Divergent Utilities of Alkynethiolate-Based Precursors for the New Synthesis of Sulfur-Containing Five- and Six-Membered Heterocyclic Compounds

Md. Ashraful Alam

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Chapter 1: Introduction

1-1 Review and general introduction on the importance of sulfur-containing heterocycles

The chemistry of sulfur is an important area in organic synthetic chemistry specially heterocycles chemistry. The famous mustard gas having sulfur atoms is a feared chemical warfare. On the other hand, a great number of chemical entities containing sulfur atoms in their molecules are invaluable agents in the field of life saving drugs for example penicillins, cephalosporins and so on. The organic chemistry of sulfur started its development since the discovery of the 'mercaptan' (ethanethiol) in 1834 and xanthates in 1823 by Zeise, W.C.[1] There are a large number of organic compounds having sulfur atoms in their molecules, e.g. cysteine, cystine, coenzyme A, biotin, sulfonamides, penicillin, cephalosporin and other antibiotic compounds, are crucial for preservation of life. The sulfur compounds are also contributing to the fields of synthetic reagents, intermediates, solvents, bio-chemicals attributed to the properties of sulfur. Meanwhile, organosulfur compounds are playing the vital roles in the field of synthetic organic chemistry. A great deal of interests, to the heteroatom chemists concerning chalcogen atoms, has focused on the reactivities, structure, and spectroscopic studies of organosulfur compounds. The rapid expansion of organosulfur chemistry has widely enriched sulfur chemistry. Thus, many organosulfur chemists are undergoing a variety of studies concerning a remarkably broad range of reactivities of organosulfur compounds such as the studies on their exposure to heat, light, and ionization by radiation. Much attention of heteroatom chemists has focused on the chemistry of the reactive species of organic compounds containing sulfur. Thus, a lot of reports on the chemistry of sulfides, sulfones, cyclic sulfones, α,β-unsaturated thioester, dithioester, isothiazoles, thiochromenes, and thiochromenones have frequently appeared in recent publications. Considering all of these facts mentioned above its revealed that studies on contemporary organosulfur chemistry is the most fascinating area of frontier research.

In this chapter, the author describes a comprehensive review on organosulfur chemistry showing the development of many studies on the typical chemistry of organosulfur.

1-2 Review and general introduction on the previous synthetic strategies of sulfur containing heterocycles

Sulfur containing heterocyclic compounds have retained the interest of organic and inorganic researchers along the decades of historical development of chemistry. The presence of heteroatoms results in significant changes in the cyclic molecular structure due to the availability of unshared pairs of electrons and the difference in electronegativity between heteroatoms and carbon. As a result, there is a unique feature of these heterocycles which are considered as promising materials in different areas of pharmaceutical and agrochemical research and also more recently as compounds with interesting physical properties.

Ethylene sulfide, is the cyclic chemical compound with the formula C_2H_4S. It is the smallest sulfur-containing heterocycle and the simplest episulfide. Like many organosulfur compounds, this species has a stench. It is known as thiirane. Thiirane is also used to describe any derivative of the parent ethylene sulfide. Cyclic sulfides of 8 or more members can be prepared conveniently using ring expansion methods. Several methods are available, depending on the ring size desired. To prepare 8-10 membered rings, q-vinyl thiolanes, thianes, or thiepanes may be converted to sulfur ylides by an alkylation-deprotonation sequence. The resulting ylides undergo 2,3 sigmatropic shift at room temperature or below, resulting in ring expansion by three carbons.

Sulfoxides are classical functional groups for directing the stoichiometric metalation and functionalization of C-H bonds. In recent times, sulfoxides have been given a new lease on life owing to the development of modern synthetic methods that have arisen because of their unique reactivity. They have recently been used in catalytic C-H activation proceeding via coordination of an internal sulfoxide to a metal or through the action of an external sulfoxide ligand. Furthermore, sulfoxides are able to capture nucleophiles and electrophiles to give sulfonium salts, which subsequently enable the formation of C-C bonds at the expense of C-H bonds.

Many reactions of cyclic sulfur compounds have interesting synthetic potential, but relatively few have enjoyed widespread use. Various ethylene sulfides were reported to react with triphenyl- and triethyl-phosphine to give the corresponding phosphine sulfide and with triethyl phosphite to produce the thionophosphate.

1-2-1 Synthesis of Alkynyl Propargyl Sulfones and their conversion into six-membered Cyclic β-ketosulfones

The sulfone is a chemical compound containing a sulfonyl functional group attached to two carbon atoms. The central hexavalent sulfur atom is double bonded to each of two oxygen atoms and has a single bond to each of two carbon atoms, usually in two separate hydrocarbon substituents (Figure 1).[2] All the building blocks processing cyclic sulfone moiety have some common features that make the design of potential drug candidates particularly efficient.

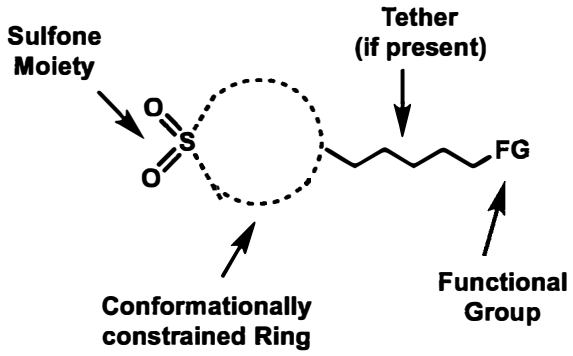


Figure 1. General structure of cyclic sulfones

There are some characteristic features of the sulfone moiety, some of them are like a) Sulfone moiety, a strong H-bond acceptor which is considered as carbonyl group bioisostere, enforces interaction of the molecule with potential biological target. b) Conformationally constrained five-, six- or seven-membered ring fixes the functional group responsible for linking the sulfolane part to other fragments of the molecule, thus reducing entropy of binding of the latter with potential biological target. In some cases, an additional flexible or conformationally constrained tether is also present. c) Functional group allows tethering cyclic sulfone building block to other fragments of the potential drug candidate molecule; moreover, it is often also capable of interaction with potential biological target through H-bonding. d) A distance between two H-bonding units mentioned above (2–5 bonds) is relevant for the most efficient interaction with different biomolecules

There are many types of cyclic sulfone compounds. These may be different numbered of cyclic sulfones. Some simple six membered cyclic sulfone types of compounds (Figure 2).

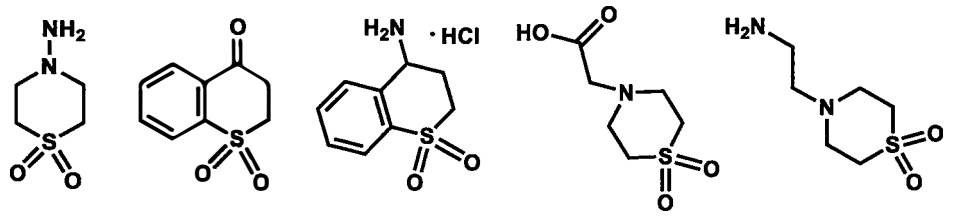
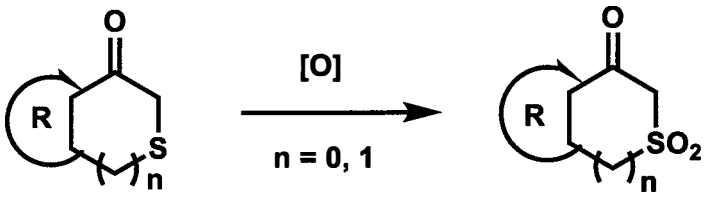


Figure 2. Some examples of six-membered cyclic sulfones.

Sulfones are a major class of organosulfur compounds[3] that have been extensively used as versatile intermediates in organic synthesis.[4] The importance of the sulfone functional group in synthetic organic chemistry warrants significant interest in the development of new methodologies related to the introduction of the sulfone functionality into an organic molecule as well as the further synthetic transformation of the sulfone intermediate, and, when desirable and possible, its eventual elimination from the target. Cyclic sulfones, in particular, have unique synthetic utilities. Different types of substituted sulfolenes are an excellent source of conjugated dienes through SO_2 extrusion and have been employed as masked dienes for intramolecular Diels-Alder reactions in numerous complex syntheses.[5] Medium ring cyclic sulfones can be used as precursors for the construction of cyclic olefins[6] by the well-established Ramberg-Bäcklund reaction.[7,8] Cyclic sulfones have also been investigated as the key subunit and scaffold for the construction of biologically active molecules such as protease and β-lactamase inhibitors.[9,10] Although a plethora of methods for the synthesis of cyclic sulfones exists in the literature,[3,4] a generally applicable and highly efficient approach to the synthesis of cyclic sulfones of various ring sizes and different substitution patterns is still highly desirable. The majority of the existing methodologies for the synthesis of cyclic sulfones involve the construction of the corresponding cyclic sulfides from appropriately functionalized precursors that often require tedious multistep manipulations, followed by oxidation of the sulfides to sulfones.

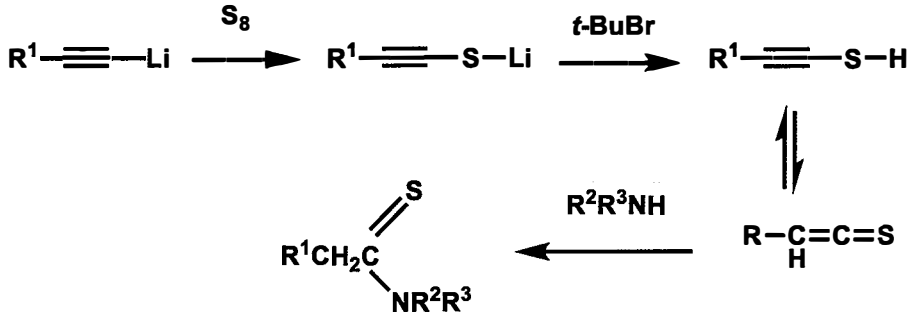
1-2-1-1 Synthesis and Reactions of Cyclic Sulfones

The most widely used method for the synthesis of the cyclic sulfone compounds is oxidation of the sulfur atom in the thiophene, thiopyran, benzothiophene, or isothiochroman ring and the peroxides are mainly used as oxidizing agents. Methods for the production of cyclic β-keto sulfones in which the sulfur oxidation stage precedes the cyclization stage have also been widely used (Scheme 1).[11]



Scheme 1. Simple oxidation method for the synthesis of cyclic β-keto sulfones

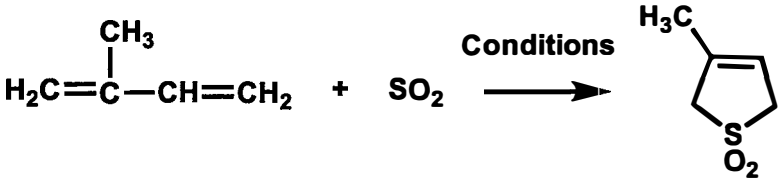
A communication[12] was described the synthesis of *N,* N-diethylphenylthioacetamide from phenylacetylene, sodium, sulfur and diethylamine by Schuijl, P. J. W. and Brandsma, L. and prompted them to communicate the results of similar investigations carried out in their laboratory as an extension of earlier work. Then they reported, that the reaction of alkynethiolates with thiols furnishes dithioesters,[13] and on analogy they prepared thioamides[14] (Scheme 2) from alkynethiolate and a secondary amine.[15] The favorable results were obtained when *t*-butyl bromide was used as the proton donor.[16]



Scheme 2. Preparation of thioamides from alkynethiolates and amines

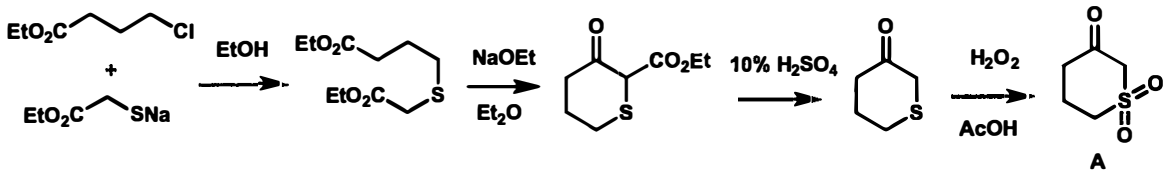
In 1914, G. de Bruin described some properties of a pure, crystalline monoadduct obtained by allowing isoprene to react with liquid sulfur dioxide at room temperature. There were earlier

observations of crystalline products from the reaction of dienes with sulfur dioxide in aqueous solution, but no analytical data were reported. While de Bruin was not positive in his assignment of structure for the isoprene-sulfur dioxide adduct, his characterization of the compound and a consideration of Thiele's explanation of other 1,4-additions to conjugated dienes led him to suggest that a cyclic sulfone structure **A** for the product was not improbable. Subsequent investigations by other workers showed that structure **A** is correct, and that analogous cyclic sulfones can be obtained from the reaction of sulfur dioxide with a variety of conjugated dienes (Scheme 3).[17]



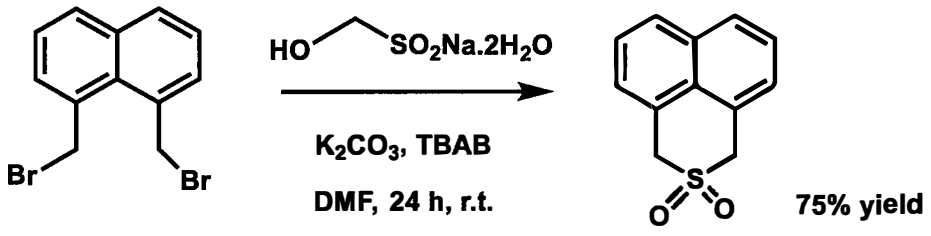
Scheme 3. Formation of five-membered cyclic sulfones

Dihydro-2*H*-thiopyran-3-(4*H*)-one 1,1-dioxide (**A**) was synthesized (Scheme 4) in four stages with up to 72% yield by the reaction of ethyl γ-chlorobutyrate with the sodium salt of ethyl thioglycolate.[18]



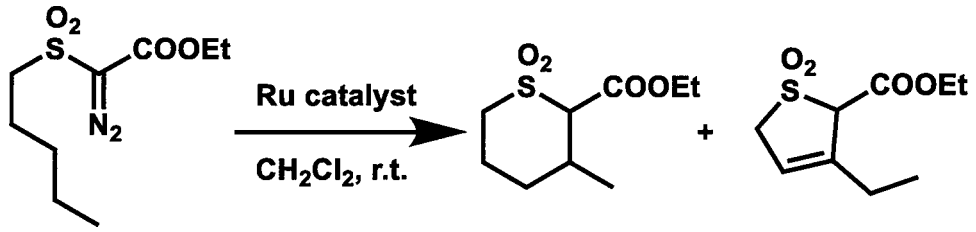
Scheme 4. Synthesis of *β*-keto cyclic sulfone

A series of symmetrical sulfones[19] were prepared by Kotha, A. *et al.* from rongalite (sodium hydroxymethanesulfinate) (Scheme 5).



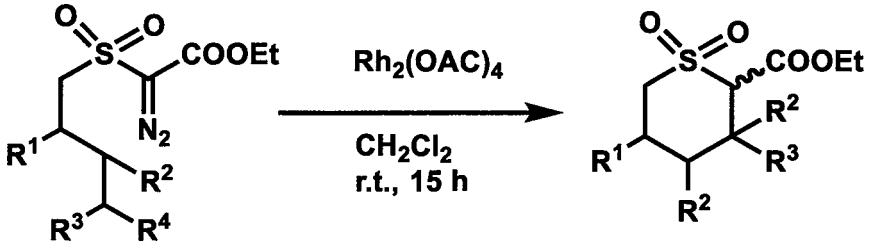
Scheme 5. Preparation of cyclic sulfone from rongalite

C–H insertion on the alkylsulfonyl diazoacetate substrates has demonstrated by Jungong, C. S. *et al.* A sensitive nature of the earlier discovered preference for formation of six-membered sulfone rings (Scheme 6). Substitution next to sulfone was found to tilt it toward the formation of five-membered sulfones. Unexpectedly, same influence is also exerted by $Rh_2(pfb)_4$ catalyst. This permits a degree of control over the reaction outcome to form either thiofuran or thiopyran 1,1-dioxides, both of which are useful intermediates in synthesis.[20]



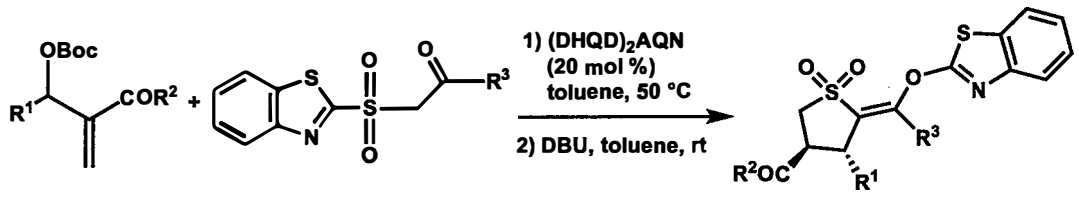
Scheme 6: Synthesis and catalyst effectivity on five- versus six-membered sulfone rings

The preferential formation of six membered cyclic sulfones and sulfonates through C-H insertion demonstrated by John, J. P. and Novikov, A. V. Carbethoxy diazosulfones and sulfonates, easily available from corresponding sulfones and sulfonates, undergo C-H insertion with preferential formation of six membered cyclic sulfones and sulfonates[21] (Scheme 7).



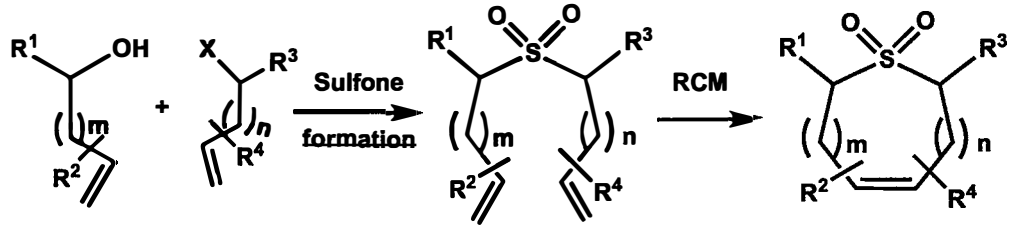
Scheme 7. Formation of the preferential six-membered cyclic sulfones by C-H insertion

An asymmetric allylic alkylation of Morita_Baylis_Hillman carbonates and β-keto sulfones was investigated by the catalysis of modified cinchona alkaloids by Chen, Y. C. *et al.*, whose products underwent a Smiles rearrangement_sulfinate addition cascade to furnish highly functionalized five-membered cyclic sulfones[22] in moderate to excellent enantioselectivity and good diastereoselectivity after treatment with DBU (Scheme 8).



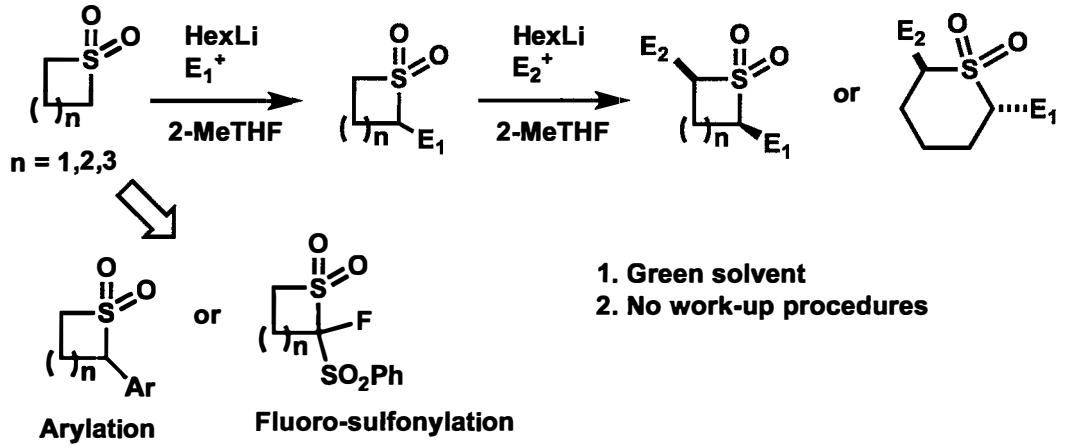
Scheme 8. Construction of chiral cyclic sulfones

A novel and versatile strategy was constructed by Qingwei, Y. for the synthesis of cyclic sulfones based on the ring-closing metathesis (RCM) of acyclic sulfones which can be readily prepared from alkenyl alcohols and alkenyl halides through standard functional group transformations (Scheme 9).[23]



Scheme 9. Ring-Closing Metathesis (RCM) approach to cyclic sulfones

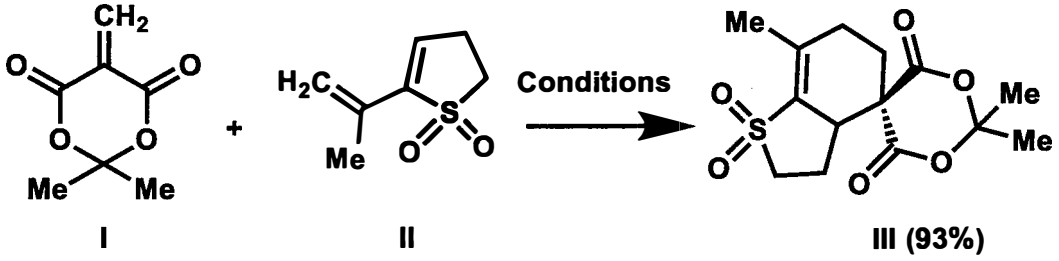
The regioselective functionalization of four- and six-membered cyclic sulfones (Scheme 10) was investigated by Luisi, R. and co-workers[24] using a lithiation/electrophile trapping strategy. The protocol features an interesting eco-compatibility profile because of the use of 2-MeTHF as a solvent (more eco-friendly than other organic solvents) and *n*-hexyllithium as a lithiating agent safer than other alkyllithium compounds. Several derivatives were prepared with different stereochemistry and substitution patterns. A number of selected derivatives, spanning a range of 5 log *P* units, were characterized for their lipophilicity through RP-HPLC. A good linear correlation, with a slope close to 1.0, was observed between the experimentally determined RP-HPLC lipophilicity parameters ($\log k'_w$) and calculated log *P* (clog *P*) values, whereas a systematic difference in absolute values between the chromatographic parameters and *in silico* lipophilicity descriptors can be attributed mainly to silanophilic interactions between the H-bond acceptor SO_2 group and free silanol groups on silica-based C18 columns, which results in increased retention times.



Scheme 10. A greener and efficient access to substituted four- and six-membered cyclic sulfones

1-2-1-2 Diels–Alder reactions with cyclic sulfones:

Diels–Alder reactions with 2,3-dihydrothiophene 1,1-dioxide derivatives as dienophiles and dienes were used previously to obtain various tri- and tetracyclic compounds containing a fused tetrahydrothiophene 1,1-dioxide fragment.[25-30] Some of the prepared compounds were found to exhibit a high antiphlogistic, antiulcer, and psychotropic activity together with low toxicity.[31-33] Here, Shul'ts, E. E. *et al.* synthesized such compounds[34] by cycloaddition of 5-methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (**I**)[35] and 5-isopropenyl-2,3-dihydrothiophene1,1-dioxide (**II**).[36] The reaction of diene **II** with dienophile **I** was regioselective, and it resulted in formation of 93% of adduct **III** (Scheme 11).



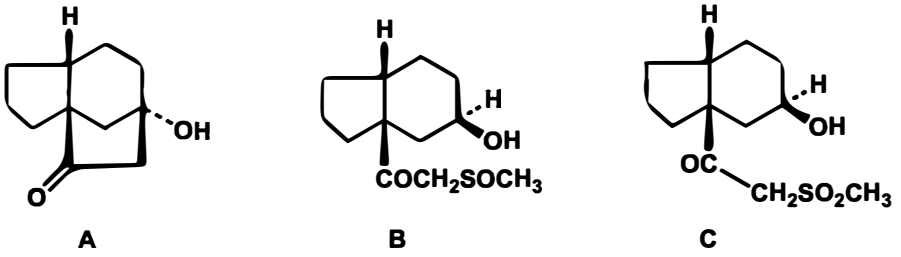
Scheme 11. Diels-Alder reactions of cyclic sulfones

1-2-1-3 Synthetic utilities of *β*-keto-sulfones and cyclic *β*-keto-sulfones

The sulfone-containing molecule plays an important role in many classes of biologically active compounds and marketed drugs.[37] The sulfone moiety also serves as a versatile building block, especially as a carbon nucleophile owing to its electron-withdrawing character.[38] As a consequence, the considerable effort has been paid to exploring practical access to this framework. Moreover, *β*-ketosulfones have attracted significant attention due to their important applications in a large array of natural products and important organic compounds.[39]

The *β*-keto sulfones are an important class of compounds in organic synthesis.[40] Several useful compounds are prepared *via* the intermediacy of *β*-keto sulfones, such as olefins,[2] disubstituted acetylenes,[41] vinyl sulfones,[42] allenes,[43] and polyfunctionalized 4*H*-pyrans.[44] Facile reductive elimination of *β*-keto sulfones leads to the formation of ketones.[45] Additionally, *β*-keto sulfones are precursors for optically active *β*-hydroxy sulfones.[46] Some of the *β*-keto sulfones are found to possess fungicidal activity.[47] The common routes to *β*-keto sulfones involve oxidation of *β*-keto-sulfides,[48] reactions of sulfonyl chlorides with silyl enol ethers,[49] reactions of diazo sulfones with aldehydes,[50] alkylation of arene sulfonate salts with a-haloketones,[51] acylation of alkyl sulfones, reaction of alkyl sulfones with N-acylbenzotriazoles,[52] and a more recent approach involving the reaction of sulfonyl chloride with arylacetylenes.[53] An easy solvent-free method is described for the preparation of *β*-keto sulfones from ketones in high yields that involves the ***in situ*** generation of α-tosyloxyketones, followed by nucleophilic substitution with sodium arene sulfinate in the presence of tetrabutylammonium bromide at room temperature by Kumar D. *et al.*[54]

The β-keto sulfone **C** was found to be a more satisfactory intermediate than the corresponding β-keto sulfoxide **B** for the preparation of the tricyclic hydroxy ketone **A**. Examination of several simpler β-keto sulfones **D**, **E**, and **F** (Figure 3) indicated that the preparation and C-alkylation of these materials occur as readily as the reactions involving the corresponding β-keto sulfoxides. The β-keto sulfones are more stable to oxidation and reduction procedures than the β-keto sulfoxides.[55]



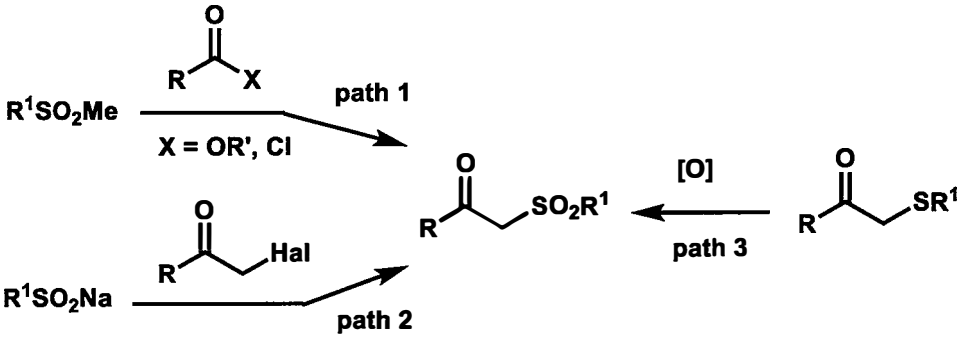
$CH_3(CH_2)_{16}COCH_2SO_2CH_3$ $C_6H_5COCH_2SO_2CH_3$ $CH_3(CH_2)_4COCH_2SO_2CH_3$

D E F

Figure 3. Some of the structures of β-keto sulfones

Cyclic β-keto sulfones are a class of new chemical subjects with a broad spectrum of biological activity. Substances with antibacterial,[56] antiviral,[57,58] anti-inflammatory,[59] antitumor,[60] and bronchodilatory[61] properties, calcium channel antagonists[62] and potassium channel agonists,[63-68] DNA gyrase inhibitors,[56] and compounds effective in the treatment of osteoporosis[59] have been found among them. At the same time progress in medicinal chemistry depends largely on the availability of a large number new structures for pharmacological trials. This is achieved largely through effective methods of modifying existing compounds. On the other hand, cyclic β-keto sulfones are convenient model compounds for the study of such fundamental aspects as reactivity and conformational analysis.

The synthesis of β-keto sulfones can be carried out in several ways. The most available and broadly used synthetic routes to β-keto sulfones include acylation of methyl sulfones (path **1**),[69,70] alkylation of metallic arene sulfinates with α-halo ketones (path **2**)[71,72] and oxidation of β-keto sulfides[73] (path **3**) (Scheme 12). Acylation of methyl sulfones with excess amounts of either esters or carboxylic acid chlorides in the presence of base such as *n*-butyllithium, LDA or sodium hydride (path **1**) is the most explored and demanded method to provide β-keto sulfones to date. Recently, *N*-acylbenzotriazoles have been found to be effective *C*-acylation reagents for this purpose, which can be used in stoichiometric ratios affording high yields of β-keto sulfones.[74]



Scheme 12. General routes to β-keto sulfones

1-2-2 Synthesis of α, β-unsaturated carbodithioate esters and their conversion into isothiazoles

Carbon-sulfur bond formation is a fundamental approach to introduce sulfur into organic compounds. This received considerable attention due to its occurrence in various molecules that are of biological, pharmaceutical and material interest.[75]

1-2-2-1 α, β-unsaturated thioesters and carbodithioate esters

Thioesters and α, β-unsaturated thioesters have attracted much attention as active esters for syntheses of different compounds. Synthetic methods for α, β-unsaturated dithioesters have received considerable interest in view of their increased reactivity, compared to their carboxylic analogues, as potential dienes or dienophiles in hetero Diels–Alder cycloadditions.[76] Moreover, the cycloaddition products, thiochromenes, are potential precursors of a wide range of thioheterocycles with interesting biological properties. There are very few general methods available for the synthesis of α, β-unsaturated dithioesters and those known are mostly specific to certain substrate classes. The methods available in the literature include (i) alkylation of thiolate anions obtained by the addition of vinyl cuprates to carbon disulfide,[77] (ii) isomerization of α,β-

unsaturated dithioesters,[78] (iii) base catalyzed elimination of β-hydroxy dithioesters,[79] and (iv) Wittig–Horner, Peterson or Mukaiyama type condensation reactions of aldehydes and ketones.[80] Hartke et al. have also shown that α, β-unsaturated amides can be transformed into the corresponding dithioesters by a sequence of reactions involving thionation, alkylation and sulfhydrolysis.[81] Although dithioesters have been known for many years,[82] it is only recently that α, β-unsaturated dithioesters have attracted attention. We were interested in that α, β-unsaturated dithioesters as potential heterodienes or in cycloaddition reactions.[83]

1-2-2-2 Synthesis and reactions of α, β-unsaturated dithioate esters

In 1978, the preparation of the β-hydroxydithioester **(1)** was described[84] involving the treatment of ethyl dithioacetate with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) followed by isobutyraldehyde at -78 °C. It is recently that α, β-unsaturated dithioesters have attracted attention. Preparative approaches to these compounds **(2)** which have been investigated include: *(a)* reaction of a vinyl cuprate with carbon disulphide followed by methyl iodide,[85] this is successful for compounds **(2a-c),** but attempts to make the dithioester **(2d)** in this way gave its dimer; ***(b)*** sulphydrolysis at -75 **°C** of the immonium salt derived by *S*-methylation of the thioamide gave the phenyl derivative **(2e)**[86] which dimerized above -30 °C; (c) base-catalysed isomerisation of β,γ-unsaturated dithioesters,[87] in turn prepared from N-phenyliminothioesters, gave **(2a)** and, at -40 °C, **(2f)** which dimerized at room temperature; and flash pyrolysis of the bridged anthracene and trapping of the product in a matrix at -196 °C gave the parent dithioacrylate **(2g)** (Figure 4). Lawson, K. R. *et al.* were interested in α, β-unsaturated dithioesters as potential heterodienes or heterodienophiles in cycloaddition reactions,[88] and they describe their preparation from β-hydroxydithioesters and some cycloadditions in which they are involved. Subsequent to the completion of their work it was reported that addition of Grignard reagents to β-ketodithioesters gave 3,3-disubstituted β-hydroxydithioesters, and the latter were dehydrated to 3,3-disubstituted α, β-unsaturated dithioesters on treatment with *p*-toluenesulfonic acid in benzene at reflux.[89]

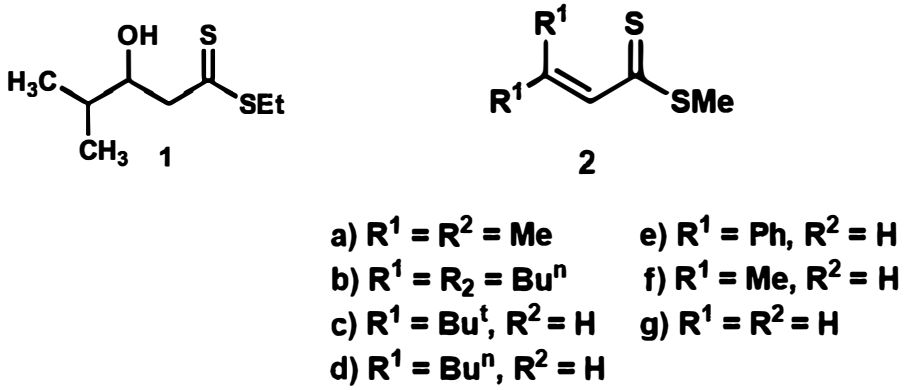
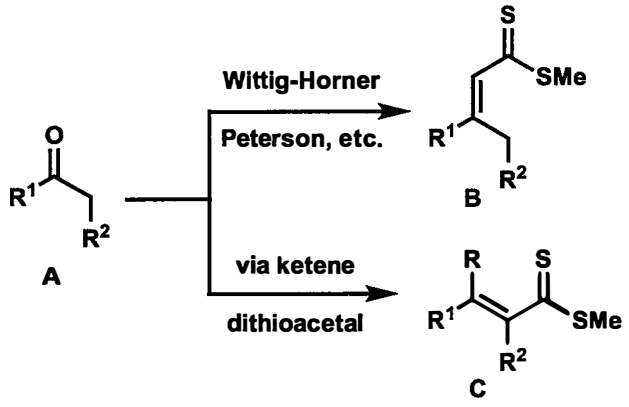


Figure 4. β-Hydroxydithioester **1** and α, β-unsaturated dithioesters **2**

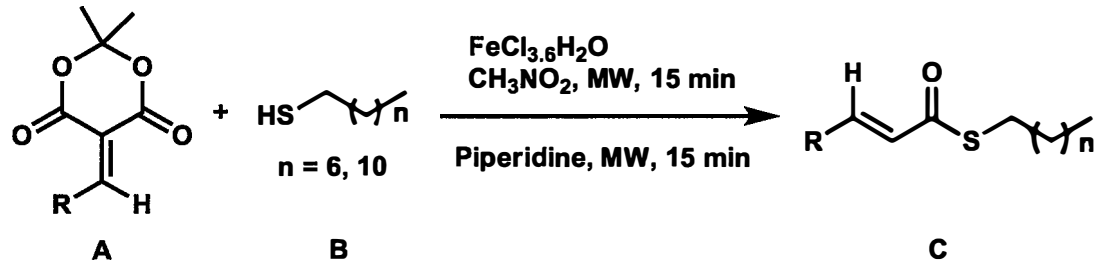
In most of the known methods[80] of preparation of α, β-unsaturated dithioesters **9** starting from carbonyl compounds (**A**), the dithioester functionality is introduced along with the α-methylene group to form (**B**). The present method provides an opportunity to introduce dithioester functionality at the α-position of the carbonyl group of the starting ketone to afford (**C**) (Scheme 13).



Scheme 13. Synthesis of α, β-unsaturated dithioesters from ketones **A** through Wittig-Horner method and *via* ketene dithioacetal

Interestingly, α, β-unsaturated thioesters have marked reactivity as Michael acceptors and they are proved to be excellent substrates in the synthesis of several natural products.[90] Although, it is a

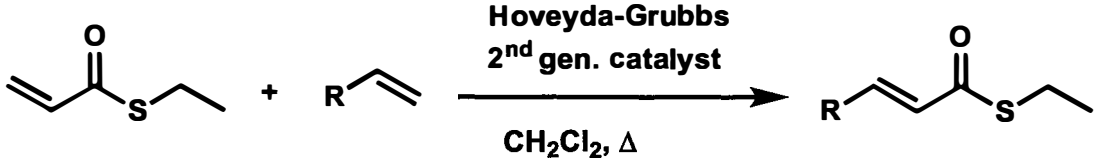
very useful intermediate, traditional syntheses of thioesters are encountered with the occasional difficulties such as 1,4-addition of thiolate and subsequent separation from the main product.[91] Olefin cross-metathesis has been elegantly explored to construct α, β-unsaturated thioesters using thioacrylate.[92] Encouraged by the success of synthesis of α, β-unsaturated esters, A.R. Mohite *et al.*[93] planned to extend the protocol for the straightforward synthesis of α, β-unsaturated thioesters using the optimized reaction conditions for esters. To compare the reactivity and to extend the application, thiols (**B**) (1 eq.) were treated with a few benzylidene derivative of MA (**A**) under optimized reaction conditions (Scheme 14). The corresponding α, β-unsaturated thioesters (**C**) were obtained in good to excellent yields (76–90%) under a short time microwave irradiation.



Scheme 14. One-pot direct synthesis of α, β-unsaturated thioesters **C**.

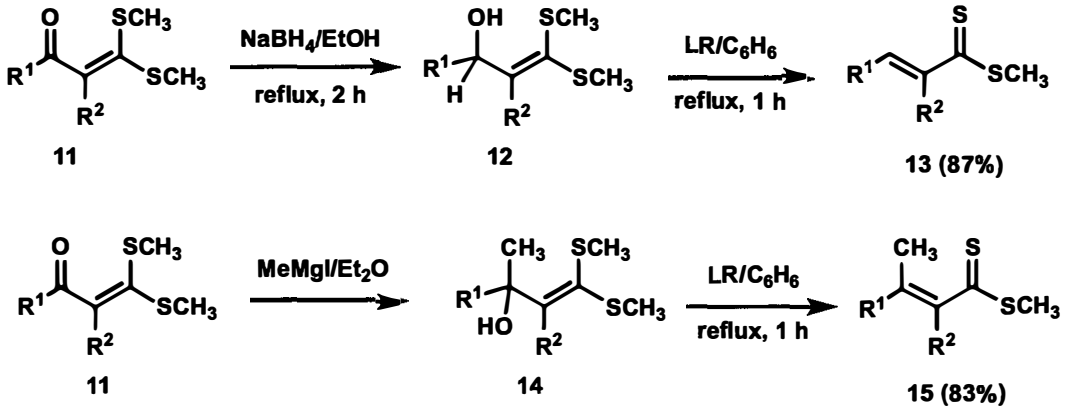
Thioesters are highly relevant compounds due to their distinctive chemical properties: the reduced electron delocalization provides for enhanced reactivity compared to oxoesters.[94] The importance of thioesters in the cell is well established: biological systems use their relative reactivity in many enzymatic reactions by employing, for example, acetyl coenzyme A, cysteine proteases, or polyketide and fatty acid synthases.[95] Their enhanced reactivity compared to that of oxoesters has been employed successfully in a wide range of synthetic organic transformations, some inspired directly by related biosynthetic pathways. Stereoselective aldol reactions often depend on the distinctive reactivity of thioesters[96] and their synthetic versatility is further illustrated by many other well-known transformations including α-alkylations,[50] selective reductions,[97,98] and Pd-catalyzed coupling reactions[99] among others.[100] Considering these importance, van Zijl, A. W. and his coworkers[101] found a mild and scalable new route to *S*-ethyl thioacrylate (Scheme 15). The feasibility of the use of this olefin in cross-metathesis reactions with the Hoveyda-Grubbs second

generation catalyst is demonstrated. The high functional group tolerance of the reaction allows the preparation of a broad range of versatile functionalized α, β-unsaturated thioesters.



Scheme 15. Cross-metathesis reaction of *S*-ethyl thioacrylate with a variety of olefins to give substituted α, β-unsaturated thioesters

Nair, S. K. and his coworkers have developed a facile two-step process for the conversion of a α-oxoketene dithioacetals to α, β-unsaturated dithioesters, which are valuable intermediates in organic synthesis and the method described here provides a valuable alternative to the previous methods for the synthesis of these compounds. The α-hydroxyketene dithioacetals **12** and 14, obtained from a-oxoketene dithioacetals by the 1,2-reduction or the 1,2-addition of carbon nucleophiles, on treatment with Lawesson's reagent afforded α, β-unsaturated dithioesters **13** and 15 in good yields (Scheme 16).[102]

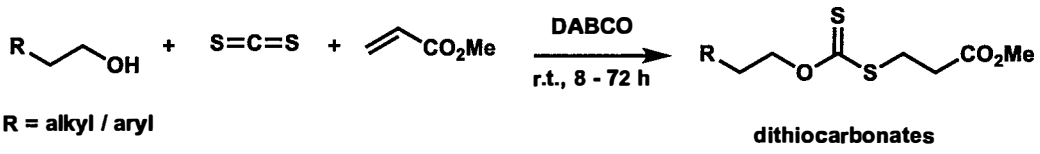


Scheme 16. Synthesis of α, β-unsaturated dithioesters 13 and 15 through the reactions of α-hydroxyketene dithioacetals 11 with Lawesson's reagent.

O, S-dialkyldithiocarbonates are a class of organo-sulfur compounds which are frequently used as versatile source of radicals[103] and useful intermediates in the synthesis of thiols,[104] thiocarbonates[105] alkenes,[106] alkanes,[107] α, β-unsaturated esters through *S*-activated carbanions[108] and as photosensitizer[109] of vinyl monomers. Besides, these are used as vulcanization accelerators[110] and in the syntheses of ionic liquids.[111] These are also used to prepare *S*-containing natural products[112] and find use in Claisen rearrangements leading to interesting derivatives.[113]

Normally these (*viz.* dithiocarbonates) are prepared from a three-step process from alcohol, alkyl halide and CS_2 using a strong base.[114] Recently efficient one-pot processes of their preparation have been reported using basic resin (Amberlite IRA)[115] or Trion B.[116] But in those communications only a non-functional alkyl group was used for alkylation of the sulfur center, and the syntheses are stepwise processes.

Multicomponent reactions (MCRs)[117] involve combination of three or more starting materials in a single operation, and are gaining popularity in the synthesis of complex compounds due to their high atom economy,[118] synthetic convergence and reduced effort in preparation and workup.[119] The early MCRs were mostly discovered by chance or serendipity. But rational design strategies for these reactions are currently being devised.[120] Patra, G. C. *et al.*[121] has developed an easy and effective preparation of dithiocarbonates in which the *S*-alkyl part is functionalized with an ester or nitrile group employing a three-component single step procedure (Scheme 17).



Scheme 17. Synthesis of functionalized *O, S*-dialkyldithiocarbonates

1-2-2-3 Isothiazoles

Many reviews have been published in the literature regarding the isothiazoles chemistry and their fused derivatives.[122,123] Comprehensive reviews[124] and other recent articles on the synthesis and chemistry of isothiazoles have been reported.[125-131] There is also a dissertation about selected features of the chemistry of these type of compounds.[132,133] A literature[124] survey revealed that isothiazole **A** was first prepared in 1956, and since then its chemical and physical properties have been extensively studied. Due to their peculiar reactivity, isothiazoles have recently emerged as useful synthetic compounds and their applications in the search for alternative synthetic strategies and the development of novel molecular structures have been steadily growing. The synthetic versatility of isothiazole has stemmed also from the interest in the biological and pharmacological properties of its derivatives. Isothiazoles **M** (1,2-thiazole), isothiazole 1,1-dioxides (sultams) **N** and the two classes of 1,2-benzisothiazole **O** and 2,1-benzisothiazole **P** are numbered (Figure 5).[134]

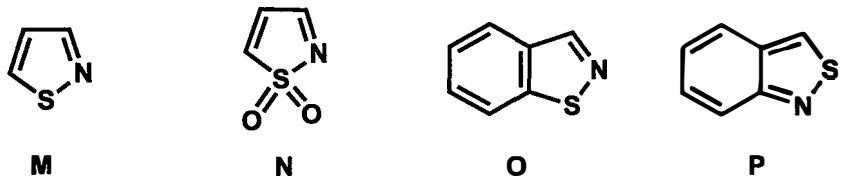
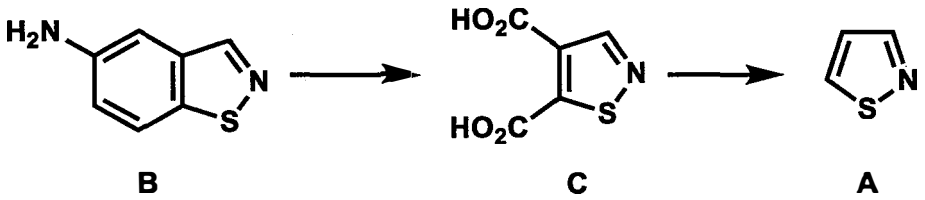


Figure 5. Structural features of isothiazoles and their benzo-derivatives

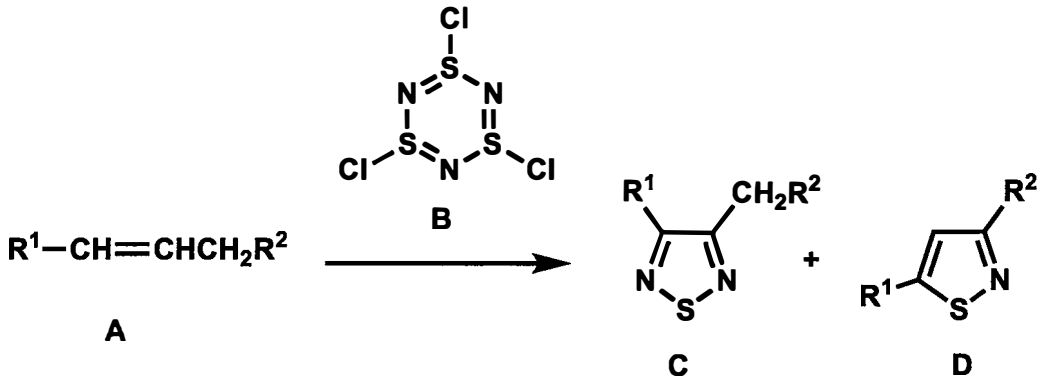
1-2-2-4 Synthesis and reactions of isothiazoles

Isothiazole (**A**) was first prepared by the oxidation of 5-amino-1,2-benzoisothiazole (**B**) with an alkaline solution of potassium permanganate with subsequent decarboxylation of isothiazole-4,5-dicarboxylic acid (**C**) (Scheme 18).[135,136] This synthetic procedure has a purely historical significance. Later, isothiazoles were synthesised from simpler and more accessible compounds.



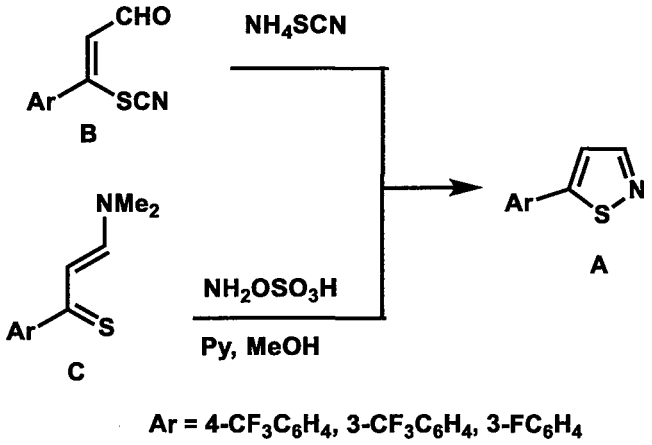
Scheme 18. Preparation of isothiazoles **A**

The use of 1,3,5-trichloro-1,3,5,2,4,6-trithiatriazine (**B**) seems to be very promising for the synthesis of isothiazoles. It was found that ordinary allylic compounds of the type (**A**) react with the reagent (**B**) as two-carbon units to give 1,2,5-thiadiazoles (**C**) and as three-carbon units to give isothiazoles (**D**). The ratio of compounds (**C**) and (**D**) depends on the reaction conditions and the nature of the substituents (Scheme 19).[137]



Scheme 19. Synthesis of isothiazoles **C**, **D** from ordinary allylic compounds **A**

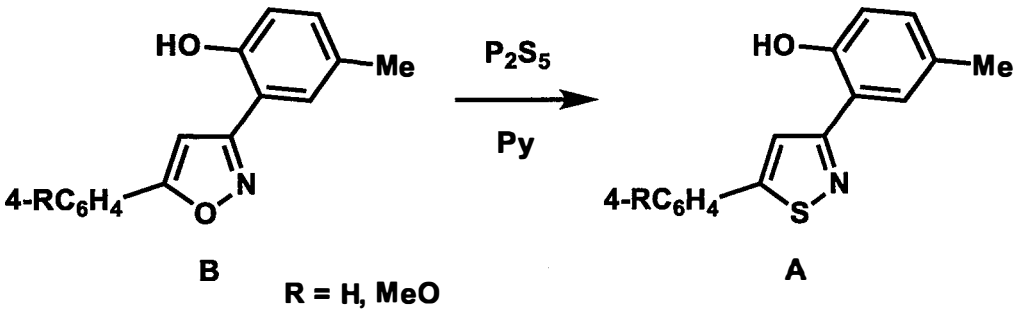
Schulze *et al.*[138] have developed two procedures for the synthesis of isothiazoles (**A**) containing fluoro-substituted aryl groups. The first of them is based on the reaction of *β*-thiocyanatocinnamaldehydes (**B**) with ammonium thiocyanate. Isothiazoles (**A**) were obtained in good yields. In this case, ammonium thiocyanate acts as a source of ammonium required for ring closure. It is noteworthy that ammonium thiocyanate was employed previously for the preparation of 4- and 5-alkylisothiazoles.[139] The second route is based on the use of enamino thiones (**C**) as starting compounds; their reaction with hydroxylamine-O-sulfonic acid gives isothiazoles (**A**) (Scheme 20). In this case, the yields reached to 98%.



Scheme 20. Synthesis of isothiazoles **A** from *β*-thiocyanatocinnamaldehydes **B** and enamino thiones **C**

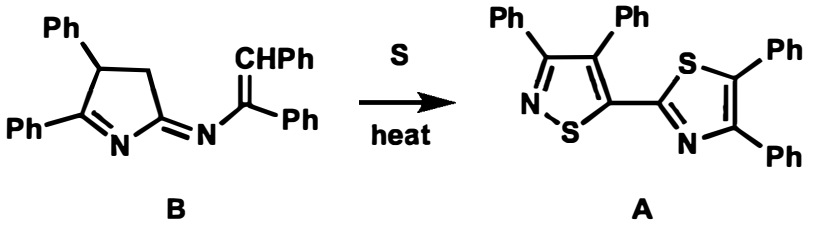
1-2-2-5 Synthesis of isothiazoles from some of the heterocyclic compounds

Methods for the synthesis of substituted isothiazoles from other heterocyclic compounds find wide application despite the fact that they belong to the most ancient ones. Thus 3,5-disubstituted isothiazoles (**A**) were prepared from isoxazoles (**B**) by the reaction with phosphorus pentasulfide in pyridine (Scheme 21).[140]



Scheme 21. Synthesis of isothiazoles **A** from isoxazoles **B**

The reaction of 2-imino-3,4-dihydro-2H-pyrrole (**B**) with sulfur on heating is accompanied by dehydrogenation and incorporation of the sulfur atom into the pyrrole ring resulting in the previously unknown thiazolylisothiazoles (**A**) (Scheme 22).[141]

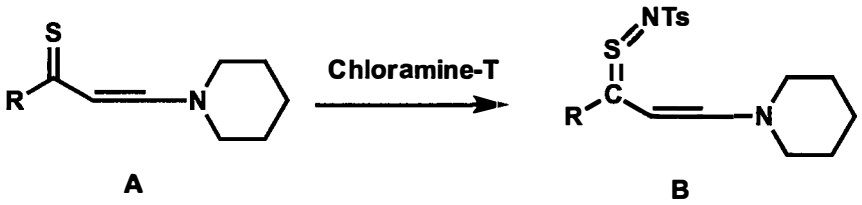


B A

Scheme 22. Synthesis of isothiazoles from 2-imino-3,4-dihydro-2*H*-pyrrole (B)

1-2-2-6 Previous synthesis of thione S-imides

The treatment of thiones **A** (10 mmol) with chloramine-T (hydrate, 11 mmol) in ethanol (35-40 ml) at -10-0 °C for lh afforded thione S-imides **B** as yellow crystals in fairly good yields by Saito, T. *et al.* which is shown below (Scheme 23).[142]



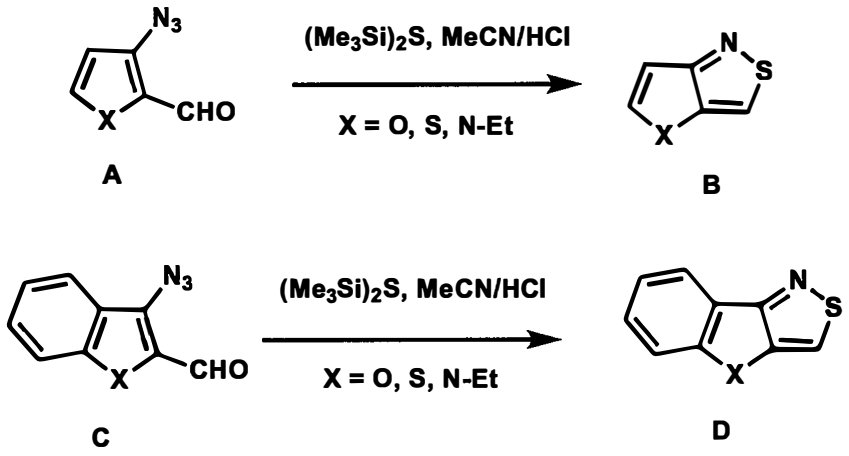
A B

R = C_6H_5, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, 2-Thienyl

Scheme 23. Synthesis of thione S-imides

1-2-2-6 Synthesis of isothiazoles from five-membered heterocycles having one heteroatom

Degl'Innocenti *et al.* have reported[143,144] a novel route to fused isothiazole ring systems through intramolecular trapping of o-azidoaldehydes such as **A** and/or **C** through thionation by the highly chemoselective reagent hexamethyl-disilathiane (HMDST) in the presence of HCl. The azido group seemingly represents a good trapping agent for the thioaldehydes, giving direct access to the fused isothiazoles **B** and **D** (Scheme 24).[145]



Scheme 24. Isothiazoles from five-membered heterocycles

1-2-3 Synthesis of Thiochromenes *via* oxidative ring closure of *α, β*-unsaturated carbodithioates

Sulfur-containing compounds are widely present in natural products and synthetic bioactive molecules as well as in materials.[146] Carbon-sulfur bond formation is a fundamental approach to introduce sulfur into organic compounds. This received considerable attention due to its occurrence in various molecules that are biological, pharmaceutical and material interest.[147] Some of the structural features of thiochromenes are shown in below (Figure 6).

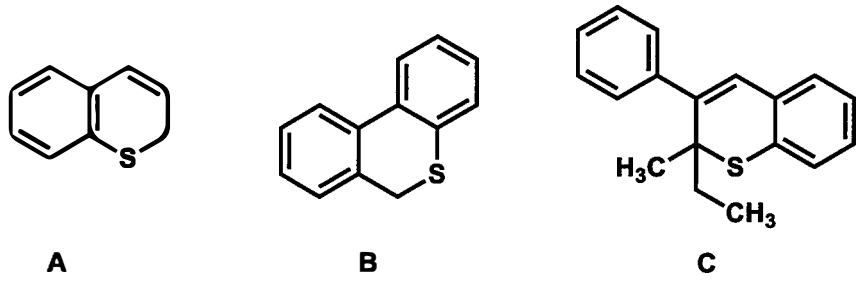


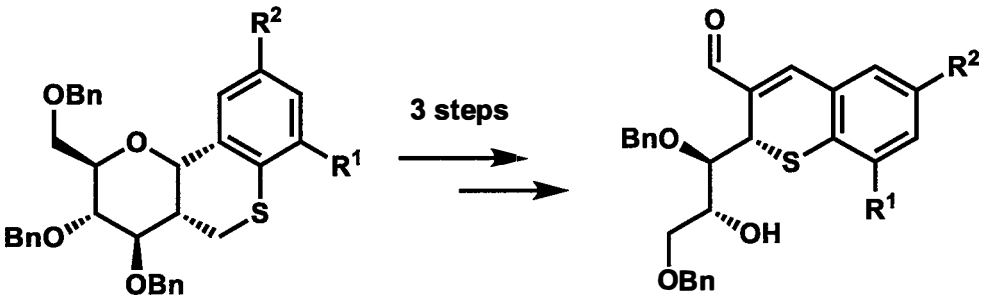
Figure 6. Some of the structural features of thiochromenes

There is currently an increasing interest towards the synthesis of heterocycles containing sulfur such as thiochromanes and 2*H*-thiochromenes. For these compounds,[148] a wide range of biological activities has been identified and used in research and development of new pharmaceutical products.[149] Moreover, preparation of new 2*H*-thiochromenes is an active area of research[150] because of the recent finding of their anticancer activity.[151] Although there have been different methods describing the preparation of thiochromanes or thiochromenes,[148] their asymmetric synthesis either by using optically pure starting materials[152] or chiral auxiliaries[153] are rather scarce. In most cases, the initial step in the mechanism of their formation is a conjugate addition of thiols to electron-deficient olefins or a sulfa-Michael addition,[153f-h] and the second process is a nitroaldol reaction.[154] This way to generate carbon-sulfur bonds has found many applications in chemistry and biology,[155] being one of the most valuable synthetic methods for preparing optically active chiral thiocompounds which are widely used in organic and medicinal chemistry.[156]

1-2-3-1 Synthesis and reactions of thiochromenes and their derivatives

2*H*-1-Benzothiopyrans, commonly known as thiochromenes, are an important heterocyclic class of compounds found in a number of pharmaceutical agents,[157-161] including anticancer,[162,163] anticonvulsant,[164] anti-HIV,[165] and antibacterial agents.[163] Owing to their pharmacological importance, a number of synthetic protocols have been reported for the synthesis of thiochromenes.[166-171] However, there have been very few literature reports on stereoselective synthetic approaches to such compounds. Kobayashi and co-workers reported on the synthesis of thiochromenes in 92–93% ee via condensation of 2-mercaptobenzophenone and α, β-unsaturated

carboxylates in the presence of (diisopropylamino)magnesium reagent followed by dehydration.[172] Kinfe, H. H. and his coworkers have shown an efficient and highly stereoselective strategy for the synthesis of 2,3-substituted thiochromenes via a tandem thio-Michael addition reaction (Scheme 25). This protocol is superior to reported protocols in that the carbohydratederived substituent at the stereogenic center of the thiochromene is versatile and is amenable for further transformation.[173]



Scheme 25. Stereoselective synthesis of thiochromenes *via* intramolecular tandem thio-Michael addition

1-3 Review and general introduction on the synthetic utilities of alkynethiolate derivatives

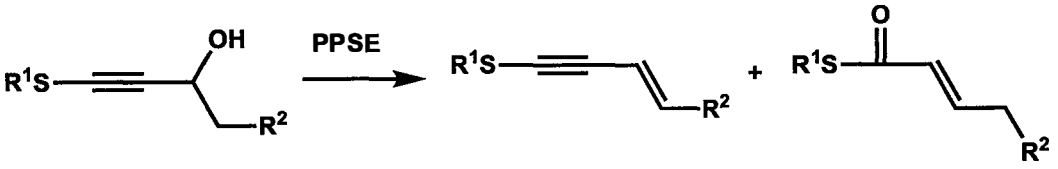
The alkynethiolate precursors are the important compounds in the heterocyclic synthetic chemistry. These are using from many years by the researchers of different fields of chemistry. From the inorganic to organic chemists, they used these alkynethiolate compounds as the important substrates in their preparation for the targeted findings. The use of organosulfur ligands in transition metal chemistry has been of interest due to the importance of the formation or cleavage of C-S bonds either from biological, industrial or environmental point of view.[174] Besides the thiolate or acetylide chemistry has been widely explored, a few complexes containing alkynethiolate ligands are also known.[175] Ara, I. *et al.* reported on the preparation and properties of several mononuclear alkynethiolate titanocene complexes and described their reactivity towards several metal complexes containing labile ligands.[176]

Transition metal chemistry with organosulfur ligands is an attractive subject due to its relevance in biological, industrial and environmental applications.[177-180] The metal chemistry of Alkynethiolate is almost unknown compared with the related aryl or alkyl thiolates, although alkynethiolate compounds are known as important intermediates in the synthesis of basic organic compounds like dithiolenes[181,182] and tetrathiafulvalenes,[183,184] which are excellent starting materials for the building of more complicated coordination solids. A series of alkynethiolate gold(I) derivatives have been synthesised by the cleavage of 4-monosubstituted 1,2,3-thiadiazoles in the presence of strong bases by Lardi´es, N. *et al.*[185]

Thus, from the above discussion it can be said that the alkynethiolate metal complexes, such as the corresponding alkali metal salts of alkynethiolate and selenolate, and other inorganic and organic compounds have been prepared and described. But in the fileds of organic synthetic chemistry, the alkynethiolate precursors have not been used so much. So, we planned and tried to work with the help of these alkynethiolate precursors and found satisfactory results.

The use of organosulfur chemistry has been of interest due to the importance of the formation or cleavage of C-S bonds either from biological, industrial or environmental point of view.[186] Although thiolate or acetylide chemistry has been widely explored, just a few complexes containing alkynethiolates are known.[187] Although the synthesis of a few mononuclear ruthenium complexes containing alkynethiolate ligands has been previously reported, the synthesis of heterocyclic alkynethiolate compounds are still remained in deep interest. The cleavage of ring type of compounds in the presence of strong bases in situ gives alkynethiolates. An effective way of obtaining the alkynylthiolates is the ring cleavage of thiocompounds. Schuijl P. J. W. and Brandsma L. have reported that the reaction of alkynethiolates with thiols furnishes dithioesters,[188] and on analogy they prepared thioamides[189] from alkynethiolate and a secondary amine. Favorable results were obtained when t-butyl bromide was used as proton donor.[190]

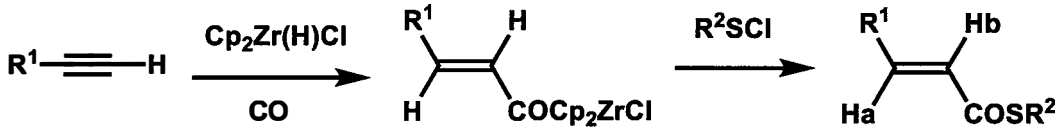
There are many ways to synthesize α, β-unsaturated thioesters and dithioesters. The treatment of y-chalcogen-substituted propargyl alcohols with polyphosphoric acid trimethylsilyl ester (PPSE) gave α, β-unsaturated thioesters *via* the Meyer-Schuster type rearrangement[191] instead of γ-chalcogen-substituted enynes (Scheme 26). γ-Sulfur-substituted propargyl alcohols reacted with PPSE to give the α, β-unsaturated thioesters in good yields. However, the reactions also gave the enyne sulfides.[192]



Scheme 26. Meyer-Schuster rearrangement of γ-sulfur-substituted propargyl alcohols to synthesis of α, β-unsaturated thioesters

Coupling reactions of acylzirconocene chlorides with organic halides afforded the corresponding ketones.[193] Considering the high electrophilicity of arylsulfenyl chlorides, P. Zhongt and his coworkers[194] attempted to react them with the α, β-unsaturated acylzirconocene chlorides **2.** Experimental results show that, $Cp_2Zr(H)Cl$[195] adds to terminal alkynes **1** in CH_2C1_2 at room temperature stereospecifically with high regioselectivity to yield vinylic Zr^{IV} complex, which was stirred under CO atmosphere to give the α, β-unsaturated acylzirconocene chlorides the adducts **2.**

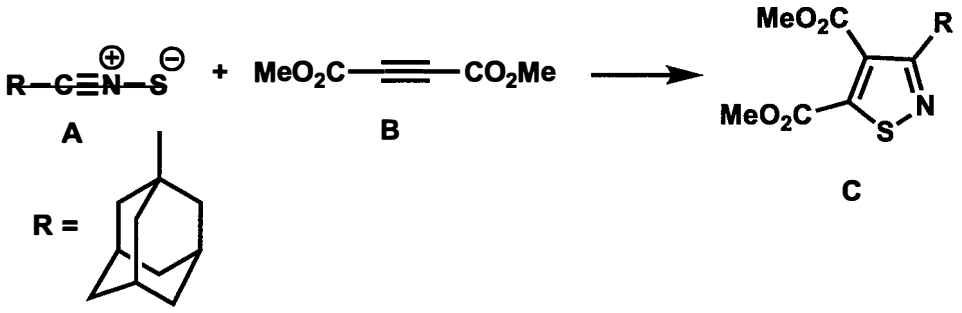
2 react with arylsulfenyl chlorides[196] rapidly at O°C to afford α, β-unsaturated thioesters 3 with good to excellent yields (Scheme 27).



R^1 = Ph, 4-ClC_6H_4, n-C_4H_9, n-C_5H_{11}; R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4

Scheme 27. A stereoselective synthetic route to (*E*)-α, β-unsaturated thioesters

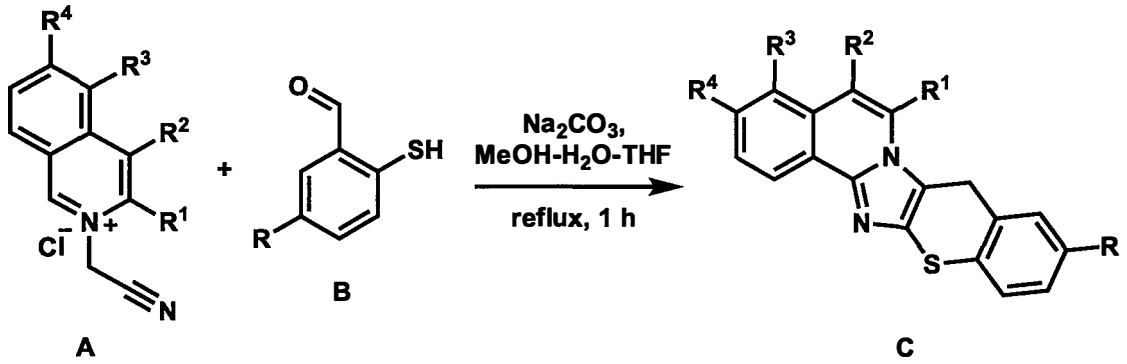
The methods for the synthesis of isothiazoles using cycloaddition and condensation reactions of compounds containing a set of essential fragments are the most well-studied and attract, as before, the attention of investigators. Thus the 1,3-dipolar cycloaddition of nitrile sulfide (**A**) to dimethyl acetylenedicarboxylate (**B**) yields the isothiazole derivative (**C**) the structure of which has been confirmed by X-ray diffraction analysis (Scheme 28).[197]



Scheme 28. Synthesis of isothiazoles *via* 1,3-dipolar cycloaddition

Domino reactions have emerged as a powerful tool for the effective creation and expansion of molecular diversity.[198] Carbon–carbon and carbon–heteroatom bond-forming reactions are crucial to organic synthesis. Domino processes are important for generating high levels of diversity and complexity giving rise to complex structures by simultaneous formation of two or more bonds from simple substrates. These advantages are of particular interest in pharmaceutical research for the construction of libraries of biologically active compounds. Thus, developing new,

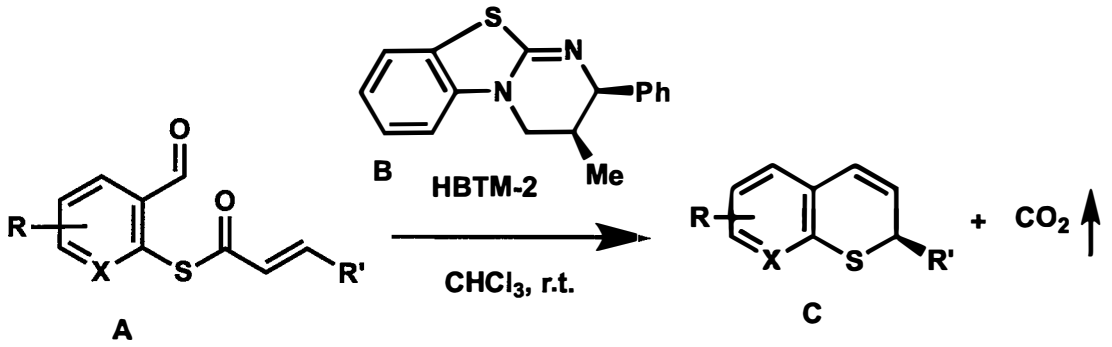
environmentally benign domino reactions is an important topic of green chemistry.[199] Herein, Voskressensky, L. G. and his coworkers present a novel reaction which provides an easy access towards functionalized thiochromeno [2′,3′:4,5] imidazo[2,1-α]isoquinoline derivatives, that means a one-pot protocol towards previously unreported derivatives of thiochromeno [2′,3′:4,5] imidazo[2,1-α]isoquinoline via a domino reaction of isoquinoline-derived iminium salts and α-mercapto benzaldehydes is elaborated (Scheme 29).[200]



R = NO_2, R^1 = H, R^2 = H, R^3 = H, R^4 = H; 66%
R = NO_2, R^1 = H, R^2 = H, R^3 = H, R^4 = OH; 29%
R = NO_2, R^1 = H, R^2 = H, R^3 = OH, R^4 = H; 22%
R = NO_2, R^1 = Me, R^2 = H, R^3 = H, R^4 = H; 21%
R = Br, R^1 = H, R^2 = H, R^3 = H, R^4 = OH; 30%

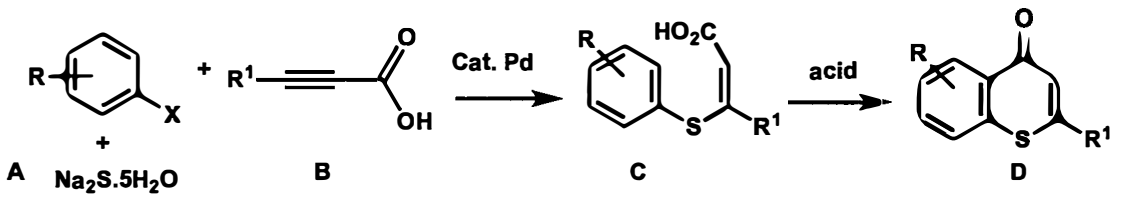
Scheme 29. The reaction of isoquinolinium salts **A** with thiosalicylic aldehyde **B** to form thiochromenes **C**

Enantioselective synthesis of 2-substituted thiochromenes and thiochromans has attracted some attention because of the potential of their derivatives in drug design.[201] Ahlemeyer, N. A. and Birman, V. B. has developed a novel, reagent-free catalytic transformation of α, β-unsaturated thioesters into 2-substituted thiochromenes,[202] with carbon dioxide as the only byproduct. Amidine-based catalysts, particularly homobenzotetramisole and its analogues, achieve high enantioselectivities and yields in this process (Scheme 30).



Scheme 30. Catalytic asymmetric synthesis of thiochromenes

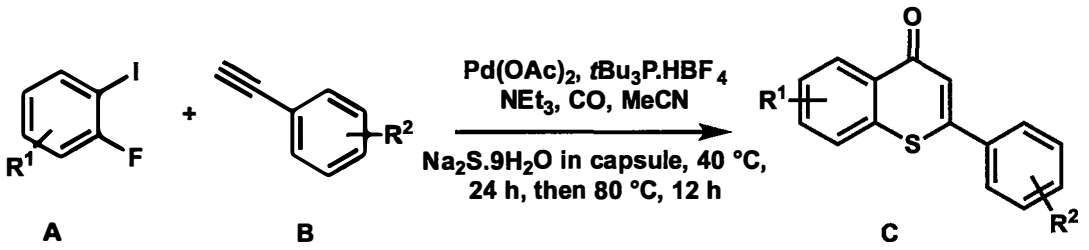
1-Alkenyl sulfides are important intermediates in the synthesis of organic and polymeric materials due to their ease of transformation,[203] and are key structure units in natural products and biologically active compounds.[204] T. Palani *et al.*[205] have developed a stereoselective synthesis of (*Z*)-arylthioacrylic acids from the three-component reaction of aryl halides, $Na_2S·5H_2O$, and propiolic acid. They suggested that the C-S bond formation of aryl iodide and $Na_2S·5H_2O$ occurred first, and then reacted with propiolic acid. They also found that $Na_2S·5H_2O$ has key role in the highly stereoselective formation of (*Z*)-isomer. In addition, the resulting arylthioacryl acids were easily transformed into thiochromenones (Scheme 31). The method is free of toxic and smelly thiols, and this report is the first on the one-pot direct synthesis of thiochromenones from aryl halides.



Scheme 31. Synthesis of alkenyl sulfides and thiochromenes

Purification processes probably are the most time-consuming, cost-ineffective, and waste-producing manual operations in modern organic synthesis. However, to improve compatibility and to ensure that the consecutive reaction proceeds smoothly, the purification of intermediates seems to be inevitable. As an advancement of this conventional "stop-and-go" synthetic approach,

multistep one-pot strategies, which are more compact, less time-consuming, and less waste-generating, can dramatically improve synthetic efficiency.[206] In this respect, significant progress has been achieved in the area of multicomponent reactions (MCR),[207] as illustrated by various examples of three-component reactions.[208] Considering these points, C. Shen and his coworkers[209] have developed an efficient palladium-catalyzed carbonylative method for preparing thiochromenones in a four-component reaction that makes use of an reagent capsule (Scheme 32). The reagent capsule was essential to solving problems related to the poisoning of the transition-metal catalyst as well as the compatibility of the various reagents in the one-pot process. It also helped to reduce the total number of manual operations, rendering the purification of intermediates unnecessary, and greatly facilitated the development of a highly efficient, environmentally friendly multicomponent reaction.



Scheme 32. Palladium-catalyzed four-component reaction of substituted 1-fluoro-2-iodobenzenes and substituted phenylacetylene derivatives

1-4 The research purpose of this work

There are many applications of these type of sulfur containing compounds in the fields of specially the biological and pharmaceutical sectors. Because of these many applications in the synthetic organic study, we planned to synthesyze some of the sulfur containing heterocyclic compounds and found good results.

1-4-1 Biological and Pharmaceutical Importance of Cyclic Sulfones

Sulfones are useful synthons for the construction of carbon–carbon bonds via anionic, cationic, and radical intermediates.[210] Fused or 3-substituted sulfolenes are a latent source of conjugated dienes. Therefore, they are useful partners in Diels–Alder reactions for the synthesis of complex synthetic targets containing six-membered rings.[211] Due to the electron-withdrawing nature of the sulfone moiety, neighboring methylene or methyl group(s) can be alkylated with various electrophiles. This unique reactivity coupled with the ease of desulfonylation has been exploited in several instances for the construction of various theoretically interesting and biologically active molecules.[212] Although sulfones are used widely in organic synthesis,[213] most of the methods involve multistep synthetic sequences.[214] The importance of sulfones encouraged us to search for alternate synthetic routes.

Chiral cyclic sulfones are the key scaffolds in a number of pharmaceutically important compounds and natural products as those exemplified in Figure 7,[215] which exhibit broad biological activities such as inhibiting HIV-1 protease, hepatitis C virus, influenza neuraminidase, and human carbonic anhydrase II, etc.

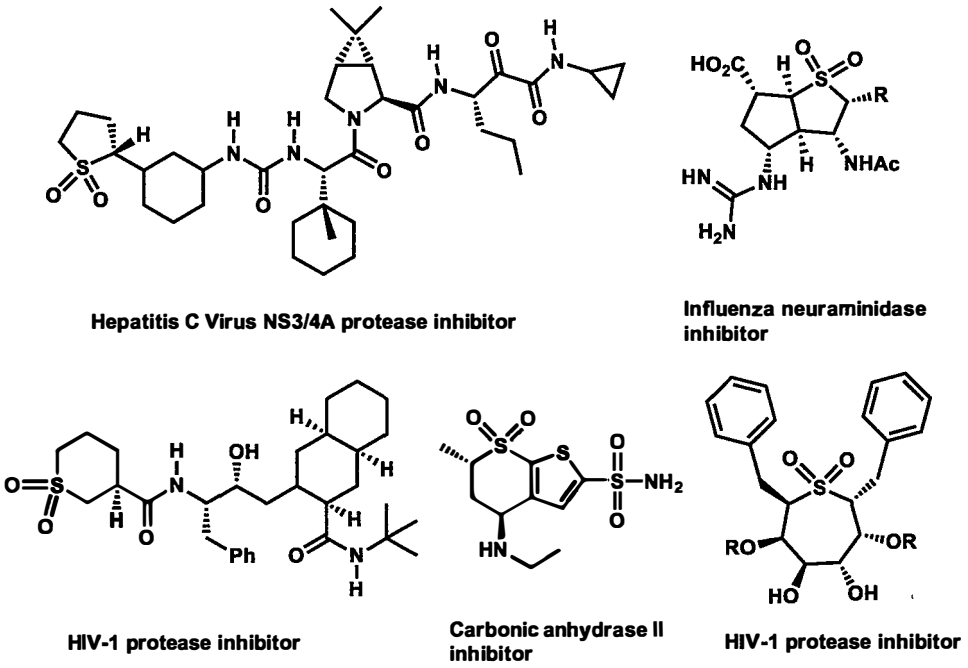


Figure 7. Biologically active compounds containing a cyclic sulfone motif.

Hepatitis C virus (HCV) infection remains a public health burden by afflicting more than 170 million people worldwide.[216] Chronic HCV infection is the leading cause for liver failure and liver cancer. The health care costs associated with HCV are expected to increase substantially as the majority of patients reach the end stage complications of the disease. The current standard of care for HCV infection is a combination of peginterferon and ribavirin.[217] This treatment is effective and can successfully deliver sustained virologic response (SVR) in >75% of patients infected with genotype-2 and -3. However, patients infected with genotype-1, which include most of the patients in U.S., Europe, and Japan, achieve only 40% SVR. Therefore, tremendous efforts have been directed to develop new and more effective therapeutic agents for the treatment of HCV infection. Therefore, novel treatments are needed to combat the infection. Francisco Vel_azquez and his research group continued for the discovery of more and more potent compounds[218] with improved pharmacokinetic profiles. A new series of HCV NS3 protease inhibitors like P having a cyclic sulfone P3-cap have been discovered. Compounds showed Ki values in the single-digit nM range and their cellular potency was improved (Figure 8).

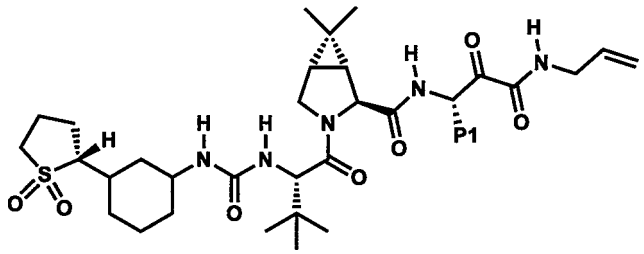


Figure 8. Five- and six-membered cyclic sulfone inhibitors: Evaluation of P1-allyl group

Structure-based design of a series of cyclic hydroxyethylamine BACE1 inhibitors (shown in Figure 9) allowed the rational incorporation of prime- and nonprime-side fragments to a central core template without any amide functionality. The core scaffold selection and the structure–activity relationship development were supported by molecular modeling studies and by X-ray analysis of BACE1 complexes with various ligands to expedite the optimization of the series. The direct extension from P1-aryl- and heteroaryl moieties into the S3 binding pocket allowed the enhancement of potency and selectivity over cathepsin D. Restraining the design and synthesis of compounds to a physicochemical property space consistent with central nervous system drugs led to inhibitors with improved blood–brain barrier permeability. Guided by structure-based optimization, H. Rueeger and his coworkers were able to obtain highly potent compounds[219] such as 60p with enzymatic and cellular IC_{50} values of 2 and 50 nM, respectively, and with >200-fold selectivity over cathepsin D. Pharmacodynamic studies in APP51/16 transgenic mice at oral doses of 180 μmol/kg demonstrated significant reduction of brain Aβ levels.

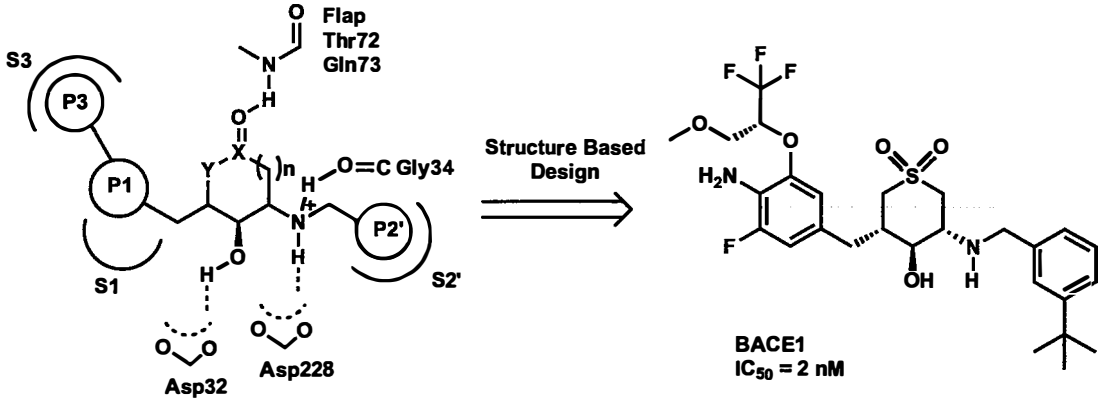
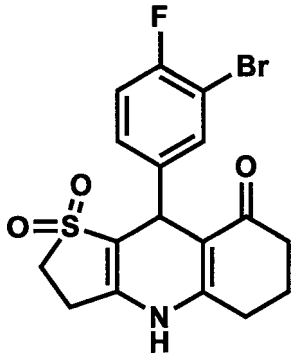


Figure 9. Designed the structure based cyclic sulfones which acts as potent and selective β-Site APP-cleaving enzyme 1 (BACE1) inhibitors

1-4-1-1 Biological activity of β-Keto Sulfones

A constantly increasing number of papers describing preparation, properties and application of β-keto sulfones indicate their growing importance as building blocks of high synthetic potential. β-keto sulfone type substances are widely used in the synthesis of novel biologically active compounds. Derivatives of thiopyran-3-one and dihydrothiophen-3-one 1,1-dioxides are antagonists of calcium channels, and this gives rise to their coronaro- and bronchodilatory activity.[220-222] It is interesting that there are also potassium channel modulators among these compounds.[223] In[224] the relation between the structure of thiopyran-3-one 1,1-dioxides and their ability to act as agonists of these channels was analyzed. One of the most powerful modulators of ATP-dependent potassium channels is compound A-278637 (Figure 10), which is at present undergoing preclinical trials.[225-228]



A-278637

Figure 10. Compound A-278637

1-4-2 Biological Importance of Isothiazoles

A sulfur-containing five-membered ring compound is a partial structure contained in many pharmacological activities, physiologically active substances, and many bioactive organic compounds having an isothiazole ring have been reported so far. For example, JE-2147 derivative **B** having HIV protease inhibitory activity synthesized by Lu et al.,[229] Isothiazole derivative **E**[230] having HCV NS5B polymerase inhibitory activity synthesized by Yao *et al.*, Viral herpes simplex synthetically synthesized by Clerici et al 2'-dioxy-5-(isothiazol-5-yl) uridine **A**[233] having virus

(HSV-1) kinase inhibitory activity, VRX 0466617 **C** having selective Chk2 inhibitory activity reported by Carlessi et al.,[232] Synthesized by Beebe et al. (VEGFR-2) inhibitory activity inhibitor CP-547,632 **D** have been reported (**Figure 11**)[231], respectively.

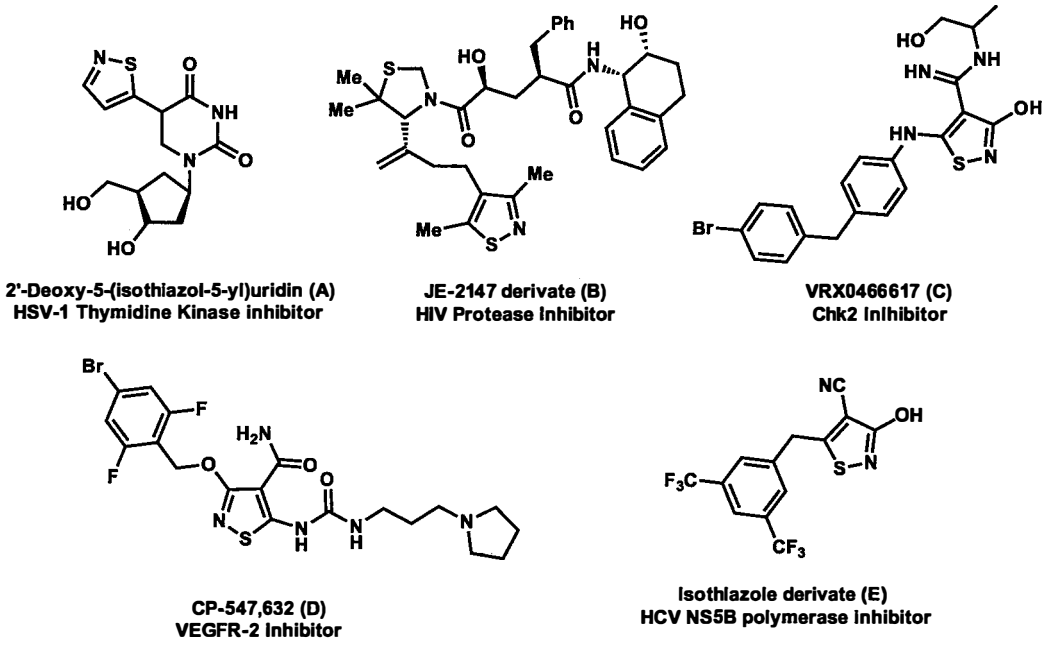
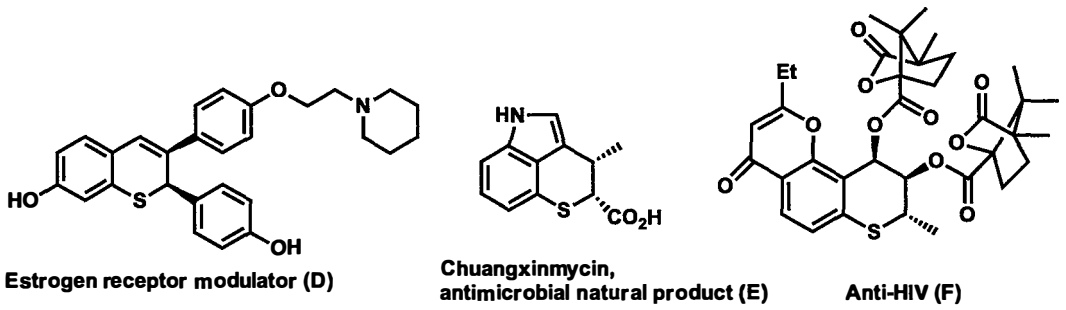


Figure 11. The importance of isothiazoles in medicinal and pharmaceutical sectors

1-4-3 Biological importance of thiochromenes and their derivatives

Thiochromenes, thiochromanes and their derivatives are valuable compounds due to their potential applications in pharmaceutical industries.[234-236] Particularly, thiochromenes are the important heterocyclic scaffold which is present in many biologically important molecules and has been used as valuable building block for the synthesis of pharmaceutical active compounds. Over the past decade, thiochromenes have attracted increasing attention owing to their diverse bioactivities specially in medicinal chemistry and drug discovery. Previous studies revealed that thiochromene derivatives possess a wide variety of biological activities including estrogen receptor modulator, chuangxinmycin as antimicrobial natural product (Figure 12), Anti-inflammation,[237] Anti-HIV,[238] anti-bacteria,[239] anti-hyperplasia,[240] anti-psychiatric[241] and anti-cancer[242] activities. As a result, a number of strategies have been devised for the synthesis of such heterocycles.



Estrogen receptor modulator (D)

Chuangxinmycin, antimicrobial natural product (E)

Anti-HIV (F)

Figure 12. Biologically and pharmaceutically active Substituted thiochromene derivatives

Chapter 2:

Synthesis of Alkynyl Propargyl Sulfones and their Conversion into six-membered Cyclic β-ketosulfones

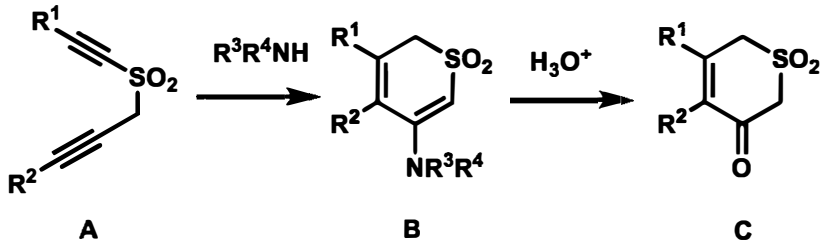
Chapter 2: Synthesis of Alkynyl Propargyl Sulfones and their conversion into six-membered Cyclic β-ketosulfones

2-1 Introduction

Sulfones belong to a known class of organosulfur compounds, which found various applications in organic synthesis. Among other derivatives of sulfones, a special attention of synthetic chemists is drawn to sulfones containing functional group. In particular, 2-oxo-sulfones (*β*-keto sulfones) bearing carbonyl function in the *β*-position to sulfonyl group are versatile synthetic intermediates used for the preparation of diverse classes of organic compounds. Thus, the syntheses of cyclic sulfones have been a deep interest for their potent biological activities as drugs, useful synthetic intermediates, and the potentiality as the building blocks for heterocyclic compounds, and varoius synthetic methods for these compounds have been explored. However, for the synthesis of unsaturated cyclic β-ketosulfones, the limited methods have been reported till now due to the difficulty in preparation of suitable precursors in spite of their potentiality as the new synthetic intermediates bearing an active methylene group bound to sulfonyl and carbonyl functionalities are exist in the compounds. It was expected that the cyclic *β*-ketosulfones would be formed from alkynyl propargyl sulfones *via* the ring closure of some synthetic equivalents of propargyl *α*-sulfonyl carbanion and the electrondeficient alkynyl sulfone moiety. The conversion of propargyl sulfones into the corresponding enaminosulfones were reported by Skatteboel previously, and several groups also reported Michael-type nucleophilic addition of alkynyl sulfones forming *β*-functionalized vinyl sulfones. Actually, in the course of this synthetic research works on the chemistry of alkynechalcogenolates and their derivatives, the researchers have already found a thermal conversion of alkynyl propargyl sulfones into alleneynes *via* [3,3] sigmatropic rearrangement and the subsequent SO_2 extrusion from the intermediary allenylthioketene *S,S*-dioxides, and, therefore, the main problem on thermal reaction of alkynyl propargyl sulfones in the presence of amine is the competition of two possible pathways. Based on these previous data we planned to find out a new and convenient synthesis of cyclic β-ketosulfones *via* cyclic enaminosulfones formed through a synchronous amine-induced cyclization of alkynyl propargyl sulfones.

2-2 Results and Discussion

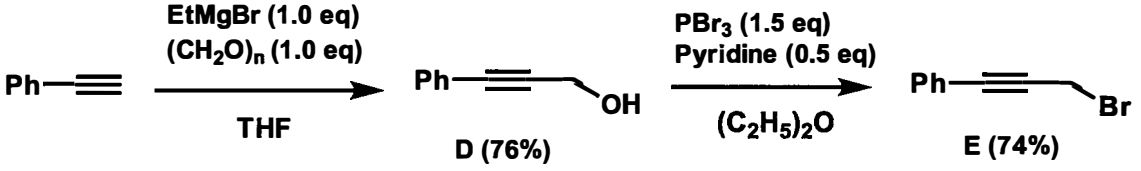
Here, a novel and convenient two-step synthesis of six-membered cyclic β-ketosulfones **C** by the treatment of alkynyl propargyl sulfones **A** with a secondary amine and the subsequent acidic hydrolysis of the resulting enaminosulfones **B** has been described (Scheme 33) in this chapter.



Scheme 33. Formation of six-membered cyclic *β*-ketosulfones **C** from alkynyl propargyl sulfones **A**

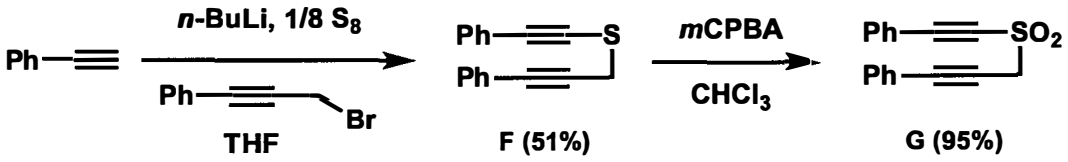
2-2-1 Preparation of substrates

At first, for the preparation of the substrates like alkynyl propargyl sulfides, some procedures were followed. Firstly, 3-phenyl-2-propyn-1-ol **D** and 3-bromo-1-phenyl-1-propyn, **E are prepared following the usual procedures. Then** alkynyl propargyl sulfide **F** were prepared (Scheme 34).



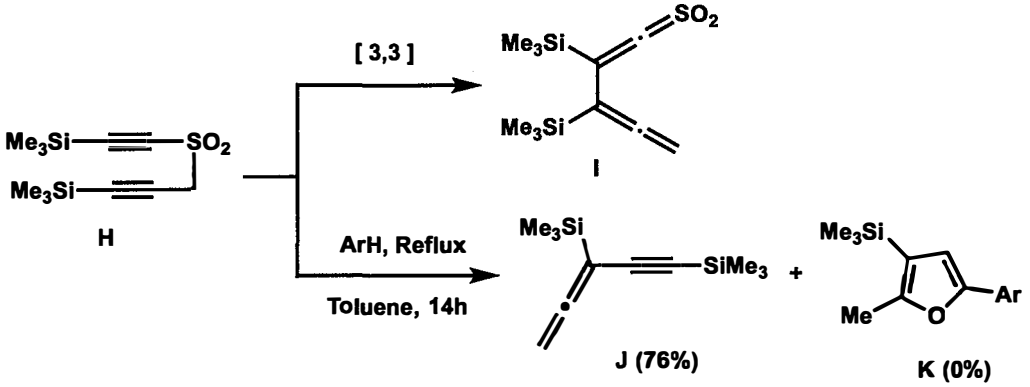
Scheme 34. Preparation of 3-phenyl-2-propyn-1-ol **D** and 3-bromo-1-phenyl-1-propyn, **E**

The alkynyl propargyl sulfides **F 1** were then prepared by following some procedures and by the treatment of terminal alkynes with a base, elemental sulfur, and substituted propargyl bromides according to the previous reports, and sulfides **F 1** were efficiently converted into the corresponding sulfones **G 2** by treating with *m*CPBA (2.2 eq.) in $CHCl_3$ at 0 °C (Scheme 35).



Scheme 35. Preparation of alkynyl propargyl sulfide **F** and alkynyl propargyl sulfone **G**

The application of highly reactive species to organic synthesis is desired to the end of efficient and straightforward transformation of complicated target molecules. Aoyagi, S. *et al.* in 2007 described a novel generation and trapping of allenylthioketene S,S-dioxides[243] **I** by thermal reaction of alkynyl propargyl sulfones **H**, and the formation of allenynes **K** through spontaneous SO2 extrusion of 2. They also prepared the allenynes **J** or furans **K** as colorless oils in moderate yields. Before that Aoyagi, S. *et al.* in 2006 prepared alkynyl propargyl sulfones **H** in excellent yields by the treatment of alkynyl propargyl sulfides[244,245] with *m*-CPBA (2.2 equiv) in chloroform at 0 °C for 30 min.

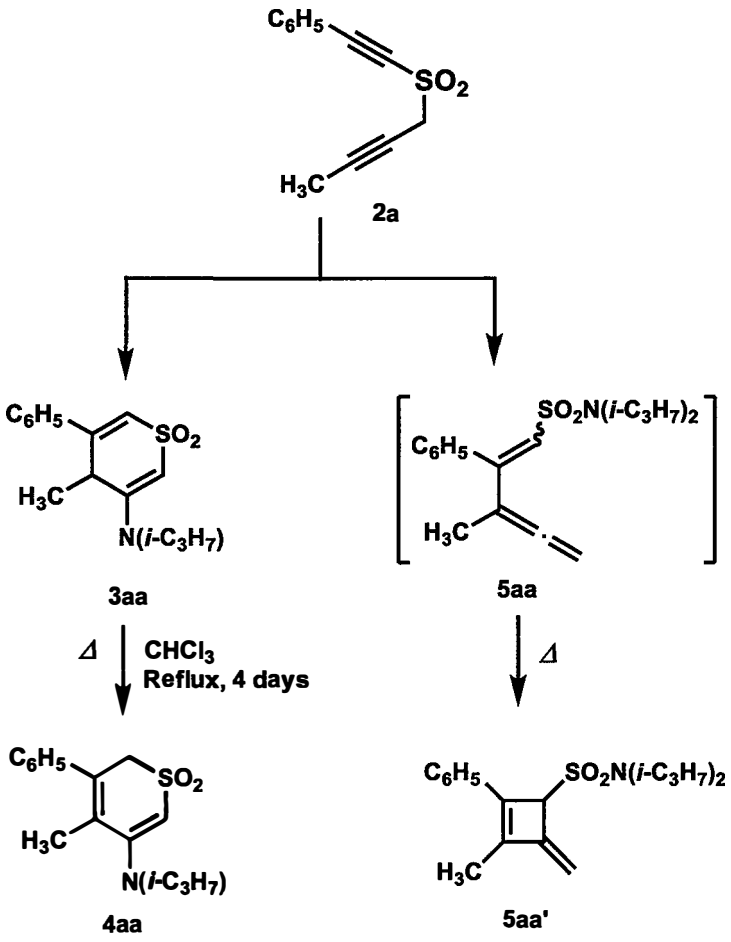


Scheme 36. Preparation of allenylthioketene S,S-dioxides **I,** allenynes **J** and furans **K**

2-2-2 Details Explanation

A new product was obtained in 50% yield as a sole product when a $CHCl_3$ solution of sulfone **2a** ($R^1 = C_6H_5$, $R^2 = CH_3$) was treated with $(i\text{-}C_3H_7)_2NH$ (3.0 mol amt.) at 0 °C to R.T: for 3 h, and the treatment of a $CHCl_3$ solution of **2a** in the presence of $(i\text{-}C_3H_7)_2NH$ at refluxing temperature for 3 h in a similar manner afforded a separable mixture of **3aa** ($R^1 = C_6H_5$, $R^2 = CH_3$, $R_3 = i\text{-}C_3H_7$) and **4aa** ($R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = i\text{-}C_3H_7$) in 61% and 17% yields, respectively. Moreover, the

compound **4aa** was exclusively obtained in 76% yield by heating of a toluene solution of sulfone **2a** under refluxing temperature for 24 h. All physical and spectral data of products, as well as their elemental analysis data, were fully consistent with the structures of cyclic enaminosulfones **3aa** and **4aa**. Irreversible isomerization of **3aa** into $\alpha,\beta,\gamma,\delta$-unsaturated enaminosulfone **4aa** bearing a higher conjugation system was also observed by heating under refluxing temperature in $CHCl_3$ (Scheme 36). It is noteworthy that sulfones **2** were stable enough at R.T. and underwent [3,3] sigmatropic rearrangement by heating under refluxing temperature in toluene or benzene. Therefore, the preferable formation of cyclic enaminosulfones **3aa** and **4aa** was explained by a base-induced isomerization of **2a** into allenyl sulfone **5a** rather than thermal [3,3] sigmatropic rearrangement and the subsequent nucleophilic addition of an amine to the resulting sulfene-type intermediates.



Scheme 37. Thermal reaction of alkynyl propargyl sulfone **2a** ($R^1 = C_6H_5$, $R^2 = CH_3$) in presence of $(i\text{-}C_3H_7)_2NH$.

The corresponding six-membered cyclic $\alpha,\beta,\gamma,\delta$-unsaturated enaminosulfones **4** were obtained in moderate to high yields as sole products when the sulfones **2** bearing various substituents at the R^1 and R^2 positions were treated with an excess amount of $(i\text{-}C_3H_7)_2NH$ or $(c\text{-}C_6H_{11})_2NH$ in $CHCl_3$, 1,2-dichloroethane (DCE), benzene, or toluene at ambient temperature in a similar manner. The structure of cyclic $\alpha,\beta,\gamma,\delta$-unsaturated enaminosulfones **4** was confirmed through the NOE experiment of **4ba**, by which a positive NOE was observed between the vinyl proton and the methyl proton of diisopropylamino group along with the absence of NOE between the methylene protons adjacent to SO_2 group with the methyl proton of diisopropylamino group. Therefore, the alternative structure **4a'** was excluded out for the products. Especially, the final structural

determination of enaminosulfones **4** was performed by X-ray crystallographic analysis. All the results of the reactions are summarized and shown in Table 1.

X-ray crystallographic data of cyclic enaminosulfone 4da:

$C_{23}H_{37}NO_2SSi$, M_w = 419.70, Colorless prismatic, Triclinic, P$\bar{1}$ (#2), a = 11.576(1) Å, b = 13.525(2) Å, c = 8.377(2) Å, α = 97.20(2) °, β = 90.28(1) °, γ = 108.025(9) °, V = 1235.9(3) Å^3, Z = 2, D_{calc} = 1.128 g/cm3, μ(MoKα) = 1.96 cm^{-1}, R = 0.056, R_w = 0.060. Bond lengths (Å): S(1)-O(1), 1.431(3); S(1)-O(2). 1.448(3); S(1)-C(1), 1.774(4); S(1)-C(5), 1.697(4); Si(1)-C(2), 1.912(3); Si(1)-C(12), 1.862(5); Si(1)-C(13), 1.872(5); Si(1)-C(14), 1.909(4); N(1)-C(4), 1.351(4); N(1)-C(6), 1.491(4); N(1)-C(9), 1.484(4); C(1)-C(2), 1.565(5); C(1)-H(1), 0.94(3); C(1)-H(2), 1.09(3); C(2)-C(3), 1.332(4); C(3)-C(4), 1.520(4); C(3)-C(18), 1.499(4); C(4)-C(5), 1.362(5); C(5)-H(2), 0.77(4); C(6)-C(7), 1.502(5); C(6)-C(8), 1.527(5); C(6)-H(4), 0.96(3); C(7)-H(5), 0.92(3); C(7)-H(6), 0.94(4); C(7)-H(7), 1.05(5); C(8)-H(8), 0.96(4); C(8)-H(9), 0.85(4); C(8)-H(10), 1.09(4); C(9)-H(10), 1.539(6); C(9)-C(11), 1.546(6); C(9)-H(11), 0.98(3); C(10)-H(12), 1.06(4); C(10)-H(13), 1.09(4); C(10)-H(14), 1.00(5); C(11)-H(15), 0.97(4); C(11)-H(16), 0.89(6); C(11)-H(17), 1.11(5); C(12)-H(18), 0.87(5); C(12)-H(19), 0.88(4); C(12)-H(20), 0.92(4); C(13)-H(21), 0.88(5); C(13)-H(22), 0.90(5); C(13)-H(23), 1.04(5); C(14)-C(15), 1.506(7); C(14)-C(16), 1.553(6); C(14)-C(17), 1.530(7); C(15)-H(27), 0.88(5); C(15)-H(28), 1.12(5); C(15)-H(29), 0.94(5); C(16)-H(30), 0.88(5); C(16)-H(31), 0.88(6); C(16)-H(32), 1.15(6). Bond angles (deg): O(1)-S(1) -O(2), 116.0(2); O(1)-S(1)-C(1), 108.3(2); O(1)-S(1)-C(5), 114.2(2); O(2)-S(1)-C(1), 109.8(2); O(2)-S(1)-C(5), 107.9(2); C(1)-S(1)-C(5), 99.2(2); C(2)-Si(1)-C(12), 115.7(2); C(2)-Si(1)-C(13), 106.2(2); C(2)-Si(1)-C(14), 108.7(1); C(12)-Si(1)-C(13), 107.2(2); C(12)-Si(1)-C(14), 109.2(2); C(13)-Si(1)-C(14), 109.8(2); C(4)-N(1)-C(6), 120.0(2); C(4)-N(1)-C(9), 122.5(3); C(6)-N(1)-C(9), 115.3(3); S(1)-C(1)-C(2), 106.5(2); S(1)-C(1)-H(1), 108(2); S(1)-C(1)-H(2), 106(2); C(2)-C(1)-H(1), 111(2); C(2)-C(1)-H(2), 115(2); H(1)-C(1)-H(2), 110(3); Si(1)-C(2)-C(1), 113.0(2); Si(1)-C(2)-C(3), 129.4(2); C(1)-C(2)-C(3), 116.8(3); C(2)-C(3)-C(4), 121.9(3); C(2)-C(3)-C(18), 123.3(3); C(4)-C(3)-C(18), 113.7(3); N(1)-C(4)-C(3), 117.9(3); N(1)-C(4)-C(5), 125.6(3); C(3)-C(4)-C(5), 116.3(3); S(1)-C(5)-C(4), 120.9(3); S(1)-C(5)-H(3), 111(3); C(4)-C(5)-H(3), 126(3); N(1)-C(6)-C(7), 112.4(3); N(1)-C(6)-C(8), 110.8(3); N(1)-C(6)-H(4), 102(2); C(7)-C(6)-C(8), 112.9(3); C(7)-C(6)-H(4), 112(2); C(8)-C(6)-H(4), 106(2); C(6)-C(7)-H(5), 110(2); C(6)-C(7)-

H(6), 120(3); C(6)-C(7)-H(7), 112(3); H(5)-C(7)-H(6), 107(3); H(5)-C(7)-H(7), 113(3); H(6)-C(7)-H(7), 94(4); C(6)-C(8)-H(8), 105(2); C(6)-C(8)-H(9), 105(3); C(6)-C(8)-H(10), 109(2); H(8)-C(8)-H(9), 88(4); H(8)-C(8)-H(10), 121(4); H(9)-C(8)-H(10), 125(4); N(1)-C(9)-C(10), 110.9(3). Torsion angles (deg): S(1)-C(1)-C(2)-Si(1), 120.2(2); S(1)-C(1)-C(2)-C(3), -50.5(3); S(1)-C(5)- C(4)-N(1), 166.9(3); S(1)-C(5)-C(4)-C(3), -18.3(4); Si(1)-C(2)-C(3)-C(4), -169.1(2); Si(1)-C(2)-C(3)-C(18), -1.6(5); O(1)-S(1)-C(1)-C(2), -59.3(3); O(1)-S(1)-C(5)-C(4), 87.4(3); O(2)-S(1)-C(1)-C(2), 173.0(2); O(2)-S(1)-C(5)-C(4), -142.0(3); N(1)-C(4)-C(3)-C(2), -145.0(3); N(1)-C(4)-C(3)-C(18), 46.4(4); C(1)-S(1)-C(5)-C(4), -27.6(4); C(1)-C(2)-Si(1)-C(12), -156.8(3); C(1)-C(2)-Si(1)-C(13), -38.1(3); C(1)-C(2)-Si(1)-C(14), 80.0(3); C(1)-C(2)-C(3)-C(4), -0.2(4); C(1)-C(2)-C(3)-C(18), 167.3(3); C(2)-Si(1)-C(14)-C(15), 63.7(3); C(2)-Si(1)-C(14)-C(16), -176.0(3); C(2)-Si(1)-C(14)-C(17), -59.3(3); C(2)-C(1)-S(1)-C(5), 60.1(3); C(2)-C(3)-C(4)-C(5), 39.8(4); C(2)-C(3)-C(18)-C(19), -107.6(4); C(2)-C(3)-C(18)-C(23), 71.5(4); C(3)-C(2)-Si(1)-C(12), 12.4(4); C(3)-C(2)-Si(1)-C(13), 131.1(3); C(3)-C(2)-Si(1)-C(14), -110.8(3); C(3)-C(4)-N(1)-C(6), 35.5(4); C(3)-C(4)-N(1)-C(9), -162.4(3); C(3)-C(18)-C(19)-C(20), 177.7(3); C(3)-C(18)-C(23)-C(22), -178.6(3); C(4)-N(1)-C(6)-C(7), -128.7(3); C(4)-N(1)-C(6)-C(8), 104.0(3); C(4)-N(1)-C(9)-C(10), 61.4(4); C(4)-N(1)-C(9)-C(11), -67.6(5); C(4)- C(3)-C(18)-C(19), 60.8(4); C(4)-C(3)-C(18)-C(23), -120.1(3); C(5)-C(4)-N(1)-C(6), -149.8(3); C(5)-C(4)-N(1)-C(9), 12.3(5); C(5)-C(4)-C(3)-C(18), -128.8(3); C(6)-N(1)-C(9)-C(10), -135.7(3); C(6)-N(1)-C(9)-C(11), 95.4(4); C(7)-C(6)-N(1)-C(9), 67.9(4); C(8)-C(6)-N(1)-C(9), -59.4(4); C(12)-Si(1)-C(14)-C(15), -63.3(4); C(12)-Si(1)-C(14)-C(16), 57.0(4); C(12)-Si(1)-C(14)-C(17), 173.7(3); C(13)-Si(1)-C(14)-C(15), 179.4(3); C(13)-Si(1)-C(14)-C(16), -60.2(4); C(13)-Si(1)-C(14)-C(17), 56.4(4); C(18)-C(19)-C(20)-C(21), 1.1(6).

Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 1826547.

The ORTEP drawing of cyclic enaminosulfone (Figure 13) are shown in below.

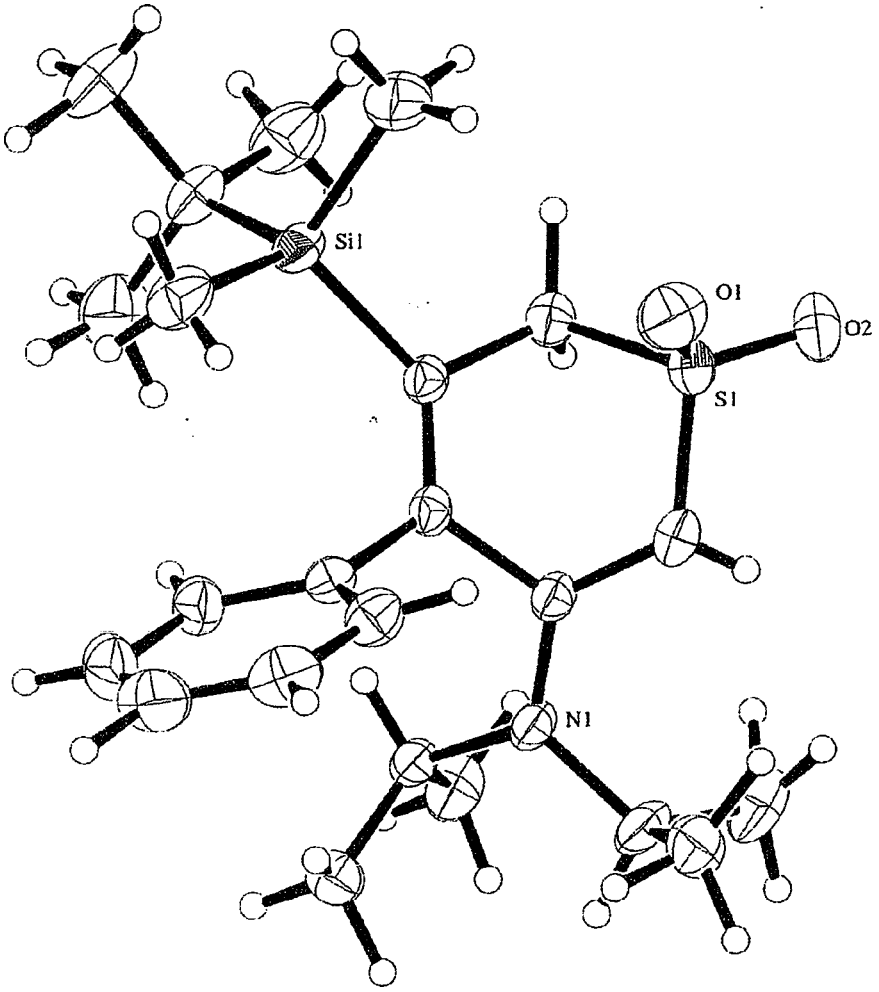
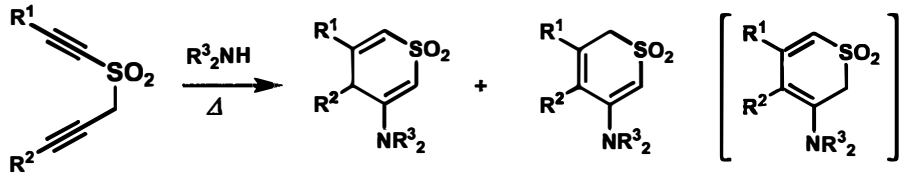


Figure 13. ORTEP drawing of cyclic enaminosulfone (R^1 = *t*-$C_4H_9(CH_3)_2Si$, R^2 = C_6H_5, R^3 = *i*-C_3H_7)

Table 1. Reaction of alkynyl propargyl sulfones **2** with secondary amines



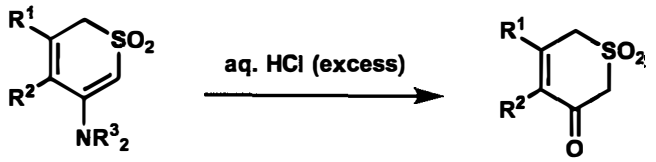
2 **3** **4** **4'**

Substrate			R^3_2NH (3.0 mol amt.)	Solvent	Temp (°C)	Time (h)	Yield (%)	
R^1	R^2	**2**	R^3				**3**	**4**
C_6H_5	CH_3	**2a**	*i*-C_3H_7	$CHCl_3$	0 - R.T.	3	50 (**3aa**)	0
C_6H_5	CH_3	**2a**	*i*-C_3H_7	$CHCl_3$	Reflux	3	61 (**3aa**)	17 (**4aa**)
C_6H_5	CH_3	**2a**	*i*-C_3H_7	Toluene	Reflux	24	0	76 (**4aa**)
C_6H_5	C_6H_5	**2b**	*i*-C_3H_7	$CHCl_3$	-60 to 0	3	0	51 (**4ba**)
n-C_4H_9	C_6H_5	**2c**	*i*-C_3H_7	Toluene	Reflux	10	0	73 (**4ca**)
t-Bu$(CH_3)_2$Si	C_6H_5	**2d**	*i*-C_3H_7	Benzene	Reflux	0.5	0	29 (**4da**)
t-Bu$(CH_3)_2$Si	C_6H_5	**2d**	*c*-C_6H_{11}	DCE	Reflux	2.5	0	29 (**4db**

The results shown above indicated that the less conjugated cyclic enaminosulfone **3aa** was the kinetic product of the ring closure of sulfone **2a** and the preferable isomerization of **3** into **4** by heating was reasonably explained by the thermodynamic stability of cyclic enaminosulfones **4** having the highest π-conjugation system among the possible double bond isomers of **4**. On the other hand, treatment of a CH_2Cl_2 solution of **2a** with other nucleophiles or bases, such as ethanol or Et_3N, only afforded the recovery of substrate at R.T., and the treatment of **2a** with *t*-BuOK (3.0 mol amt.) at R.T. for 1 h just resulted in the formation of a complex mixture.

Moreover, cyclic enaminosulfones **4** were converted into the corresponding cyclic γ,δ-unsaturated β-ketosulfones **6** in high yields through an acidic hydrolysis of the enamine moiety by treating with aqueous HCl solution (12 mol/L, excess) in a mixed solvent of THF/EtOH/H_2O (0.3:1:1) at R.T. for 1 - 2 days. All physical and spectral data of the products involving MS, IR, ^1H NMR, and ^{13}C NMR spectra, as well as their elemental analysis data, were fully consistent with the structures of products **6**. All the results of the synthesis of **6** are summarized and shown in Table 2.

Table 2. Conversion of cyclic enaminosulfones **4** into cyclic γ,δ-unsaturated β-ketosulfones **6** [a]

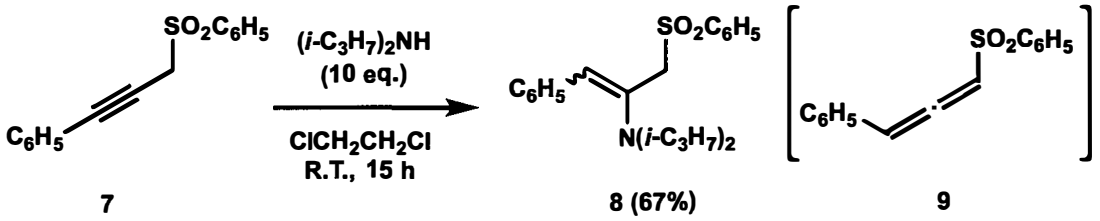


4 6

Substrate				Solvent	Temp (°C)	Time (h)	Yield (%) 6
R^1	R^2	R^3	4				
C_6H_5	CH_3	*i*-C_3H_7	**4aa**	THF:EtOH:H_2O (0.3:1:1)	R.T.	72	quant. (**6a**)
C_6H_5	C_6H_5	*i*-C_3H_7	**4ba**	THF:EtOH:H_2O (0.3:1:1)	R.T.	72	90 (**6b**)
C_6H_5	C_6H_5	*c*-C_6H_{11}	**4bb**	THF:EtOH:H_2O (0.3:1:1)	R.T.	96	85 (**6b**)
n-C_4H_9	C_6H_5	*i*-C_3H_7	**4ca**	THF:EtOH:H_2O (0.3:1:1)	R.T.	72	81 (**6c**)
t-Bu$(CH_3)_2$Si	C_6H_5	*i*-C_3H_7	**4da**	THF:EtOH:H_2O (0.3:1:1)	R.T.	72	94 (**6d**)

[a] An aqueous HCl solution (12 mol/L) was used for the hydrolysis

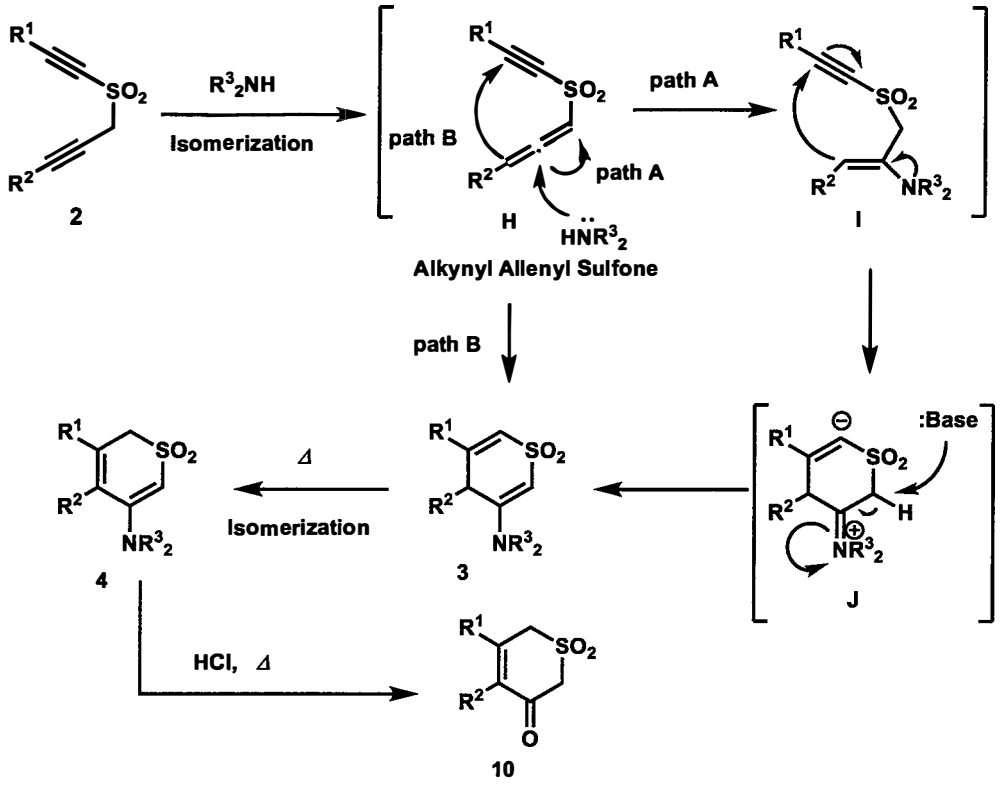
For the clarification of the role of secondary amine and for the conversion of alkynyl propargyl sulfones **2** into the corresponding cyclic enaminosulfones (**3**, **4**), it was attempted the treatment of phenyl 3-phenylpropargyl sulfone (**7**) with (*i*-C_3H_7)$_2$NH in a similar manner at R.T., by which enamine **8** was obtained in 67% yield as a single geometrical isomer in contrast to the case of reaction of amine with propargyl sulfones forming sulfonyl enamines. Especially, an allylic methylene signal assignable to the methylene group adjacent to sulfonyl group revealed at the rather low field area (δ = 4.14 (2H, s)) in the ^{1}H NMR spectrum of **8**, and therefore the alternative structure of sulfonyl enaines were excluded out. However, the newly-formed trisubstituted double bond of **8** was not confirmed well through the spectral data (Scheme 37). These results strongly suggested that phenylpropargyl sulfone **7** undergoes base-induced isomerization into allenyl sulfone **9** which were further converted into enamine **8** through a nucleophilic attack of secondary amine at the central carbon of the allenic moiety. These results indicated that the formation of allenyl sulfones *via* α-sulfonyl carbanion plays an important role for the *in situ* formation of acyclic enamine-type intermediates, which cause the nucleophilic attack to the β-position of the alkynyl sulfone moiety of the substrates as the preferable pathway.



Scheme 38. Conversion of phenyl 3-phenypropargyl sulfone (**7**) into enamine **8** *via* allenyl sulfone **9** by treating with diisopropylamine

2-2-2 Reaction mechanism for the formation of six-membered cyclic enaminosulfones and β-ketosulfones

The amine-induced ring closure of alkynyl propargyl sulfones **2** were assumed to proceed through a plausible pathway involving a base-induced isomerization of propargyl sulfones into allenyl sulfones **H**, nucleophilic addition of secondary amine to the β-position of allenyl sulfones **H**, and the final ring closure *via* Michael-type intramolecular nucleophilic attack of enamines **I** into the β-position of alkynyl sulfone moiety (Scheme 38).



Scheme 39. Plausible reaction mechanism for the formation of six-membered cyclic enaminosulfones and β-ketosulfones.

2-3 Experimental Section

Instruments: The melting points are measured in open capillary tubes with a Barnstead International MEL-TEMP and were uncorrected. ^{1}H NMR spectra were recorded on Bruker DRX-400P (400 MHz) and Bruker AVANCE III 500 (500 MHz) spectrometer. The chemical shifts of the ^{1}H NMR spectra were given in relative to internal tetramethylsilane (TMS). ^{13}C NMR spectra were recorded on a Bruker DRX-400P (100 MHz) or a Bruker AVANCE III 500 (126 MHz). Mass spectra were recorded on a JEOL JMS-700T mass spectrometer with electron-impact ionization at 20 or 70 eV using a directinlet system. High resolution mass spectra (HRMS) were also recorded on JEOL JMS-700T spectrometer. IR (FT-IR) spectra were recorded for neat or KBr disk on JASCO FT/IR-7300 spectrometer. Elemental analyses were performed using a Yanagimoto CHN corder MT-5.

2-3-1. Procedure for amine-induced cyclization of alkynyl propargyl sulfones (2):

A dry chloroform solution of alkynyl propargyl sulfone **2a** ($R^1 = C_6H_5$, $R^2 = CH_3$, 1.009 g, 4.62 mmol) was treated with $(i\text{-}C_3H_7)_2NH$ (1.40 g, 13.86 mmol) at R.T. for 3 h. The reaction mixture was subjected to evaporation in *vacuo*, and the crude products were purified by column chromatography on silica gel to obtain cyclic enaminosulfone **3a** ($R^1 = C_6H_5$, $R^2 = CH_3$, 1.034 g, yield 50 %) as colorless oil.

Physical and spectral data for cyclic enaminosulfones (3):

Compound 3aa ($R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = i\text{-}C_3H_7$)

Colorless oil.

IR (neat): 2980, 1560, 1330, 1247, 1177 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ: 1.28 (6H, d, J = 6.9 Hz), 1.35 (6H, d, J = 6.9 Hz), 1.51 (3H, d, J = 7.1 Hz), 3.80 (1H, dq, J = 7.1, 1.5 Hz), 3.81 (2H, sept, J = 6.9 Hz), 5.52 (1H, dd, J = 2.5, 1.5 Hz), 6.81 (1H, d, J = 2.5 Hz), 7.28-7.46 (5H, m).

^{13}C NMR ($CDCl_3$) δ: 19.6 (q), 22.3 (q), 22.4 (q), 36.6 (d), 48.4 (d), 97.7 (d), 125.6 (d), 125.8 (d), 127.8 (d), 129.4 (d), 136.5 (s), 150.2 (s), 159.6 (s).

MS (*m/z*): 319 (M^+; 11%), 304 (M^+-CH_3; 18%), 255 (M^+-SO_2; 39%).

Calcd for $C_{18}H_{25}NO_2S$: C, 67.61; H, 7.82; N, 4.38%. Found: C, 67.31; H, 8.01; N, 4.38%.

2-3-2 Procedure for the isomerization of cyclic enaminosulfone 3 into 4:

A dry chloroform solution of cyclic enaminosulfone **3a** ($R^1 = C_6H_5$, $R^2 = CH_3$, 1.034 g, 2.31 mmol) was heated under refluxing temperature for 3-4 days and the reaction mixture was subjected to evaporation in vacuo. The crude products were purified by column chromatography on silica gel to obtain the isomeric enaminosulfone **4a** ($R^1 = C_6H_5$, $R^2 = CH_3$, 618 mg, yield 42%) as pale yellow solid.

Physical and spectral data for cyclic enaminosulfones (4):

Compound 4aa ($R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = i\text{-}C_3H_7$)

Pale yellow needles.

MP: 145.1-145.5 °C.

IR (KBr): 2981, 1542, 1292, 1100, 756 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.98 (12H, d, J= 6.8 Hz), 1.81 (3H, s), 3.67 (2H, sept, J= 6.8 Hz), 3.92 (2H, s), 5.80 (1H, s), 7.26-7.42 (5H. m).

^{13}C NMR ($CDCl_3$) δ: 19.1 (q), 21.4 (q), 49.1 (q), 55.4 (t), 103.2 (s), 127.6 (d), 128.3 (d), 128.5 (d), 134.5 (s), 140.4 (s), 144.4 (s).

Calcd for $C_{18}H_{25}NO_2S$: C, 67.61; H, 7.82; N, 4.38%. Found: C, 67.52; H, 7.89; N, 4.43%.

Compound 4ba ($R^1 = R^2 = C_6H_5$, $R_3 = i\text{-}C_3H_7$)

Pale yellow needles.

MP: 157.3-160.4 °C.

IR (KBr): 2980, 1545, 1290, 1112, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.98 (12H, d, J= 6.8 Hz), 3.54 (2H, sept, J= 6.8 Hz), 4.04 (2H, s), 5.86 (1H, s), 6.92-6.97 (4H, m), 7.09-7.15 (6H, m).

^{13}C NMR ($CDCl_3$) δ: 20.3 (q), 49.2 (d), 56.6 (t), 101.0 (d), 127.0 (d), 127.2 (d), 127.5 (d), 127.9 (d), 128.2 (d), 130.1 (d), 133.8 (s), 135.3 (s), 137.6 (s), 140.9 (s), 153.6 (s).

MS (*m/z*): 333 (M^+; 17%), 269 (M^+-SO_2; 27%), 254 (M^+-SO_2-CH_3; bp).

Calcd for $C_{23}H_{27}NO_2S$: C, 72.40; H, 7.13; N, 3.67%. Found: C, 72.59; H, 7.18; N, 3.13%.

Compound 4ca ($R^1 = n\text{-}C_4H_9$, $R^2 = C_6H_5$)

Colorless solid.

MP: 151.1-151.7 °C.

IR (KBr): 2879, 1539, 1279, 1101 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.79 (3H, t, J = 5.6 Hz), 0.94 (12H, d, J = 5.6 Hz), 1.18-1.26 (2H, sext, J = 6.0 Hz), 1.37-1.42 (2H, m), 2.26 (2H, t, J = 6.0 Hz), 3.49 (2H, quint, J = 5.6 Hz), 3.74 (2H, s), 7.15-7.18 (2H, m), 7.24-7.28 (1H, m), 7.31-7.34 (2H, m).

^{13}C NMR ($CDCl_3$) δ: 13.9 (q), 20.6 (t), 22.6 (t), 28.7 (t), 35.8 (t), 49.2 (d), 54.3 (t), 100.9 (d), 127.3 (d), 128.0 (d), 130.0 (d), 132.0 (s), 137.1 (s), 138.1 (s), 153.9 (s).

MS (*m/z*): 361 (M^+; 12%), 254 (bp).

HRMS (EI) calcd for $C_{21}H_{31}NO_2S$: *m/z* 361.2076. Found: *m/z* 361.2068.

Compound 4da (R^1 = *t*-$C_4H_9(CH_3)_2Si$, R^2 = C_6H_5, R^3 = *i*-C_3H_7)

Colorless prisms.

MP: 160.6-162.3 °C.

IR (KBr): 2959, 2855, 1547, 1288, 1112 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.26 (6H, s), 0.94 (12H, d, J = 6.8 Hz), 0.96 (9H, s), 3.46 (2H, sept, J = 6.8 Hz), 3.84 (2H, s), 5.84 (1H, s), 7.22-7.28 (5H, m).

^{13}C NMR ($CDCl_3$) δ: -4.6 (q), 18.1 (s), 20.7 (q), 27.5 (q), 49.0 (d), 53.4 (t), 102.9 (d), 127.4 (d), 127.7 (d), 130.2 (d), 135.7 (s), 140.3 (s), 146.6 (s), 152.9 (s).

MS (*m/z*): 356 (M^+-SO_2; 4%), 41 (bp).

Calcd for $C_{23}H_{37}NO_2SSi$: C, 65.82; H, 8.89; N, 3.34%. Found: C, 65.69; H, 8.81; N, 3.49%.

Compound 4db (R^1 = *t*-$C_4H_9(CH_3)_2Si$, R^2 = C_6H_5, R^3 = *c*-C_6H_{11})

Pale pink plates.

MP: 195.1-196.6 °C.

IR (KBr): 2932, 1714, 1566, 1261, 1102, 836 cm^{-1}.

^1H NMR ($CDCl_3$) δ: -0.25 (6H, s), 0.96 (9H, s), 1.02-1.15 (10H, m), 1.57-1.70 (10H, m), 2.99 (2H, d, J= 9.2 Hz), 3.83 (2H, s), 5.94 (1H, s), 7.21-7.32 (5H, m).

^{13}C NMR ($CDCl_3$) δ: -4.6 (q), 18.1 (s), 25.5 (t), 26.6 (t), 27.5 (q), 31.1 (t), 53.5 (t), 59.7 (d), 102.9 (d), 127.3 (d), 127.6 (d), 130.1 (d), 135.1 (s), 140.4 (s), 146.8 (s), 154.1 (s).

MS (*m/z*): 499 (M^+; 2%), 435 (M^+-SO_2; 7%), 115 (*t*-$C_4H_9(CH_3)_2Si$; 14%).

Calcd for $C_{29}H_{45}NO_2SSi$: C, 69.69; H, 9.07; N, 2.80%. Found: C, 69.34; H, 9.58; N, 2.78%.

2-3-3 Reaction of phenylpropargyl sulfone (7) with diisopropylamine:

The 1,2-dichloroethane (DCE) solution of phenyl phenylpropargyl sulfone (**7**, 380 mg, 1.50 mmol) with (i-C_3H_7)$_2$NH (1.52 g, 10 eq.) at R.T. for 15 h, and the reaction mixture was subjected to evaporation *in vacuo*. The crude products were purified by column chromatography on silica gel to obtain acyclic enaminosulfone **8** (360 mg, yield 67%) as colorless plates.

Physical and spectral data for acyclic enaminosulfone 8:

Colorless plates.

MP: 137.5-137.7 °C.

IR (KBr): 2967, 1550, 1457, 1385, 1262, 1133, 1078, 1037 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ: 1.12 (12H, d, J = 6.7 Hz), 3.76 (2H, sept, J = 6.7 Hz), 4.14 (2H, s), 5.42 (1H, s), 6.91-6.93 (1H, m), 7.08-7.14 (3H, m), 7.25-7.37 (3H, m), 7.77-7.79 (2H, m).

^{13}C NMR ($CDCl_3$) δ: 20.0 (q), 34.5 (t), 48.1 (d), 97.7 (d), 126.2 (s), 126.3 (d), 127.7 ((d), 128.4 (d), 128.5 (d), 131.1 (d), 136.7 (s), 146.5 (s), 155.3 (s).

MS (*m/z*): 357 (M^+; 3%), 216 (M^+-$SO_2C_6H_5$; bp), 43 (i-C_3H_7; 48%).

Calcd for $C_{21}H_{27}NO_2S$: C, 70.55; H, 7.61; N, 3.92%. Found: C, 70.46; H, 8.51; N, 3.90%.

2-3-4 Procedure for the conversion of cyclic enaminosulfones (4) into cyclic γ,δ-unsaturated β-ketosulfones (6) through acidic hydrolysis:

A mixed solution (THF: ethanol: water = 0.3:1:1, 15 mL) of enaminosulfone **4aa** (R^1 = C_6H_5, R^2 = CH_3, R^3 = i-C_3H_7, 618 mg, 1.93 mmol) was treated with an excess amount of hydrochloric acid (12 M, 7.0 mL) at R.T. for 3 days. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ solution, and the reaction mixture was extracted with chloroform. The organic layer was washed with water and was dried over anhydrous Na_2SO_4 powder, and the organic solvent was evaporated *in vacuo*. The crude products were purified by column chromatography on silica gel to obtain cyclic γ,δ-unsaturated β-ketosulfone **6a** (R^1 = C_6H_5, R^2 = CH_3, 513 mg, quant.) as pale yellow oil.

Physical and spectral data for cyclic γ,δ-unsaturated β-ketosulfones 6:

Compound 6a ($R^1 = C_6H_5$, $R^2 = CH_3$)

Pale yellow oil.

^1H NMR ($CDCl_3$) δ: 1.84 (3H, s), 4.15 (2H, s), 4.19 (2H, s), 7.21-7.23 (2H, m), 7.40-7.48 (3H, m).

^{13}C NMR ($CDCl_3$) δ: 14.2 (q), 56.8 (t), 61.2 (t), 126.8 (d), 128.2 (d), 129.0 (d), 133.8 (s), 138.5 (s), 146.0 (s), 187.7 (s).

Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12%. Found: C, 60.95; H, 4.95%.

Compound 6b ($R^1 = R^2 = C_6H_5$)

Pale yellow needles.

MP: 208.8-209.9 °C.

IR (KBr): 1686, 1321, 1289, 1128 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 4.31 (2H, s), 4.41 (2H, s), 6.94-6.97 (2H, m), 7.03-7.04 (2H, m), 7.18-7.22 (6H, m).

^{13}C NMR ($CDCl_3$) δ: 57.0 (t), 61.8 (t), 128,0 (d), 128.6 (d), 129.1 (d), 130.7 (d), 133.5 (s), 138.3 (s), 138.9 (s), 147.7 (s), 186.8 (s).

Calcd for $C_{17}H_{14}O_3S$: C, 68.44; H, 4.73%. Found: C, 68.21; H, 4.98%.

Compound 6c ($R^1 = n\text{-}C_4H_9$, $R^2 = C_6H_5$)

Colorless solid.

MP: 151.1 -151.7 °C.

IR (KBr): 2924, 1673, 1325, 1134, 704 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.79 (3H, t, J= 6.0 Hz), 1.17-1.25 (2H, sext, J= 6.0 Hz), 1.39-1.44 (2H, m), 2.21 (2H, t, J = 6.0 Hz), 4.07 (2H, s), 4.15 (2H, s), 7.05-7.07 (2H, m), 7.36-7.37 (3H, m).

^{13}C NMR ($CDCl_3$) δ: 13.7 (q), 22.5 (t), 29.5 (t), 36.3 (t), 54.5 (t), 61.6 (t), 128.3 (d), 128.6 (d), 129.5 (d), 134.0 (s), 138.9 (s), 151.0 (s), 186.8 (s).

MS (*m/z*): 278 (M^+; bp).

HRMS (EI) calcd for $C_{15}H_{18}O_3S$: *m/z* 278.0977. Found: *m/z* 278.0976.

Compound 6d (R^1 = *t*-$C_4H_9(CH_3)_2Si$, R^2 = C_6H_5)

Colorless prisms.

MP: 162.2-164.3 °C.

IR (KBr): 2930, 1675, 1320, 1131, 839 cm^{-1}.

^1H NMR ($CDCl_3$) δ: -0.26 (6H, s), 0.95 (9H, s), 4.10 (2H, s), 4.13 (2H, s), 7.24-7.35 (5H, m).

^{13}C NMR ($CDCl_3$) δ: -4.6 (q), 18.5 (s), 27.7 (q), 54.6 (t), 62.5 (t), 127.7 (d), 128.4 (d), 130.1 (d), 136.1 (s), 149.5 (s), 168.6 (s), 187.0 (s).

Calcd for $C_{17}H_{24}O_3SSi$: C, 60.67; H, 7.19%. Found: C, 60.22; H, 7.03%.

So, the sulfones and their derivatives have vast applications in biological, pharmaceutical, medicinal and in many other fields. In conclusion, a convenient one-pot synthesis of six-membered cyclic *γ, δ*-unsaturated β-ketosulfones **6** has been found through the heating of alkynyl propargyl sulfones **2** in the presence of a secondary amine and discussed here in this chapter.

Chapter 3:

Synthesis of α, β-Unsaturated Carbodithioate Esters and their conversion into Isothiazoles

Chapter 3: Synthesis of α, β-Unsaturated Carbodithioate Esters and their conversion into Isothiazoles

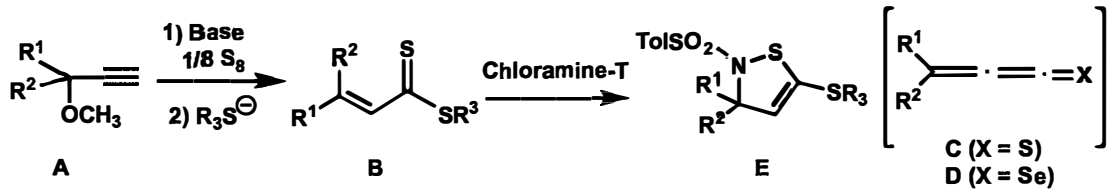
3-1 Introduction

α, β-unsaturated chalcogenocarbonyl and isothiazole compounds are valuable structural motifs found in many natural products, pharmaceutical compounds, and functional materials. As a result, so much interest has been focused onto the expansion of the synthetic utility of highly reactive species related to propadienechalcogenones as novel four-atom synthetic building blocks of a variety of five-membered heterocycles containing a chalcogen and nitrogen atoms. However, previous studies on propadienechalcogenones were carried out only in line with the structural interests, and their synthetic applications involving the strategic generation and chemical conversion of propadienechalcogenones were limited in spite of their potentiality as the precursors of α, β-unsaturated chalcogenocarbonyl compounds.

3-2 Results and Discussion

Because of getting many importance about the cumulated chalcogenocarbonyl compounds, the researchers previously reported a novel and convenient synthesis of α, β-unsaturated thioamides and selenoamides through the reaction of substituted propargyl methyl ethers **A** with a base, elemental sulfur or selenium, and a primary or secondary amine. These reactions were assumed to proceed through *in situ* generation of some heterocumulene-like intermediates related to propadienethiones **C** and selones **D** and the subsequent nucleophilic addition of amine (Scheme 39). These successful results derived to go to an extension of the method to the synthesis of 2-alkenecarbodithioate esters **B**, widely recognized as versatile building blocks for a variety of sulfur-containing heterocycles, through a similar treatment by applying a sulfur nucleophile in place of amine, and finally it was found a new one-pot preparation of compounds **B** from 3,3-disubstituted propargyl ethers **A** by the stepwise treatment of a base, elemental sulfur, and a thiol. In this chapter, the author would like to describe the details of the synthesis of 2-alkenecarbodithioate esters **B** through a plausible pathway involving the *in-situ* generation of

intermediates **C**. The successful conversion of compounds **B** into isothiazoles **E** *via* [4+1] type oxidative ring closure are also carried out and described here in this chapter.



Scheme 40. Synthsis of $\alpha\,\beta$-unsaturated carbodithioate esters **B** and subsequent conversion into isothiazoles **E**

3-2-1 Preparation of substrates

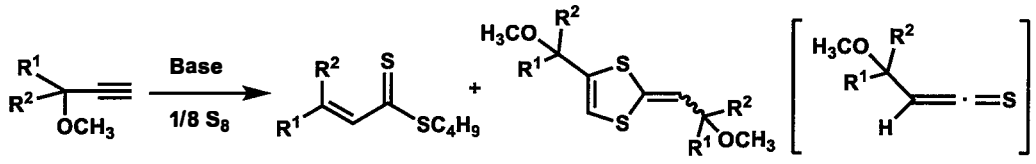
For the preparation of the substrates like the substituted propargyl methyl ethers **2** were prepared by two-step conversion from the starting ketones **1** [*i.e.* (i) acetylene gas, C_2H_5MgBr, (ii) NaH, CH_3I] according to the usual and reported methods.

3-2-2 Details explanation

S-butyl 3,3-diphenyl-2-propenecarbodithioate (**3a**, $R^1 = R^2 = C_6H_5$) was obtained in low yield as reddish-brown oil by treating the compound **2a** ($R^1 = R^2 = C_6H_5$) with butyllithium and elemental sulfur at -78 to 0°C in the absence of nucleophilic reagents. The yield of **3a** was raised up to 15% by treating a small excess amount of butyllithium, and this result suggested that the butylthio group of **3a** was originated from 1-butanethiolate ion formed through the reaction of butyllithium and elemental sulfur. On the other hand, treatment of **2** with potassium *t*-butoxide and elemental sulfur in a similar manner only gave a complex mixture, and after the concise separation, an air-unstable 1,3-dithiole **4a** was isolated in low yield. It was already reported that alkynethiolate ions, generated through the reaction of phenylacetylene with a base and elemental sulfur, afford 1,3-dithioles in high yields *via* generation and dimerization of diphenylthioketene. Therefore, this result also suggested the *in situ* generation of thioketene **F** from alkynethiolate ions under the mentioned

reaction condition. All the results of the reaction of **2** with a base and elemental sulfur are summarized and shown in Table 3.

Table 3. One-pot synthesis of *S*-butyl 2-propenecarbodithioates **3** from propargyl methyl ethers **2**



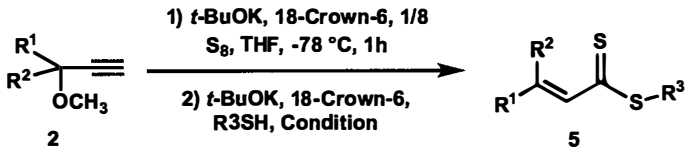
2 **3** **4** **F**

Substrate			Base (eq.)	1/8 S_8 (eq.)	Solvent	Temp (°C)	Time (h)	Yield (%)	
R^1	R^2	**2**						**3**	**4**
C_6H_5	C_6H_5	**2a**	BuLi (5.5)	2.2	THF	-78 to 0	5	15 (**3a**)	0
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	**2b**	BuLi (5.5)	2.2	THF	-78 to 0	5	15 (**3b**)	0
C_6H_5	C_6H_5	**2a**	*t*-BuOK (5.0)	2.0	THF	-78 to 0	3	-	10 (**4a**)[a]

[a] The geometry of exocyclic double bond was not confirmed

S-octyl 3,3-diphenylpropenecarbodithioate **5a** ($R^1 = R^2 = C_6H_5$) was found in low yield by the similar treatment of **2a** with potassium *t*-butoxide (5.0 eq.) and elemental sulfur (2.2 eq.) in presence of 1-octanethiol (2.0 eq.). In this case, the use of 18-crown-6 as an additive of the reaction was much effective to raise up the yields of **5a**. And finally, the yield of **5a** was improved to 62% by dropwise addition of a THF solution of the reaction mixture of **2**, potassium *t*-butoxide, and 18-crown-6 to a separately prepared THF solution of 1-octanethiolate ion by treating 1-octanethiol with potassium *t*-butoxide and 18-crown-6. It was a matter of interesting that the compound **4a** was not obtained at all as a byproduct in these cases. The synthesis of various *S*-octyl 2-alkenecarbodithioates **5** were successfully performed through the same procedure, and all the results are summarized and shown in Table 4. However, only a complex mixture involving a small amount of *S*-phenyl 3,3-diphenyl-2-propenecarboditihoate (**5f**) was obtained when benzenethiol was used as a sulfur nucleophile in place of 1-octanethiol.

Table 4. One-pot synthesis of *S*-octyl 2-alkenecarbodithioates **5**



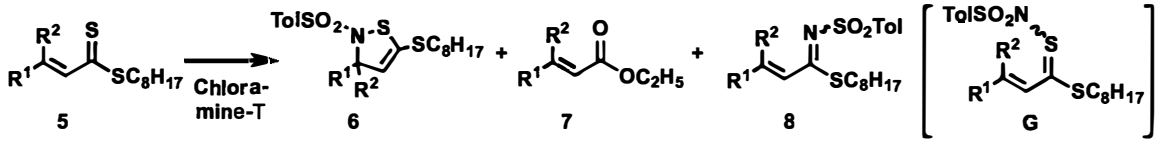
Substrate		*t*-BuOK	1/8 S_8	Thiol	18-Crown-6	Solvent	Condition		Yield (%)
R^1	R^2	(eq.)	(eq.)	R^3 (eq.)	(eq.)		Temp (°C)	Time (h)	**5**
C_6H_5	C_6H_5	4.5	2.2	C_8H_{17} (1.5)	0	Et_2O	Reflux	4	16 (**5a**)
C_6H_5	C_6H_5	3.5	2.0	C_8H_{17} (2.0)	0	THF	-78 to 0	2	9 (**5a**)
C_6H_5	C_6H_5	9.0	2.0	C_8H_{17} (2.0)	1.5	DMF	Reflux	6	10 (**5a**)
C_6H_5	C_6H_5	6.0	3.0	C_8H_{17} (2.0)	3.5	THF	Reflux	6	49 (**5a**)
C_6H_5	C_6H_5	9.0	3.0	C_8H_{17} (2.0	3.5	THF	Reflux	6	62 (**5a**)
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	9.0	3.0	C_8H_{17} (2.0)	3.5	THF	Reflux	6	49 (**5b**)
p-ClC_6H_4	*p*-ClC_6H_4	9.0	3.0	C_8H_{17} (2.0)	3.5	THF	Reflux	6	50 (**5c**)
C_6H_5	CH_3	9.0	2.0	C_8H_{17} (2.0)	3.5	THF	Reflux	6	20 (**5d**) [a]
C_6H_5	*n*-C_5H_{11}	9.0	3.0	C_8H_{17} (2.0)	3.5	THF	Reflux	6	34 (**5e**) [b]
C_6H_5	H	9.0	3.0	C_8H_{17} (2.0)	3.5	THF	Reflux	6	Complex mixture
C_6H_5	C_6H_5	9.0	3.0	C_6H_5 (2.0)	3.5	THF	Reflux	6	Complex mixture

[a] Single geometrical isomer from the ^1H NMR spectrum of the crude product. [b] E/Z ratio of the isomeric mixture was estimated to be 10:1 from the integration of the ^1H NMR spectrum of the crude product.

After finding the above results we planned to go to the further and new conversion of 2-alkenecarbodithioates **5** into substituted isothioazoles through a one-step [4+1] ring closure *via* intermediary thiocarbonyl *S*-imide **G** because of their synthetic importance as the precursors of a variety of biologically and pharmaceutically active heterocycles. When compound **5a** was treated with chloramine-T in commercial chloroform at R.T. for 8 h, *N*-tosyl-3,3-diphenyl-2,3-dihydroisothiazole (**6a**) was obtained in 8% yield besides ethyl 3,3-diphenyl-2-propenoate (**7a**, 39%), thioimidate **8a** (trace), and several uncharacterized byproducts. However, the yield of **6a** was dramatically improved by carrying out the same reaction in distilled dry chloroform, and in this case the yield of **6a** was raised up to 68%. The structural determination of **6a** ($R^1 = R^2 = C_6H_5$) was carried out from the physical and spectral data, and was finally confirmed by Birch reduction (Na / $C_3H_7NH_2$) affording *N*-propyl-3,3-diphenyl-2-propenethioamide (**9a**). It is assumed that the *in situ* generated thiocarbonyl *S*-imides **G** would undergo facile ring closure to afford products **6**

without the isomerization to thiaziridine intermediates. Other substrates **5b** and **5c** bearing *p*-methoxyphenyl and *p*-chlorophenyl substituents on the C-3 position were also converted into the corresponding isothiazole derivatives **6b** and **6c**, respectively, through a similar manner. All the results of the reactions of 2-alkenecarbodithioate esters **5** bearing several substituents with chloramine-T are summarized andshown in Table 5.

Table 5. Synthesis of substituted isothiazoles **10** through the reaction of 2-alkenecarbodithioate esters **5** with chloramine-T

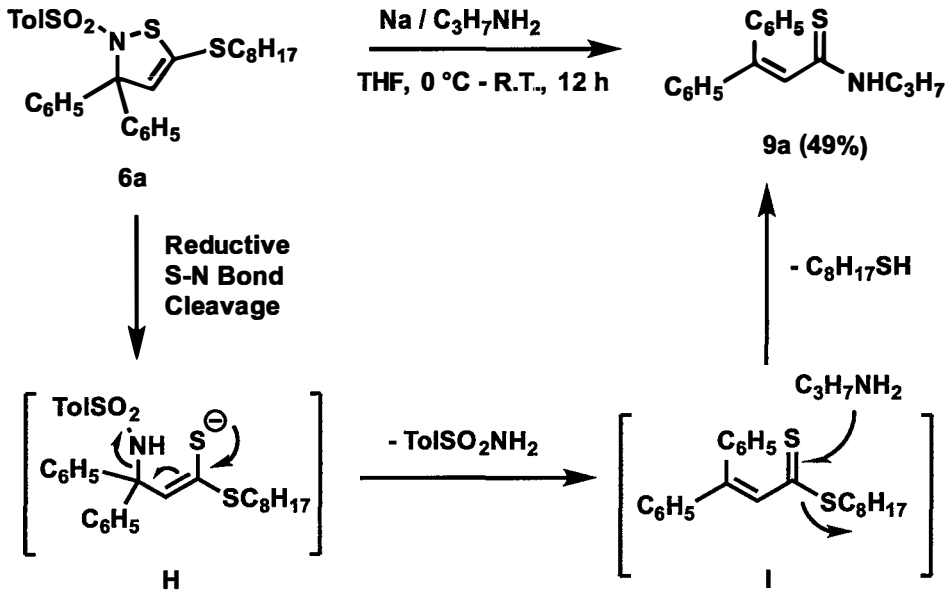


Substrate			Chloramine-T (eq.)	Solvent	Temp (°C)	Time (h)	Yield (%)		
R^1	R^2	**5**					**6**	**7**	**5**
C_6H_5	C_6H_5	**5a**	1.1	$CHCl_3$ [a]	R.T.	8	8 (**6a**)	39 (**7a**)	8 (**8a**) [b]
C_6H_5	C_6H_5	**5a**	1.1	Distilled $CHCl_3$	R.T.	6	50 (**6a**)	0	trace (**8a**)
C_6H_5	C_6H_5	**5a**	1.1	CH_2Cl_2	R.T.	8	47 (**6a**)	0	trace (**8a**)
C_6H_5	C_6H_5	**5a**	1.4	Distilled $CHCl_3$	Reflux	1.25	68 (**6a**)	0	trace (**8a**)
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	**5b**	1.4	Distilled $CHCl_3$	R.T.	1	90 (**6b**)	trace	ND
p-$ClOC_6H_4$	*p*-$ClOC_6H_4$	**5c**	1.4	Distilled $CHCl_3$	R.T.	1	60 (**6c**)	0	ND
C_6H_5	C_6H_5	**5d**	1.4	Distilled $CHCl_3$	R.T.	1	Complex mixture		

[a] Commercially available chloroform was used without any pretreatment. [b] Single geometrical isomer.

3-2-3 Structural confirmation of the compound 6a by using Birch reduction

With the help of the previous study it was assumed to form the compound **9a** through a reductive S-N bond cleavage of compound **6a** followed by the elimination of *p*-toluenesulfonamide from intermediate **H** and the subsequent nucleophilic addition of propylamine to the thiocarbonyl carbon of intermediary carbodithioate ester **I** along with elimination of 1-octanethiol (Scheme 40).



Scheme 41. Structural confirmation of compound **6a**

3-3 Experimental Section

Instruments: The melting points were determined with a Büchi 535 micro-melting-point apparatus. ^{1}H NMR spectra were recorded on a Bruker DRX-400P (400 MHz) spectrometer, and the chemical shifts of the ^{1}H NMR spectra are given in δ relative to internal tetramethylsilane (TMS). ^{13}C NMR spectra were recorded on a Bruker DRX-400P (100 MHz). Mass spectra were recorded on a JEOL MS-700T mass spectrometer with electron-impact ionization at 20 or 70 eV using a direct inlet system. High resolution mass spectra (HRMS) were also recorded on a JEOL MS-700T spectrometer. IR spectra were recorded for thin film (neat) or KBr disks on a JASCO FT/IR-7300 spectrometer. Elemental analyses were performed using a Yanagimoto CHN corder MT-5.

3-3-1 Procedure for the preparation of 3,3-disubstituted *S*-butyl 2-alkenecarbodithioates 3:
A THF solution of propargyl methyl ether **2a** ($R^1 = R^2 = C_6H_5$, 850 mg, 3.83 mmol) was treated with butyllithium hexane solution (7.8 ml, 21.1 mmol, 5.5 eq.) at -78°C for 1 h, and then elemental sulfur (269 mg, 8.40 mmol, 2.2 eq.) was added to the reaction mixture at -78°C for 1 h. The reaction temperature was gradually raised up to 0°C and after stirring for 5 h, and the reaction was quenched by addition of an excess amount of water. The reaction mixture was extracted with diethyl ether, and the organic layer was washed with water and then with brine, and was dried over anhydrous sodium sulfate powder. After removing the solvent in vacuo, the crude product was subjected to chromatographic purification on silica gel to isolate the corresponding S-butyl 2-propenecarbodithioate **3a** ($R^1 = R^2 = C_6H_5$, 179 mg, yield 15%) as reddish-brown oil along with several unidentified byproducts.

Compound 3a ($R^1 = R^2 = C_6H_5$):
Red oil.
IR (neat): 3056, 3025, 1179 cm^{-1}.
^{1}H NMR ($CDCl_3$) δ: 0.86 (3H, t, *J* = 7.2 Hz), 1.23-1.32 (2H, m), 1.46-1.53 (2H, m), 3.30 (2H, t, *J* = 7.2 Hz), 7.06 (1H, s), 7.25-7.35 (10H, m).
^{13}C NMR ($CDCl_3$) δ: 13.7 (q), 22.1 (t), 29.3 (t), 36.1 (t), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 129.0 (d), 130.2 (d), 134.1 (d), 139.0 (s), 141.5 (s), 146.3 (s), 227.0 (s).

MS (*m/z*): 312 (M^+; 25%), 256 (M^+-C_4H_9; 35%), 223 (M^+-SC_4H_9; bp).
HRMS calcd for $C_{19}H_{20}S_2$: *m/z* 312.1006. Found: *m/z* 312.1014.

Compound 3b ($R^1 = R^2 = p$-$CH_3OC_6H_4$):
Red oil.
IR (neat): 3064, 2834, 1605, 1174 cm^{-1}.
^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.4 Hz), 1.30 (2H, q, *J* = 7.4 Hz), 1.52 (2H, q, *J* = 7.4 Hz), 3.14 (2H, t, *J* = 7.4 Hz), 3.82 (3H, s), 3.84 (3H, s), 6.85 (4H, br. d, *J* = 8.4 Hz), 7.04 (1H, s), 7.18 (4H, d, *J* = 8.4 Hz), 7.27 (2H, d, *J* = 8.4 Hz).
^{13}C NMR ($CDCl_3$) δ: 13.7 (q), 22.1 (t), 29.4 (t), 36.1 (t), 55.3 (s), 55.4 (s), 113.4 (d), 113.6 (d), 113.7 (d), 128.3 (d), 130.2 (d), 131.4 (d), 131.8 (d), 132.6 (d), 134.3 (s), 146.7 (s), 160.5 (s), 160.7 (s), 226.7 (s).
MS (*m/z*): 372 (M^+; 20%), 283 (M^+-SC_4H_9; bp).
HRMS calcd for $C_{24}H_{24}O_2S_2$: *m/z* 372.1218. Found: *m/z* 372.1218.

3-3-2 Reaction of propargyl methyl ether 2a with potassium *t*-butoxide and elemental sulfur:
A THF solution of propargyl methyl ether **2a** ($R^1 = R^2 = C_6H_5$, 203 mg, 0.914 mmol) was treated with potassium *t*-butoxide (510 mg, 4.57 mmol, 5.0 eq.) and elemental sulfur (58 mg, 1.83 mmol, 2.0 eq.) at -78°C for 1 h and then at 0°C for 2 h. After quenching the reaction by addition of water, the usual workup, and purification using silica gel column chromatography, unstable 1,3-dithiole **4a** ($R^1 = R^2 = C_6H_5$, 46 mg, 10% yield) was isolated as yellow oil besides several uncharacterized products.

Compound 4a ($R^1 = R^2 = C_6H_5$):
Pale yellow oil.
^1H NMR ($CDCl_3$) δ: 3.07 (3H, s), 3.12 (3H, s), 6.62 (1H, s), 6.67 (1H, s), 7.24-7.41 (20H, m).
^{13}C NMR ($CDCl_3$) δ: 52.1 (q), 52.2 (q), 83.7 (s), 84.4 (s), 122.4 (d), 124.6 (d), 126.2 (d), 127.2 (d), 127.3 (d), 127.4 (d), 128.2 (d), 128.3 (d), 135.7 (s), 142.2 (s), 143.2 (s), 143.7 (s).
MS (*m/z*) 509 (M^++1; 4%, 508 (M^+; 11%), 254 (M^+/2; bp).
HRMS calcd for $C_{32}H_{28}O_2S_2$: *m/z* 508.1531. Found: *m/z* 509.1609 (M^++1).

3-3-3 Procedure for the preparation of 3,3-disubstituted *S*-octyl 2-alkenecarbodithioates 5:

A THF solution of propargyl methyl ether **2a** ($R^1 = R^2 = C_6H_5$, 130 mg, 0.585 mmol) was treated with potassium *t*-butoxide (400 mg, 3.52 mmol, 6.0 eq.), 18-crown-6 (236 mg, 0.834 mmol, 1.5 eq.), and elemental sulfur (58 mg, 1.78 mmol, 3.0 eq.) at -78°C for 30 min. Then a THF solution of 1-octanethiol (180 mg, 1.19 mmol, 2.0 eq.), potassium t-butoxide (198 mg, 1.76 mmol, 3.0 eq.), and 18-crown-6 (315 mg, 1.19 mmol, 2.0 eq.) was treated with the reaction mixture at refluxing temperature for 6 h. After quenching the reaction by addition of water, the usual workup, and purification using silica gel column chromatography, the corresponding S-octyl 2-alkenecarbodithioate **5a** ($R^1 = R^2 = C_6H_5$, 133 mg, 62% yield) was isolated as reddish brown oil along with several unidentified byproducts.

Compound 5a ($R^1 = R^2 = C_6H_5$, $R^3 = n\text{-}C_8H_{17}$):

Red oil.

IR (neat): 3056, 2953, 1047 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.0 Hz), 1.20-1.35 (10H, m), 1.45-1.55 (2H, m), 3.11 (2H, t, J = 7.0 Hz), 7.06 (1H, s), 7.24-7.27 (2H, m), 7.31-7.33 (8H, m).

^{13}C NMR ($CDCl_3$) δ: 14.2 (q), 22.7 (t), 27.2 (t), 29.0 (t), 29.1 (t x 2), 31.8 (t), 36.4 (t), 128.1 (d), 128.2 (d), 128.4 (d), 128.5 (d), 129.0 (d), 130.2 (d), 134.1 (d), 139.0 (s), 141.5 (s), 146.3 (s), 226.9 (s).

MS (*m/z*): 368 (M^+; 28%), 256 (M^+-C_8H_{17}; 50%), 151 (M^+-SC_8H_{17};

bp), 178 (M^+-$CS_2C_8H_{17}$; 10%).

HRMS calcd for $C_{23}H_{28}S_2$: *m/z* 368.1632. Found: *m/z* 368.1635.

Compound 5b ($R^1 = R^2 = p\text{-}CH_3OC_6H_4$, $R^3 = n\text{-}C_8H_{17}$)

Red oil

IR (neat): 3034, 1606, 1124 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.0 Hz), 1.15-1.30 (10H, m), 1.50-1.60 (2H, m), 3.13 (2H, t, J = 7.0 Hz), 3.82 (3H, s), 3.83 (3H, s), 6.83-6.87 (4H, m), 7.04 (1H, s), 7.17-7.28 (4H, m).

^{13}C NMR ($CDCl_3$) δ: 14.1 (q), 22.7 (t), 27.3 (t), 29.0 (t), 29.1 (t), 29.7 (t), 31.8 (t), 36.3 (t), 55.2 (q), 55.4 (q), 113.6 (d), 113.7 (d), 130.2 (d), 131.4 (s), 131.8 (d), 132.6 (d), 134.3 (s), 146.7 (s), 159.9 (s), 160.6 (s), 226.6 (s).

MS (*m/z*): 428 (M^+; 12%), 316 (M^+-C_8H_{17}; 23%), 283 (M^+-SC_8H_{17}; bp).

HRMS calcd for $C_{25}H_{32}O_2S_2$: *m/z* 368.1632. Found: *m/z* 368.1632.

Compound 5c ($R^1 = R^2 = p$-ClC_6H_4, $R^3 = n$-C_8H_{17})

Red oil.

IR (neat): 2935, 1582, 1092 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.0 Hz), 1.10-1.30 (10H, m), 1.50-1.57 (2H, m), 3.13 (2H, t, J = 7.0 Hz), 6.98 (1H, s), 7.16-7.24 (4H, m), 7.29-7.32 (4H, m).

^{13}C NMR ($CDCl_3$) δ: 14.1 (q), 22.6 (t), 27.1 (t), 28.9 (t), 29.0 (t), 29.1 (t), 31.8 (t), 36.4 (t), 128.6 (d), 128.7 (d), 129.6 (d), 131.5 (d), 134.3 (d), 134.5 (s), 135.2 (s), 136.9 (s), 139.5 (s), 143.6 (s), 226.2 (s).

MS (*m/z*): 438 (M^+; 9%, ^{35}Cl, ^{37}Cl), 436 (M^+; 11%, ^{35}Cl), 293 (M^+-SC_8H_{17}; 69%, ^{35}Cl, ^{37}Cl), 291 (M^+-SC_8H_{17}; bp, ^{35}Cl).

HRMS calcd for $C_{23}H_{26}Cl_2S_2$: *m/z* 436.0853. Found: *m/z* 436.0853.

Compound 5d ($R^1 = C_6H_5$, $R_2 = CH_3$, $R^3 = n$-C_8H_{17})

Red oil.

IR (neat): 3059, 1595, 1162 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.2 Hz), 1.15-1.30 (10H, m), 1.41-1.45 (2H, m), 1.66-1.72 (2H, m), 2.55 (3H, s), 3.27 (2H, t, J = 7.2 Hz), 7.00 (1H, s), 7.36-7.40 (3H, m), 7.49-7.52 (2H, m).

^{13}C NMR ($CDCl_3$) δ: 14.2, 19.8, 22.7, 29.2, 31.8, 36.0, 126.5, 128.6, 128.7, 132.9, 143.2, 147.4, 224.9.

MS (*m/z*): 306 (M^+; 10%), 193 (M^+-C_8H_{17}; bp), 161 (M^+-SC_8H_{17}).

HRMS calcd for $C_{18}H_{26}S_2$: *m/z* 306.1476. Found: *m/z* 306.1481.

Compound 5e ($R^1 = C_6H_5$, $R^2 = n$-C_5H_{11}, $R^3 = n$-C_8H_{17})

Red oil.

IR (neat): 2955, 1592, 1215 cm^{-1}.

^1H NMR ($CDCl_3$) *Z*-isomer δ: 0.83-0.90 (6H, m), 1.21-1.48 (4H, m), 1.54-1.60 (4H, m), 2.42-2.44 (2H, m), 2.50 (2H, t, J = 7.5 Hz), 6.61 (1H, s), 7.20-7.22 (2H, m), 7.25-7.30 (3H, m),

E-isomer δ: 0.83-0.90 (6H, m), 1.21-1.48 (4H, m), 1.70 (2H, sext, *J*= 7.5 Hz), 3.01-3.07 (2H, m), 3.25 (2H, t, *J* = 7.5 Hz), 6.84 (1H, s), 7.32-7.39 (3H, m), 7.44-7.47 (2H, m).

^{13}C NMR ($CDCl_3$) *Z*-isomer δ: 14.1 (q), 22.5 (t), 27.2 (t), 27.3 (t), 29.0 (t), 29.8 (t), 31.5 (t), 32.3 (t), 36.5 (t), 39.4 (t), 40.2 (t), 127.7 (d), 128.2 (d), 134.0 (d), 140.1 (s), 148.7 (s), 228.1(s),

E-isomer δ: 14.1 (q), 14.2 (t), 22.5 (t), 22.8 (t), 27.6 (t), 28.7 (t), 29.2 (t), 31.6 (t), 31.9 (t), 32.0 (t), 36.2 (t), 126.6 (d), 128.6 (d), 133.1 (d), 142.2 (s), 152.3 (s), 225.1 (s).

MS (*m/z*): 360 (M^+; 11%), 249 (M^+-C_8H_{17}; bp), 217 (M^+-SC_8H_{17}).

HRMS calcd for $C_{22}H_{34}S_2$: *m/z* 362.2102. Found: *m/z* 362.2089.

3-3-4 Procedure for the reaction of 2-alkenecarbodithioate esters 5 with chloramine-T:

A dry chloroform solution of S-octyl 2-alkenecarbodithioate **5a** ($R^1 = R^2 = C_6H_5$, 50 mg, 0.136 mmol) was treated with chloramine-T (59 mg, 0.190 mmol, 1.4 eq.) at refluxing temperature for 75 min. After quenching the reaction by addition of water, the usual workup, and purification using silica gel column chromatography, the corresponding 2,3-dihydroisothiazole **6a** ($R^1 = R^2 = C_6H_5$, 50 mg, 68% yield) was isolated as yellow oil along with a few byproducts involving ethyl 3,3-diphenyl-2-propenoate (**7a**) and thioimidate **8a**.

Physical and spectral data for 2,3-dihydroisothiazoles 6:

Compound 6a ($R^1 = R^2 = C_6H_5$):

Pale yellow oil.

IR (neat): 3060, 2926, 2857, 1351, 1162 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, t, *J*= 6.8 Hz), 1.26-1.37 (10H, m), 1.54-1.59 (2H, m), 2.36 (3H, s), 2.72 (2H, t, *J* = 7.2 Hz), 5.70 (1H, s), 6.98 (2H, d, *J*= 8.4 Hz), 7.06 (2H, d, *J*= 8.4 Hz), 7.20-7.27 (10H, m).

^{13}C NMR ($CDCl_3$) δ: 13.1 (q), 20.5 (q), 21.6 (t), 27.4 (t), 28.1 (t), 28.8 (t), 30.8 (t), 33.7 (t), 83.7 (t), 126.0 (d), 126.2 (d), 126.7 (d), 126.9 (d), 127.8 (d), 128.0 (d), 131.2 (s), 136.4 (s), 138.5 (s), 141.9 (s).

MS (*m/z*): 538 (M^++1; 19%), 537 (M^+; 14%), 460 (M^+-C_6H_5; 43%), 382 (M^+-SO_2Tol; bp), 222 (M^+-SC_8H_{17}-$SNSO_2Tol$; 97%).

HRMS calcd for $C_{30}H_{35}NO_2S_3$: *m/z* 537.1823. Found: *m/z* 538.1930 (M^++1).

Compound 6b ($R^1 = R^2 = p\text{-}CH_3OC_6H_4$):

Pale yellow oil.

IR (neat): 3061, 2926, 2852, 1349 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6.8 Hz), 1.24-1.38 (12H, m), 1.54-1.62 (2H, quint, J = 7.2 Hz), 2.36 (3H, s), 2.72 (2H, t, J = 7.2 Hz), 3.80 (6H, s), 5.67 (1H, s), 6.71 (2H, d, J = 8.8 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.12-7.17 (8H, m).

^{13}C NMR ($CDCl_3$): 14.1 (q), 21.5 (q), 22.7 (t), 28.4 (t), 29.2 (t), 29.8 (t), 31.9 (t), 34.7 (t), 55.3 (q), 84.2 (s), 113.0 (d), 127.0 (d), 127.7 (d), 128.7 (d), 130.2 (d), 131.7 (s), 132.0 (s), 137.8 (s), 142.9 (s), 159.2 (s).

MS (*m/z*): 598 (M^++1; 33%), 597 (M^+; 10%), 442 (M^+-SO_2Tol; bp), 283 (M^+-SC_8H_{17}-$SNSO_2$Tol; bp).

HRMS calcd for $C_{32}H_{39}NO_4S_3$: *m/z* 597.2041. Found: *m/z* 598.2111 (M^++1).

Compound 6c ($R^1 = R^2 = p\text{-}ClC_6H_4$):

Pale yellow oil.

IR (neat): 3065, 2926, 2857, 1352 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6.8 Hz), 1.26 (6H, s), 1.30-1.37 (4H, m), 2.39 (3H, s), 2.74 (2H, t, J = 7.6 Hz), 5.56 (1H, s), 7.04 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.17 (8H, br. s).

^{13}C NMR ($CDCl_3$) δ: 14.1 (q), 21.6 (q), 22.7 (t), 28.4 (t), 29.1 (t), 29.8 (t), 31.8 (t), 34.8 (t), 83.5 (s), 125.4 (d), 126.8 (d), 128.0 (d), 128.9 (d), 130.3 (d), 133.6 (s), 134.3 (s), 137.5 (s), 137.8 (s), 143.5 (s).

MS (*m/z*): 607 (M^+; 16%, ^{35}Cl, ^{37}Cl), 606 (M^++1; 19%), 605 (M^+; 13%, 35Cl), 450 (M^+-SO_2Tol; 50%), 305 (M^+-SC_8H_{17}-$SNSO_2$Tol; bp).

HRMS calcd for $C_{30}H_{33}Cl_2NO_2S_3$: *m/z* 605.1051. Found: *m/z* 606.1134 (M^++1).

Compound 8a ($R^1 = R^2 = C_6H_5$):

Pale yellow solid.

MP: 69.1-71.7°C.

IR (KBr): 3057, 2925, 1529, 1318, 1158 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, t, J= 7.2 Hz), 1.05-1.34 (12H, m), 2.42 (1H, s), 2.43 (3H, s), 2.72 (2H, t, J = 7.2 Hz), 7.02 (1H, s), 7.09 (1H, s), 7.10 (2H, d, J = 8.4 Hz), 7.27-7.37 (10H, m), 7.85 (2H, d, J = 8.4 Hz).

^{13}C NMR ($CDCl_3$) δ: 13.1 (q), 20.6 (q), 21.6 (d), 26.7 (t), 27.6 (t), 28.0 (t), 28.1 (t), 30.8 (t), 121.5 (d), 126.3 (d), 127.0 (d), 127.3 (d), 127.4 (d), 127.7 (d), 128.3 (d), 137.3 (s), 139.4 (s), 142.3 (s), 150.2 (s).

MS (*m/z*): 505 (M^+; 1%), 360 (M^+-SC_8H_{17}; 39%), 350 (M^+-SO_2Tol; 15%), 155 (SO_2Tol; bp).

HRMS calcd for $C_{30}H_{35}NO_2S_2$: *m/z* 505.2109. Found: *m/z* 505.2598.

3-3-5 Birch reduction of 2,3-dihydroisothiazole 6a:

A THF solution of compound **6a** ($R^1 = R^2 = C_6H_5$, 70 mg, 0.13 mmol) was treated with sodium metal (25 mg, 8.0 eq.) and propylamine (154 mg, 20 eq.) at 0°C to R.T. for 12 h. After quenching the reaction by addition of an excess amount of water, the usual workup, and purification using silica gel column chromatography, the corresponding *N*-propyl-3,3-diphenyl-2-propenethioamide **9a** ($R^1 = R^2 = C_6H_5$, 37 mg, 48% yield) was isolated as yellow oil.

***N*-propyl-3,3-diphenyl-2-propenethioamide (9a)**

Compound 9a ($R^1 = R^2 = C_6H_5$):

Yellow oil.

IR (neat): 3240, 2958, 2926, 1527, 1401, 1067, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, t, J = 7.5 Hz), 1.20 (2H, sextet, J = 7.5 Hz), 3.38 (2H, td, J = 7.5, 4.5 Hz), 6.89-6.91 (1H, m), 7.24-7.28 (2H, m), 7.29-7.34 (5H, m), 7.40-7.45 (3H, m).

^{13}C NMR ($CDCl_3$) δ: 14.1 (q), 11.4 (q), 20.9 (t), 47.7 (t), 128.2 (d), 128.6 (d), 128.9 (d), 129.1 (d), 129.2 (d), 129.6 (d), 129.7 (d), 138.2 (s), 140.7 (s), 142.8 (s), 195.0 (s).

MS (*m/z*): 281 (M^+; bp), 191 (($C_6H_5)_2C_3H$; 50%), 178 (($C_6H_5)_2C_2$; 30%), 83 (54%).

HRMS calcd for $C_{18}H_{19}NS$: *m/z* 281.1238. Found: *m/z* 281.1261.

3-3-6 Procedure for the reaction of 2-alkenecarbodithioate esters 5 with *m*CPBA:

A dichloromethane solution of S-octyl 3,3-diphenyl-2-propcarbodithioate (**5a**, $R^1 = R^2 = C_6H_5$, 126 mg, 0.342 mmol) was treated with *m*CPBA (133 mg, 0.479 mmol, 1.4 eq.) at -78°C for 30 min. After quenching the reaction by addition of saturated aq. sodium sulfite solution, the usual workup, and purification using silica gel column chromatography, *S*-octyl 3,3-diphenyl-2-propenecarbothioate (**10a**, $R^1 = R^2 = C_6H_5$, 50 mg, 8% yield) was isolated as colorless oil besides several uncharacterized byproducts.

***S*-octyl 3,3-diphenyl-2-propenecarbothioate (10a)**

Compound 10a ($R^1 = R^2 = C_6H_5$):

Colorless oil.

IR (neat): 3026, 2956, 1677 cm-1.

^{1}H NMR (CDCl3) δ: 0.78-0.81 (3H, m), 1.17-1.18 (10H, m), 1.44-1.47 (2H, m), 2.78 (2H, t, J = 7.2 Hz), 6.52 (1H, s), 7.14-7.32 (10H, m).

^{13}C NMR (CDCl3) δ: 13.1 (q), 21.6 (t), 27.9 (t), 28.0 (t), 28.1 (t), 28.2 (t), 28.5 (t), 30.8 (t), 123.0 (d), 127.0 (d), 127.4 (d), 127.5 (d), 128.4 (d), 137.7 (s), 139.7 (s), 151.9 (s), 187.9 (s).

So, α, β-unsaturated esters and dithioesters are the important compounds which are used in a number of biologically active compounds, as well as ubiquitous structural motifs to various organic fields. Isothiazoles constitute a relatively novel class of heterocyclic and biologically active compounds which are also kept a vital role in organic chemistry.

In conclusion, here a new method has been found for the synthesis of 2-alkenecarbodithioate esters **5** through the reaction of substituted propargyl methyl ethers **2** with a base, elemental sulfur, and an alkanethiol in one-pot procedure and the subsequent efficient conversion of **5** into substituted isothiazole derivatives **6** in [4+1] type oxidative ring closure.

Chapter 4:

Synthesis of Thiochromenes *via* Oxidative Ring Closure of *α*, *β*-Unsaturated Carbodithioates

Chapter 4: Synthesis of Thiochromenes *via* Oxidative Ring Closure of α, β-Unsaturated Carbodithioates

4-1 Introduction

Chromenes and their sulfur analogues like thiochrmenes are the important classes of structural motifs found in numerous naturally occurring and synthetic compounds. Due to a rich array of functionalities and chiral centers these motifs are widely recognized as useful building blocks for the synthesis of a broad and interesting range of biologically active heterocyclic compounds having antiviral, antitumor, antimicrobial, antidiabetic, sex-pheromone, diuretic, anticoagulant, anti-anaphylatic and many more activities. Therefore, the synthetic methodologies allowing rapid access to these heterocycles in optically enriched form are highly desirable in organic synthesis and chemical biology/medicinal chemistry.

4-2 Results and Discussion

4-2-1 General Discussion

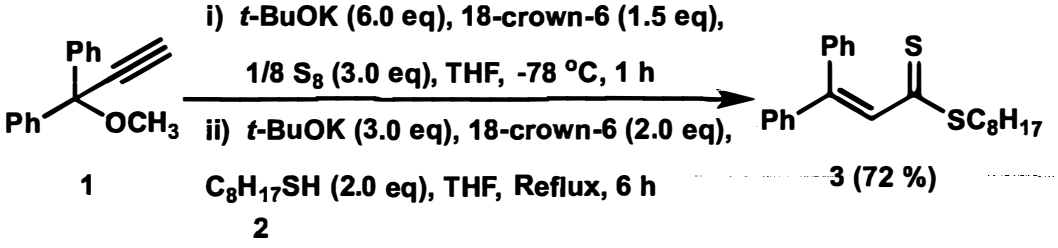
Despite the progress toward synthesis of thiochromenes, all the reported methods utilize thiols derivatives as starting materials which are less accessible, produce unpleasant smell, and concern environmental safety. Therefore, development of an alternative method which overcomes all above-mentioned difficulties would be highly desirable. There are very few general methods available for the synthesis of thiochromenes and those known are mostly specific to certain substrate classes. In recent years, considerable effort has been devoted toward the synthesis of thichromenes through different pathways. The development of elegant synthetic methods to access thiochromenes with diverse structural motifs is particularly appealing.

Due to the various applications of thiochromenes in medicinal chemistry, considerable research efforts have been focused on the development of the efficient methods for the synthesis of thiochromenes. We envisioned here a short-step preparation of thiochromene ring system by using a hetero Diels-Alder type reaction of α, β-unsaturated thiocarbonyl compounds with *in situ*

generated benzynes. As the part of our successive work, we have investigated here the formal [4+2] type oxidative ring closure of α, β-unsaturated carbodithioates with arynes *in situ* to synthesize some substituted thiochromenes starting from readily available intermediates.

4-2-2 Details explanation

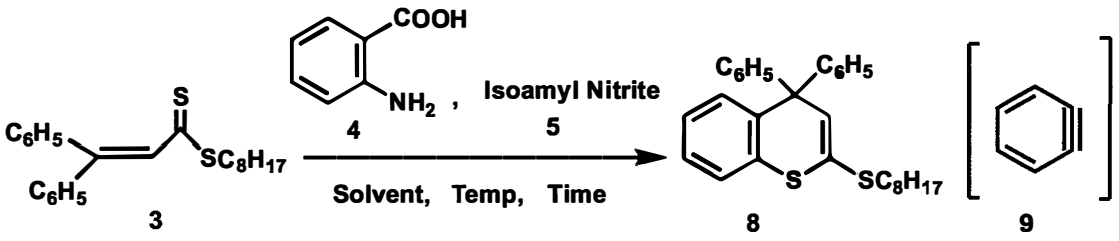
To synthesize thiochromene type of compounds, the preparation of α, β-unsaturated carbodithioates was performed before like the one-step synthesis of 2-alkenecarbodithioate esters from substituted propargyl ethers through a [4+1] type oxidative ring closure system (Scheme 41).



Scheme 42. Preparation of α, β-unsaturated carbodithioates **3**

To optimize the reaction conditions, compound **3** was subjected to the reaction with *in-situ* generated benzyne **9** to obtain the formal [4+2] cycloadduct. The yield of compound **8** was depending on the reaction conditions, and the best result was obtained in the case of treating **3** with 3.0 eq. of **4** and 3.5 eq. of **5** in dioxane under refluxing temperature for 6 hours which is shown in Table 6. These results provide us an attractive short-step approach to thiochromenes bearing various functionality, and the synthetic extension of the reaction was carried out for the substrate scope.

Table 6. Optimization of the reaction conditions for the synthesis of thiochromenes **8** [a]



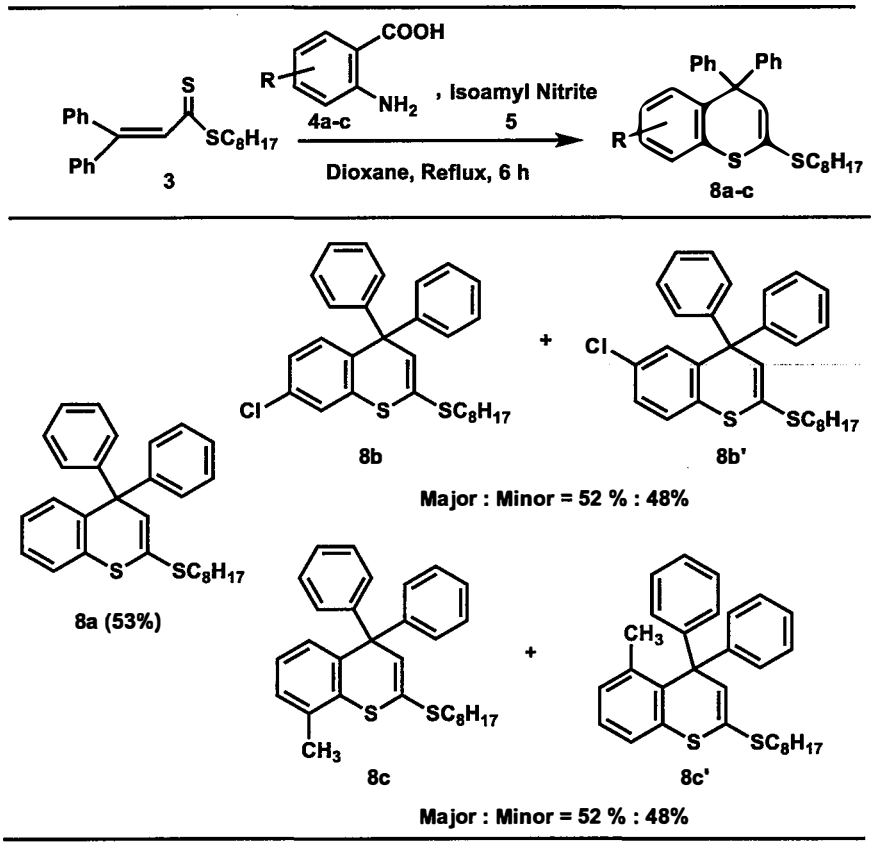
Entry	B (eq)	Isoamyl Nitrite (eq)	Solvent	Temp (°C)	Time (h)	Yield[a] (%) of 8
1	2.0	3.0	acetone	Reflux	1.5	42
2	2.5	3.0	diglyme	Reflux	3.0	47
3	3.0	3.5	dioxane	Reflux	3.0	43
4	3.0	3.5	dioxane	Reflux	6.0	53

[a] **Isolated yield.**

Having established the optimal reaction conditions, the substrate scope of this cascade reaction was explored with an array of substituted thiochromenes. Indeed, the reactions proceeded quickly to give the expected cycloadducts in moderate to good yields. This cascade reactions are considerably general and tolerates substituted thichromenes bearing both electron-rich and electron-deficient groups on the aromatic ring. Among them, one of the most important and new method is the oxidative ring closure of α, β-unsaturated carbodithioate **3** with arynes, followed by formal [4+2] cycloaddition procedure which is shown in Table 7. Different reagents have been reported to get the cycloaddition products, such as 3-methyl anthranilic acid and 4-chloroanthaniclic acid. However, the method had some disadvantages such as the use of some expensive reagents and longer reaction times. But the effective approach for the synthesis of thiochromenes is the nucleophilic substitution of appropriately substituted thiochromenes with arynes. However, this transformation utilizes the reaction conditions to provide moderate results. The substrates with electron withdrawing substituents on aryl ring led to lower yields (Table 7, **8b**), presumably due to the lower reactivity of the solvent with the substrates. In case of 3-methyl anthranilic acid and 4-chloro anthranilic acid, the regioisomeric products were found. In both cases

the major and minor products were found almost 52% and 48% respectively. Notably, satisfactory results in term of yield were also achieved with the electron donating substituents bearing methyl group in the aryne ring (Table 7, **8c**). It is mentioned that the preliminary confirmation of the products was found from the ^{1}H NMR spectra.

Table 7. Substrate scope for anthranilic acid to synthesize thiochromenes [a,b]

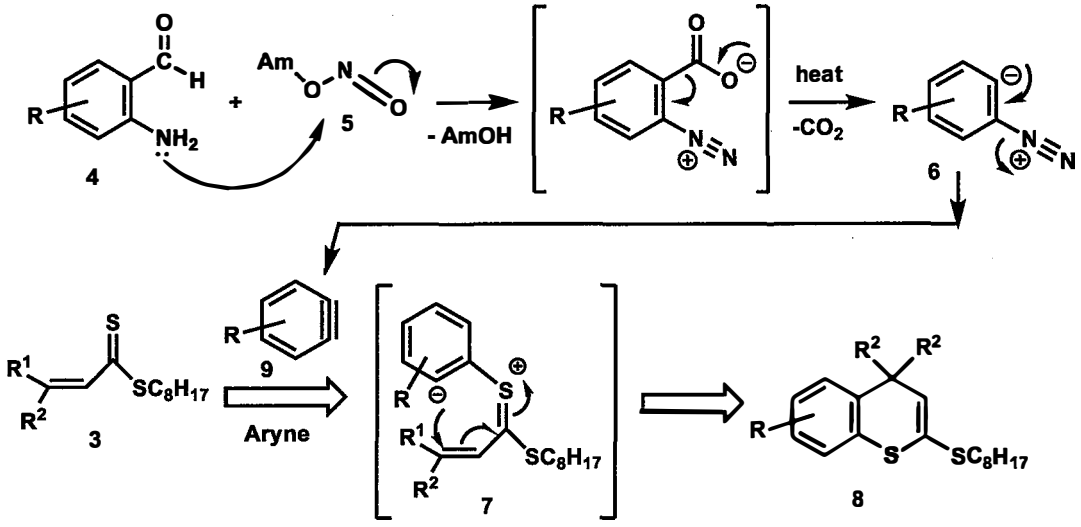


[a] Reaction conditions: all reactions were performed with **3** (0.143 mmol), **4** (0.429 mmol) and Isoamyl nitrite (0.500 mmol) in dioxane (5 mL) at reflux for 6 h. [b] Isolated yield.

4-2-3 Reaction Mechanism

Based on the reported mechanistic studies, the reaction of α, β-unsaturated carbodithioate ester **3** with arynes, **9** we proposed a plausible pathway for the formation of thiochromenes **8** (Scheme 42). Here, initially, the amino group attacks to isoamyl nitrite to form an intermediate by removing

amylalcohol which is followed by arynes through the leaving group of nitrogen molecule. Finally, the condensation of α, β-unsaturated carbodithioates **3** with arynes **9** occurs to provide thiochromenes **8** by the formation of intermediate as **7**.



Scheme 43. Plausible reaction mechanism for formal [4+2] cycloaddition of α, β-unsaturated carbodithioates **3** with arynes **9** to form thiochromenes **8**

4-3 Experimental Section

Instruments: The melting points were determined with a Büchi 535 micro-melting-point apparatus. ^{1}H NMR spectra were recorded on a Bruker DRX-400P (400 MHz) spectrometer, and the chemical shifts of the ^{1}H NMR spectra are given in δ relative to internal tetramethylsilane (TMS). ^{13}C NMR spectra were recorded on a Bruker DRX-400P (100 MHz). Mass spectra were recorded on a JEOL MS-700T mass spectrometer with electron-impact ionization at 20 or 70 eV using a direct inlet system. High resolution mass spectra (HRMS) were also recorded on a JEOL MS-700T spectrometer. IR spectra were recorded for thin film (neat) or KBr disks on a JASCO FT/IR-7300 spectrometer. Elemental analyses were performed using a Yanagimoto CHN corder MT-5.

4-3-1 Procedure for the preparation of 3,3-diphenyl *S*-octyl 2-propenecarbodithioate, 3:

The reaction procedure was performed in two stages: (1) A 50 ml 2 necked flask was dried in vacuum and nitrogen gas was passed. A dry THF solution of ^{t}BuOK (3 eq.) was treated with 18-crown-6 ether (2 eq.) and *n*-$C_8H_{17}SH$ (2 eq.) was stirred at room temperature as around 1 h. The solution was appeared as white milky colour. (2) A 100 ml 3 necked flask was dried in liquid nitrogen vacuum and nitrogen gas was passed. Then ^{t}BuOK (6 eq.) and 18-crown-6 (1.5 eq.) ether was taken and cooled at -78°C using MeOH and liquid N_2 bath. Then diphenyl propargyl methyl ether **1** (40 mg, 1.8 mmol) was added in the solution and stirred at -78°C for 1 h. Elemental sulfur (3 eq.) was incorporated to the solution and stirred again at -78°C for around 30 mins. Then the solution of (1) was transferred into the solution (2) and warm at up to RT for 20 min. and then refluxed at around 80°C for 6 h. The solution was cooled at RT and quenched with water. Extracted with $CHCl_3$, dried over anhydrous Na_2SO_4. After removing the solvent in vacuo, the crude product was subjected to chromatographic purification on silica gel to isolate the corresponding 3,3-diphenyl *S*-octyl 2-propenecarbodithioate **3** (48 mg, yield 72%) as reddish oil along with some byproducts.

Physical and spectral data of compound 3:

Reddish oil.

IR (neat): 3056, 3023, 2953, 1565, 1177, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.2 Hz), 1.23-1.29 (10H, m), 1.49-1.53 (2H, m), 3.11 (2H, t, J = 7.2 Hz), 7.06 (1H, s), 7.24-7.33 (10H, m).

^{13}C NMR ($CDCl_3$) δ: 14.2 (q), 22.8 (t), 27.3 (t), 29.0 (t), 29.2 (t), 29.3 (t), 31.9 (t), 36.5 (t), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 129.0 (d), 130.2 (d), 134.1 (d), 139.0 (s), 141.5 (s), 146.3 (s), 227.0 (s).

DEFT-135 NMR ($CDCl_3$) δ: 14.2 (q), 22.8 (t), 27.3 (t), 29.0 (t), 29.2 (t), 29.3 (t), 31.7 (t), 31.9 (t), 36.5 (t), 128.2 (d), 128.3 (d), 128.4 (d), 128.6 (d), 129.0 (d), 130.3 (d), 134.2 (d).

HRMS calcd for $C_{23}H_{28}S_2$: *m/z* 368.1632. Found: *m/z* 368.1635.

4-3-2 Procedure for the preparation of 2-(octylthio)-4,4-diphenyl-4*H*-thiochromene, 8a:

A 30-minute stirred THF solution of 3,3-disubstituted S-butyl 2-alkenecarbodithioates 2a (20 mg, 0.054 mmol) was transferred into another 30 minutes stirred dioxane solution of 3 eq. anthranilic acid (22 mg, 0.162 mmol) and 3.5 eq. isoamyl nitrite (22 mg, 0.189 mmol). Then the mixture was refluxed around around 3 h. After refluxing and TLC checking, the reaction was quenched by the addition of an excess amount of water. The reaction mixture was extracted with $CHCl_3$, and the organic layer was washed with water and then with brine, and was dried over anhydrous sodium sulfate powder. After removing the solvent in vacuo, the crude product was subjected to chromatographic purification on silica gel to isolate the corresponding product **8a** (13 mg, yield 53%) as blood reddish oil.

Physical and spectral data of 2-(octylthio)-4,4-diphenyl-4*H*-thiochromene (8a):
Blood Reddish oil.
IR (neat): 3057.6, 2954.4, 2925.5, 2854.1, 1674.9, 1110.8, 1076.1 cm^{-1}.
^1H NMR ($CDCl_3$, 500 MHz) δ: 0.86 (3H, t, J = 7.0 Hz), 1.24-1.30 (10H, m), 1.51-1.55 (2H, m), 2.85 (2H, t, J = 7.25 Hz), 6.59 (1H, s), 7.21-7.42 (14H, m).
^{13}C NMR ($CDCl_3$, 500 MHz) δ: 14.23 (s), 22.78 (s), 29.03 (s), 29.29 (t), 29.70 (s), 31.92 (s), 124.15 (d), 127.14 (d), 127.63 (d), 128.10 (d), 128.24 (d), 128.55 (d), 128.71 (d), 129.56 (d), 131.95 (d), 138.88 (s), 140.88 (s), 153.03 (s), 189.11 (s).
DEFT-135 NMR ($CDCl_3$, 500 MHz) δ: 14.23 (s), 22.77 (s), 29.03 (s), 29.24 (t), 29.30 (s), 29.35 (d), 31.91 (s), 124.13 (d), 127.13 (d), 127.63 (d), 128.09 (d), 128.24 (d), 128.54 (d), 128.71 (d), 129.54 (d), 129.71 (s).

Physical and spectral data of 2-(octylthio)-4,4-diphenyl-4*H*-thiochromene (8b):
Blood Reddish oil.
IR (neat): 2957.3, 2927.4, 2856.1, 1662.3, 1164.8, 1091.5 cm^{-1}.
^1H NMR ($CDCl_3$, 500 MHz) δ: 0.86 (3H, t, J = 7.0 Hz), 0.91-0.96 (10H, m), 1.24-1.36 (2H, m), 4.02 (2H, t, J = 7.25 Hz), 6.36 (1H, s), 7.21-7.38 (14H, m).

^{13}C NMR ($CDCl_3$, 500 MHz) δ: 14.3 (s), 22.54 (s), 29.03 (s), 29.29 (t), 29.70 (s), 31.92 (s), 124.15 (d), 127.14 (d), 127.63 (d), 128.03 (d), 128.11 (d), 128.42 (d), 128.50 (d), 128.72 (d), 129.23 (d), 129.50 (d), 129.57 (d), 130.21 (s), 132.56 (s).

Physical and spectral data of 2-(octylthio)-4,4-diphenyl-4*H*-thiochromene (8c):

Blood Reddish oil.

IR (neat): 2954.4, 2925.5, 2856.1, 1672.0, 1118.5, 1032.7 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (3H, t, J = 7.0 Hz), 1.24-1.45 (10H, m), 1.46-1.48 (2H, m), 2022 (s), 3.45 (2H, t, J = 7.25 Hz), 6.59 (1H, s), 7.11-7.32 (14H, m).

^{13}C NMR ($CDCl_3$, 500 MHz) δ: 26.37 (s), 26.42 (s), 29.23 (s), 29.36 (t), 29.70 (s), 31.92 (s), 38.73 (s), 69.47 (s), 110.99 (s), 124.15 (d), 126.83 (d), 126.94 (d), 127.44 (d), 128.10 (d), 128.49 (d), 128.55 (d), 128.77 (d), 129.56 (d), 130.70 (s).

So, the thiochromenes are of considerable pharmacological and material interest because they display a wide range of biological activities and are occasionally used as scaffolds or synthetic intermediates of functional dyes.

Considering these circumstances, here in this chapter an efficient method has been reported for the synthesis of thiochromenes **8** by the reaction of α, β-unsaturated carbodithioates with arynes *in situ* from the substituted anthranilic acid and amyl nitrite in optimized reaction conditions. Here in this work, the usage of economically reasonable reagents, mild reaction conditions and good yields of the synthesized products prove that the present protocol is a good alternative to the previously reported methods.

Chapter 5: Summary

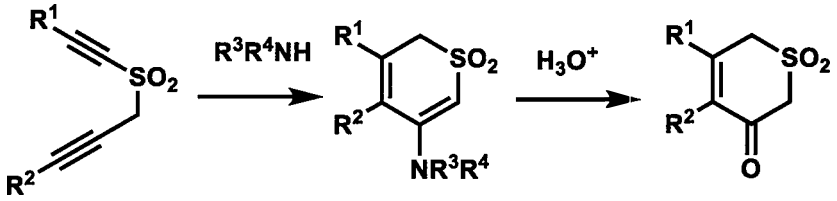
Summary

5-1 Introduction

Sulfur-containing compounds are widely present in natural products and synthetic bioactive molecules as well as in materials. Carbon-sulfur bond formation is a fundamental approach to introduce sulfur into organic compounds. This received considerable attention due to its occurrence in various molecules that are biological, pharmaceutical and material interest.

5-2 Synthesis of alkynyl propargyl sulfones and their conversion into six-membered cyclic *β*-ketosulfones

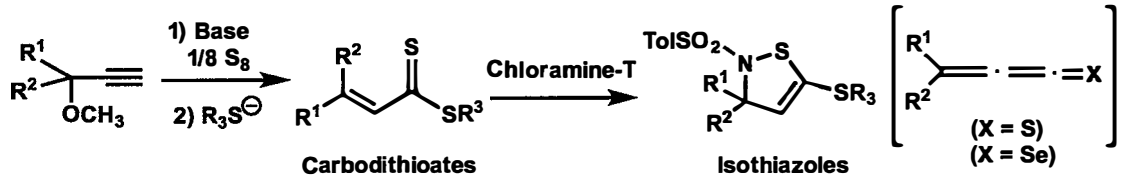
Sulfones belong to a known class of organosulfur compounds, which found various applications in organic synthesis. Among the other derivatives of sulfones, a special attention of synthetic chemists is drawn to sulfones containing functional group. In particular, 2-oxo-sulfones (*β*-keto sulfones) bearing carbonyl function in the *β*-position to sulfonyl group are versatile synthetic intermediates used for the preparation of diverse classes of organic compounds. Here, it was found a convenient one-pot synthesis of six-membered cyclic *γ, δ*-unsaturated β-ketosulfones through the heating of alkynyl propargyl sulfones in the presence of a secondary amine.



5-3 Synthesis of *α, β*-unsaturated carbodithioate esters and their conversion into isothiazoles

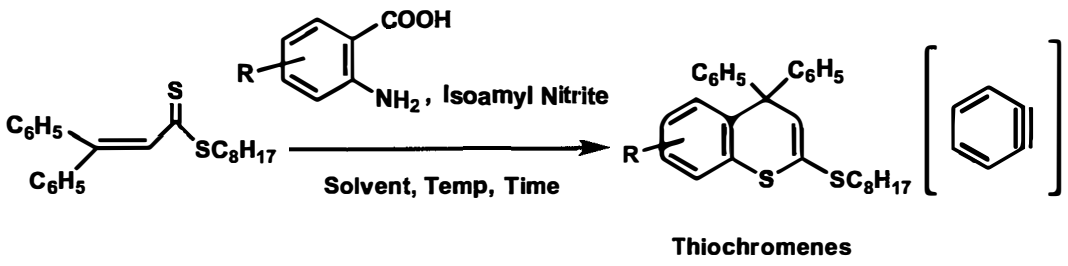
There are many importancy of carbodithioate esters and isothiazoles are found in different sectors. As a result, the active investigation of the chemistry of these compounds and their derivatives has

come to the researchers for many years. During this time, a number of routes have been devised for the preparation of these kind of various substituted compounds. Hence, here it is found a new method for the synthesis of 2-alkenecarbodithioate esters through the reaction of substituted propargyl methyl ethers with a base, elemental sulfur, and an alkanethiol in one-pot procedure and the subsequent efficient conversion of 2-alkenecarbodithioate esters into substituted isothiazole derivatives in [4+1] type oxidative ring closure.



5-4 Synthesis of thiochromenes *via* oxidative ring closure of *α, β*-unsaturated carbodithioates

Sulfur containing heterocycles like thiochromemes are found in a variety of biologically active molecules that can be used in different sectors. Hence, here in it is reported an efficient method for the synthesis of thiochromenes by the reaction of α, β-unsaturated carbodithioates with arynes *in situ* from substituted anthranilic acid and amyl nitrite in optimized reaction conditions. The usage of economically reasonable reagents, mild reaction conditions and good yields of the synthesized products prove that the present protocol is a good alternative to the previously reported methods. Further studies on the applications of these thiochromenes to thiochromenones and in drug discovery will be conducted in future.



5-5 Conclusion

Recently, the enormous increase in the synthesis of heterocyclic compounds containing chalcogen atoms has been leading to develop new methods and compounds. In summary, the synthesis of alkynyl propargyl sulfones and their conversion into six-membered cyclic β-ketosulfones, synthesis of α, β-unsaturated carbodithioate esters and their conversion into isothiazoles and synthesis of thiochromenes *via* oxidative ring closure of α, β-unsaturated carbodithioates are reported here in this thesis dissertation.

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List of Publications

1. **A Short Step Conversion of Alkynyl Propargyl Sulfones into Six-Membered Cyclic β-Ketosulfones *via* an Amine-Induced Novel Ring Closure,**

   Md. Ashraful Alam, Kazuaki Shimada, Hironobu Kamoto, Kasumi Shingo, Toshinobu Korenaga, and Chizuko Kabuto, *Natural Product Communications*, **2018**, *13*, 593-598.

2. **One-Step Synthesis of 2-Alkenecarbodithioate Esters from Substituted Propargyl Ethers, and Their Conversion into Isothiazole Ring through a [4+1] Type Oxidative Ring Closure,**

   Kazuaki Shimada, Fumiya Ishikawa, **Md. Ashraful Alam**, and Toshinobu Korenaga. *Natural Product Communications*, **2017**, *12*, 951-956.

List of Presentations

1. **Novel Synthesis of Thiochromenes *via* Oxidative Ring Closure of α, β-Unsaturated Carbodithioates**

   Md. Ashraful Alam, Kazuaki Shimada. The 98th CSJ Annual Meeting (Chemical Society Japan), Tokyo, **Japan** on March 21, 2018 (**Oral**).

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