**).⁶⁶

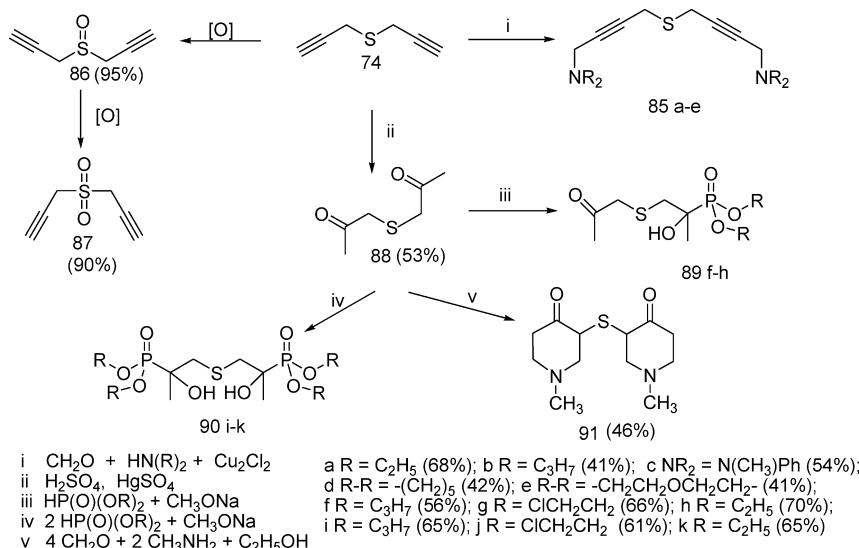
In addition, the reactivity of the resulting **88** was further studied under Abramov's reaction conditions.⁶⁸ The reaction of the sulfide and dialkyl phosphites (diethyl, dipropyl, and bis(β -chloroethyl) phosphites), which took place in the presence of sodium alcoholates, was dependent on the reagent ratio. The products monoalkyl phosphones **89f–h** and dialkyl phosphones **90i–k** were formed in good yields. In other studies, **88** was used in constructing various heterocycles, such as bis(1-

Scheme 46

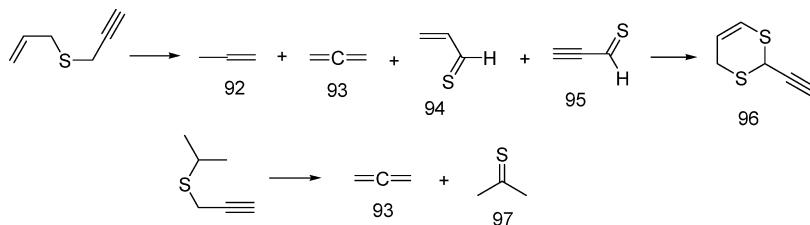


i Na₂S, CH₂Cl₂/MeOH; ii Na₂S/Al₂O₃, THF, reflux; iii KOH, MeOH/THF, rt

Scheme 49



Scheme 50



methyl-4-oxopiperidin-3-yl) sulfide (**91**), which were obtained by treatment of **88** with paraform and primary amines (ammonium acetate, ethylamine, propylamine, and butylamine, 25% methylamine aqueous solution).^{69,70} Interestingly, biologically active compounds were afforded among these products, particularly in growth-promoting activity.⁷¹

3.6. Pyrolytic Behavior of Propargyl Sulfides

Martin and co-workers^{72a} investigated the pyrolytic behavior of allyl propargyl and isopropyl propargyl sulfides in the gaseous phase in the temperature range of 312–402 °C. Under these conditions, a mixture of propene, allene, and propene- and propynethials (**92**–**95**) was generated, which in turn either polymerized or underwent intramolecular Diels–Alder reaction to give the cyclized product **96**. Additionally, pyrolysis of isopropyl propargyl sulfide resulted in formation of thioacetone (**97**) and allene (**93**) (Scheme 50).

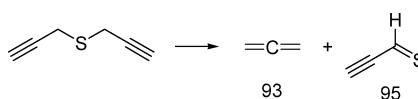
The same authors^{72b} studied pyrolysis of crotyl propargyl sulfide in a stirred-flow system over the same temperature range

(340–402 °C) and at pressures of 2–12 Torr, yielding olefins together with thioaldehydes (Scheme 51). The Arrhenius parameters were consistent with unimolecular mechanisms involving six-centered cyclic transition states.

A flash pyrolysis of dipropargyl sulfide gave $\text{HC}\equiv\text{CCHS}$. The IR spectra of the major isotopic species of $\text{HC}\equiv\text{CCHS}$ and $\text{HC}\equiv\text{CCHS}^3$ were obtained. The derived rotational constant for these species and the measured dipole moments of the component were used to eliminate any alternative structure during pyrolysis.⁷³

Conditions of selective thermal fragmentation of dipropargyl sulfide to propynethial (**95**) and allene (**93**) were optimized by

Scheme 52

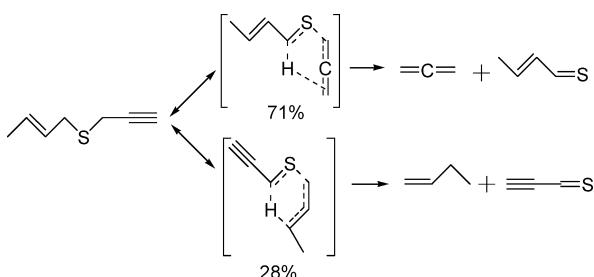


semiempirical methods based on surface energy calculation and photoelectron spectroscopy in the gaseous phase.⁷⁴ A suggested mechanism for this fragmentation is based on hydrogen atom intermolecular transfer (Scheme 52).

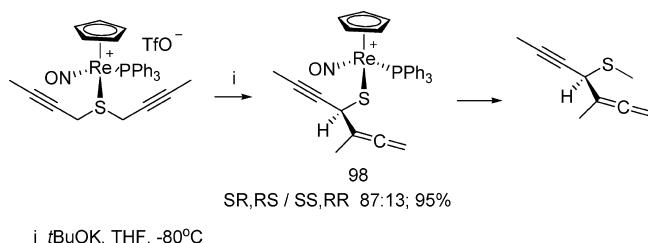
3.7. Enantioselective Synthesis of Organosulfur Compounds

The syntheses of various allyl (propargyl) alkyl (aryl) sulfide complexes were reported by Gladysz et al.,^{75a,b} including sulfide complex **98**, which was obtained in 95% yield (with 87:13 enantioselectivity) as shown in Scheme 53. The chiral Re-containing Lewis acid $[(\eta_5-\text{C}_5\text{H}_5)\text{Re}(\text{NO})(\text{PPh}_3)]^+$ not only was a highly effective auxiliary for asymmetric synthesis of

Scheme 51



Scheme 53



diallyl, dipropargyl, and dibenzyl sulfides but also was easily recovered with retention of configuration. Addition of *t*-BuOK to the air-stable cationic sulfide adducts gave neutral thiolate complexes with high diastereomeric selectivity according to their crystalline structural data. In addition, the thiolate ligands can be S-alkylated and detached as sulfides with a high enantiomeric ratio.

4. CYCLIZATIONS OF PROPARGYL SULFIDES, SULFOXIDES, AND SULFONES

Propargyl sulfides of arenes and heteroarenes are increasingly used for the syntheses of sulfur-containing heterocyclic compounds which provide additional synthetic methods for thiopyran and thiophene derivatives.

4.1. Formation of Thiophene Derivatives

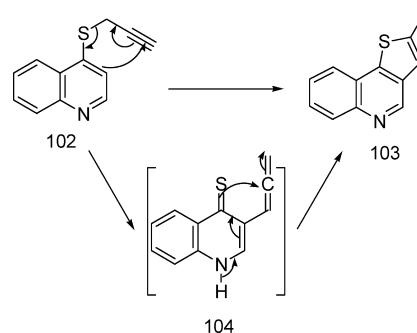
Rearrangement of alk-1-ynyl alk-2-ynyl sulfides was done at room temperature ($R' = H$) or by heating ($R' = \text{alkyl}$) with either dialkylamines or dialkylphosphines.⁷⁶ In the presence of dialkylamines the rearrangement started at 10–20 °C to give methylthiophene 101 (Scheme 54). However, a gummy mixture was obtained as a result of polymerization of allenyl and dienyl thioamides 99 and 100 and methylthiophene 101 in the presence of dialkylphosphines.

Makisumi and Murabayashi showed that propargyl 4-quinolyl sulfide (102) underwent thio-Claisen rearrangement.⁷⁷ Thus, 2-methylthieno[3.2-*c*]quinoline (103) was obtained in 80% yield when propargyl sulfide 102 was heated to 200 °C for 2 h in dimethylaniline. It was proposed that the formation of 103 by the thermal rearrangement of sulfide 102 was interpreted as a novel [3,3]-sigmatropic rearrangement of aryl propargyl sulfide to give 3-allenyl-4(1*H*)-quinolinethione (104), which can undergo prototropic cyclization (Scheme 55).

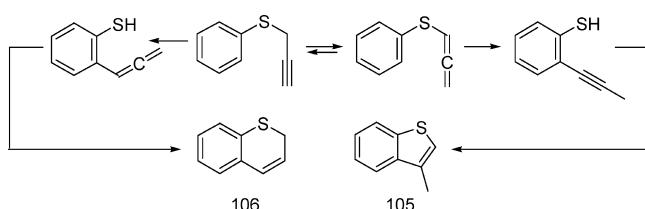
Kwart and George⁷⁸ did a comprehensive study on the cyclization of phenyl propargyl sulfide to 3-methylbenzothiophene (105) and benzothiopyran (106) as shown in Scheme 56. Phenyl propargyl sulfide in quinoline medium at 200 °C was selectively converted to 3-methylbenzothiophene by thio-Claisen rearrangement through allenyl phenyl sulfide, but benzothiopyran was also detected at temperatures above 250 °C.

A thermal rearrangement of aryl propargyl sulfoxides 107 and 109 to dihydrobenzothiophenes 108 and dihydronaph-

Scheme 55



Scheme 56



thothiophenes 110 has been discussed with a comprehensive description of all the intermediates^{79a,b} (Scheme 57). Initially, [2,3]-sigmatropic rearrangement of sulfoxide 107 to the unstable allene intermediate containing a S–O bond took place followed by [3,3]-sigmatropic rearrangement, which led to dihydrobenzothiophenes 108 and dihydronaphthothiophenes 110.

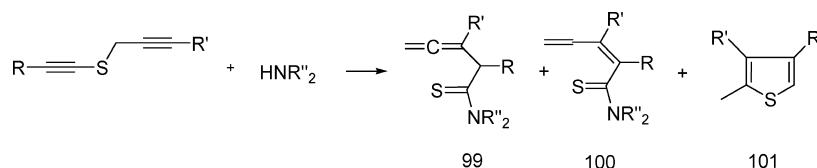
The rearrangements of (propargylthio)benzimidazoles 111 and 114 led to the formation of tricyclic compounds 112, 113, and 115⁸⁰ (Scheme 58).

Anisimov and Viktorova⁸¹ utilized thio-Claisen rearrangement of allyl and propargyl sulfides for the synthesis of heterocyclic compounds. Accordingly, the synthesis of thienofuran 116 from 2-(propargylthio)furan using subsequent intramolecular Diels–Alder reaction was well investigated⁸² (Scheme 59).

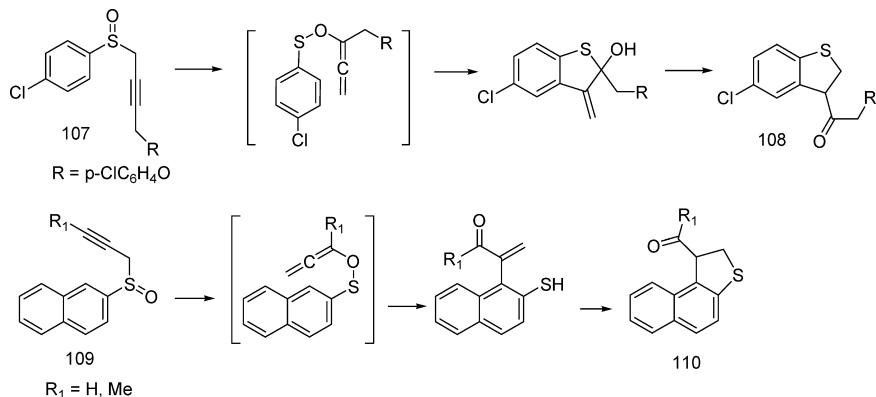
On the other hand, the product 3-methylene-2,3-dihydrobenzo[*b*]thiophene (117) was obtained by Pd-catalyzed cyclization of *o*-iodophenyl propargyl sulfide, which in turn reacted with an enophyl as shown in Scheme 60.⁸³

Schwan and co-workers⁸⁴ described transition-metal-free cyclization of benzyl 1-alkynyl sulfides. This base-induced reaction proceeded without the necessity for activating the electron-withdrawing substituents which are directly bonded to the carbon skeleton. The 2,3-dihydrothiophene products 118 were readily transformed to 2-arylthiophenes 119 (Scheme 61). The authors were assisted by a computational study to understand the cyclization mechanism and suggested that the intermediate allenyl tautomer possessed a lower benzylic proton affinity than the propargyl moiety, favoring the base-induced cyclization of the former.

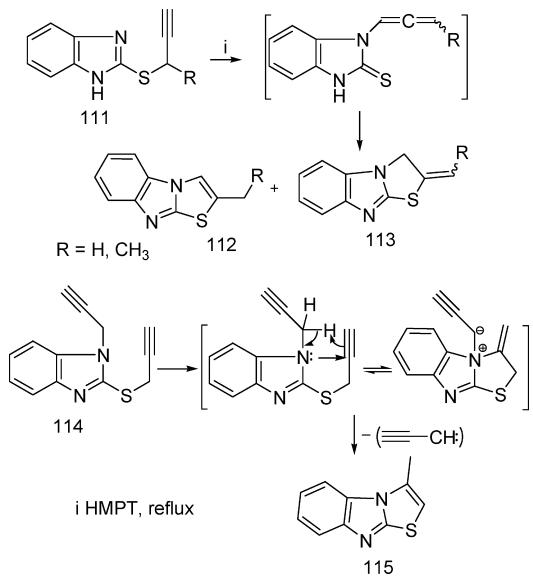
Scheme 54



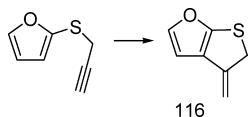
Scheme 57



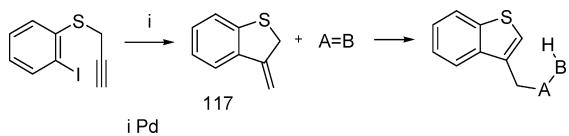
Scheme 58



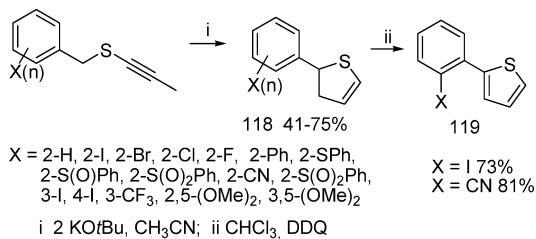
Scheme 59



Scheme 60

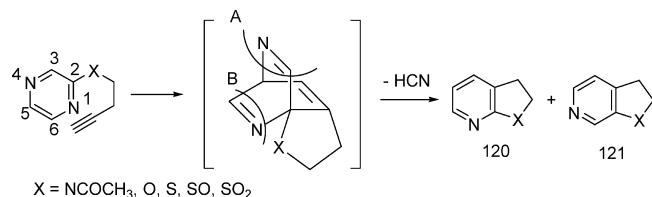


Scheme 61



Cyclization ofaza- or diazacyclic ethers of propargyl heteroatomic derivatives was carried out at high temperature in acidic media in numerous studies.^{85,86} Thus, heating of pyrazines with an *ω*-alkynyl substituent in nitrobenzene or cumene resulted in an intramolecular Diels–Alder reaction.⁸⁷ Pyrazines with an electron-donating substituent X on the side chain preferentially produced [c]-annulated pyridines, whereas the pyrazines with an electron-withdrawing group X gave [b]-annulated pyridines. The authors proposed that the reaction proceeded through intermediates resulting from [2 + 4]-

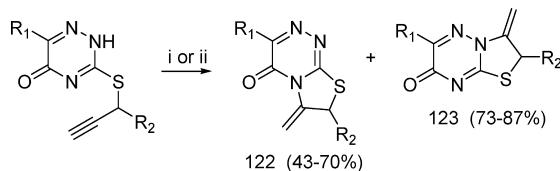
Scheme 62



cycloaddition of the C≡C group and fragment C(2)N(1)-C(6)C(5) of the pyrazine cycle. Splitting off HC(3)N(4) (route A) or HC(6)N(1) (route B) afforded the annulated products 120 and 121, respectively (Scheme 62).

Palladium(II) complexes selectively catalyzed cyclization of 3-(propargylthio)-1,2,4-triazin-5(2*H*)-ones in boiling acetoni-

Scheme 63

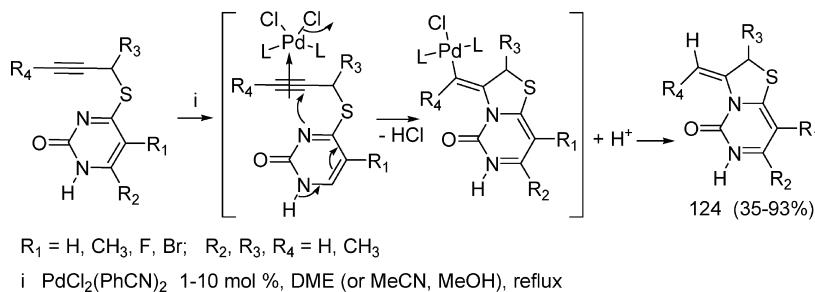


i PdCl₂(PhCN)₂ 2-5 mol %, MeCN or DME, reflux.
ii NaOH 10-50 mol %, MeOH, reflux.

trile or DME to the *regio* isomers thiazolo[1,2,4]triazinones 122. Interestingly, the *regio* isomers 123 were obtained as sole products when sodium hydroxide was used as a catalyst in boiling methanol⁸⁸ (Scheme 63).

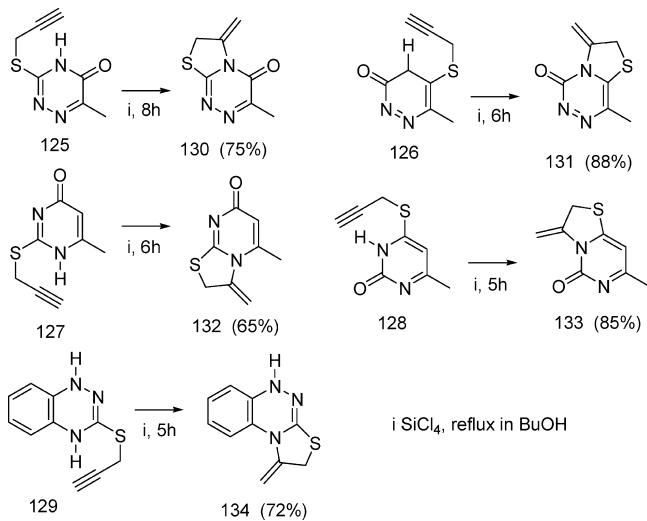
Similarly, 4-(propargylthio)pyrimidin-2(1*H*)-ones were cyclized and transformed to thiazolopyrimidin-5-ones 124 in

Scheme 64



good yields by intramolecular nucleophilic addition in the presence of a palladium catalyst (Scheme 64).⁸⁹

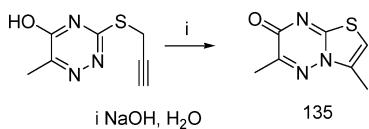
Scheme 65



Silicon tetrachloride-catalyzed intramolecular cyclization reaction of acetylenic fragments in the substrates 125–129 resulted in condensed thiazoles 130–134 in good to high yields (Scheme 65).⁹⁰

Regioselective isomerization of 6-substituted 5-hydroxy-3-(propargylthio)-1,2,4-triazine to the sole isomer 135 was also achieved by sodium hydroxide catalysis. This regioselectivity

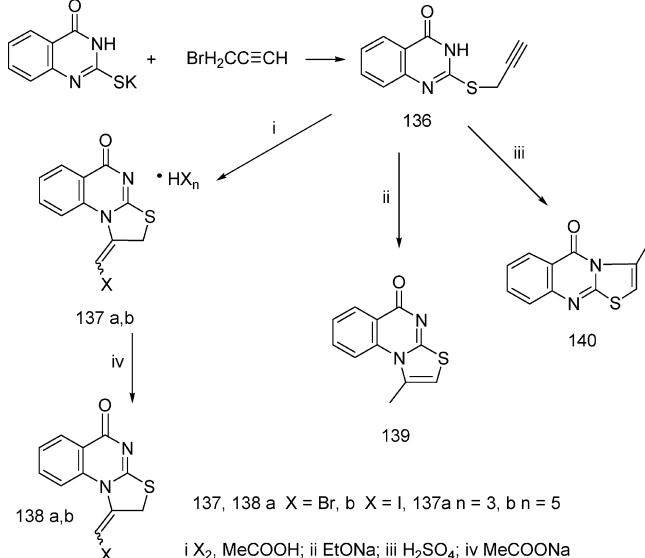
Scheme 66



is evidence that the isomerization happened directly through propynyl rearrangement. The product structure was confirmed by NMR spectroscopy ($^1H/^{15}N$ HMBC spectra) (Scheme 66).⁹¹

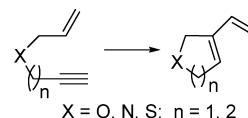
To develop an alternative method for the synthesis of thiazoloquinazolinone derivatives, Zborovskii et al.⁹² studied heterocyclization of 2-(propargylthio)quinazolin-4-ones by treatment with a number of electrophilic and nucleophilic reagents which enabled the production of condensed heterocyclic systems with both linear and angular structures (Scheme 67). Thus, it was described that the reaction of quinazolinone 136 with bromine or iodine in acetic acid

Scheme 67



produced the angular 2-(halomethylidene)-dihydrothiazoloquinazolin-5-ones 137a,b. Treatment of the latter with an aqueous solution of sodium acetate yielded the corresponding bases 138a,b. Such cyclization can also be carried out by treatment with sodium ethoxide in which the angular structure product thiazoloquinazolinone 139 was formed. However, when concentrated sulfuric acid was used, thiazoloquinazolinone 140 with a linear structure was obtained. This variation in products is due to the differences in the mechanistic courses.

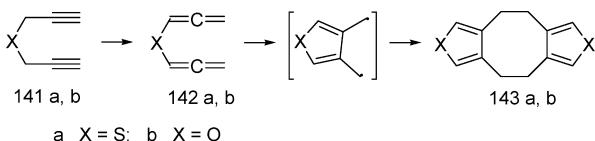
Scheme 68



Majumdar et al.⁹³ described the formation of five- and six-membered heterocyclic rings of various compounds, including sulfides, by intramolecular cyclization through enyne metathesis (Scheme 68).

Braverman et al.⁹⁴ showed that isomerization of dipropargyl sulfide (141a) to diallenyl sulfide (142a) occurred readily upon treatment of 141a with freshly prepared *t*-BuOK in *t*-BuOH at 0 °C. The authors observed that compound 142a was unstable and gradually dimerized to bisthiocyclooctadiene 143a. The same product was also obtained (20–30% yield) when dipropargyl sulfide was treated with basic activated alumina

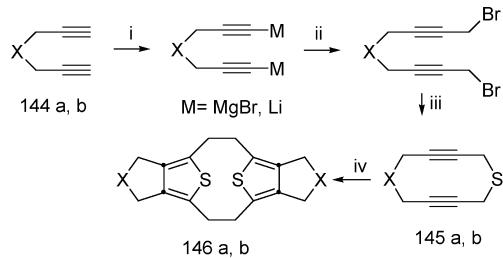
Scheme 69



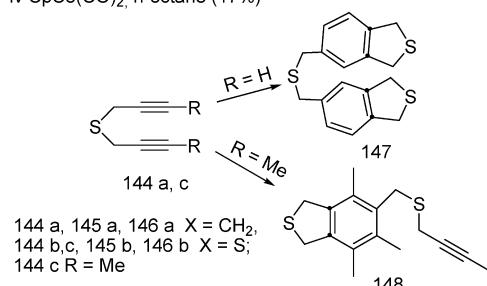
and sodium ethoxide in ethanol at 50 °C as well as under other base-catalyzed conditions (Scheme 69).

Gleiter and Rittinger^{95a} reported the synthesis of thia- and dithiadecadiynes **145a** and **145b** via a cyclization sequence of diynes **144a,b**. Oligomerization of **145a** and **145b^{95b}** with catalytic as well as stoichiometric amounts of CpCo(CO)₂ was done in refluxed *n*-octane to yield the [2,2](2,5)-

Scheme 70



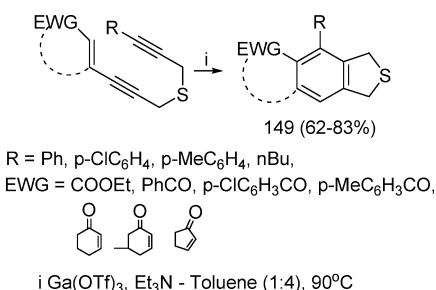
i CH₃MgBr or BuLi, ii 1) CH₂O; 2) PBr₃; iii (145 a) : Na₂S·9H₂O, Cs₂CO₃, C₆H₆, EtOH (38%)
iii (145 b) : (Bu₃Sn)₂S, CsF, 18 crown 6, CH₃CN (36%)
iv CpCo(CO)₂, n-octane (17%)



thiophenophane derivatives **146a,b**. Under different reaction conditions, dipropargyl sulfide (**144b**) and dibut-2-diynyl sulfide (**144c**) led to the anticipated [2 + 2 + 2]-cycloaddition products **147** and **148** (Scheme 70).

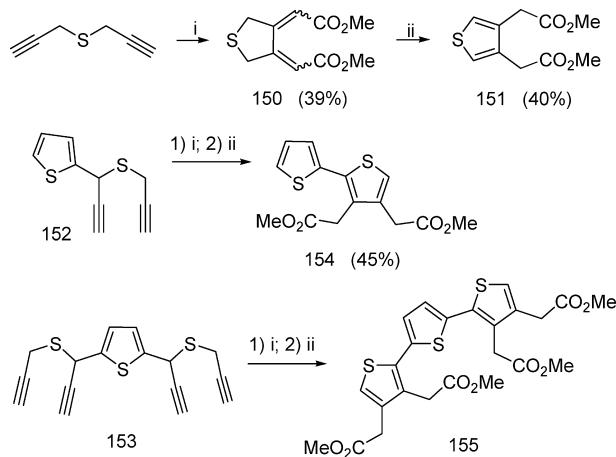
Zhou et al.⁹⁶ developed Ga(OTf)₃-promoted sequential reactions via sulfur-assisted propargyl–allenyl isomerizations and intramolecular [4 + 2]-cycloaddition for the synthesis of 1,3-dihydrobenzo[c]thiophenes **149** in moderate to good yields under mild conditions (Scheme 71).

Scheme 71



Fasio et al.⁹⁷ synthesized 3,4-bis[(methoxycarbonyl)methylene]tetrahydrothiophene (**150**) as a mixture of (Z,Z)-

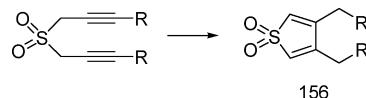
Scheme 72



i CO (15-20 atm), MeOH, air, PdI₂, KI, 40-70°C, 4.5 - 15h
ii Et₃N, 60°C, 3 h

and (*E,Z*)-isomers which rearranged to 3,4-bis[(methoxycarbonyl)methyl]thiophene (**151**) in good yields using diprop-2-ynyl sulfide transformations (Scheme 72). The same sequence of oxidation, dicarbonylation, and isomerization was studied on 2-[1-(prop-2-ynylthio)prop-2-ynyl]thiophene (**152**) and 2,5-bis[1-(prop-2-ynylthio)prop-2-ynyl]thiophene (**153**) and (**154**) and (**155**) were gained in moderate yields.

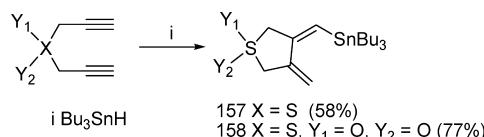
Scheme 73



(**153**) in which the novel bis- and terthiophene derivatives **154** and **155** were gained in moderate yields.

Isomerization and cyclization of dipropargyl sulfone resulted in the production of pharmacologically active products **156**, which possessed potential antitumor activity (Scheme 73).⁹⁸

Scheme 74

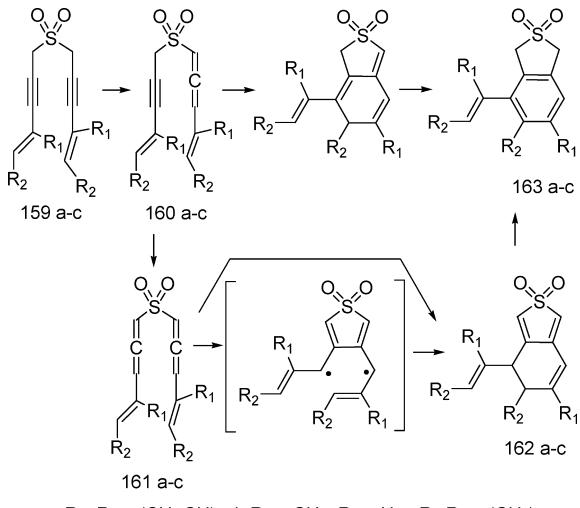


Lautens et al.⁹⁹ carried out the cyclization of dipropargyl sulfide and its sulfone in the presence of the homogeneous catalyst Bu₃SnH. As a result, 3,4-dialkylidenetetrahydrothiophenes **157** and **158** were obtained in good yields (Scheme 74).

Braverman et al.¹⁰⁰ showed that the base-catalyzed rearrangements of dipropargyl selenides, sulfides, sulfoxides, and sulfones conjugated in their γ -positions to the substituted carbon–carbon double bond led to polycyclic aromatic (dihydrobenzo- or naphtha[c]selenophenes, -thiophenes, -thiophene S-oxides, and -thiophene S,S-dioxides) products.¹⁰¹ Thiophene dioxide intermediates **163b,c** formed by a mild tandem isomerization/

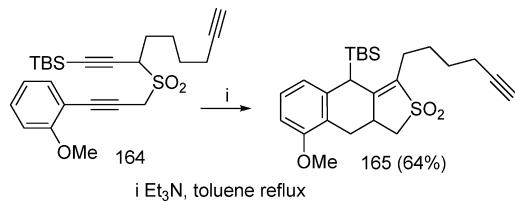
cyclization/aromatization of bis(π -conjugated propargyl) sulfones **159a–c** to dihydrothiophene dioxides **163a–c**. Other

Scheme 75



monoallene (**160b,c**) and diallene (**161b**) intermediates were also detected by NMR analysis. A kinetic study of rearrangements of dipropargyl sulfones **159a–c** revealed that the unusual facile tandem process was highly dependent on the nature of γ -substitution (Scheme 75).

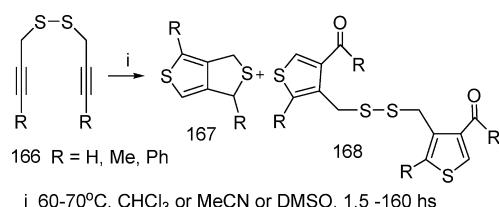
Scheme 76



Base-mediated bicyclization of unsymmetrical dipropargyl sulfone **164** gave dihydroisobenzothiophene dioxide **165** through a presumed diradical intermediate (Scheme 76). However, attempts to trap a putative thiophene dioxide via Diels–Alder reaction with a pendant alkyne were unsuccessful.¹⁰²

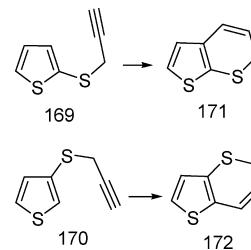
Braverman et al.¹⁰³ found that dipropargylic disulfides **166** can rearrange and cyclize under mild thermal conditions. The reaction involved elusive thiosulfoxide intermediates and produced novel thienothiophene (**167**) and thienyl disulfide (**168**) derivatives in 40–80% yields. The selectivity was dependent on the reaction conditions; i.e., increasing the

Scheme 77



polarity of the solvent not only enhanced the reaction but also increased the yield of **168** (Scheme 77).

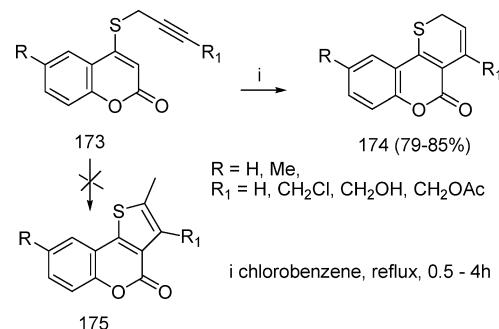
Scheme 78



4.2. Formation of Thiopyran Derivatives

Thio-Claisen rearrangement of both 2-(propargylthio)-thiophene (**169**) and 3-(propargylthio)thiophene (**170**) in HMPT or DMF at 170–180 °C led to the formation of thiophenothiopyrans **171** and **172** in good yield¹⁰⁴ (Scheme 78).

Scheme 79



Majumdar and Ghosh¹⁰⁵ reported a regioselective synthesis of 2*H*-thiopyrano[3,2-*c*][1]benzopyran-5-ones **174** in high yields by thio-Claisen rearrangement of 4-(propargylthio)[1]benzopyran-2-ones **173**. Under the common thermal rearrangement conditions, propargyl sulfide **173** preferentially yielded **174** without detection of any traces of other isomers **175** (Scheme 79).

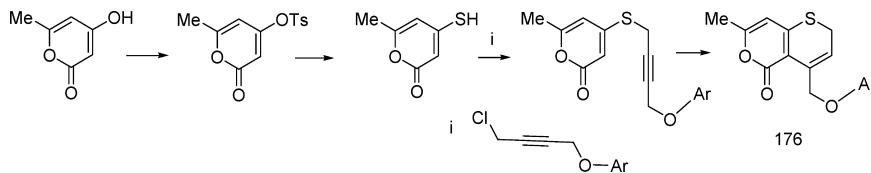
In addition, cyclization of [((aryloxy)but-2-ynyl)thio]pyrans was investigated by the same authors.^{106a,b} They obtained the starting acetylene product by the reaction of 4-mercapto-6-methylpyran-2-one with 1-(aryloxy)-4-chlorobut-2-yne at room temperature in the presence of benzyltriethylammonium chloride as a phase transfer catalyst. Then annulation was carried out in chlorobenzene at 131–132 °C for 5 h to yield **176** (Scheme 80).

A suggested mechanism of the thermal cyclization is shown in Scheme 81, in which the major step was [3,3]-sigmatropic rearrangement.

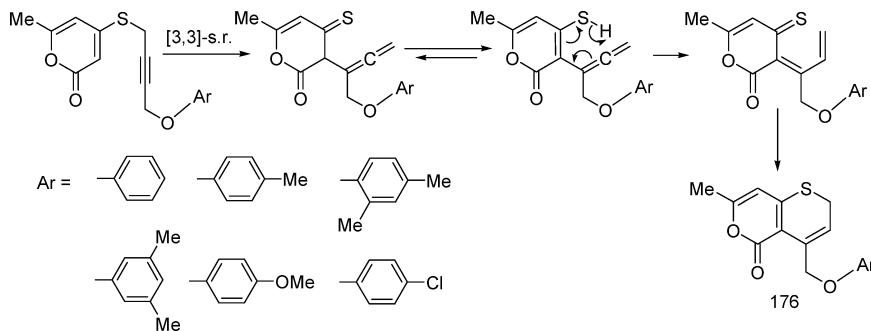
Similarly, Claisen's rearrangement of indol-2-yl propargyl sulfide gave 4-(aminomethyl)tetrahydrothiopyrano[2,3-*b*]-indole **177**, which showed high analgesic activity.¹⁰⁷ A detailed mechanism of the cyclization process was also proposed (Scheme 82).

Thiopyran derivatives **179** and **180** were obtained in high stereoselectivity by Pd-catalyzed sulfinylzincation of diarynes **178**¹⁰⁸ (Scheme 83).

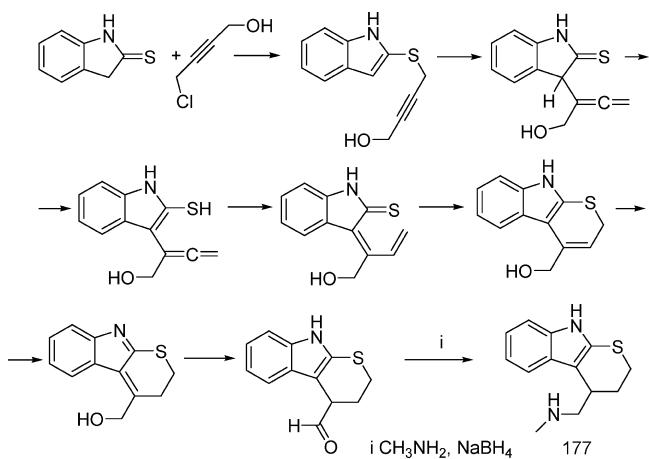
Scheme 80



Scheme 81



Scheme 82



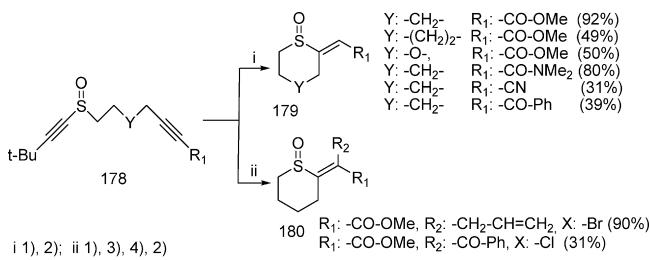
Scheme 84

R_1 ,	R_2 ,	R_3	%, yield
I,	H,	Me	66
I,	H,	nBu	61
Br,	H,	Me	55
Me,	H,	Me	13
CF ₃ ,	H,	Me	51
O <i>i</i> Pr,	H,	Me	47
Ph,	H,	Me	80
H,	Ph,	Me	71
2-thienyl,	H,	Me	69
H,	Ph,	nBu	91

R_2 ,	R_3	%, yield
Ph,	nBu	83
H,	Ph	80
Ph,	Ph	90
H,	Me	83

i 1) LDA, -78°C, 2) warm to rt over 45 min

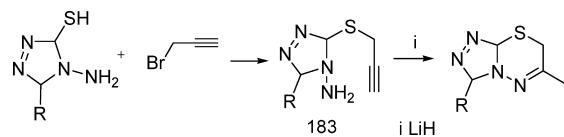
Scheme 83



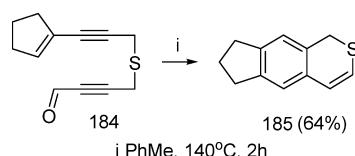
Hossain and Schwan¹⁰⁹ demonstrated a new lithium diisopropylamide (LDA)-induced conversion of benzyl 1-alkynyl sulfones to 1*H*-2-benzothiopyran S,S-dioxides 181. A benzyl carbanion is believed to cyclize by temporary disruption of aromaticity according to the intermediates detected by FTIR analysis. Similarly, thiophene derivatives successfully cyclized to 7*H*-thieno[2,3-*c*]thiopyran S,S-dioxides 182 (Scheme 84).

Propynyl sulfide 183 was obtained by the reaction of 5-substituted 4-amino-3-mercaptop-1,2,4-triazole with propargyl

Scheme 85



Scheme 86

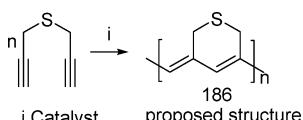


bromide, which upon lithiation with lithium hydride produced 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine¹¹⁰ (Scheme 85).

Mikami et al.¹¹¹ primarily established the cyclization of 10-(2,4-ene conditions to afford the bicyclic subunit of the neocarzinostatin chromophore, which triggers in tandem the Bergman cycloaromatization reaction. Therefore, thermal

cyclization of cyclopentenylthiaoctadiynal (**184**) in toluene in a sealed tube gave indenothiopyran (**185**) (Scheme 86).

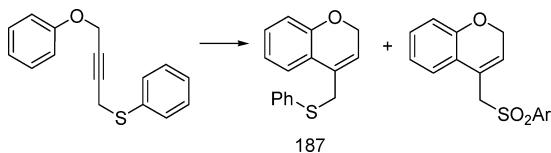
Scheme 87



Another W and Co catalytic method for cyclopolymerization of dipropargyl sulfide was obtained from potassium sulfide and propargyl bromide in a water–methanol medium.¹¹² Thus, polymerization of dipropargyl sulfide using WCl_6 - and MoCl_5 -based catalysts under various reaction conditions was investigated, and a polymer with the proposed structure **186** was afforded (Scheme 87). The yields of various MoCl_5 -based catalysts were in the range of 24–61%, whereas higher yields were obtained when WCl_6 was used under the same conditions (i.e., 91%).¹¹³

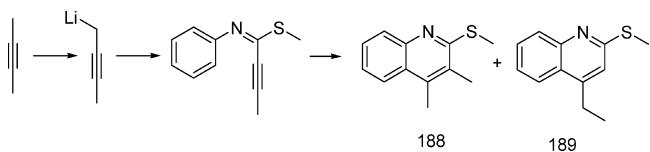
The regio- and stereoselective cyclopolymerizations of different diarynes using Mo catalysts were also studied. Various

Scheme 88



heterocyclic polymerization products were gained using different dipropargyl structures, including dipropargylaniline, dipropargyl sulfide, 1,8-diethynylnaphthalene, and 1,2-diethynyltetramethylsilane. In addition, the electrical conductivity and thermal stability of the products were investigated.¹¹⁴

Scheme 89



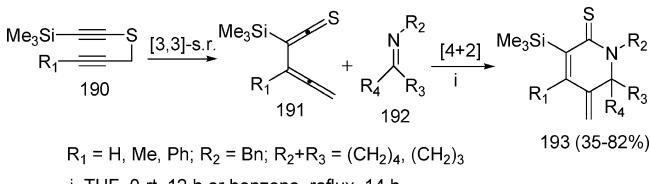
4.3. Formation of Other Cyclic Organosulfur Compounds

Mercury catalyzed the cyclization of 1-phenoxy-4-(phenylthio)-but-2-yne in acetic acid, which produced 4-[(phenylthio)methyl]chromene (**187**) rather than the thiochromene *regio* isomer (Scheme 88).¹¹⁵

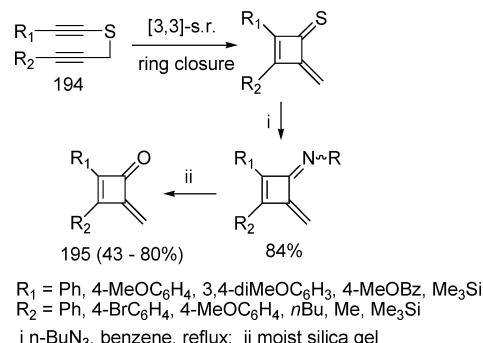
The synthesis of 2-(methylthio)quinolines **188** and **189** was performed with lithiated acetylenes and phenyl isothiocyanate.¹¹⁶ Therefore, acetylenic thioimine which was obtained by metalation of but-2-yne followed by addition of phenyl isothiocyanate in the presence of methyl iodide was cyclized to the corresponding quinolines **188** and **189** upon heating at 100 °C in 70% overall yield (Scheme 89).

Aoyagi et al.¹¹⁷ reported that allenyl(trimethylsilyl)-thioketenes **191**, which were generated *in situ* through [3,3]-

Scheme 90

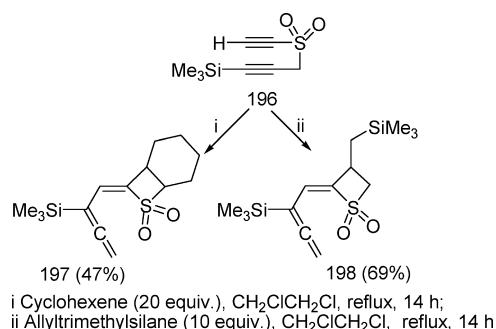


Scheme 91



sigmatropic rearrangement of (trimethylsilyl)ethynyl propargyl sulfides **190** underwent a facile [4 + 2]-cycloaddition with

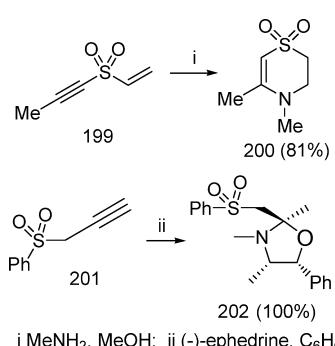
Scheme 92



imines **192** to afford the corresponding thiolactams **193** in good to high yields (Scheme 90).

Then the same authors¹¹⁸ showed that thermal rearrangement of alk-1-ynyl propargyl sulfides **194** in the presence of *n*-butyl azide followed by moist silica gel treatment gave 4-methylenecyclobutenones **195** in moderate yields (Scheme 91).

Scheme 93

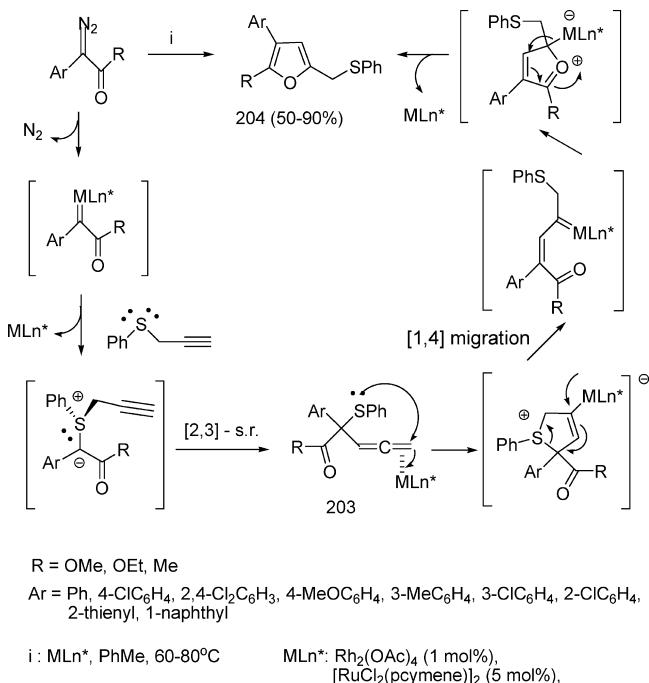


i MeNH_2 , MeOH ; ii $(-)$ -ephedrine, C_6H_6

Thermal rearrangement of ethynyl propargyl sulfone **196** in the presence of cyclohexene (20 equiv) in refluxing 1,2-dichloroethane afforded the cycloadduct **197**. Under similar conditions, but using 10 equiv of allyltrimethylsilane instead of cyclohexene, furnished the [2 + 2]-cycloadduct **198** in high yield (Scheme 92).¹¹⁹

Doubly conjugated addition of amines to bifunctional acetylenic sulfones such as **199** took place to afford the cyclic product **200**.¹²⁰ Also, chiral cyclic amine **202** was formed by

Scheme 94



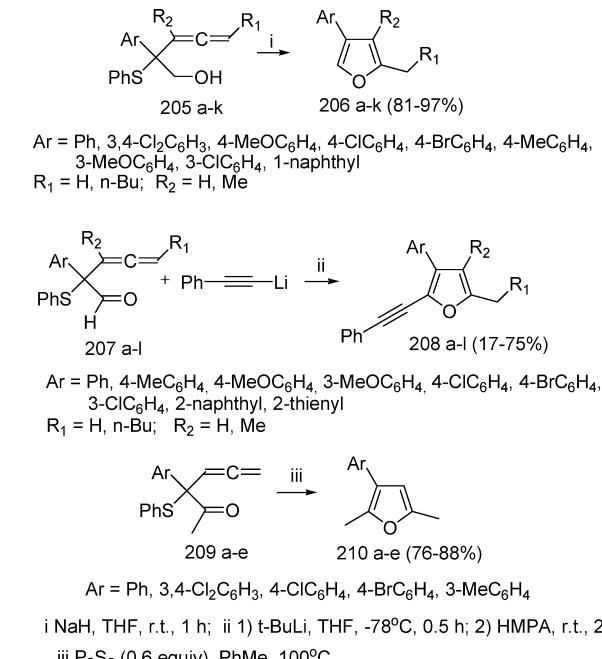
double Michael additions of (*−*)-ephedrine to propargyl sulfone **201** or to the corresponding allenyl and 1-propynyl derivatives (Scheme 93).^{120c}

Allenyl sulfides **203**, which were obtained from the [2,3]-sigmatropic rearrangement of sulfonium ylides (originally generated from rhodium(II) carbene and phenyl propargyl sulfide) were further utilized in Ru(II)-catalyzed reaction to give furan derivatives through 1,4-migration of the sulfonyl group and formation of ruthenium carbene intermediates. This method is considered a unique one-pot sequential catalytic transformation of α -diazocarbonyl compounds to furan derivatives **204** (Scheme 94).¹²¹

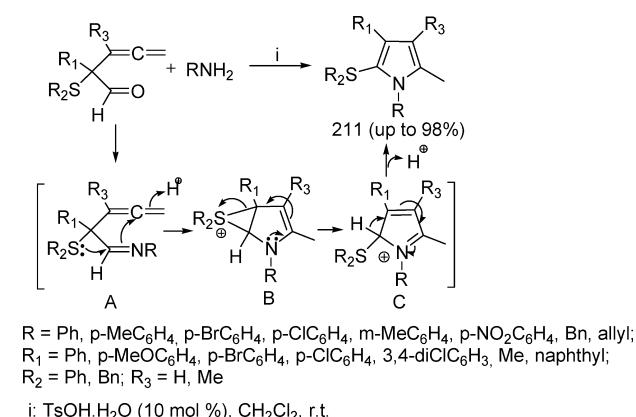
Then Peng et al.¹²² reported the synthesis of multisubstituted furan derivatives **206a–k**, **208a–l**, and **210a–e** from various classes of allenic sulfides **205a–k**, **207a–l**, and **209a–e**, respectively. Furan products **206a–k** were generated by the reaction of β -hydroxyl allenic sulfides **205a–k** with NaH through the elimination of the phenylthio group in excellent yields. β -Aldehyde allenic sulfides **207a–l** gave the more substituted furan products **208a–l** upon treatment with *n*-BuLi. β -Ketone allenic sulfides **209a–e** were also cyclized but with the promotion of P₂S₅ to give furan derivatives **210a–e** (Scheme 95).

The same authors¹²³ developed an acid-promoted cyclization reaction of thioallenic aldehydes with amines which gave various 2-thio-substituted pyrrole products **211** in good to excellent yields (Scheme 96). Lewis acids such as BF₃·Et₂O,

Scheme 95



Scheme 96

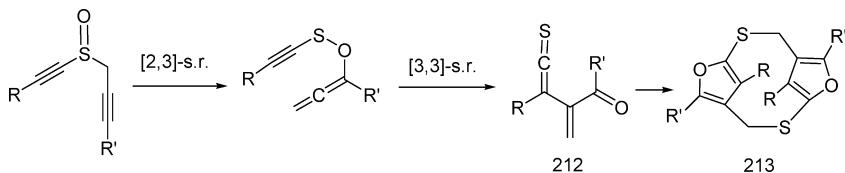


AuCl, and AgOTf and protonic acids such as TsOH·H₂O and HCl enhanced the reaction. The authors proposed that imine intermediates A were initially generated by the reaction of thioallenic aldehydes with amine followed by nucleophilic attack of the thiophenyl group on the imine to form intermediate B, which rearranged to intermediate C. Then deprotonation of C furnished pyrrole **211**. This reaction for providing such a class of substituted pyrroles is also considered of particular interest.

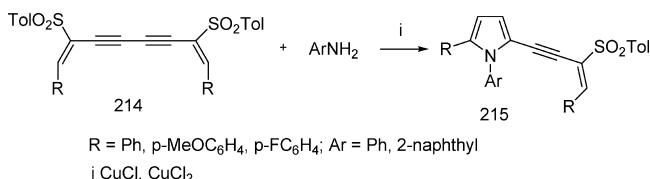
The (α -ketovinyl)thioketenes **212** were synthesized by a thermal reaction of alkynyl propargyl sulfoxides through tandem [2,3]/[3,3]-sigmatropic rearrangement. These products were successfully utilized in the synthesis of furanophane compounds **213** (Scheme 97).¹²⁴

Another interesting reaction for the construction of a pyrrole ring was developed.¹²⁵ Thus, when 1,8-disubstituted 2,7-bis(*p*-tolylsulfonyl)-1,7-octadiene-3,6-dynes **214** were treated with an aniline derivative in the presence of cuprous chloride (1.6 equiv) and cupric chloride (0.16 equiv) in DMF at 90 °C, they were regioselectively converted to a 1-arylpyrrole skeleton (**215**) in a reasonable yield. It is worth noting that only half of

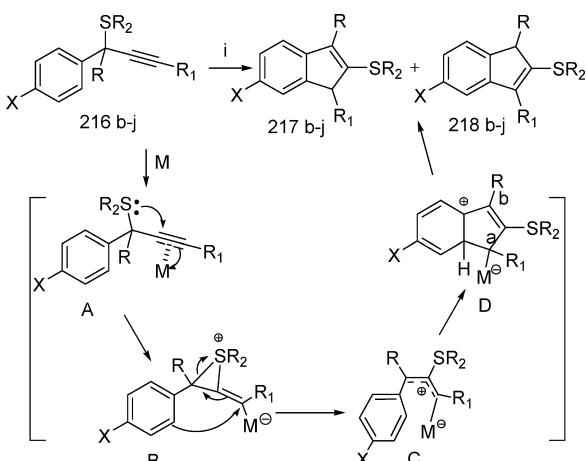
Scheme 97



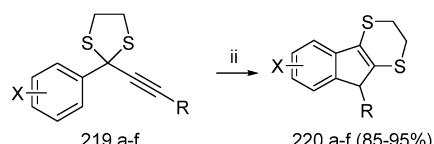
Scheme 98



Scheme 99



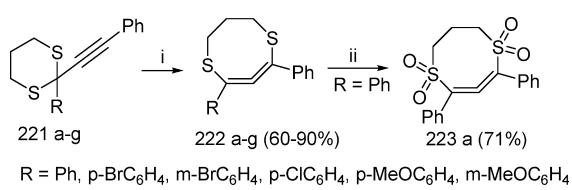
R = Me, H; R₁ = H, Me, CO₂Et;
 R₂ = o-C₆H₄, 2-naphthyl, Bn, CH₂C₆H₄Cl-o, Ph;
 X = H, Br



the 214 molecule was involved in the annulation reaction (Scheme 98).

Aryl propargylic sulfides 216a–j and aryl alkynyl dithioacetals 219a–f were found to undergo intramolecular cyclization when catalyzed by transition-metal catalysts such as AuCl,

Scheme 100



AuCl₃, and PtCl₂, affording indene derivatives 217a–j, 218a–j, and 220a–f in high yields through pentannulation of the aromatic rings.¹²⁶ The reaction presumably involves a three-centered trienium intermediate (**B**) followed by metal carbene **C** and cyclic intermediate **D**. Demetalation and proton transfer to the *a* or *b* position furnished 217a–j and 218a–j, respectively (Scheme 99).

In the same context, Wang et al.¹²⁷ reported a novel rearrangement of propargylic dithioacetals 221a–g catalyzed by Au(PPh₃)Cl/AgSbF₆, which formed 1,5-dithio-substituted cyclic allenes 222a–g in good yields (Scheme 100). This novel structure of eight-membered 1,5-dithio-substituted cyclic allenes is stable enough to be characterized by X-ray crystallography. Then it was observed that cyclic allene 222a can be easily oxidized to the corresponding sulfone 223a.

5. APPLICATIONS OF PROPARGYL SULFIDES

5.1. Industrial Applications of Propargyl Sulfides

Not only are synthetic organosulfur compounds widely used,^{128–130} but also natural sulfur-containing compounds are applied in various fields.^{131–133} They have many industrial applications.¹³⁴ For instance, in 1959 the Dow Chemical Co. patented dipropargyl sulfide for corrosion resistance for black metals in aqueous acidic media. It was proved that a 0.4% content of dipropargyl sulfide almost completely prevented corrosion in acetic, sulfuric, and phosphoric acids.¹³⁵ Another study devoted to the investigation of the electrical conductivity of poly(propargyl sulfide) and poly(dipropargyl ester/ether) with iodine additives showed that the electrical conductivity of dipropargyl sulfide was higher than that of its oxygen analogue.¹³⁶ In addition, imidazolyl, oxazolyl, thiazolyl, and other sulfides are used as inhibitors of the colored veil in color photos.¹³⁷ Moreover, utilization of propargyl sulfides in solar batteries, polymers, semiconductors, conductors, and power supplies has also been documented.¹³⁸

5.2. Agricultural Applications of Propargyl Sulfides

A large number of organic sulfur compounds are used in agriculture as effective pesticides, such as 2,4-dichlorophenyl (4-nitrophenyl)propargyl sulfide, which is a herbicide that is selectively effective against the chicken millet in water-meadow fields without influencing rice.¹³⁹ Also, sulfides with propargyl radicals and a crotyl group exhibited an insecticide activity against harmful insects; i.e., external treatment of sheep with 0.01–5.00% solutions of imidopropargyl thiocarbonate and ethylthiophosphinyl propargyl sulfide protects them from a fly maggot infection. Moreover, synergistic insecticidal activity of 2-

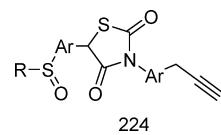
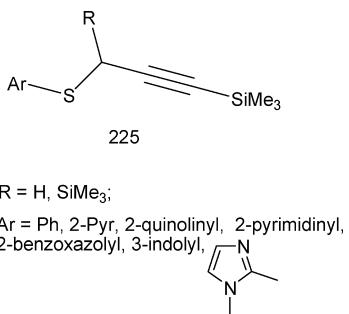
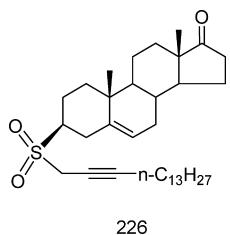


Figure 1. Antihyperglycemic agent.

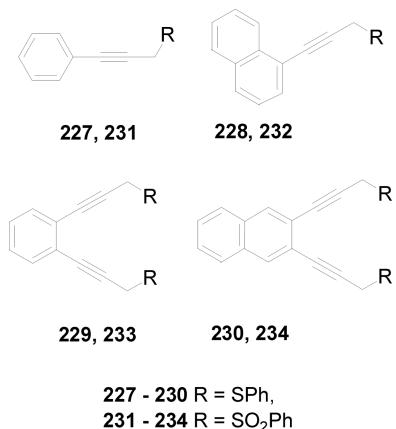
**Figure 2.** Hetaryl propargyl sulfide anticonvulsant.

(4-*tert*-butylphenoxy)cyclohexyl prop-2-ynyl sulfite was observed.¹⁴⁰

**Figure 3.** Inhibitor of glucose-6-phosphate dehydrogenase.

5.3. Applications of Propargyl Sulfides in Medicine

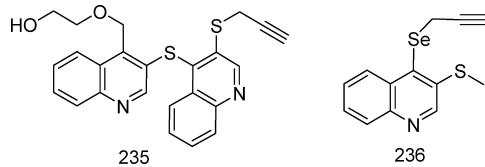
Propargyl sulfides are utilized as antituberculous, antimicrobial, antiulcerous, and anticancer remedies.^{141–144} Precisely, thiazo-

**Figure 4.** Anticancer agents.

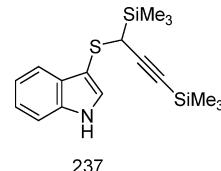
line-2,4-diones **224** (Figure 1) have been found to be antihyperglycemic agents.¹⁴⁵

Silicon derivatives of hetaryl propargyl sulfides **225** (Figure 2) possessed anticonvulsant and memory-improving activities.¹⁴⁶

Cyclic and aliphatic dipropargyl sulfones are used as functional starting materials for the production of anticancer compounds.¹⁴⁷ The steroidal propargyl sulfone derivative **226** has potential for inhibiting the glucose-6-phosphate dehydrogenase (G6PDH) enzyme (Figure 3).¹⁴⁸

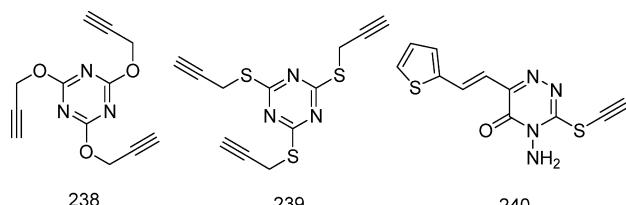
**Figure 5.** Compounds with anticancer activity.

Additionally, mono- and dipropargyl sulfides **227–230** in addition to sulfones **231–234** showed high cytotoxic activity

**Figure 6.** Thioindole **237** possessing cytotoxic activity.

against a series of leukemia (Molt-4), colon (Colo 205), epidermoid (HA22T), and melanoma (SK-BR-3) cells (Figure 4).¹⁴⁹

Anticancer activity of 3,4-disubstituted thioquinolines was reported. Among them, 4-[((2-hydroxyethyl)oxy)methyl]-3'-(propargylthio)-3,4'-diquinolinyl sulfide (**235**) and 3-(methylthio)-4-(propargylseleno)quinoline (**236**), containing propargyl sulfide (selenide) groups, were promising because of their high *in vivo* anticancer properties (Figure 5).¹⁵⁰

**Figure 7.** Potential antimetabolites and anticancer compounds.

Abele and coauthors¹⁵¹ developed a two-step method for the syntheses of [3-(hetarylthio)-1-propynyl]trimethylsilanes from thiols under phase transfer catalysis in which 3-[(1,3-bis(trimethylsilyl)-2-propynyl)thio]indole (**237**) was synthesized and showed high cytotoxic activity against HT-1080 and MG-22A cancer cells (Figure 6).

The derivatives 2,4,6-tris(propargyloxy)-1,3,5-triazine (**238**) and 2,4,6-tris(propargylthio)-1,3,5-triazine (**239**) not only are convenient synthones for the synthesis of carboranes, which are potential antimetabolites, but also are of major interest for delivery and accumulation of boron-containing fragments into tumor tissues in boron neutron capture therapy (BNCT) (Figure 7).¹⁵² Besides, synthetic compound **240** showed cytotoxicity (IC_{50} , $\mu\text{g/mL}$) against three different human cancer cell lines: Hep-G2 (31.64), MCF-7 (28.88), and HCT-116 (40.08).¹⁵³

5.4. Naturally Occurring Sulfides of the Propargyl Type and Their Applications

Cyclohexadiene polyacetylene 1,2-dithiins are a group of naturally occurring metabolites which are primarily synthesized in roots and exhibit a wide range of antibiotic activities.¹⁵⁴ Some dithiopolyynes known to be active in the dark and in the

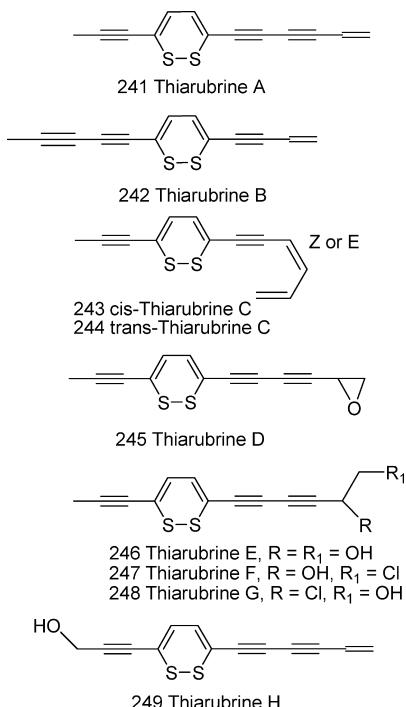


Figure 8. Family of thiarubrines exhibiting several pharmacological activities.

presence of ultraviolet light are active against fungi and insects. The thiarubrines A–H (241–249) (Figure 8) exist in a variety of plant species from the Asteraceae family and possess potential antiviral, antibiotic, anticancer, antibacterial, antifungal, and nematicidal activity.¹⁵⁵

Thiarubrine A (241), dithiacyclohexadiene polyyne, is found in the roots of common ragweed, belonging to the genus *Ambrosia* (*Ambrosia artemisiifolia*, *Ambrosia maritima*, *Ambrosia chamissonis*),¹⁵⁶ in the leaves of *Aspilia* species (*Aspilia mossambicensis* and *Aspilia rufa*, Tanzania),¹⁵⁷ in the roots of *Eriophyllum lanatum* and *Chaenactis douglasii*, and in the roots and leaves of *Am. chamissonis*,^{156,157} exhibiting a strong antifungal activity toward *Candida albicans* and *Aspergillus fumigatus* organisms, which are human pathogens at concentrations compatible with those of a currently used antifungal agent, amphotericin B.¹⁵⁸ Thiarubrine A from the roots of *Ch. douglasii* and a related dithiacyclohexadiene from *Rudbeckia hirta* showed a strong light-independent antibacterial and antifungal activity.¹⁵⁹ Thiarubrines A–C (241–244) were successfully isolated from the roots of *Aspilia mossambicensis*, *R. hirta*, *Am. chamissonis*, *Ambrosia psilostachya*, and *Ambrosia coniferiflora*.¹⁶⁰ Two mammalian viruses, murine *Cytomegalovirus* and *Sindbis virus*, were extremely sensitive to thiarubrine A only in the presence of UV-A. The bacteriophage T4 was slightly affected in UV-A only, whereas the bacteriophage M13 was completely unaffected.¹⁶¹ Thiarubrines A and D showed good activity against human immunodeficiency virus (HIV-1) in micromolar concentrations, which was dependent upon UV-A radiation.¹⁶² Besides the inhibition activity of thiarubrine A against fungi, certain viruses, and nematodes,¹⁶³ it also killed cancer cells in solid tumors commonly found in the breast and the lung.¹⁶⁴ Thiarubrines A, B, and D which were isolated from the roots of *Am. chamissonis* (Asteraceae) are photolabile, yielding thiophenes and elemental sulfur upon exposure to UV or visible light.¹⁶⁵ Thiarubrine C was found to have potent

antibacterial and antifungal activity¹⁶⁵ and unlike other natural thiarubrines can cleave DNA strands.¹⁶⁶ Thiarubrine C which was isolated from the roots of *R. hirta* (Asteraceae) exhibits a strong nematicidal in vitro activity in growth chamber assays. In

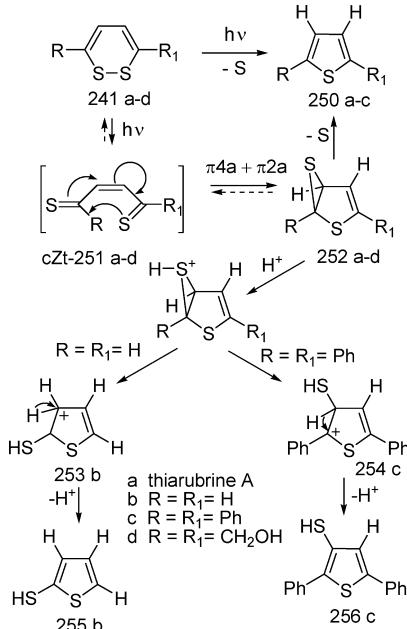


Figure 9. Suggested mechanism of thiarubrine conversion to thiophenes.

the absence of light, thiarubrine C was toxic to the plant-parasitic nematodes *Meloidogyne incognita* and *Pratylenchus penetrans* at $LC_{50} = 12.4$ and 23.5 ppm, respectively.¹⁶⁷ Moreover, thiarubrines D–H inhibit *Ca. albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Enterobacter aerogenes*, *Escherichia coli*, *Mycobacterium*, *Staphylococcus aureus*, *Streptococcus faecalis* growth in the nanogram per milliliter range.¹⁶⁸

The thiarubrines are easily converted to the corresponding thiophenes when exposed to light or heat under either acidic or alkali media. Thiarubrine A and related wine-red antibiotic pigments (thiarubrines B–H) found in the Asteraceae family^{155–157} are unique among natural products in containing an eight- π -electron (1,2-dithiin) ring.¹⁶⁹ A notable property of 1,2-dithiins 241a–d is their light sensitivity under brief exposure to visible or ultraviolet light, giving the corresponding thiophenes 250a–c (Figure 9).¹⁷⁰ Hitherto, little was known about the mechanism of this desulfurization process.^{159,171} The quantitative yield for conversion of 3,6-diphenyl-1,2-dithiin (241c) to 2,5-diphenylthiophene (250c) and ring opening of 241c to (Z)-butenedithione derivative 251c was determined.^{170,172} Also, various substituents in the desulfurization of 161 were involved.¹⁷³ Similarly, direct extrusion of singlet sulfur from 241b is calculated to be disfavored by ca. 80 (kcal mol)⁻¹.¹⁷⁴ Exposure of 241a to visible light led to desulfurization, which enhanced the biological activity. In addition, the observation that irradiation of 241a resulted in a colorless solution which upon standing retained some of its red color led to the postulation of the presence of a labile intermediate between 1,2-dithiins and thiophenes.^{159,171}

Block and coauthors examined the photochemistry of 241a and synthesis of 1,2-dithiins 241b–d in solution and under matrix isolation conditions. They suggested that the formation of the novel sulfur compounds provided an explanation for the

light-induced conversion of 1,2-dithiins to thiophenes.¹⁷⁵ In particular, irradiation of **241** with visible light at -60 to -75 °C afforded a previously unknown class of compounds, 2,6-dithiabicyclo[3.1.0]hex-3-enes **252**, in excellent yields.¹⁷⁶ On the other hand, matrix isolation and flash photolysis techniques were used to identify and determine the in solution lifetime of *s-cis,s-trans-(Z)-2-butenedithial* (*cZt-251b*), which is a presumed intermediate in the formation of dithiabicyclohexenes **252** to provide an alternative low-temperature photochemical pathway to butenedithial *cZt-251b* (Figure 4). The products dithiabicyclohexenes **252**, thiophenes **250**, and sulfur were afforded upon warming or further exposure to light, whereas, under catalytic acid conditions, dithiabicyclohexenes **252b** and

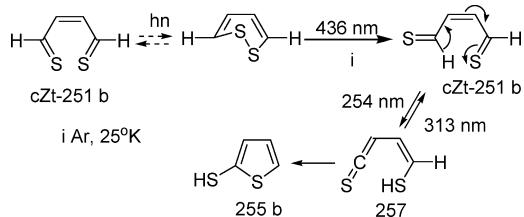


Figure 10. Possible mechanism of *cZt-251b* conversion to thiophene.

252c rearranged to 2-mercaptopthiophene (**255b**) and 2,5-diphenyl-3-mercaptopthiophene (**256c**).¹⁷⁶

The authors proposed that photoproducts **252a–d**, which were identified by spectroscopy as 2,6-dithiabicyclo[3.1.0]hex-3-enes, were formed by a $\pi_{4a} + \pi_{2a}$ rearrangement from initially formed (*Z*)-2-butenedithials **251**. An analogous process was reported by Padwa for photolysis of 4-phenylisothiocromene (*cZt-251b*) (Figure 9).¹⁷⁷ At least in the cases of **252a** and **252c** the process was partially reversible under thermal conditions in which dithiins **241a** and **241c** were regenerated. Rearrangement of photoproducts **252b** and **252c** to mercaptopthiophenes **255b** and **256c** presumably involved acid-catalyzed ring opening, giving the most stable carbocations **253b** and **254c**, respectively. It was also found that when compound *cZt-241b* was further irradiated at 254 nm, it was transformed to **257** and thiophene **255b** (Figure 10).^{178,179}

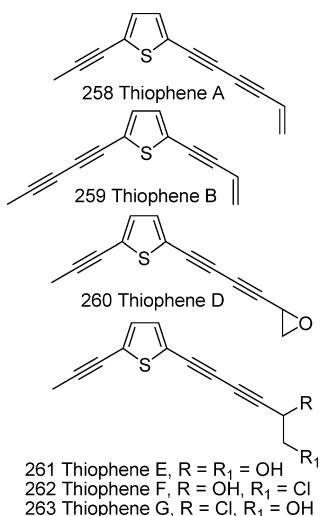


Figure 11. Selected natural bioactive thiophenes.

Thiophene A (**258**) possessed in vitro antiviral activities precisely against *Si. virus* and murine *Cytomegalovirus* infection of murine 3T3-L1 cells.¹⁷⁰ Also, British Columbia reported that thiophene E (**261**) which was isolated from *Balsamorhiza sagittata* exhibited antibacterial and antifungal properties.¹⁸⁰ In addition, thiophenes A (**258**), B (**259**), D (**260**), and E (**261**) which were isolated from the leaves and roots of *Aspi. mossambicensis* showed antifungal activity against *Ca. albicans*.¹⁸¹ Also, the biological activity of the natural products thiophenes with acetylenic moieties and related compounds was screened and showed that they are photosensitizers; i.e. their activities against fungi, bacteria, viruses, nematodes, insects, mammalian cells, and other organisms are augmented by UV-A light (Figure 11).¹⁸²

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Notes

The authors declare no competing financial interest.

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Valery M. Dembitsky received his M.S. degree in organic synthesis from the Far East State University (now the Far East Federal University), Vladivostok, USSR, in 1973. He received a Ph.D. degree in biological chemistry from the USSR Academy of Sciences, Leningrad, in 1981 and his D.Sc. degree in bioorganic chemistry and chemistry of natural products from the M. V. Lomonosov Moscow State Academy of Fine Chemical Technology in 1997. From 1989 to 1991, he was an associate professor in the Organic Chemistry and Biochemistry Department, Samara State University. He also was a visiting professor in the Department of Scientific and Industrial Research, The Massey University, Palmerston North, New Zealand (1990), Department of Organic and Biological Chemistry, Auckland University, Auckland, New Zealand (1990), Department of Plant Chemistry, Institute of Organic Chemistry with Phytocentre, Bulgarian Academy of Science (1990, 2006), Department of Natural Biogenesis, Institute of Microbiology, Czechoslovakia Academy of Science, Prague (1989, 1990, 2002), and Department of Marine Chemistry, Institute of Oceanology, Polish Academy of Science, Sopot (1989) and at Nantes University, France (2004, 2013). From 1991 to 1992, he held a guest professorship at the School of Chemistry, Melbourne University, Australia, and in 1993, he moved to the Department of Organic Chemistry, Hebrew University, Jerusalem. In 2000, he joined the

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