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RECENT DEVELOPMENTS IN THE CHEMISTRY OF SULFUR- AND NITROGEN-CONTAINING HETEROCYCLES AND RELATED COMPOUNDS

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Interesting ring transformation reactions of thiazolines, thiazines and related compounds are described. Thiazoline derivatives and their sulfoxides undergo ring expansion under various reaction conditions to afford the corresponding thiazine derivatives. Photochemical and thermal addition reactions of benzisothiazoles, benzothiazoles, and their derivatives with alkenes or alkynes give various types of addition products, depending on the substrates. Photochemical or metal-catalyzed ring contractions of thiazines afford thiazolines, thiazetidines, or thiazoles, respectively. Thiazine derivatives undergo ring expansion by treatment with acid or base to give the corresponding thiazepine derivatives. The stereospecificity of the ring expansion of benzothiazine sulfoxides is also described. Preparation, properties and reactions of azathiabenzene derivatives are described. Recently reported interesting reactions of thiazine derivatives and thiazine formation reactions are described.

KEY WORDS: Thiazine, Thiazoline, Benzothiazepine, Azathiabenzene, Ring expansion, Ring contraction

INTRODUCTION

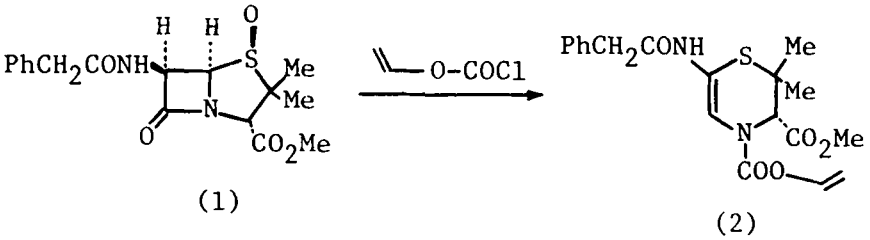
Sulfur- and nitrogen-containing heterocycles have attracted very strong attention since among them there are many biologically important compounds such as vitamine B_{12}, penicillins, cephalosporins and so on, and moreover interesting chemical reactivities can be expected. Tremendously great numbers of reports on the chemistry of this field have appeared so far. In this short review, special attention is drawn to current work published during these five years concerning the chemistry of five- and six-membered sulfur- and nitrogen-containing heterocyclic compounds including thiazoles, thiazolines, benzothiazoles, benzothiazolines, thiazines, benzothiazines, and related heterocycles. Especially, detailed descriptions are focused on ring transformation reactions of the above heterocycles.

I. CHEMISTRY OF SULFUR- AND NITROGEN-CONTAINING FIVE-MEMBERED HETEROCYCLES

I.1. Rearrangement of Thiazoline Derivatives and Related Compounds

There have been reported many reactions that result in the conversion of the thiazoline skeleton into other heterocycles. In this section, recently found new transformation reactions of the thiazoline skeleton are described.

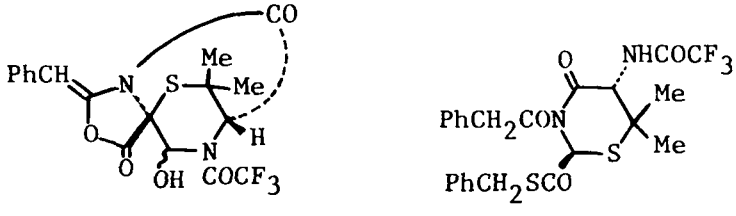
I.1.A. Ring expansion of penicillin derivatives Unusual ring cleavages and rearrangements of penicillin derivatives to the corresponding thiazines or other heterocycles have been reported.[1] The penicillin G β-sulfoxide methyl ester (**1**) reacts readily, at 0 °C or room temperature, with excess vinyl chloroformate in anhydrous alcohol-free chloroform to give the 1,4-thiazine derivative (**2**) in 56% yield. Although the mechanism of this rearrangement has not yet been determined, a cleavage of the C^5—S bond, initiated by attack of chloroformate, is suspected to be involved.



(1) (2)

SCHEME 1

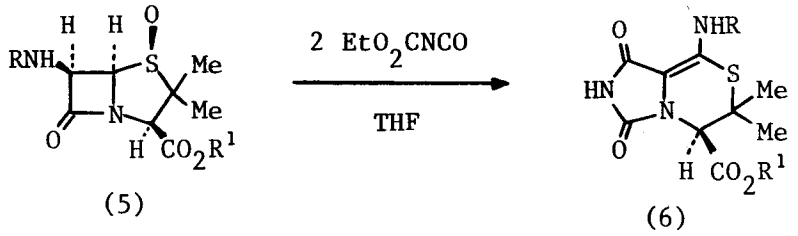
Penicillin G sulfoxide undergoes a novel rearrangement upon treatment with trifluoroacetic anhydride to afford a tricyclic spiro compound (**3**), which affords phenylthioacetaldehyde and the thiazinone derivative (**4**) when treated with benzylmethanethiol.[2]



(3) (4)

SCHEME 2

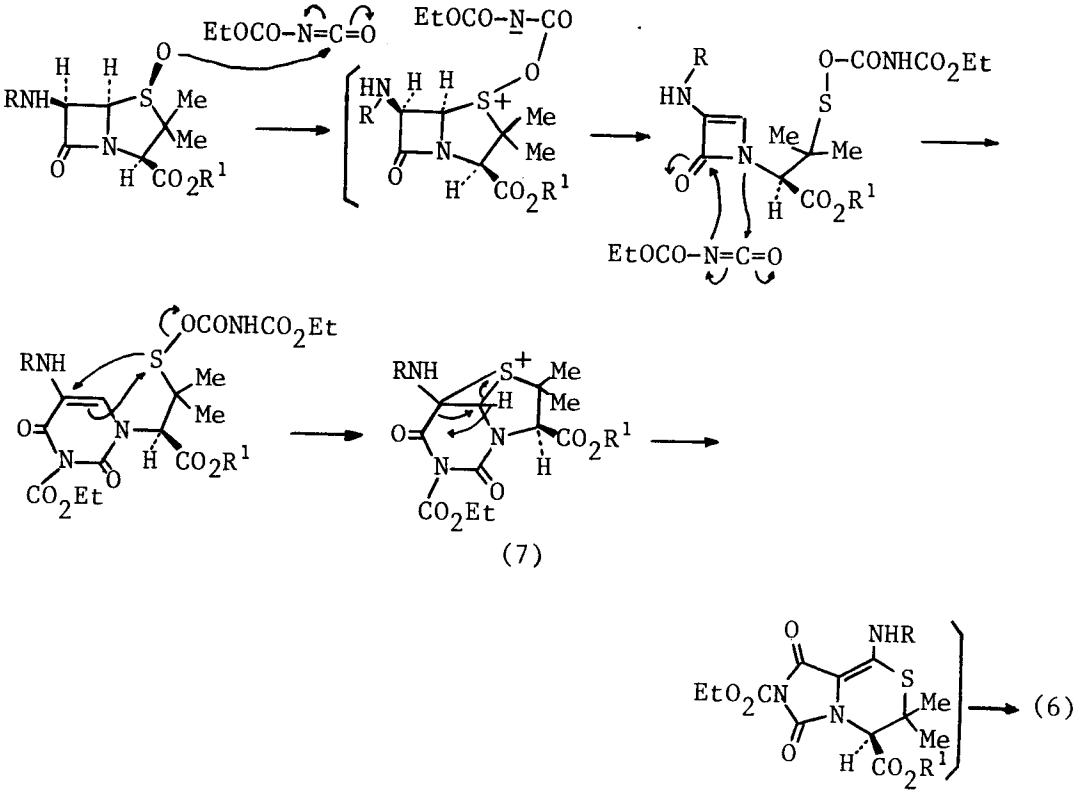
Another example of a new ring expansion of penicillin sulfoxides was reported by Nudelman et al.[3] When treated with two equivalents of ethoxycarbonyl isocyanate, the penicillin sulfoxides (**5**) are transformed to novel imidazo-1,4-benzothiazines (**6**).



(5) (6)

SCHEME 3

A mechanism involving C^5—S bond cleavage by the isocyanate and formation of an episulfonium ion intermediate (**7**) has been proposed as shown in Scheme 4.

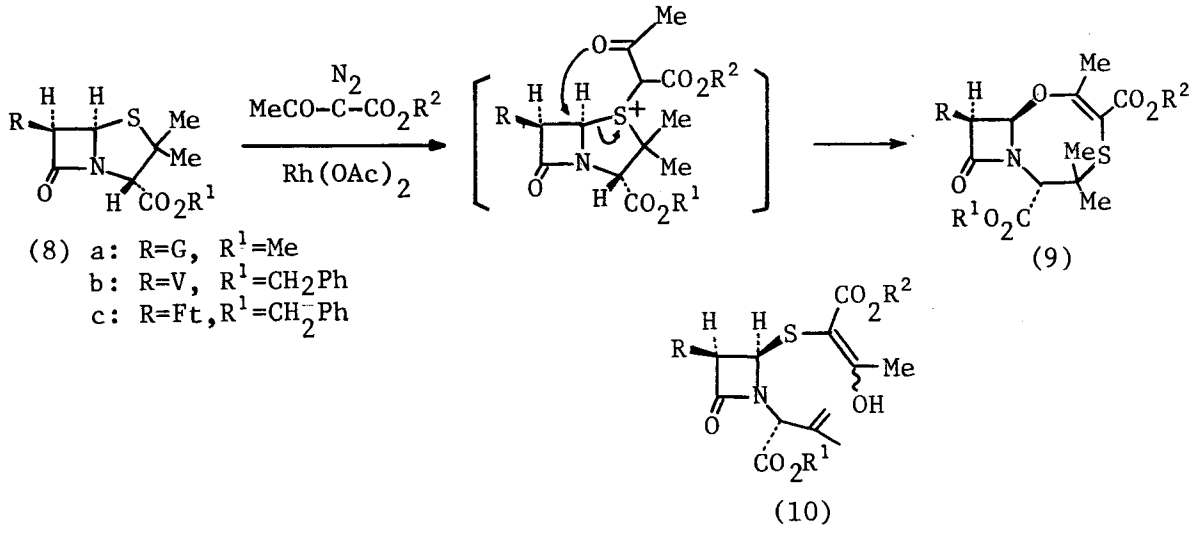


SCHEME 4

Penicillins are also cleaved between S and C^5 to afford new seven- and eight-membered heterocycles.[4]

The reaction of penicillin G methyl ester (**8a**) or penicillin V benzyl ester (**8b**) with *p*-nitrobenzyl α-diazoacetoacetate in dichloromethane-benzene solution in the presence of rhodium acetate at 70—80 °C yields the corresponding ring-expanded

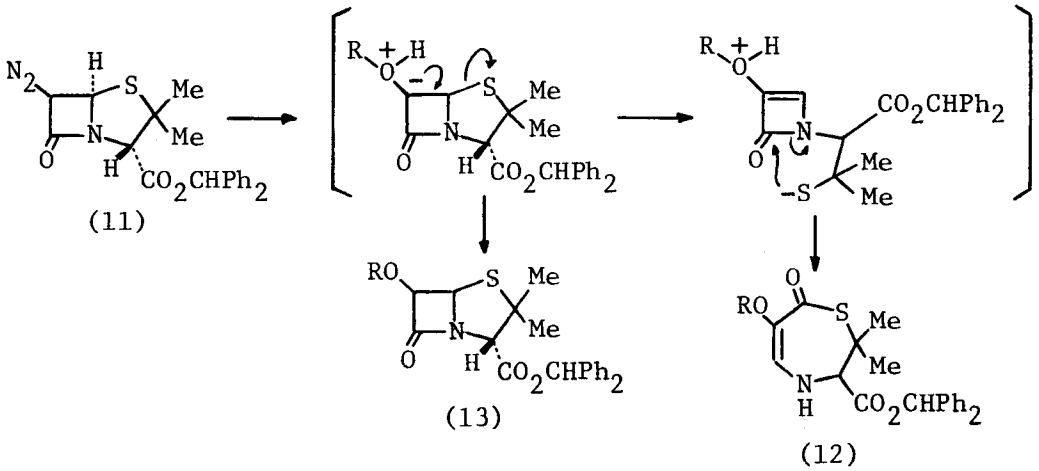
oxa-β-lactam derivatives (**9**) in moderate yield. This ring expansion reaction proceeds stereoselectively. Under the same reaction conditions, benzyl 3,4-*cis*-6-phthalimidylpenicillanate (**8c**) undergoes a cleavage of the C^2—S bond to give the ring-opened product (**10**) in 81% yield.



(8) a: R=G, R^1=Me
b: R=V, R^1=CH_2Ph
c: R=Ft, R^1=CH_2Ph

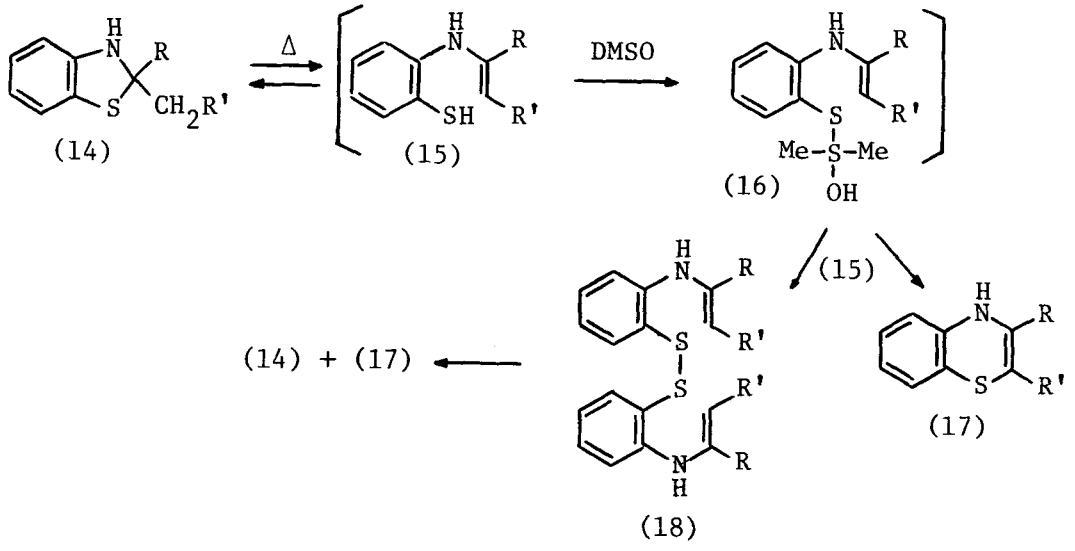
SCHEME 5

Treatment of the 6-diazopenicillanate ester (**11**) with alcohols in the presence of a rhodium ($Rh_2(OAc)_4 \cdot 2H_2O$) or copper catalyst ($Cu(acac)_2$) causes ring expansion of the ester and gives the corresponding thiazepines (**12**) as major products along with the alkoxypenicillanates (**13**) as minor products.[5] The thiazepines and alkoxypenicillanates are formed by rearrangement of oxonium ylide intermediates and proton transfer, respectively.

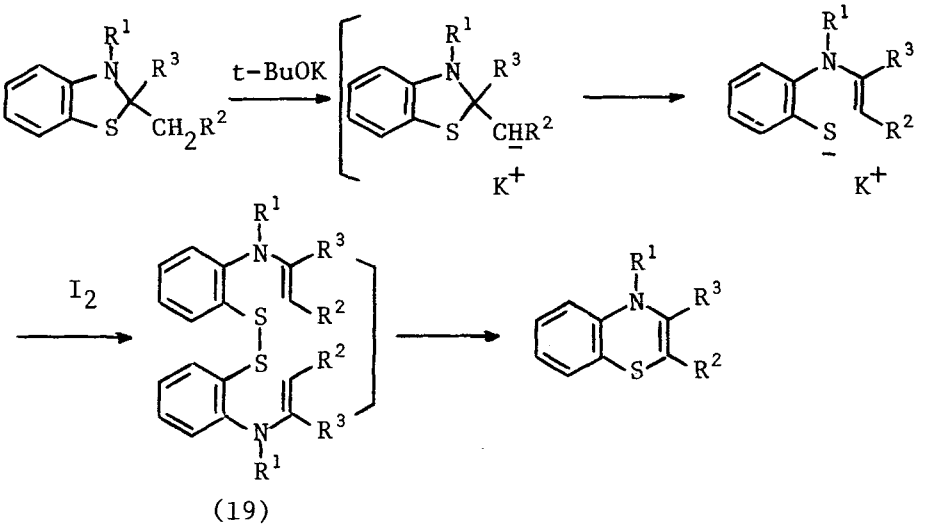


SCHEME 6

I.1.B. Ring expansion of thiazoline derivatives Direct conversion of *N*-unsubstituted 2,2-dialkylbenzothiazolines into 1,4-benzothiazines was found to occur in boiling dimethyl sulfoxide (DMSO) by Liso *et al.*[6] This oxidative ring expansion can be rationalized by invoking the intermediacy of the enamine species (**16**) which cyclizes to afford 1,4-benzothiazines (**17**). An alternative mechanism lets intermediate (**16**), by reaction with the ring-opened species (**15**), give the bis-enamine disulfide species (**18**) which in turn yields benzothiazines together with recovery of starting material.



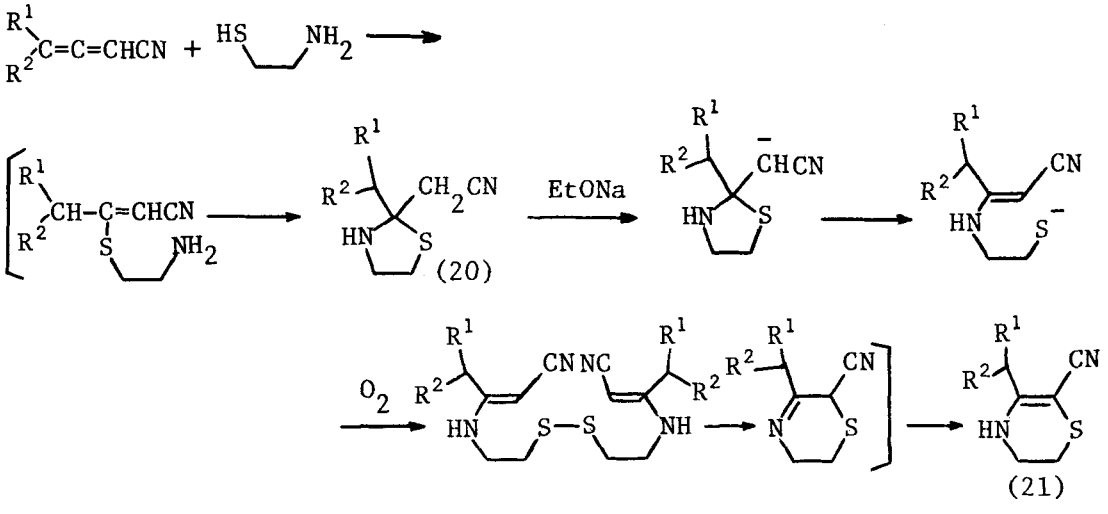
SCHEME 7



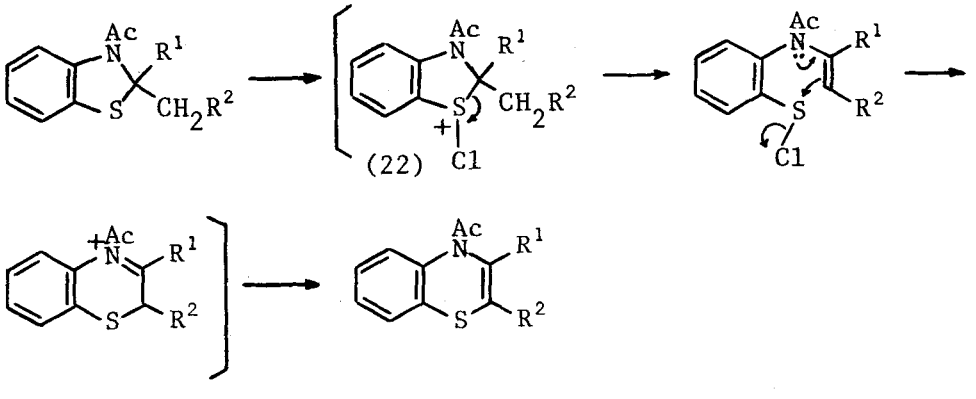
SCHEME 8

An improved oxidative ring expansion of benzothiazolines with electron-withdrawing groups in the 2-position into 1,4-benzothiazines was achieved by the same group.[7] The procedure consists in treating at room temperature under nitrogen a toluene solution of benzothiazolines with one equivalent of potassium *t*-butoxide, followed by one equivalent of powdered iodine. This reaction pathway may be explained by the cyclization of the bis-enamine sulfide (**19**) formed by iodine oxidation of an initially formed ring-opened enamine thiolate anion.

A similar type of ring expansion of thiazolidines to 1,4-thiazines via a bis-enamine disulfide intermediate has been reported.[8] Unisolable thiazolidines (**20**), which may be intermediates of the reaction of allenyl nitriles and 2-aminoethanethiol, undergo ring transformation upon treatment with two equivalents of sodium methoxide for 24 hr under reflux in alcohol and afford 5-alkyl-6-cyano-2,3-dihydro-4*H*-1,4-thiazines (**21**) in more than 90% yield.



SCHEME 9

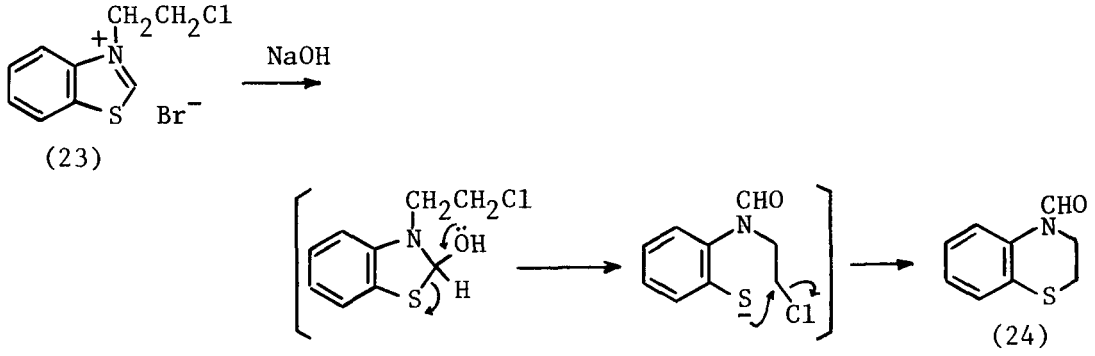


SCHEME 10

A one-step conversion of *N*-acylbenzothiazolines to 1,4-benzothiazines can be easily accomplished by treatment with sulfuryl chloride in dry dichloromethane at

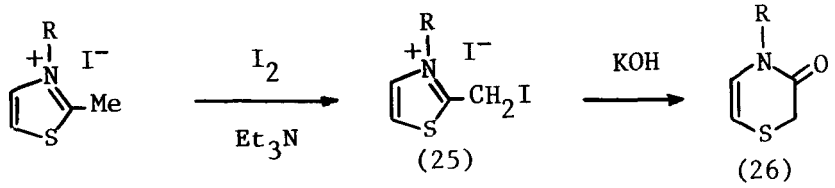
room temperature.[9] This ring expansion proceeds possibly via the chlorosulfonium salt (**22**) of benzothiazolines as shown in Scheme 10. This type of ring expansion has been reported in the ring conversion of 1,3-oxathiolanes[10] and 1,3-dithiolanes[11] to the corresponding 1,4-oxathiins and 1,4-dithiins, respectively, by treatment with chlorine and ethyl *N*-chlorocarbamate, respectively.

Base-induced ring expansion of 3-haloalkylbenzothiazolium salts has been achieved to give 6-, 7-, and 8-membered heterocycles.[12] For example, treatment of 3-chloroethylbenzothiazolium bromide (**23**) in trichloroethane and water with sodium hydroxide at 0-40°C gives 4-formyl-1,4-benzothiazine (**24**).



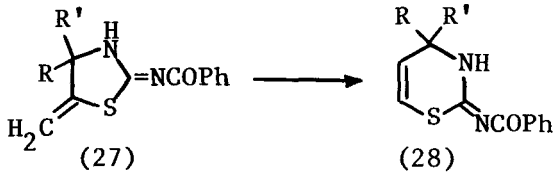
SCHEME 11

The reaction of 3-alkyl-2-iodomethylthiazolium iodide (**25**), prepared from 3-alkyl-2-methylthiazolium iodide and iodine in the presence of triethylamine, with potassium hydroxide in MeOH at room temperature gives the ring-expanded six-membered heterocyclic 4-alkyl-2*H*-1,4-thiazin-3-ones (**26**).[13]



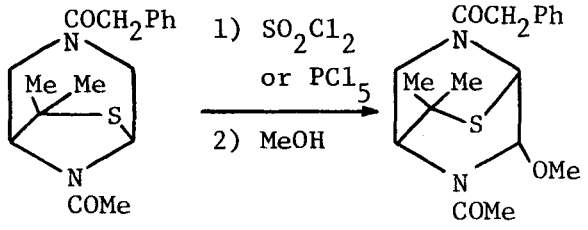
SCHEME 12

Methylenethiazolines (**27**), without a substituent at the nitrogen atom, rearrange on storage to give 1,3-thiazine derivatives (**28**).[14]



SCHEME 13

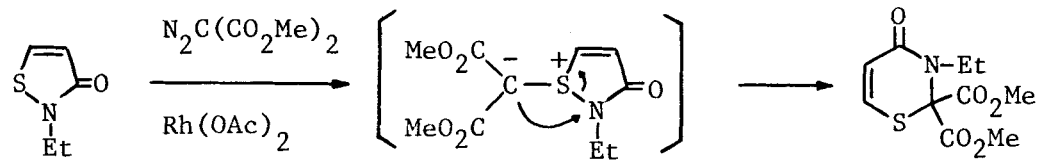
The thiadiazabicyclo[3.2.1]octane (**29**), with thionyl chloride or phosphorus pentachloride, followed by methanol, gives the ring-expanded product (**30**), containing a thiazolidine skeleton.[15]



(29) (30)

SCHEME 14

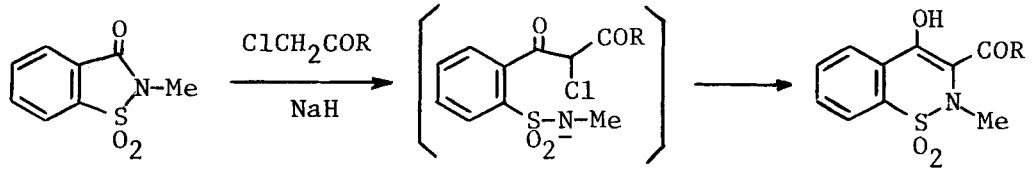
A Rh(II)-catalyzed insertion reaction of a diazo compound with isothiazol-3-ones gives 1,3-thiazin-4-ones in high yield.[16] For example, *N*-ethylisothiazol-3-one (**31**) with dimethyl diazomalonate in refluxing benzene in the presence of $Rh(OAc)_2$ for 4 hr gives a 70% yield of 1,3-thiazin-4-one (**33**), the most likely mechanism involving the trapping of a carbene species to form an intermediate sulfonium ylide (**32**) which undergoes ring expansion by a 1,2-shift.



(31) (32) (33)

SCHEME 15

A Darzens-like condensation of *N*-methylsaccharin (**34**) with α-haloacetate in the presence of sodium hydride affords 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (**35**) in high yield.[17] The use of two equivalents of base in DMF or DMSO has proved useful.

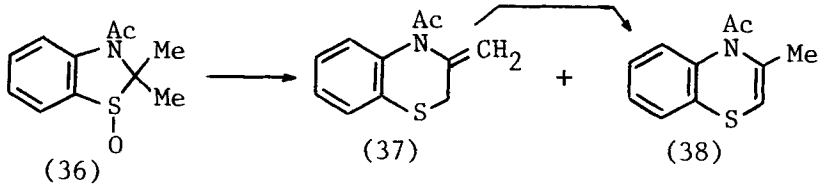


(34) (35)

SCHEME 16

I.1.C Ring expansion of benzothiazoline sulfoxides 2-Alkyl- or 2,2-dialkyl-3-acetylbenzothiazoline 1-oxides, including 2-spiro derivatives, undergo ring expansion to yield 4-acetyl-1,4-benzothiazines in good yield upon treatment with refluxing acetic

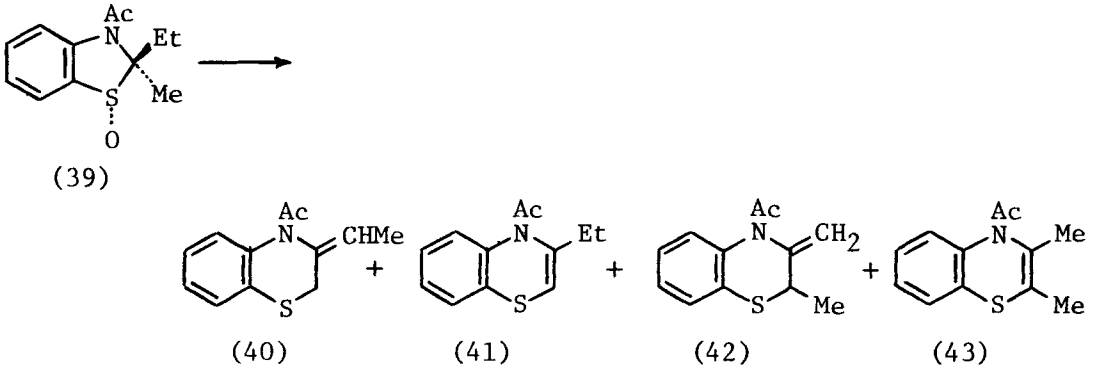
acid anhydride or trifluoroacetic acid anhydride at 0–25 °C.[18] Thus, 3-acetyl-2,2-dimethylbenzothiazoline 1-oxide (**36**) was refluxed in acetic anhydride to give the two 1,4-benzothiazines (**37**) and (**38**) in yields of 31.5% and 48.6%, respectively. Compound **37** is converted quantitatively into **38** when heated above 150 °C.



SCHEME 17

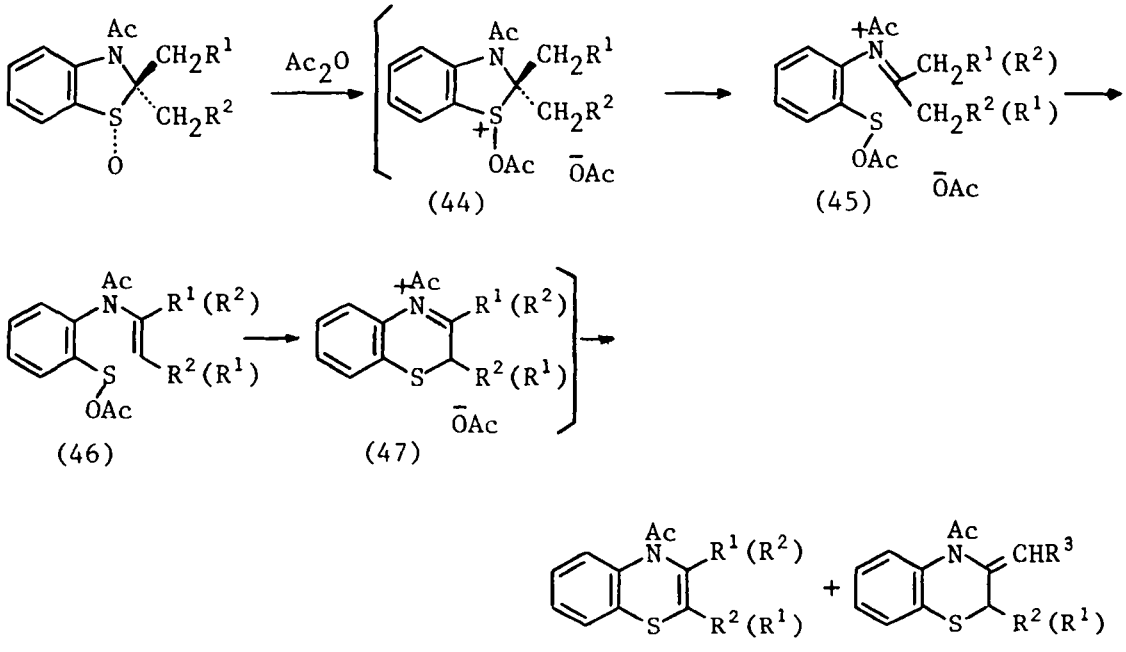
A similar ring expansion of the thiazoline skeleton by reaction with acetic anhydride, the ring transformation of penicillin sulfoxides to cephalosporins, found by Morin *et al.*, is well-known, and it is well established that the reaction is stereospecific by virtue of a thermal 2,3-sigmatropic ring-opening.[17]

In order to elucidate the stereospecificity of the ring expansion of benzothiazoline sulfoxides based on the configuration of the sulfoxide moiety, the reaction of various types of 3-acetylbenzothiazoline sulfoxides, having two different substituents in the C^2-position, with acetic acid anhydride has been examined in detail.[20,21] For example, *trans*-3-acetyl-2-ethyl-2-methylbenzothiazoline 1-oxide (**39**) yielded the four 1,4-benzothiazines (**40**), (**41**), (**42**), and (**43**). Compounds (**40**) and (**41**) are the products expanded in the direction of the methyl group *cis* to the sulfoxide oxygen. On the contrary, compounds (**42**) and (**43**) are the products expanded in the direction of the ethyl group having *trans* configuration with respect to the sulfoxide. The ratio of the products ring-expanded in the two directions is ca. 4:3. These results indicate that the ring expansion proceeds equally with either the *cis*- or the *trans*-sulfoxide, and that the reaction is non-stereospecific. It seems reasonable to assume that this non-stereospecificity could result by easy cleavage of the C^2—S bond in the thiazoline ring due to participation of the lone electron pair on the nitrogen atom in the 3-position of the benzothiazoline 1-oxide.



SCHEME 18

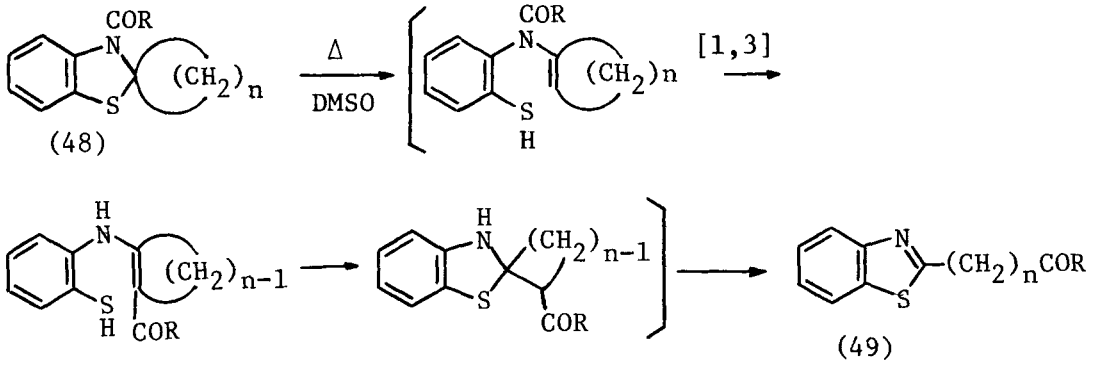
The reaction paths are explained by a mechanism involving initial acetylation of the oxygen of the sulfoxide moiety with acetic acid anhydride, forming an acetoxysulfonium ion intermediate (**44**), followed by C^2—S bond cleavage due to participation of the lone pair on the nitrogen atom to form an intermediate (**45**) which leads to the mixed sulfenic acid anhydride intermediate (**46**). Compound **46** furnishes the immonium ion (**47**) by recyclization with loss of acetate ion. Collapse of the immonium ion (**47**) leads to benzothiazines by deacetylation in the *endo*- and *exo*-directions. A similar ring expansion of benzothiazoline and thiazolidine sulfoxides upon treatment with *p*-toluenesulfonic acid as a catalyst has been reported independently by Prota *et al.*[22]



SCHEME 19

As a corollary to this non-stereospecific ring expansion of benzothiazoline sulfoxides the stereospecificity of the ring expansion of 5-membered heterocyclic sulfoxides, having another heteroatom in the β-position relative to the sulfinyl group, such as 1,3-benzodithiole sulfoxide, 1,3-benzoxathiole sulfoxide, and 1,3-dithiolane sulfoxide with acetic acid anhydride or *p*-toluenesulfonic acid has been examined by Hori *et al.*[23] Thus, all the sulfoxides underwent non-stereospecific ring expansion to give the corresponding six-membered heterocycles. It is concluded that the ring expansion of five-membered heterocyclic sulfoxides having a hetero atom in the β-position relative to the sulfoxide moiety proceeds non-stereospecifically and acetic acid anhydride or *p*-toluenesulfonic acid act as strong reaction initiators. The non-stereospecificity arises from the easy cleavage of the C^2—S bond of the five-membered ring due to the electronic effect of a heteroatom in the β-position.

I.1.D. Other rearrangement reactions of benzothiazolines *N*-Acylspirocycloalkylbenzothiazolines (**48**) undergo thermal [1,3] N-C acyl migration to give the synthetically useful ω-(benzothiazolyl)alkyl aryl (or alkyl) ketones (**49**) in good yields.[24]

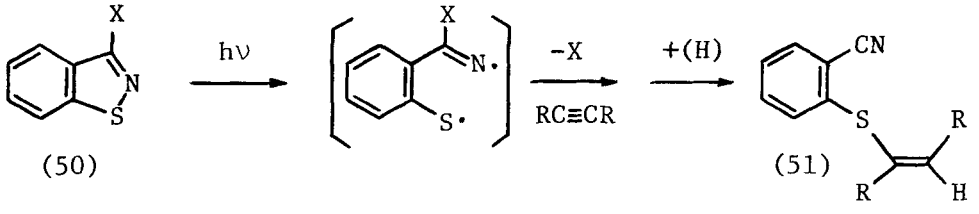


SCHEME 20

I.2. Cycloadditions with 1,2- and 1,3-Thiazole Derivatives

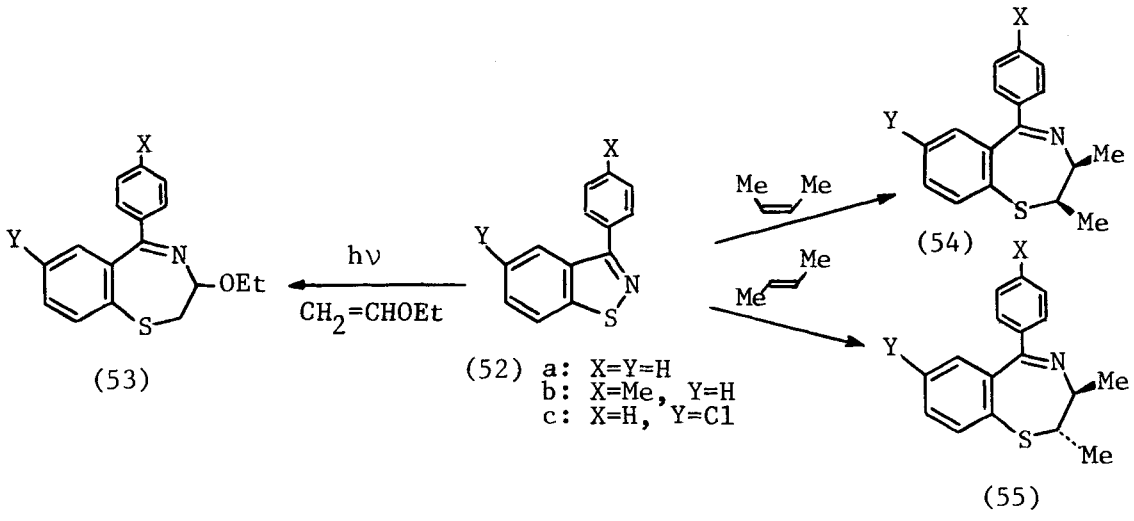
The photocycloaddition reaction of benzisothiazoles to alkynes such as dimethyl acetylenedicarboxylate (DMAD) or alkenes such as ethyl vinyl ether has been investigated by Neckers *et al.*[25,26,27,28]

Although 3-aryl-1,2-benzisothiazoles give no photochemical addition products with alkynes, 3-unsubstituted and 3-chloro-1,2-benzisothiazoles (**50**) afford linear addition products (**51**) and benzothiophenes as by-products. These photoproducts are explained as resulting from homolytic cleavage of the S—N bond of the benzisothiazole followed by transfer of the labile H or Cl originally located at the 3-position. On the



SCHEME 21

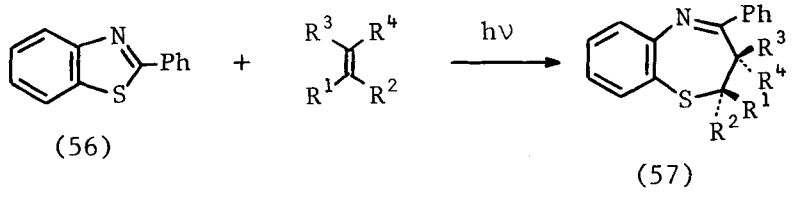
other hand, 3-phenylbenzisothiazole (**52a**) and its derivatives, when irradiated together with alkenes such as ethyl vinyl ether or *cis*- and *trans*-2-butenes, form ring-expanded products, the 1,4-benzothiazepine derivatives (**53**, **54**, **55**), in good yield.



SCHEME 22

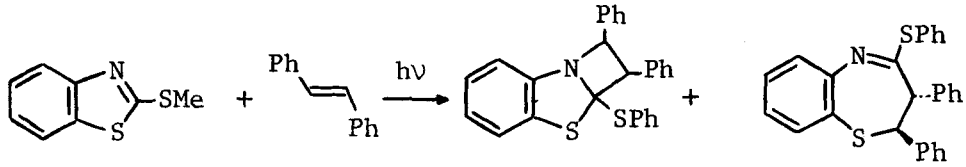
These photoadditions of alkenes to 3-aryl-1,2-benzisothiazoles are formally [$\pi 2 + \sigma 2$] additions and are regiospecific with respect to the direction of the addition of ethyl vinyl ether and stereospecific with respect to the reaction with *cis*- and *trans*-2-butene.

In the case of the photoreaction of benzothiazole derivatives with several alkenes [$\pi 2 + \sigma 2$] cycloaddition has also been observed. Thus, irradiation of 2-phenylbenzothiazole (**56**) with alkenes gives cyclic adducts, the 2,3-dihydro-1,5-benzothiazepine derivatives (**57**), their structures being suggested by spectroscopic evidence and chemical conversion to the corresponding ring-opened products. This reaction also proceeds both regioselectively and stereospecifically.



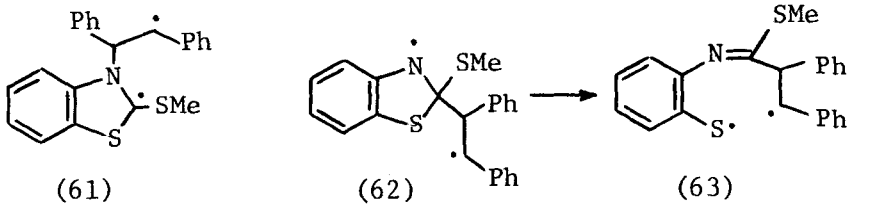
SCHEME 23

The photoreaction of stilbene with benzothiazoles has been investigated by Kaupp *et al.*[29] Photoaddition of 2-methylthiobenzothiazole (**58**) to stilbene gave the azetidine derivative (**59**) and the 1,5-benzothiazepine (**60**). This reaction has been proposed to occur via the 1,4-diradical (**61**) for the formation of **59** and the 1,7-diradical (**63**), derived from the initially formed 1,4-diradical (**62**), for the formation of **60**. The 1,5-benzothiazepine (**60**), upon heating to 200 °C, eliminates methanethiol to yield the benzothiazole derivative (**64**).[30] This unique reaction is called a [2,1,3]-elimination.

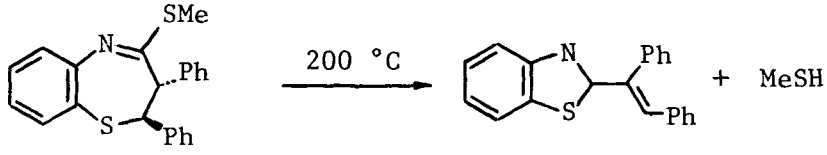


(58) (59) (60)

SCHEME 24



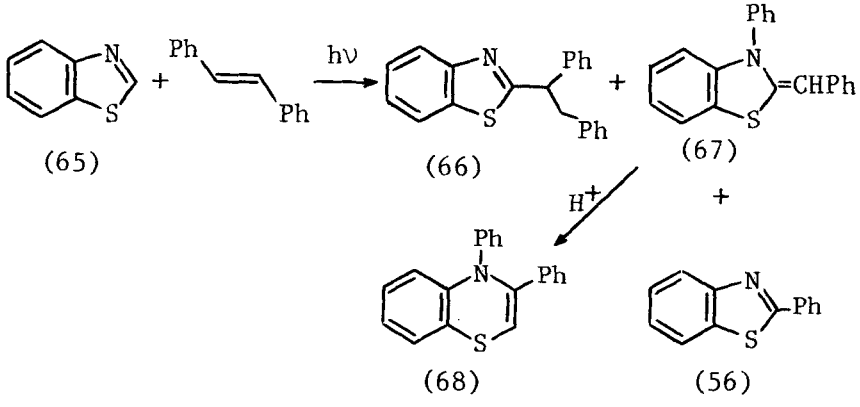
(61) (62) (63)



(60) (64)

SCHEME 25

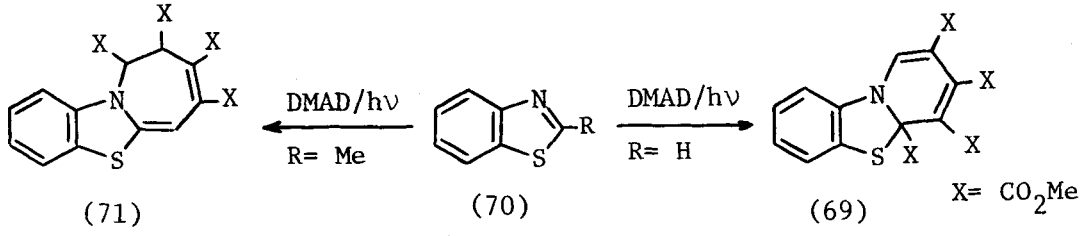
On the other hand the photoreaction of the 2-unsubstituted benzothiazole (**65**) with stilbene followed a different reaction mode and gave the three addition products (**66**), (**67**), and (**56**). These products are also assumed to be formed via 1,4-diradicals. Interestingly, product (**67**) is easily ring-enlarged in $CDCl_3$ solution in the presence of a catalytic amount of acid and affords 3,4-diphenyl-4*H*-1,4-benzothiazine (**68**) in 58% yield.



(65) (66) (67) (68) (56)

SCHEME 26

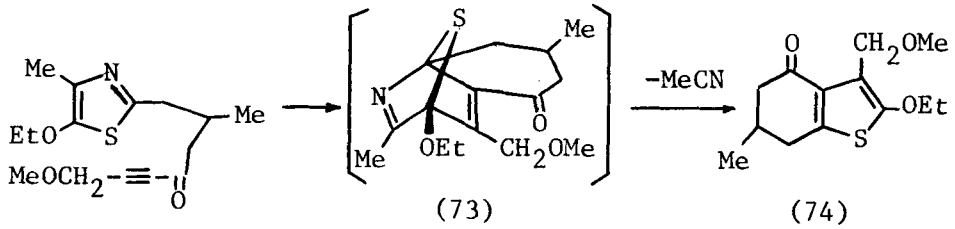
Photochemical cycloaddition of benzothiazole (**65**) to DMAD in acetone or acetonitrile affords the pyridobenzothiazole derivative (**69**). 2-Methylbenzothiazole (**70**), upon irradiation in the presence of DMAD, gives the azepinobenzothiazole (**71**).[31]



(71) (70) (69)

SCHEME 27

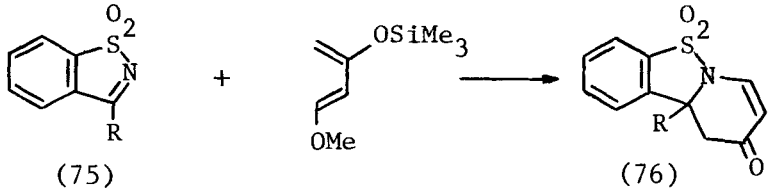
The first example of an intramolecular Diels-Alder reaction involving a thiazole ring and an acetylenic dienophile was reported by Jacobi *et al.*[32] In the presence of a catalytic amount of methylene blue the thiazole (**72**) gives a 60% yield of the thiophene (**74**), after 3 days reflux in degassed mesitylene, via the intermediate (**73**).



(72) (73) (74)

SCHEME 28

Diels-Alder reactions of 3-methyl- or 3-chloro-1,2-benzisothiazole 1,1-dioxide (**75**) with 1-methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene) in boiling toluene gave 5a-methyl- or 5a-chloro-5,5a-dihydro-4-oxopyrido[1,2-b]-1,2-benzisothiazoline 1,1-dioxide (**76**).[33]

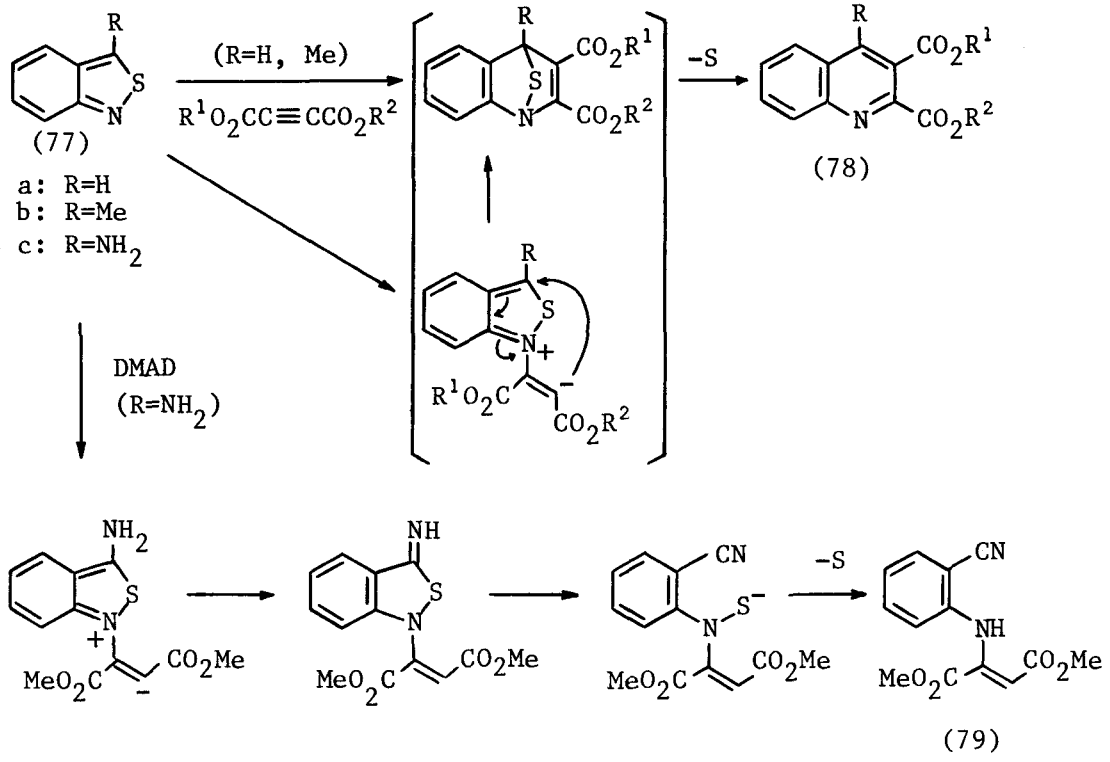


(75) (76)

SCHEME 29

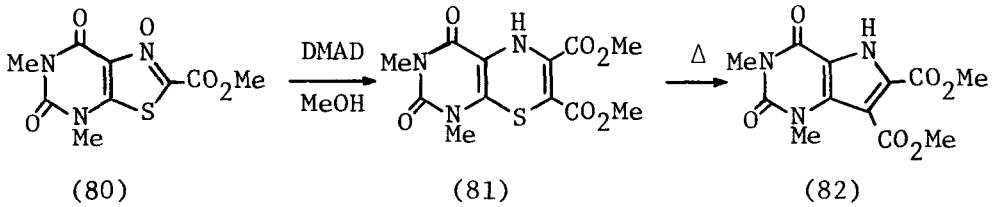
The 2,1-benzisothiazoles (**77**) react with DMAD by addition across the heterodiene and subsequent loss of sulfur to yield dimethyl 2,3-quinoline dicarboxylates (**78**).[34]

Diethyl acetylenedicarboxylate and methyl propiolate (MP) react similarly. These reactions involve initial Michael-type attack of the acetylenic ester at the heterocyclic nitrogen or a concerted cycloaddition. The 3-amino derivative, however, reacts with DMAD to give a ring-opened product, dimethyl 2-cyanoanilinofumarate (**79**).



SCHEME 30

1,3-Dipolar cycloaddition of thiazolopyrimidine *N*-oxide (**80**) to DMAD in refluxing methanol for 10 hr gives a 38% yield of a ring-expanded product, the pyrimidothiazine (**81**) which is converted into the pyrrolopyrimidine (**82**) up on reflux in methanol for 3 hr in 75% yield.[35]

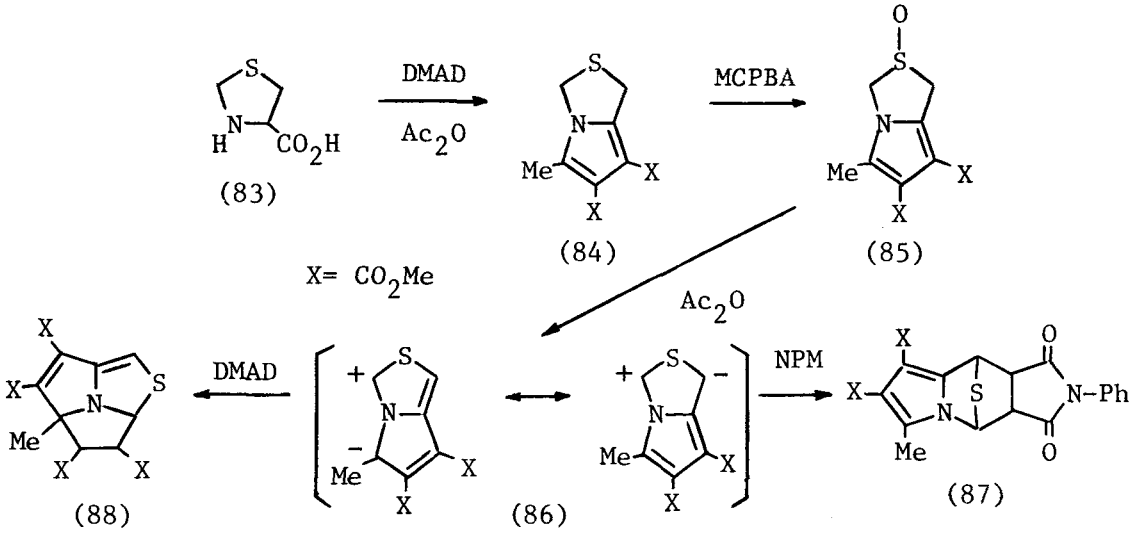


SCHEME 31

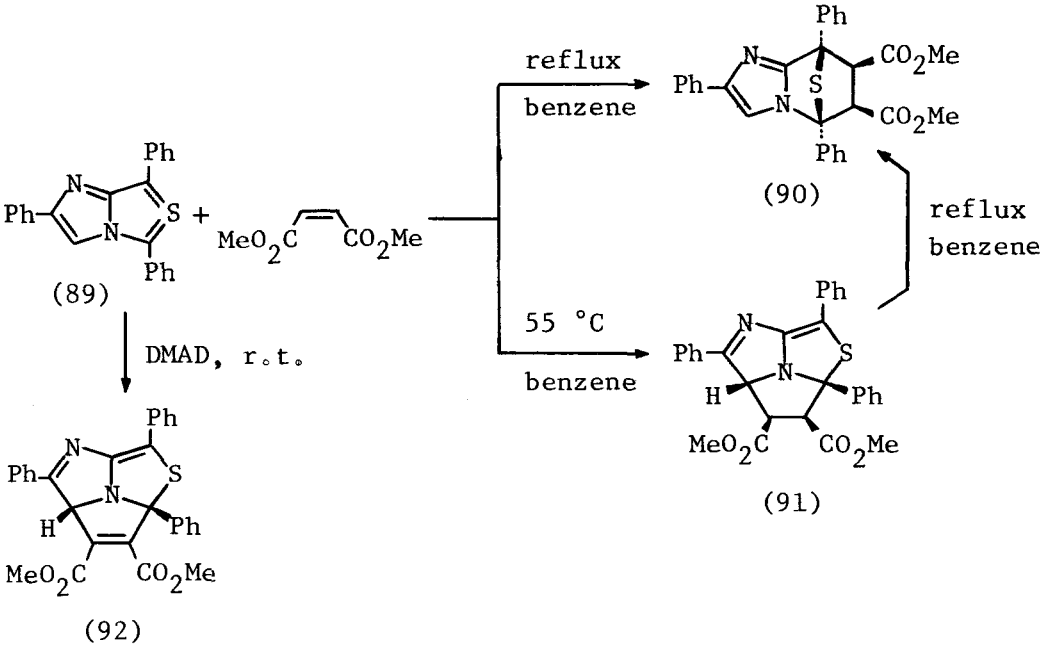
4-Thiazolidinecarboxylic acid (**83**) reacts with acetic acid anhydride in the presence of DMAD to afford the 1*H*,3*H*-pyrrolo[1,2-c]thiazole (**84**). The thiazole (**84**) can form

the unstable non-classical thiazole (**86**) upon treatment with acetic acid anhydride, via the sulfoxide (**85**).[36,37]

Non-classical thiazoles undergo cycloaddition with various type of dipolarophiles. The thiazole (**86**) was trapped with *N*-phenylmaleimide to give the 1:1-cycloadduct (**87**), derived from the thiocarbonyl ylide structure of **86** as an *exo*- and *endo*-adduct mixture in a combined yield of 59%. On the other hand trapping with DMAD affords the azomethine ylide adduct (**88**) in 15% yield.



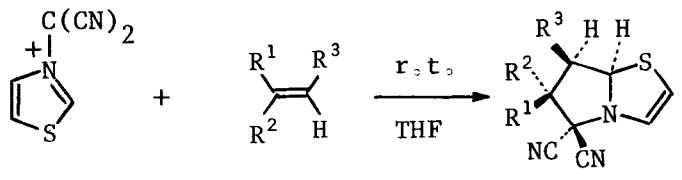
SCHEME 32



SCHEME 33

Tsuge *et al.* also investigated another type of a nitrogen-bridged tetravalent sulfur compound, 1,3,6-triphenylimidazo[1,2-c]thiazole (**89**), and its reactions with olefinic and acetylenic dipolarophiles.[37,38,39] For example, the reaction of **89** with dimethyl maleate under reflux in benzene affords the *cis-exo*[3+2] cycloadduct (**90**) to the thiocarbonyl ylide form of **89** in 77% yield. The same reaction under milder conditions (55°C) gives another type of *cis-exo*[3+2] cycloadduct, (**91**), to the azomethine ylide form of **89** in 27% yield along with **90**. The adduct (**91**) is converted to **90** when refluxed in benzene. This result indicates that the thiocarbonyl ylide adduct (**90**) is formed via the azomethine ylide adduct (**91**) through a reversible 1,3-dipolar cycloaddition. The reaction of **89** with DMAD in dry benzene at room temperature gives the red 1:1-adduct (**92**) to the azomethine ylide dipole of **89**.

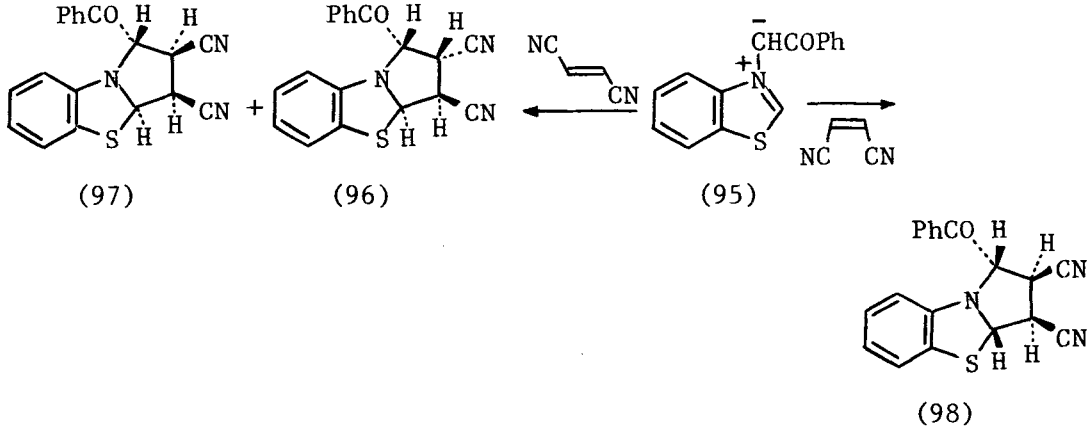
Cycloadditions of *N*-methylides of the thiazolium and benzothiazolium systems have been investigated recently. Reaction of thiazolium *N*-dicyanomethylide (**93**) with acyclic olefinic dipolarophiles such as dimethyl fumarate, maleate, and *trans*-1,2-dibenzoylethylene proceeds in a stereoselective manner to give only the corresponding *endo*[3+2] cycloadducts (**94**).[40]



(93) (94)

SCHEME 34

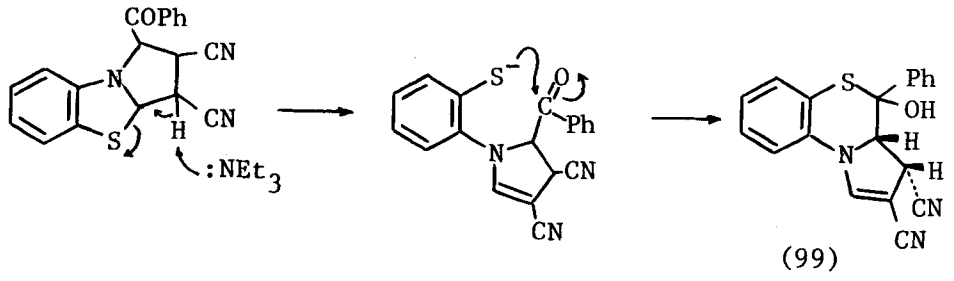
Benzothiazolium *N*-phenacylide (**95**) also reacts stereoselectively with a variety of olefinic dipolarophiles to afford the corresponding cycloadducts in good yield.[41] Some examples are shown below. Interestingly, the cycloadducts (**96**), (**97**), and (**98**) are easily transformed into the 1,4-benzothiazine derivative (**99**) on treatment with an equimolar amount of triethylamine in chloroform.



(97) (96) (95) (98)

SCHEME 35

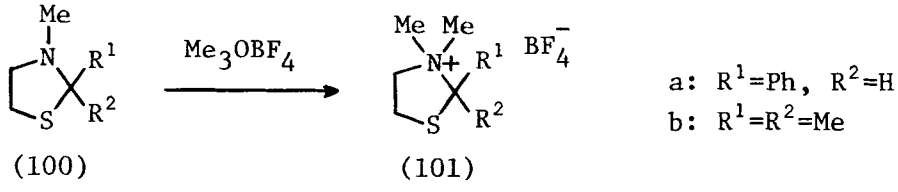
The intermediate thiolate anion arising by deprotonation of a cycloadduct would give rise to **99** through nucleophilic attack on the carbonyl group.



SCHEME 36

I.3. Alkylation and Arylation of Thiazoline Derivatives

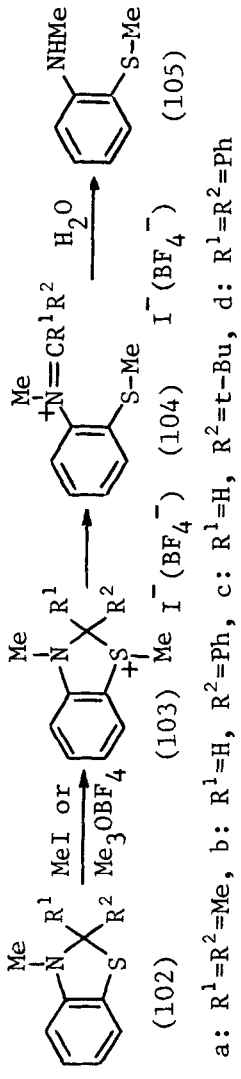
In an alkylation of thiazoline derivatives which have sulfur and nitrogen in the same molecule, it is possible to obtain a thionia or an azonia compound. Alkylation of 2-substituted 3-alkylthiazolines or 3-alkylbenzothiazolines (**100**) with Meerwein reagent gives 2-substituted 3,3-dialkylbenzothiazolium salts (**101**).[42,43,44]



SCHEME 37

It was expected that some benzothiazolines would be alkylated at the sulfur atom if a bulky group occupies the 2-position because of steric congestion around the nitrogen due to the shorter length of the C—N bond compared to the C—S bond. Thus, methylation of 2,2,3-trimethylbenzothiazoline (**102a**) with methyl iodide afforded the ring-opened product *N*-methyl-*N*-(*o*-methylthiophenyl)-*N*-isopropylideneiminium iodide (**104a**) in 65% yield, presumably by initial alkylation at sulfur, followed by ring cleavage.[42] Other attempts of methylation of 3-methyl-2-phenylbenzothiazoline (**102b**) with Meerwein reagent and of 3-methyl-2-*t*-butylbenzothiazoline (**102c**) with methyl iodide-silver perchlorate resulted in the formation of *N*-methyl-(o-methylthio)aniline (**105**), a decomposition (hydrolysis) product of the primary *S*-methylated product (**103c**). However, very recently, Akiba *et al.* succeeded in the isolation of the *S*-methylated product (**103d**) by reaction of 3-methyl-2,2-diphenylbenzothiazoline (**102d**) with Meerwein reagent.[45]

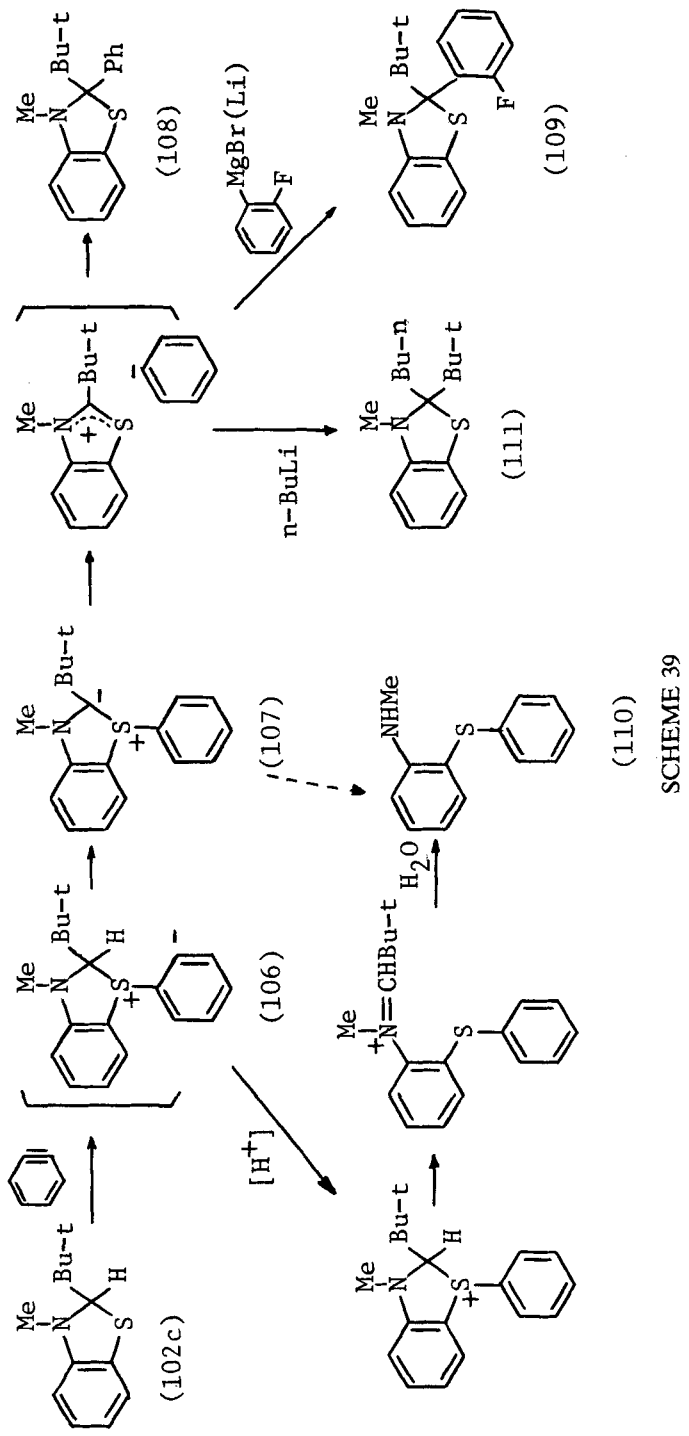
In studies of the arylation of benzothiazolines a novel nitrogen-containing cyclic sulfur ylide, benzothiazolium *S*-ylide, was generated as an intermediate in the reaction of 2-substituted 3-methylbenzothiazolines with benzyne.[46] 2-*t*-Butyl-3-methylbenzothiazoline (**102c**) was allowed to react with benzyne, generated from



(102) (103) (104) (105)

a: $R^1=R^2=Me$, b: $R^1=H$, $R^2=Ph$, c: $R^1=H$, $R^2=t\text{-}Bu$, d: $R^1=R^2=Ph$

SCHEME 38

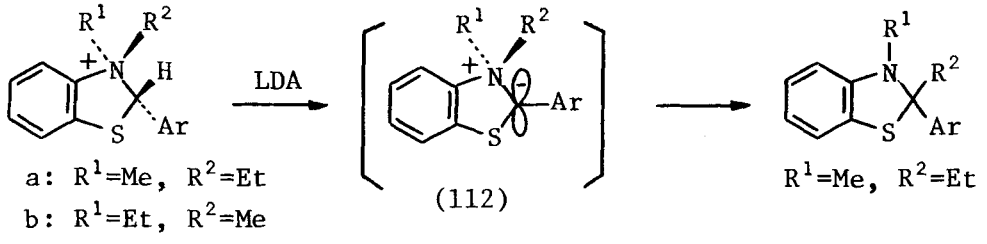


(102c) (106) (107) (108) (109) (110) (111)

SCHEME 39

o-bromofluorobenzene and magnesium, at room temperature for 4 hr in dry THF to give 2-*t*-butyl-3-methyl-2-phenylbenzothiazoline (**108**, 34% yield) along with other by-products. With benzyne generated from *o*-bromofluorobenzene and an excess of *n*-butyllithium, 2-*n*-butyl-2-*t*-butyl-3-methylbenzothiazoline (**111**) was isolated in low yield besides **108**, **109**, and **110**. For the formation of the reaction products, the following mechanism involving an intermolecular [1,2] shift of the phenyl group of the initially generated sulfur ylide (**107**) can be proposed.

Benzothiazolium *N*-ylides, generated by treatment of 2-aryl substituted 3,3-dialkylbenzothiazolium salts with LDA, undergo Stevens rearrangement to give 2-aryl-2,3-dialkylbenzothiazolines.[44] Interestingly, in the rearrangement of 2-aryl-3-ethyl-3-methylbenzothiazolium ylides (**112**), generated from the corresponding two stereoisomeric benzothiazolinium salts, the ethyl group migrates exclusively, irrespective of the stereochemistry of the starting ammonium salt, inconsistent with a concerted S_Ni type mechanism.

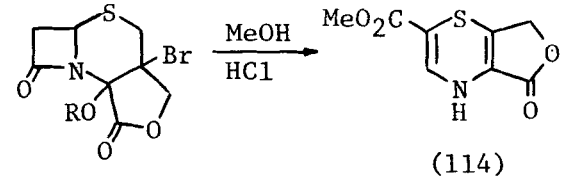


SCHEME 40

II. THE CHEMISTRY OF SULFUR- AND NITROGEN-CONTAINING SIX-MEMBERED HETEROCYCLES

II.1. Rearrangement of Thiazine Derivatives and Related Compounds

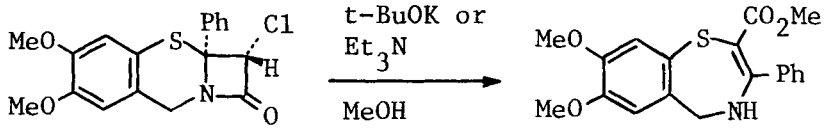
The cephem bromohydrin (**113a**) and its acetate (**113b**), on reflux in methanolic HCl solution, give the methyl ester of the ring-expanded compound, the thiazepine derivative (**114**), in high yield.[47]



SCHEME 41

Basic treatment in methanol of 6α-phenyl-7α-chloro-2,3(2′,3′-dimethoxybenzo)-1-thiaoctem (**115**) causes a new ring expansion to give the corresponding 1,4-

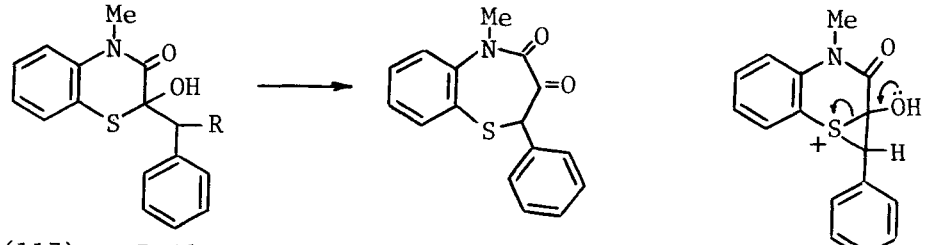
benzothiazepine derivative (**116**).[48] The rate of the reaction depends on the base involved. A 100% yield was achieved with 1 mol *t*-BuOK in 0.5 hr or with 1 mol triethylamine in 24 hr.



(115) (116)

SCHEME 42

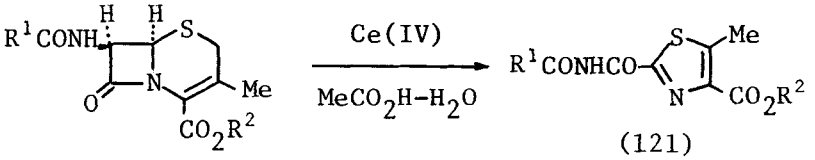
Maki *et al.* recently found a new ring expansion of 1,4-benzothiazines to 1,5-benzothiazepins.[49] Treatment of the chlorohydrin (**117a**), prepared from 2-phenylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-one by reaction with trimethylsilyl-hydroperoxide, with silver carbonate in THF for 30 min at 0 °C afforded the 1,5-benzothiazepin-4(5*H*)-one (**118**) in 88% yield. The same product was also obtained in 75% yield by treatment of the dihydroxy derivative (**117b**) with thionyl chloride in THF. The ring expansion of **117** to **118** is reasonably explained by assuming the intermediacy of the episulfonium ion (**119**).



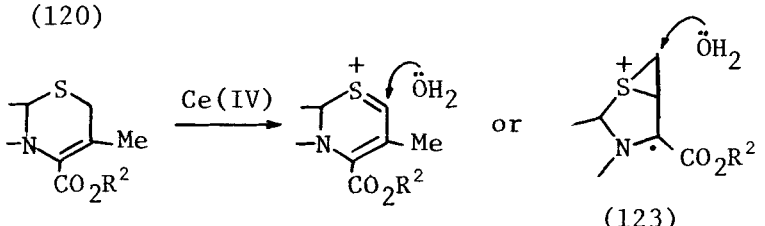
(117) a: R=Cl
b: R=OH

(118) (119)

SCHEME 43



(120) (121)



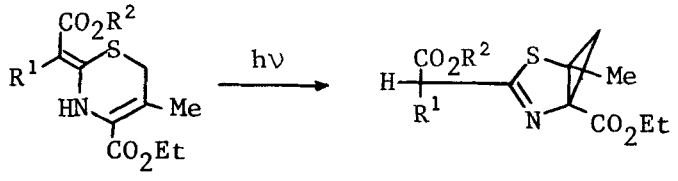
(122) (123)

SCHEME 44

A novel ring contraction reaction of cephalosporin yielding thiazole derivatives was reported by Fletton *et al.*[50] Reaction of cephalosporin esters (**120**) with excess cerium (IV) ammonium nitrate in 50% aqueous acetic acid afforded the thiazole derivatives (**121**). Regarding the mechanism of this reaction, electron transfer from sulfur to Ce(IV) to form intermediate (**122**) or (**123**) was proposed as an initial step.

Next, photochemical ring contractions of the thiazine skeleton are described.

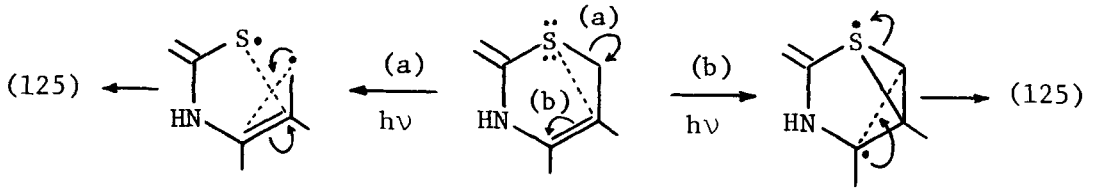
Photolysis of 1,3-thiazine derivatives (**124**) gives the fused cyclopropanothiazolines (**125**).[51]



(124) (125)

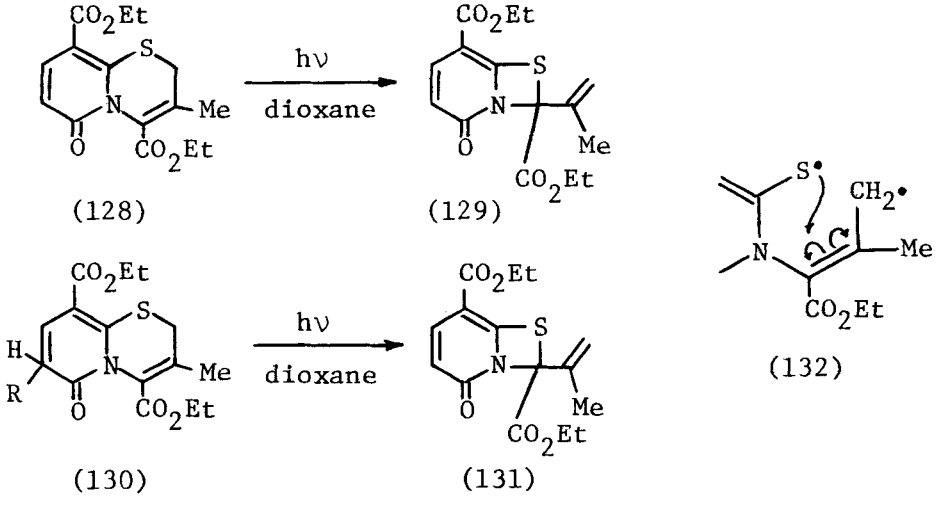
SCHEME 45

This interesting reaction would be feasible via the bond fission (a) in Scheme 46 leading to the radical intermediate (**126**) which could then yield the product by forming bonds as shown. Another possible mechanism involving diradical intermediate (**127**) was also proposed.



(126) (127)

SCHEME 46



(128) (129) (132)

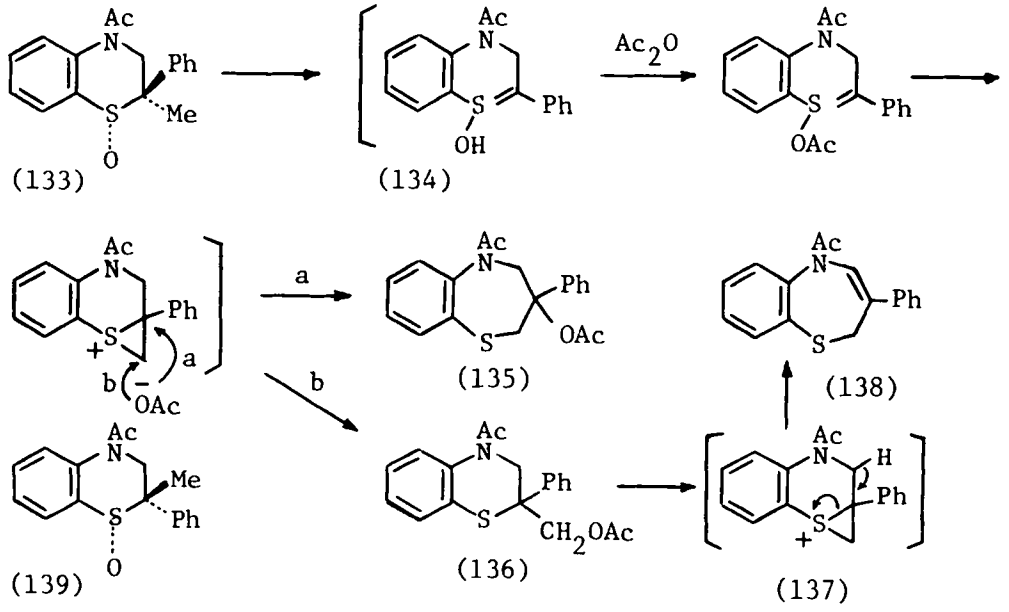
(130) (131)

SCHEME 47

In the *N*-acylated 1,3-thiazine derivatives (**128**) and (**130**) the photolysis takes an entirely different course and affords the fused 1,3-thiazetidines (**129**) and (**131**), respectively.[52] A plausible mechanism for the reaction would involve cleavage of the CH_2—S bond to give the diradicals (**132**). These would then couple as shown in Scheme 47 to yield the observed products.

Ring expansion reactions of 1,3- and 1,4-benzothiazine sulfoxides have been reported by Hori *et al.*[20,21]

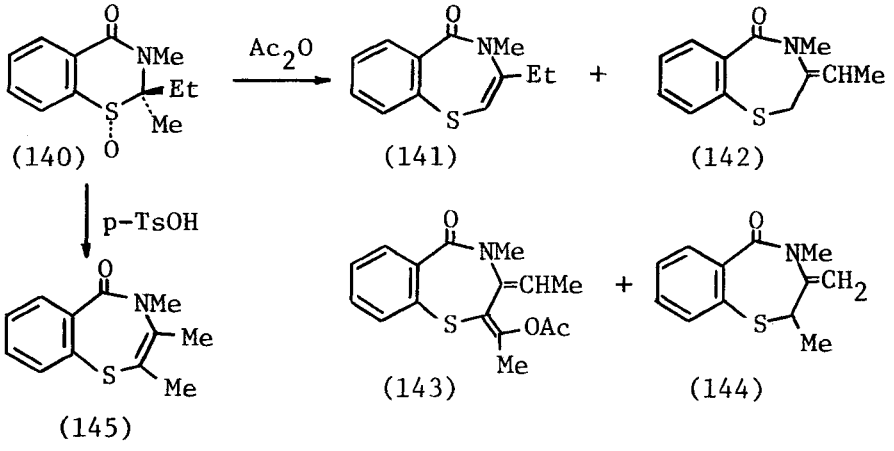
Refluxing *trans*-4-acetyl-2-methyl-2-phenyl-2,3-dihydro-4 *H*-1,4-benzothiazine 1-oxide (**133**) in acetic acid anhydride for 1.5 hr affords the ring-expanded product (**135**) in 26% yield along with 4-acetyl-2-acetoxymethyl-2-phenyl-2,3-dihydro-4*H*-1,4-benzothiazine (**136**) in 52% yield. On the other hand, the *cis*-sulfoxide (**139**) is unaffected under the same reaction conditions. This stereospecific reaction can be explained in terms of a mechanism involving the sulfenic acid (**134**) as a first intermediate formed by thermal 2,3-sigmatropic rearrangement of **133**, similar to the mechanism proposed for the ring expansion of penicillin sulfoxides to cephalosporins as shown in Scheme 48. Treatment of **136** with a few drops of concentrated sulfuric acid in refluxing benzene causes ring expansion to give the 1,5-benzothiazepine derivative (**138**) in 56% yield, possibly via the episulfonium ion intermediate (**137**).



SCHEME 48

In the case of 1,3-benzothiazine sulfoxides, a non-stereospecific ring expansion takes place to give the corresponding 1,4-benzothiazepine derivatives. For example, *trans*-2-ethyl-2,3-dimethyl-4-oxo-2,3-dihydro-1,3-benzothiazine 1-oxide (**140**) was refluxed in acetic acid anhydride for 2.5 hr to give the four ring-expanded products (**141**, 10.3%), (**142**, 25%), (**143**, 23.4%), and (**144**, 10.3%). Compounds **141**, **142**, and **143** are the products expanded in the direction of the methyl group *cis* to the sulfoxide, while the compound **144** is the product expanded in the opposite direction. On the other hand, when the sulfoxide (**140**) was refluxed in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, two ring expansion products (**141**) and

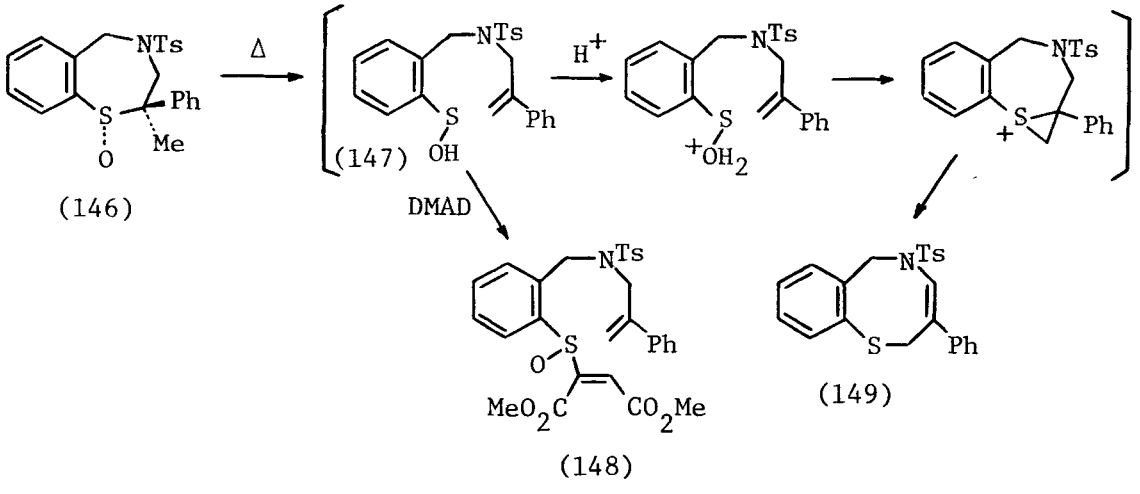
(**145**) in yields of 15 and 21%, respectively, were obtained. These results show that the ring expansion occurs non-stereospecifically. The ring expansion proceeds via a mechanism involving an acetoxysulfonium ion intermediate followed by ring opening just as in the case of the benzothiazoline sulfoxides described in Section I.1.



SCHEME 49

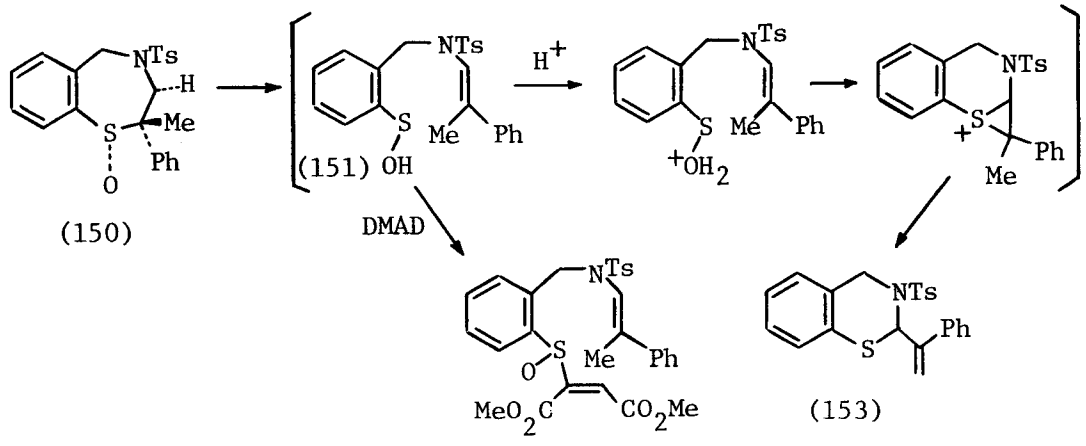
Hori *et al.* also found a remarkable contrast between *cis* and *trans* geometry in the ring transformations of seven-membered heterocyclic sulfoxides.[53]

Refluxing *trans*-1,4-benzothiazepine 1-oxide (**146**) in benzene for 10 hr in the presence of 0.1 eq of *p*-toluenesulfonic acid caused ring expansion to afford the 1,5-benzothiazocine derivative (**149**) in 73% yield. The sulfenic acid intermediate (**147**) was trapped with DMAD to give a 89% yield of the 1:1-adduct (**148**). The ring expansion of **146** to **149** can be explained by a mechanism involving the sulfenic acid intermediate (**147**) generated by 2,3-sigmatropic rearrangement of the sulfoxide as shown in Scheme 50.



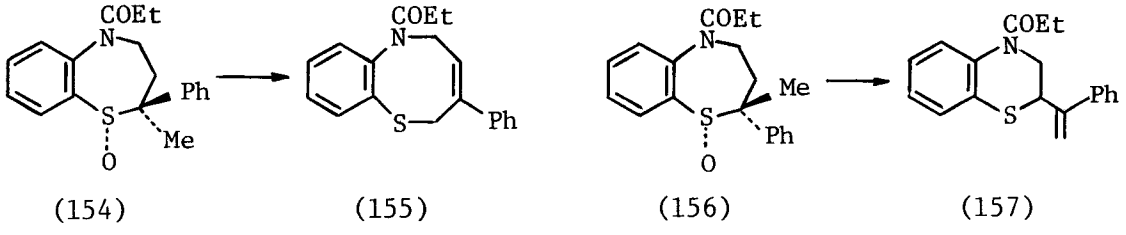
SCHEME 50

The *cis*-sulfoxide (**150**) formed a ring contraction product, a 1,3-benzothiazine derivative (**153**, 17%), along with recovered sulfoxide, (**150**, 80%), under the same reaction conditions. The sulfenic acid intermediate (**151**) was trapped with DMAD and gave the 1:1-adduct (**152**) in 92% yield. The 2,3-sigmatropic rearrangement of the 2-methyl group of **150** is highly retarded because of its *trans* configuration, leading to the recovery of large amounts of **150**, and consequently the other β-proton, one of the C^3-protons of the ring which occupies a *syn*-position with regard to the sulfoxide oxygen, undergoes a 2,3-sigmatropic shift to give the intermediate (**151**).



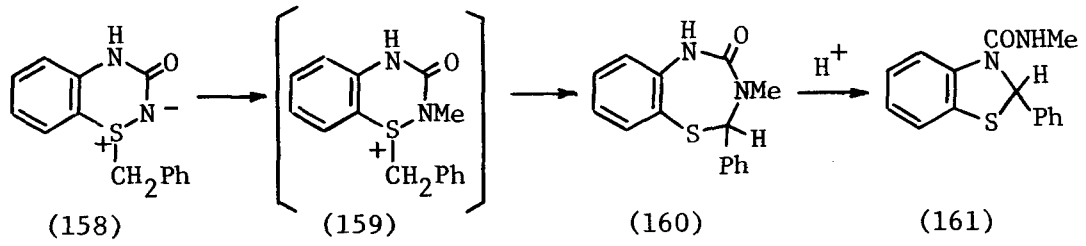
SCHEME 51

Similarly, the *trans*-1,5-benzothiazepine 1-oxide (**154**) gives a ring expansion product, the 1,6-benzothiazocine (**155**), in 57% yield whereas *cis*-1,5-benzothiazepine 1-oxide (**156**) affords a ring contraction product, the 1,4-benzothiazine (**157**), in 10% yield together with recovered **156** (81%).



SCHEME 52

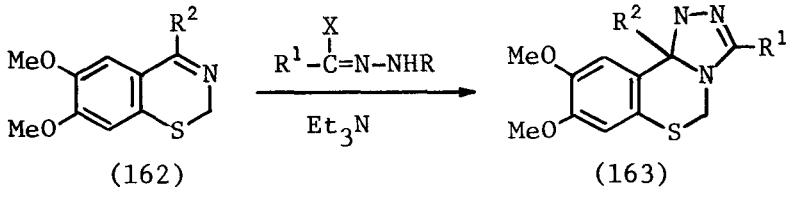
Methylation of the benzothiadiazine sulfilimine (**158**) with trimethyloxonium tetrafluoroborate in dichloromethane or with methyl fluorosulfonate affords a ring expansion compound, the 1,3,5-benzothiadiazepine derivative (**160**), in 25% yield, possibly resulting from a Pummerer-type rearrangement of the initially formed aminosulfonium salt intermediate (**159**). Interestingly, treatment of **160** with a trace of acid causes ring contraction to give the benzothiazoline derivative (**161**), via protonation of the urea moiety and cleavage of the C^2—N bond.[54]



SCHEME 53

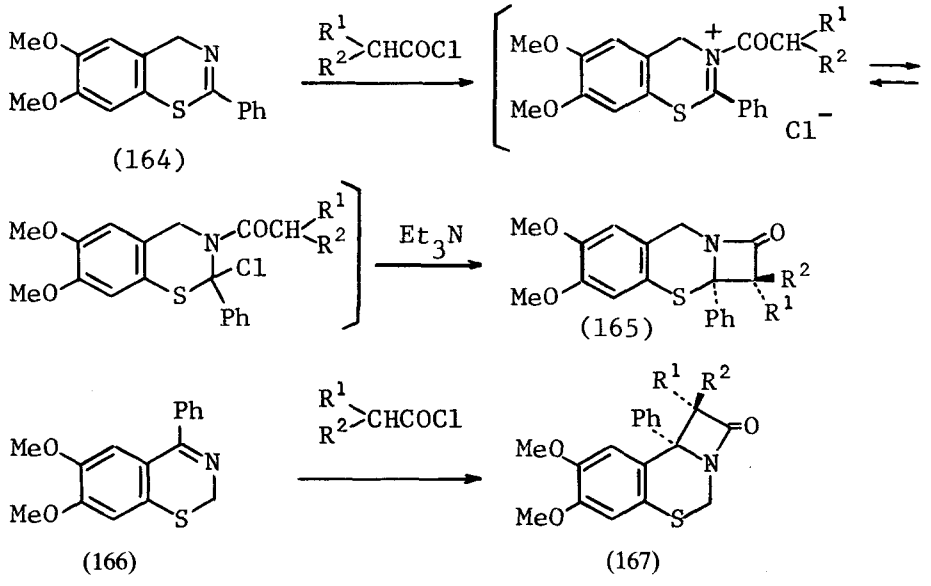
II.2. Cycloadditions of Thiazine Derivatives and Related Compounds

Thermal [3+2] intermolecular cycloaddition of nitrileimines to 2*H*-1,3-benzothiazines (**162**) gives the new fused triazolobenzothiazines (**163**).[55]



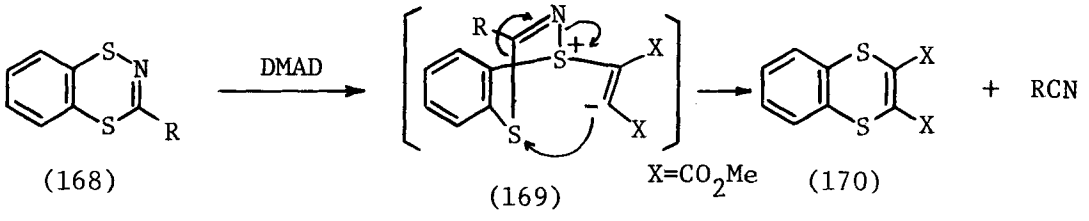
SCHEME 54

Cycloaddition of 6,7-dimethoxy-2-phenyl-4*H*-1,3-benzothiazine (**164**) and 6,7-dimethoxy-4-phenyl-2*H*-1,3-benzothiazine (**166**) with acetyl chloride took place in the presence of triethylamine to give the linearly and angularly condensed β-lactam derivatives (**165**) and (**167**), respectively.[56]



SCHEME 55

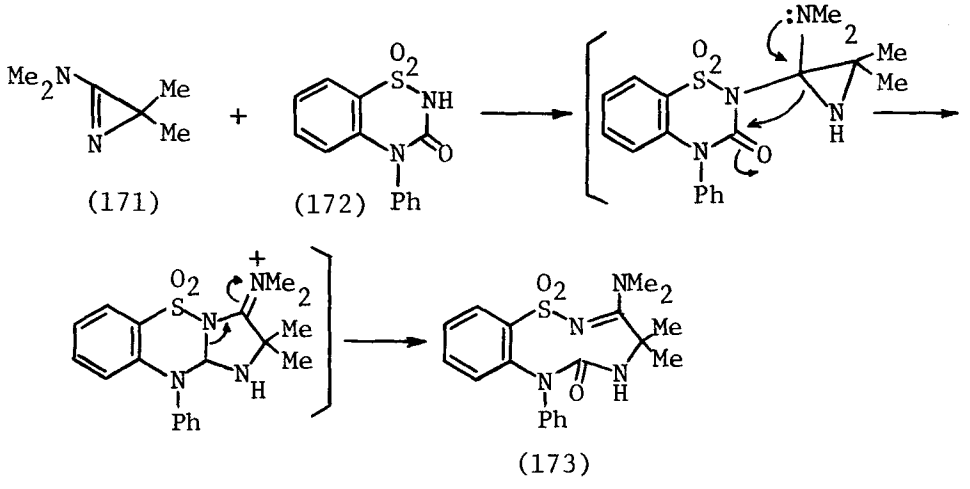
1,4,2-benzodithiazines (**168**) react with 3 eq. of DMAD in boiling *o*-dichlorobenzene for 6 hr to give 2,3-bis(methoxycarbonyl)-1,4-benzodithiins (**170**) in 75–80% yield with elimination of hydrogen cyanide or a nitrile.[57] The intermediate (**169**) has been proposed for this cycloaddition-elimination of DMAD with 1,4,2-benzodithiazines.



(168) (169) (170)

SCHEME 56

3-Dimethylamino-2,2-dimethyl-2*H*-azirine (**171**) reacts below room temperature with 4-phenyl-3,4-dihydro-2*H*-1,2,4-benzothiaziazin-3-one 1,1-dioxide (**172**) to give the nine-membered heterocyclic product (**173**) in quantitative yield.[58] The reaction mechanism for this ring expansion is given in Scheme 57.



(171) (172) (173)

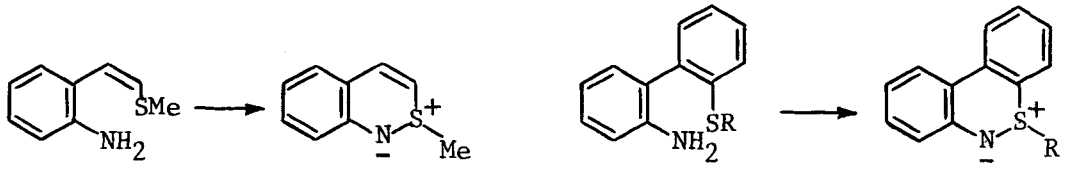
SCHEME 57

II.3. Azathiabenzenes (Cyclic Sulfilimines)

In this Section syntheses and properties of "azathiabenzenes" in which a sulfur-nitrogen bond forms part of a cyclic conjugated ring system containing six π-electrons are described.

Syntheses. The first synthesis of this novel class of heterocycles, the 2-azathiabenzenes, was achieved by Hori *et al.*[59] Treatment of *cis-o*-aminostyryl methyl

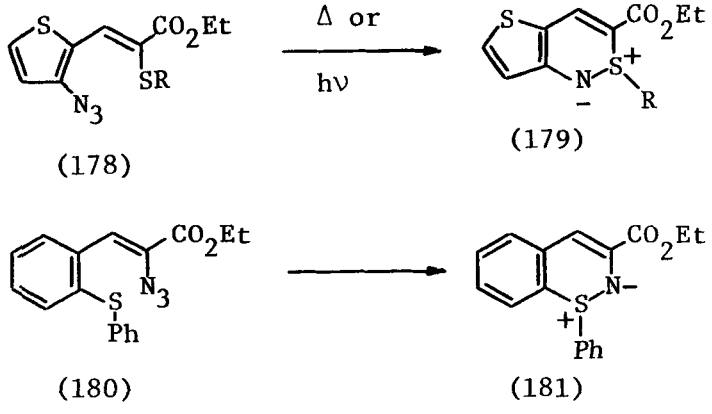
sulfide (**174**) with an equivalent amount of NCS in dry dichloromethane at −50 °C, followed by aqueous KOH solution gives a 76% yield of 2-methyl-1-aza-2-thianaphthalene (**175**) as yellow crystals. Under the same conditions the tricyclic 9-alkyl-10-aza-9-thiaphenanthrenes (**177**) can be synthesized in quantitative yield from the 2-amino-2′-alkylthiobiphenyls (**176**).



(174) (175) (176) (177)

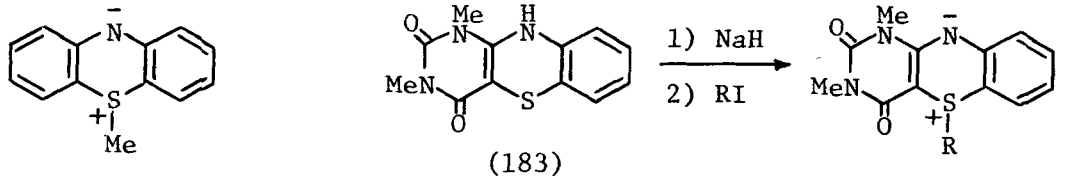
SCHEME 58

Two years later, Moody *et al.* developed a different synthetic method for these heterocycles.[60] Decomposition of azidothiophenes (**178**) in boiling toluene gives azathiabenzene derivatives (**179**) in 90% yield. Photolysis of the azides (**178**) also affords **179** in lower yield. In a similar decomposition reaction of the azide (**180**) another type of azathiabenzene, the 2-aza-1-thianaphthalene (**181**), can be prepared.



(178) (179) (180) (181)

SCHEME 59

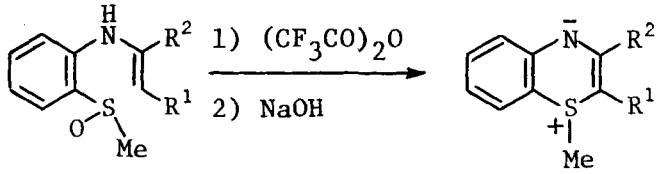


(182) (183) (184)

SCHEME 60

Contrary to the previous example, the history of 4-azathiabenzene derivatives is very old. About sixty years ago the synthesis of the phenothiazine sulfonium ylide (**182**) was reported by Kehrmann.[61] Later, pyrimido-1,4-benzothiazine sulfonium ylides (**184**) were synthesized by Schaefer *et al.*,[62] Maki *et al.*,[63] and Fenner *et al.*[64] by treatment of pyrimido-1,4-benzothiazine (**183**) with NaH, followed by alkyl iodide.

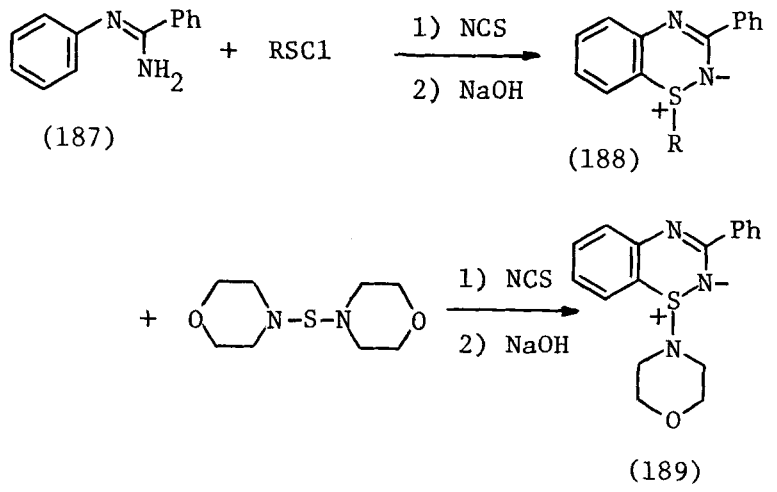
Recently, Gilchrist *et al.* have developed a new synthesis of 4-azathiabenzene derivatives.[65] Intramolecular dehydration of 2-(alkenylamino)phenyl methyl sulfoxides (**185**) with trifluoroacetic acid anhydride, followed by treatment with base affords the 1,4-benzothiazine sulfonium ylides (**186**) in good yield.



(185) (186)

SCHEME 61

Azathiabenzene derivatives having two nitrogen atoms in a conjugated ring system have also been synthesized.[66] *N*-Arylbenzamides (**187**) react with sulfenyl chlorides and NCS to give 1-alkyl- or 1-aryl-1,2,4-benzothiaziazine sulfonium ylides (**188**). Analogously, treatment of **187** with 4,4′-thiobismorpholine and NCS yields 1-morpholino-1,2,4-benzothiadiazine sulfonium ylide (**189**).



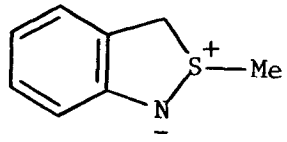
(187) (188)

(189)

SCHEME 62

Properties. The nature of the S—N bond in azathiabenzenes has been shown to be ylidic rather than ylenic by ^1H and ^{13}C NMR spectral data and some chemical evidence.[59,60] For example, the ^1H NMR spectrum to **175** shows a doublet (J = 9 Hz)

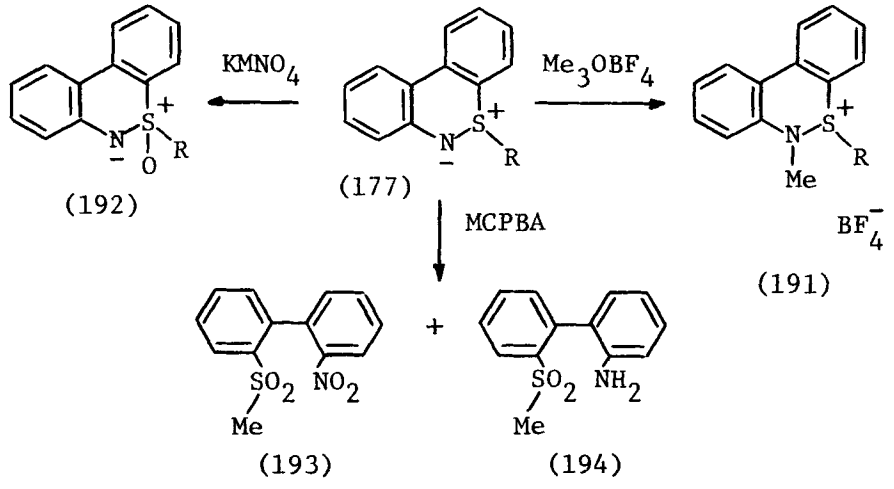
of C^3—H at δ 5.70, corresponding to olefinic, not aromatic, character. The ^{13}C NMR spectrum of **179** shows quaternary carbon signals at δ 85.5 and 116.2 ppm for C-3 and C-4a, respectively, indicating delocalization of the negative charge from nitrogen to carbon. Treatment of **175** or **177** with picric acid affords the corresponding *N*-protonated picrates in quantitative yield. The ylidic structure of the azathiabenzenes was also confirmed by an X-ray crystal structure determination of **179** by Moody *et al.*[60] recently. The S—N bond length of 1.63 Å is within the range for acyclic sulfilimines, and is intermediate between the S—N (1.74 Å) and S=N (1.53 Å) distances. Azathianaphthalene (**175**) seems to be much more stable than the non-conjugated cyclic sulfilimine (**190**), which is reported to decompose easily even at room temperature. This stabilization can be attributed to the delocalization of the negative charge from nitrogen to olefinic bond carbon (C^3-position) through the benzene ring.



(190)

CHART 1

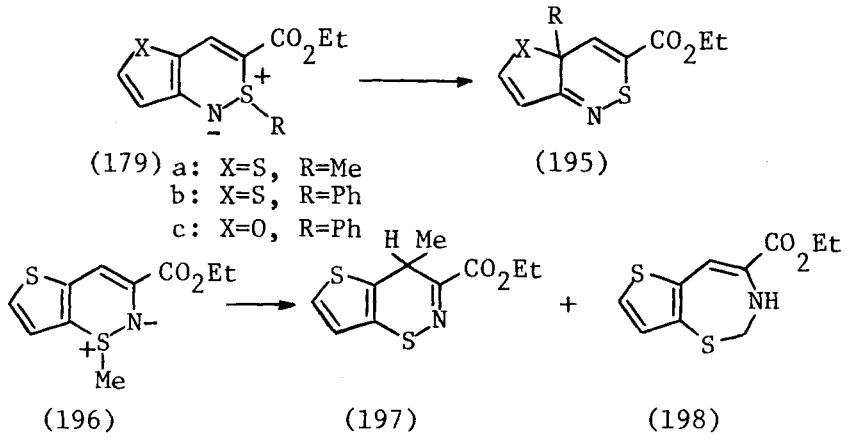
Reactions. The azathiaphenanthrene (**177a**) can be methylated with trimethyloxonium tetrafluoroborate to give the *N*-methyl sulfonium salt (**191**) in 93.4% yield. Oxidation of **177a** with potassium permanganate gives the azathiaphenanthrene oxide (**192**) in 90% yield, whereas treatment with *m*-chloroperbenzoic acid causes ring opening, resulting in the formation of 2-nitro-2′-mesylbiphenyl (**193**) and 2-amino-2′-mesylbiphenyl (**194**) in yields of 11 and 6%, respectively.



(192) (177) (191) (193) (194)

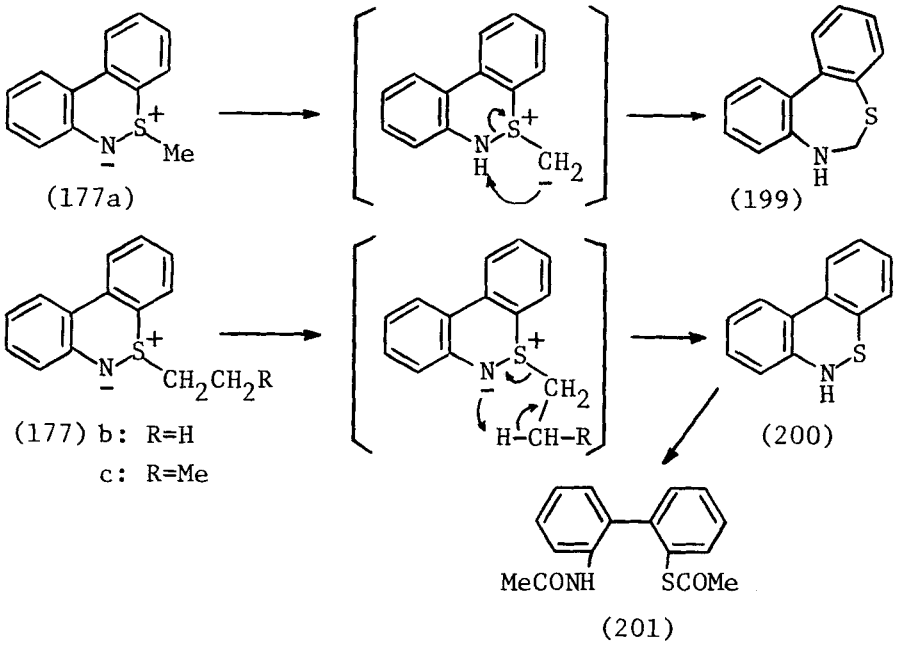
SCHEME 63

Thermal rearrangements of azathiabenzenes have been observed. Although the azathianaphthalenes (**175**) give an unidentified complex mixture, the thieno (**179a**) or furo derivative (**179c**), on heating in bromobenzene (156 °C) or in xylene (140 °C), gives the 1,4-rearranged product, the 4a*H*-thienothiazine (**195a**) or the 4a*H*-furothiazine (**195c**) in 40% and 95% yield, respectively.[69] Thermolysis of the isomeric azathiabenzene derivative (**196**) in boiling toluene gives the 1,4-rearranged product (**197**) and the ring expanded product (**198**), but no 1,2-rearranged product.[69]



SCHEME 64

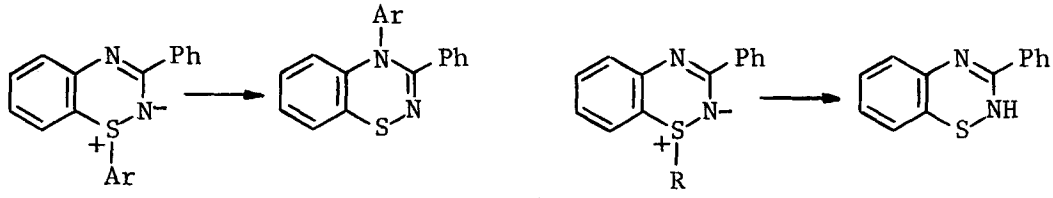
9-Methylazathiaphenanthrene (**177a**) affords the ring expansion product (**199**) in 26% yield on heating in xylene, while the 9-ethyl (**177b**) or 9-propyl derivative (**177c**)



SCHEME 65

is dealkylated, possibly by β-elimination, to afford the dibenzo-1,2-thiazine derivative (**200**) in high yield, easily diacetylated by refluxing in acetic acid anhydride to give a ring-opened biphenyl derivative (**201**).[68]

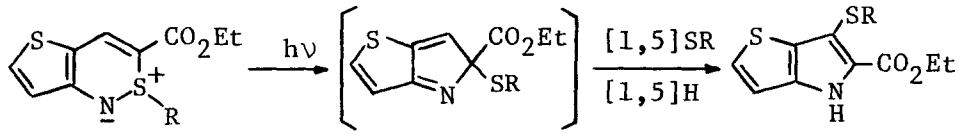
1-Arylbenzothiadiazine derivatives (**202**) rearrange, when heated above 80 °C, to give the corresponding 4-aryl-4*H*-benzothiadiazines (**203**).[70] This 1,4-rearrangement has been shown to proceed via an intramolecular pathway, a 1,4-sigmatropic shift, according to a crossover experiment. 1-Alkyl- (**204**) and 1-morpholinobenzothiadiazine (**189**) afford the 2*H*-benzothiadiazine (**205**) with loss of the 1-substituent.



(202) (203) (204) R=Me (205)
(189) R=Morpholino

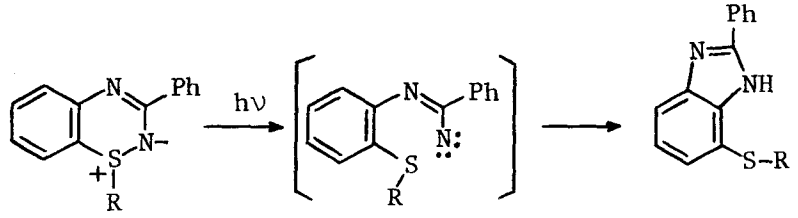
SCHEME 66

Photochemical rearrangements of azathiabenzenes have also been investigated. Photolysis of the azathiabenzenes (**179**) in acetonitrile gives the thienopyrroles (**207**) in good yield.[60] Cleavage of the S—N bond, followed by electrocyclic ring closure of the resulting nitrene would give the intermediate (**206**). The thienopyrroles (**207**) then arise by 1,5-sigmatropic shifts of RS and of hydrogen.



(179) (206) (207)

SCHEME 67

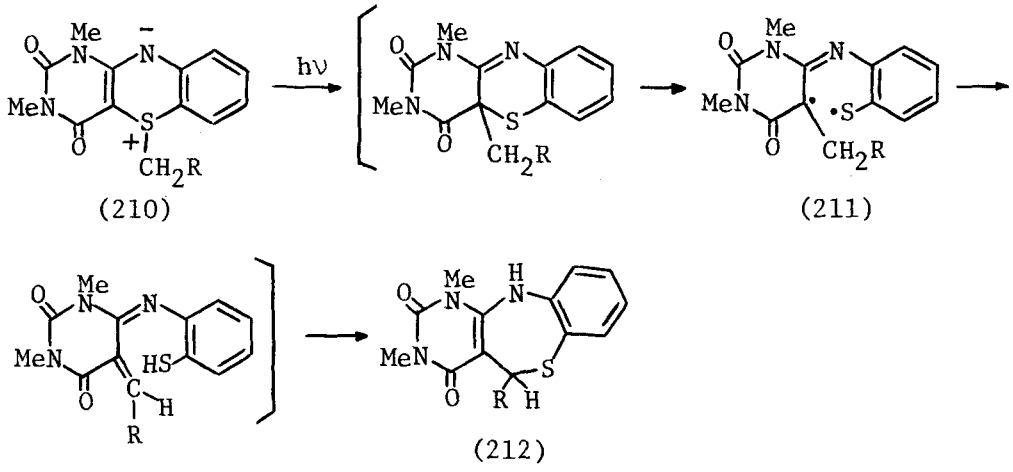


(188) (208) (209)

SCHEME 68

On irradiation in acetonitrile, 1-aryl- and 1-alkylbenzothiadiazines (**188**) rearrange to give benzimidazoles (**209**) by cleavage of the S—N ylide bond.[70] An intermediate nitrene (**208**) can be trapped with dimethyl sulfoxide.[70]

Photolysis of pyrimido-1,4-benzothiazine sulfonium ylides (**210**) results exclusively in a 1,2-rearrangement followed by ring expansion leading to the pyrimido-1,4-benzothiazepines (**212**) via the radical intermediate (**211**).[63]

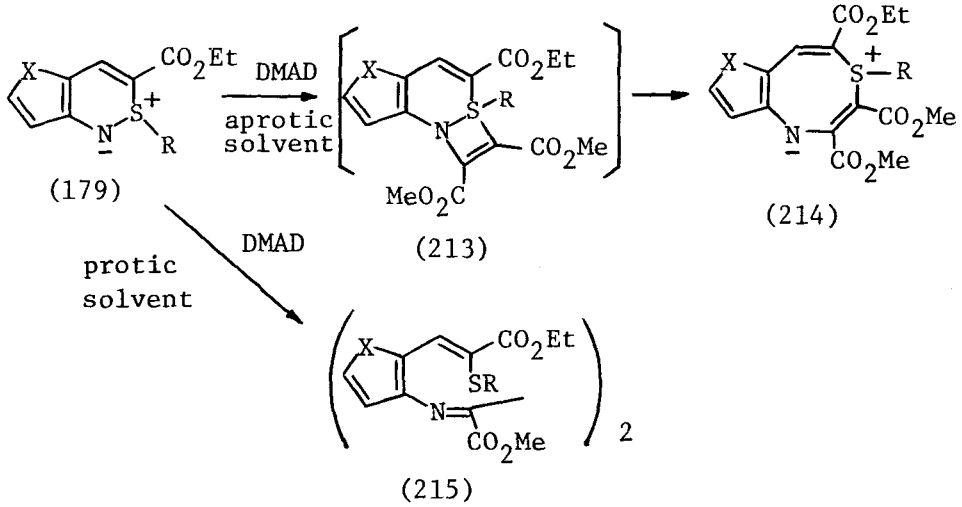


(210) (211) (212)

SCHEME 69

Some interesting ring enlargement reactions of azathiabenzenes with electrophiles have been reported.

Treatment of azathiabenzenes (**179**) with 1 eq. of DMAD in aprotic solvents such as benzene, toluene, or acetonitrile at room temperature gives 1,4-thiazocine derivatives (**214**), the structures of which were determined by X-ray analysis.[71] The

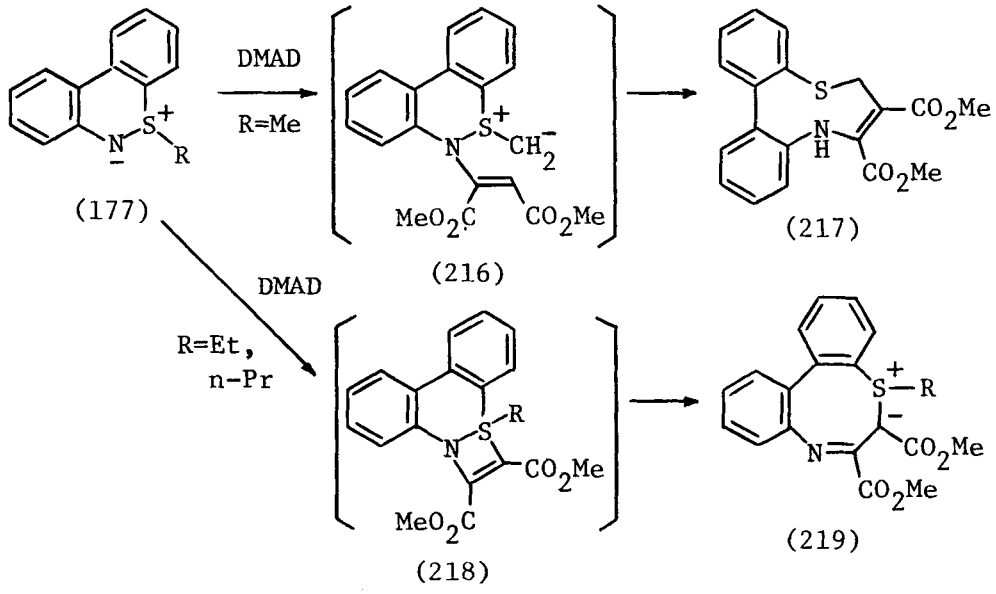


(179) (213) (214) (215)

SCHEME 70

same reaction in a protic solvent such as ethanol affords exclusively the 2:1-adducts (**215**).

The formation of the thiazocines (**214**) is thought to proceed via σ-sulfurane intermediate (**213**) as shown in Scheme 70. The reaction of 9-methylazathiaphenanthrene (**177a**) with DMAD in benzene at room temperature affords another type of 1:1-adduct, *i.e.* the 1,5-thiazonine derivative (**217**), in 24% yield.[68] 9-Ethyl- (**177b**) and 9-propylazathiaphenanthrene (**177c**), however, yield the 1,4-thiazocine derivatives (**219b**) and (**219c**) in 52% and 17% yield, respectively.[72] The remarkable difference between *S*-methyl and *S*-ethyl or *S*-propyl compounds with respect to their reaction mode can presumably be attributed to the acidities of the α-protons of the *S*-alkyl group, leading to different intermediates (**216** from **177a**, **218** from **177b** or **177c**) as shown in the reaction mechanism.

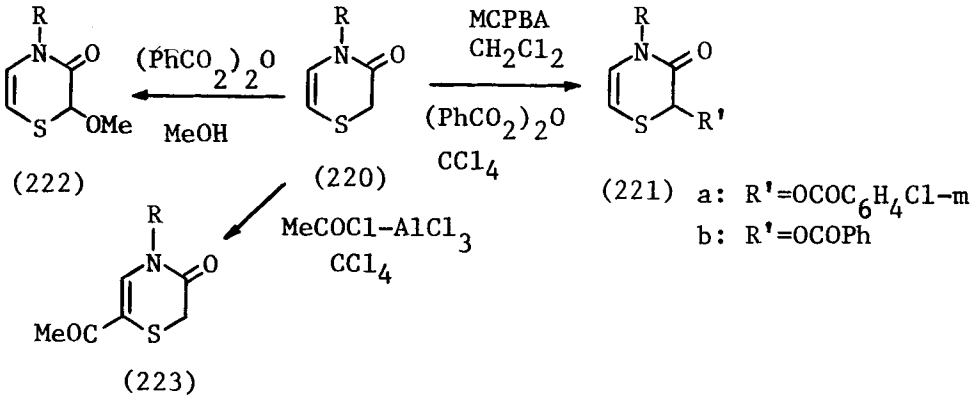


SCHEME 71

II.4. Other Reactions of 1,4-Thiazine Derivatives

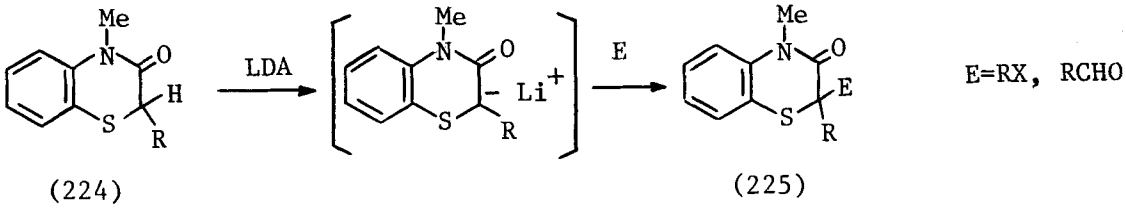
MCPBA is usually used as a versatile reagent for oxidation of sulfides to sulfoxides. However, an unusual reaction of 4-alkyl-1,4-thiazine-3-ones (**220**) with MCPBA was found to yield the 2-(*m*-chlorobenzoyloxy)-1,4-thiazin-3-ones (**221a**). Similarly, benzoyl peroxide reacts with **220** in carbon tetrachloride to afford the 2-benzoyloxy derivatives (**221b**) in high yield.[73] These reactions are strongly accelerated by light. Reaction of **220** with an equivalent amount of benzoyl peroxide in refluxing methanol instead of carbon tetrachloride for 4 hr gives the 2-methoxy derivatives (**222**) in high yield.[74]

Electrophilic substitution reactions of **220** take place at the 6-position: in the presence of aluminum chloride acetyl chloride reacts with **220** to afford the 6-acetyl derivatives (**223**) in 88–89% yields.[73]

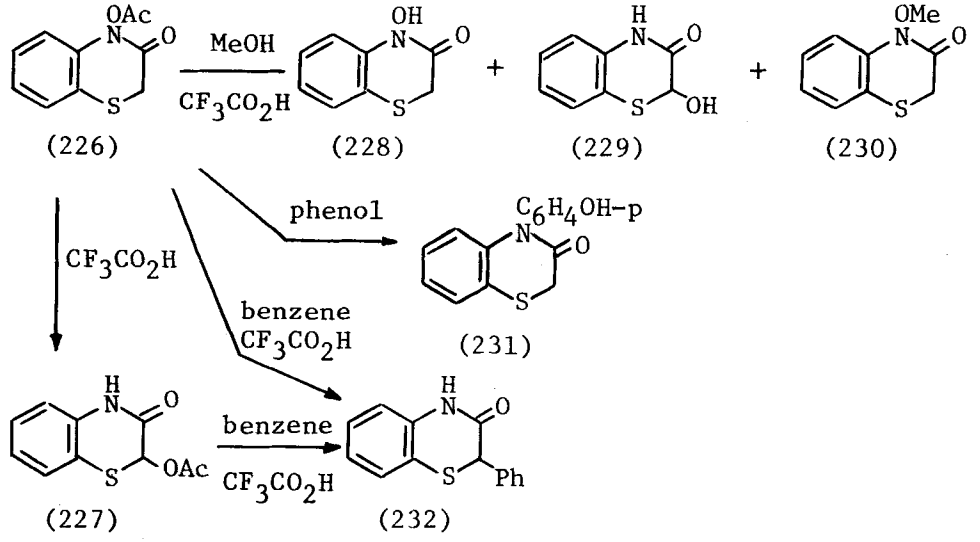


SCHEME 72

4-Methyl-1,4-benzothiazin-3-ones (**224**) can be easily lithiated in the 2-position with lithium diisopropylamide (LDA) in THF-hexane at −78 °C. Subsequent reaction with several electrophiles provides a new and direct route for the synthesis of 2-substituted 1,4-benzothiazin-3-ones (**225**).[75,76]



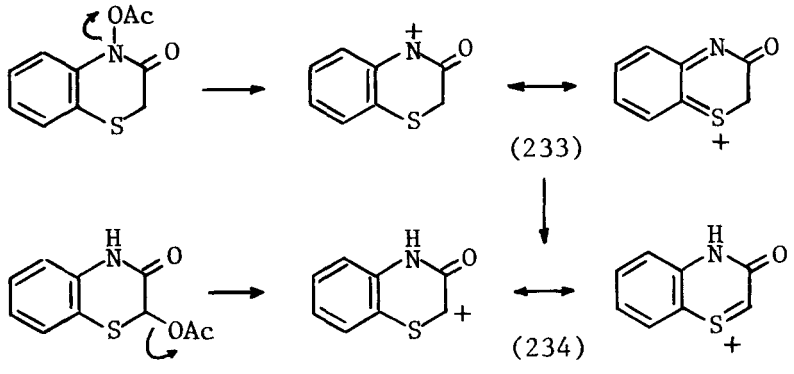
SCHEME 73



SCHEME 74

The reaction of 4-acetoxy-1,4-benzothiazin-3-one (**226**) with some nucleophiles has been reported by Kugai *et al.*[77] Reaction of **226** with trifluoroacetic acid gives the 2-acetate (**227**) by migration of the 4-acetoxy group to the 2-position. Treatment of **226** with methanol containing trifluoroacetic acid gives three major products, (**228**), (**229**), and (**230**). Compounds (**228**) and (**229**) are thought to be formed by hydrolysis of the corresponding acetoxy or trifluoroacetoxy derivatives. Compound (**230**) is the product resulting from nucleophilic attack of methanol on **226**, concerted with the hydrolysis of the N—O bond. Compound **226** reacts with phenol at the 4-position to yield compound (**231**), while the reaction with benzene, catalyzed by trifluoroacetic acid, occurs at the 2-position to give the 2-phenyl derivative (**232**) in 48% yield. The 2-acetoxy derivative (**227**) also yields compound (**232**) in its reaction with benzene-trifluoroacetic acid.

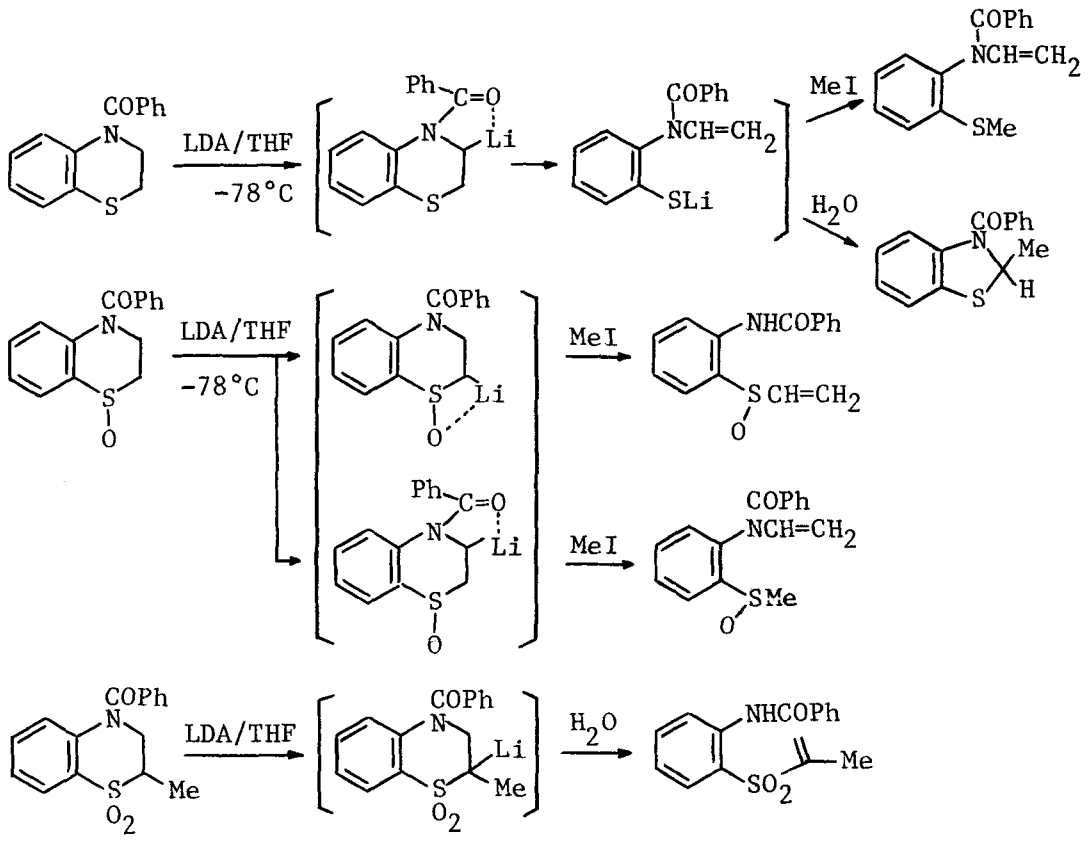
Reactions of nucleophiles at the 4-position are explained in terms of formation of a cation (**233**) by heterolytic cleavage of the N—O bond of **226**. Regarding the reaction with benzene, yielding a 2-substituted benzothiazin-3-one, participation of the cation (**234**), formed from cation (**233**) by tautomerization, is considered.



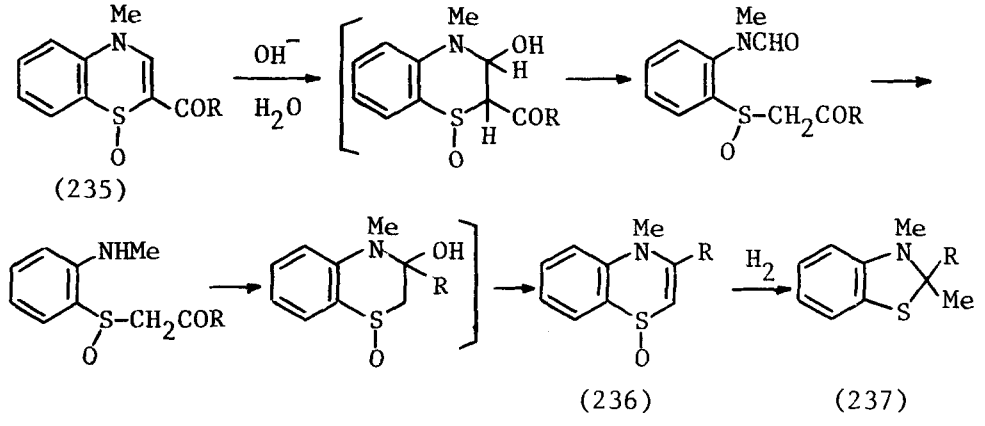
SCHEME 75

4-Acyl-1,4-benzothiazines as well as their sulfoxides and sulfones undergo facile eliminative ring fission simply on treatment with LDA or an organolithium compound.[78,79] Since 4-alkyl-1,4-benzothiazines are not subject to ring fission, the acyl group provides activation for proton removal to generate a carbanionic center α to the nitrogen atom. The presence of substituents in the 2- and 3-positions of the thiazino moiety and the oxidation state of the sulfur atom at the 1-position, which can change the acidity of the hydrogen at the 2- and 3-positions, markedly affects the direction of the ring fission. Unsubstituted and monosubstituted derivatives readily undergo eliminative ring fission, but 2,3-disubstituted derivatives do not react at all. *syn*-Coplanarity between the C^3—H bond and the carbonyl group is necessary for the ring opening reaction. Some examples are shown in Scheme 76.

Treatment of 2-acyl-4-alkyl-1,4-benzothiazine sulfoxides (**235**) with aqueous alkali causes a ring opening followed by recyclization to give 3-substituted 1,4-benzothiazine sulfoxides (**236**).[80] The sulfoxides (**236**) are easily ring-contracted to benzothiazolines (**237**) on reduction with zinc-acetic acid or by catalytic hydrogenation.[80]



SCHEME 76



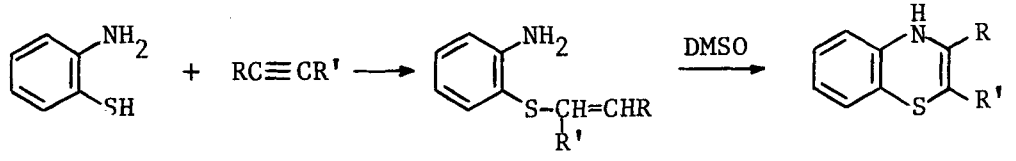
SCHEME 77

II.5. Thiazine Formation Reactions

Many synthetic methods for the formation of the thiazine skeleton have been reported so far. In this Section, recently reported new synthetic methods for thiazine

skeleton formation, except ring transformation reactions of thiazoline derivatives, are described.

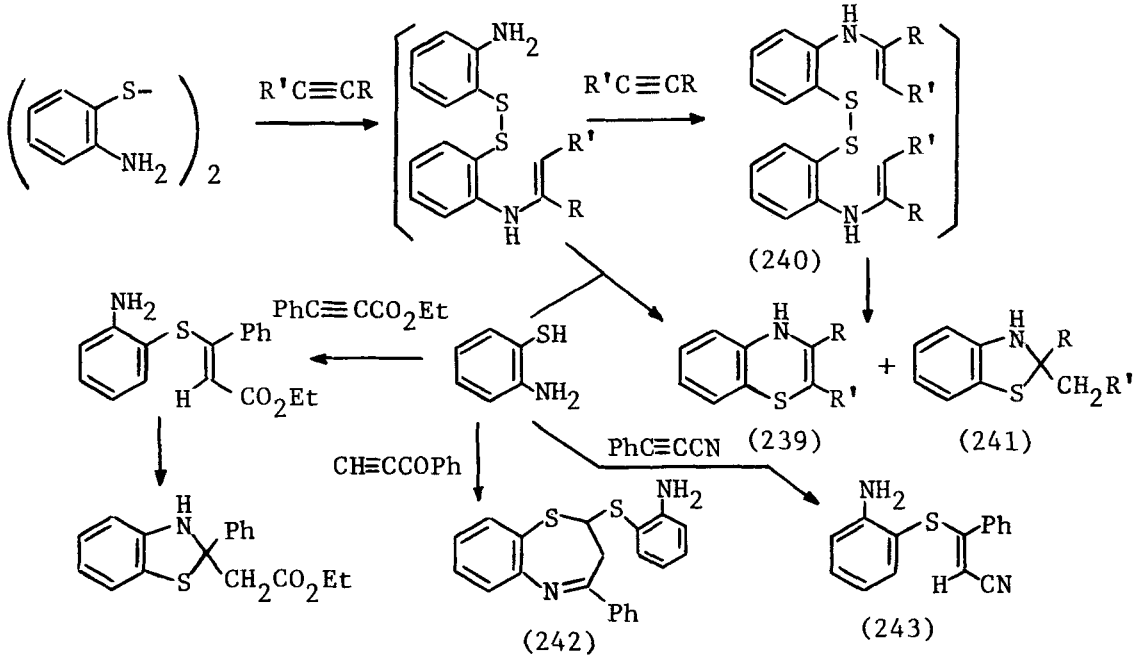
The reaction between *o*-aminobenzenethiol and acetylenic nitriles or esters leads to the vinyl sulfides (**238**). The sulfides (**238**) are easily converted to 1,4-benzothiazines (**239**) in boiling DMSO.[81]



(238) (239)

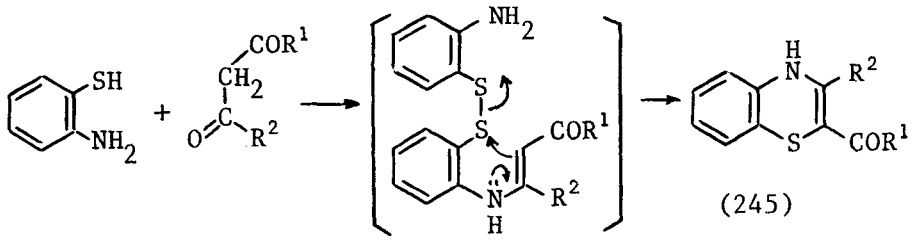
SCHEME 78

The reactions of 2,2'-dithiodianiline with activated alkynes (acetylenic esters, ketones, and nitriles) give in all cases the corresponding 4*H*-1,4-benzothiazines (**239**), together with benzothiazolines (**241**) and/or benzothiazoles, benzothiazepines such as (**242**) and vinyl sulfides such as (**243**). In particular cases the intermediate bis-enamine compound (**240**) has been isolated and found to collapse to give the corresponding benzothiazine by scission of the S—S bond upon attack by the nucleophilic enamine moiety.[82]



SCHEME 79

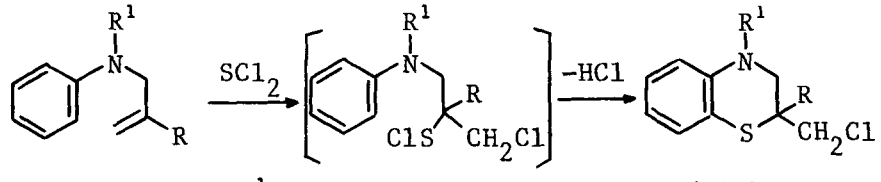
Condensation of *o*-aminobenzenethiol with 1,3-diketones in DMSO also affords 1,4-benzothiazines (**245**).[83,84] The reaction is considered to proceed via the intermediate (**244**). This reaction has been applied to the synthesis of 2,3-dihydro-1*H*-phenothiazin-4(10)-one by using a cyclic 1,3-dione.



(244) (245)

SCHEME 80

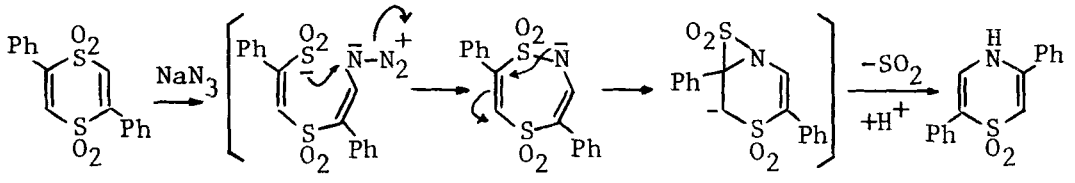
By reaction of *N*-allylanilines (**246**) with sulfur dichloride 1,4-benzothiazines (**247**) can be synthesized.[85]



(246) R=H, Me: R^1=Tos, CO_2Et (247)

SCHEME 81

Treatment of the 1,4-dithiin tetraoxide (**248**) with sodium azide leads to addition-elimination with sulfinate displacement to give the 1,4-thiazine sulfone (**252**) in 43% yield. The mechanism is regarded to hinge upon the vinyl azide (**249**) which gives the second intermediate (**250**) upon ring closure. Subsequent intramolecular Michael addition leading to **251** and loss of sulfur dioxide results in the formation of the final product.

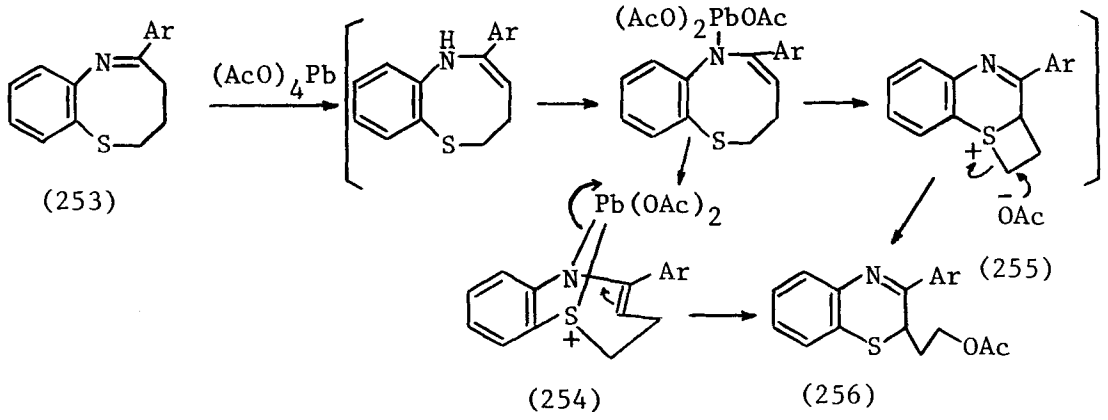


(248) (249) (250) (251) (252)

SCHEME 82

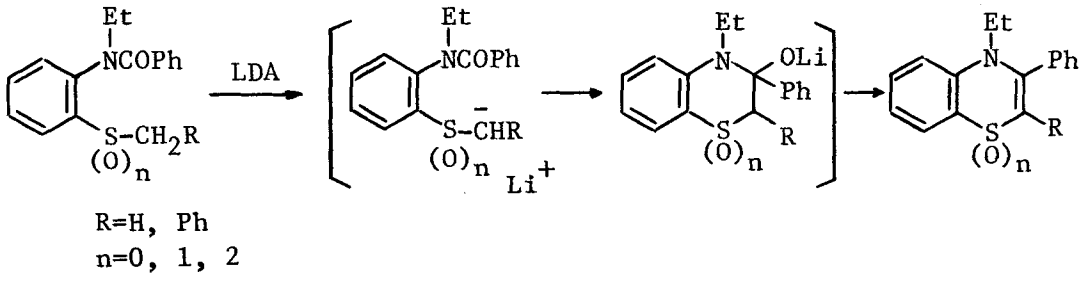
The ring contraction of the 8-membered 1,6-benzothiazocines (**253**) upon action of lead tetraacetate affords 1,4-benzothiazine derivatives (**256**), the structures of which have been determined by X-ray analysis.[87] Reaction pathways involving intermediate (**254**) or (**255**) have been proposed.

4*H*-1,4-Benzothiazines as well as their monoxides and dioxides can readily be prepared from 2-acylaminophenyl alkyl sulfides, sulfoxides, and sulfones by a



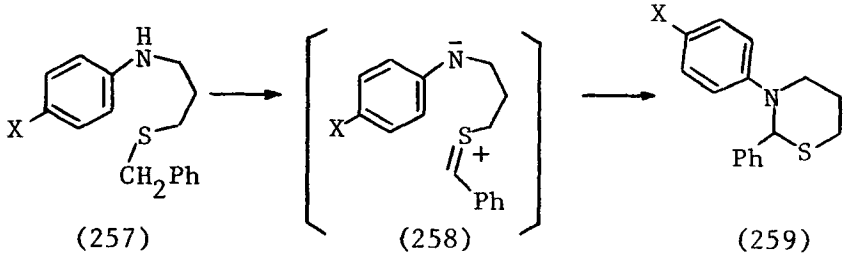
SCHEME 83

procedure involving lithiation α to the sulfur with LDA in THF at −50 °C, cyclization at the amido function, and dehydration.[88]



SCHEME 84

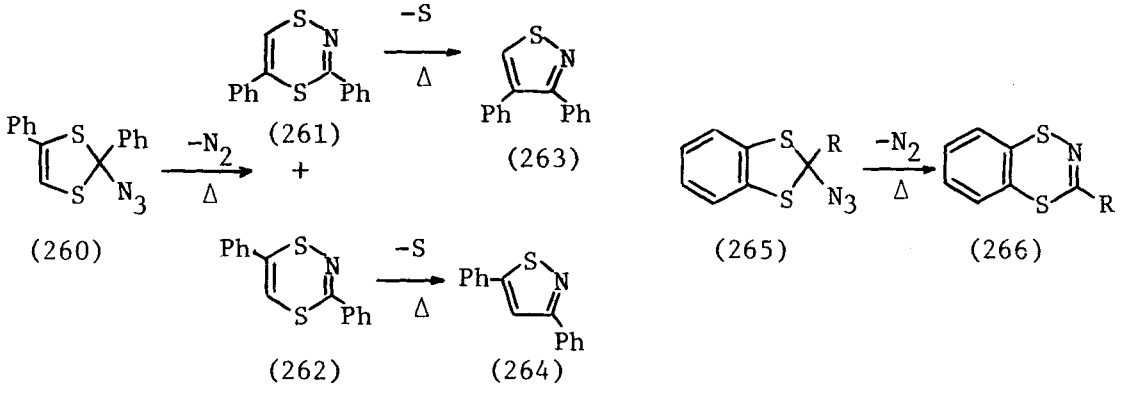
Treatment of the *N*-(3-benzylthiopropyl)anilines (**257**) with NCS in dichloromethane below 0 °C and subsequent addition of triethylamine affords the 1,3-thiazines (**259**) in 19-32% yield, presumably by an intramolecular Pummerer-type reaction of the intermediate (**258**).[89]



SCHEME 85

Upon thermolysis in refluxing toluene the 2-substituted 1,3-dithiol-2-yl azide (**260**) is converted to the 3-substituted 1,4,2-dithiazines (**261**) and (**262**) by insertion of the

nitrogen into the C—S bond.[90] These dithiazines thermally extrude the sulfur atom in the 4-position selectively to give the 3-substituted isothiazoles (**263**) or (**264**), respectively. 1,3-Benzodithiol-2-yl azides (**265**) also decompose thermally and give 1,4,2-benzothiazines (**266**) in good yields.[91]



SCHEME 86

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