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SYNTHETICALLY USEFUL EXTRUSION REACTIONS OF ORGANIC SULFUR, SELENIUM AND TELLURIUM COMPOUNDS

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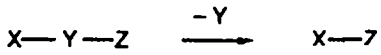
1. INTRODUCTION

Extrusion reactions have until recently not been recognized as having wide application in organic synthesis. While the extrusion process was often theoretically interesting, in many cases the required intermediates for such extrusions were not readily available. This significantly limited the preparative utility of these reactions. Recent advances in organosulfur, organoselenium and organotellurium chemistry have overcome many of these obstacles. Applying new methods novel substrates for extrusion reactions are much more readily available. The synthesis of a variety of complex molecules is now possible using extrusions. These reactions have proved to be especially useful in the preparation of extremely strained organic molecules previously unattainable when using standard synthetic procedures. This review will attempt to summarize recent applications of extrusion reactions of organic sulfur, selenium and tellurium compounds in organic synthesis, concentrating on non-traditional preparations of strained organic molecules.

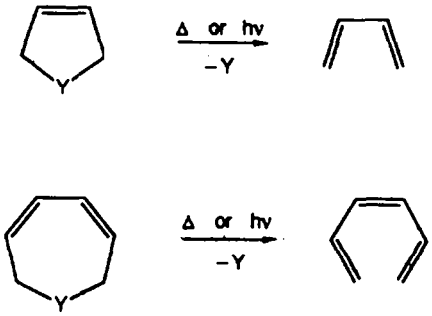
Extrusion reactions have been defined as reactions in which an atom or molecular fragment **Y** connected to two other atoms **X** and **Z** is lost from a molecule, leading to a product in which **X** is

directly bonded to Z.[1] In general the substrate is a cyclic organic molecule, and the extruded fragment is a very stable inorganic species. The reaction is most often induced thermally or photochemically. A number of classes of extrusion reactions have been excellently surveyed in a monograph by Stark and Duke.[2]



Direct removal of such an extrudable group from acyclic systems, although not unknown, is less common because of the lowered likelihood of eventual bonding between the remaining atoms X and Z. Note that in general, in cases where acyclic products are formed – for example in the Ramberg–Backlund and related reactions – cyclic structures are, in fact, intermediates in the reaction. Cheletropic reactions involving formation of a conjugated π system via loss of a stable fragment are sometimes also classed as extrusion reactions (**Scheme 1**).[3]

Scheme 1



A number of atoms or groups can be chosen for Y in extrusion reactions. For related substrates with similar extrusion mechanisms, Stark and Duke empirically ranked the ease of extrusion of a number of inorganic species as follows:

$$N_2 > CO_2 \geq CO \geq SO > SO_2 > O_2 \geq S > O$$

Paine and Warkentin subsequently confirmed these observations quantitatively based on thermodynamic considerations.[4]

Despite these results sulfur species prove to be very amenable to extrusion. While the ease of extrusion of these species is clearly not so great as that reported for molecular nitrogen, the numerous methods available for the preparation of sulfur containing substrates make such molecules extremely useful precursors for extrusions. The selenium analogues of such molecules until recently have been less-widely studied than the corresponding sulfur compounds (and the tellurium compounds even less so). As expected selenium and tellurium systems normally exhibit

closely related chemistry, however selenium or tellurium substitution often requires milder conditions for the desired extrusions. Higher yields and therefore greater synthetic applicability often are a result of such substitutions.

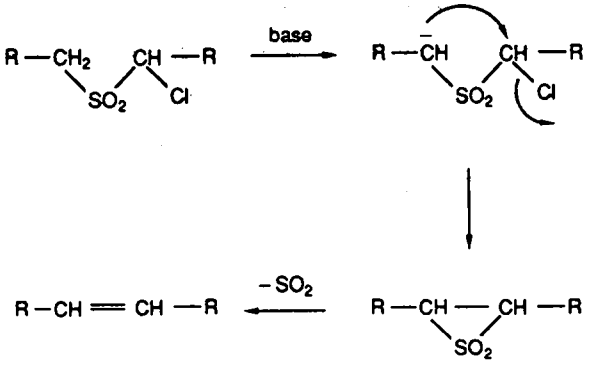
A wide variety of new synthetically useful extrusion reactions utilizing sulfur, selenium and tellurium – containing molecules as substrates have been reported since the Stark and Duke review. We have limited our survey to those reactions that follow the previously described definitions for extrusion reactions, and which also appear to have real synthetic utility. We do not attempt to discuss the complex extrusion chemistry of polysulfides or polyselenides, nor will we cover reactions in which a reactive intermediate obtained by an extrusion is trapped in a further intermolecular reaction. The reactions are classified based on the extruded groups. In addition we will indicate how those reactions have been applied to functional group preparations. Finally we will give a detailed report on applications of twofold extrusions in the synthesis of extremely sterically hindered molecules.

2. EXTRUSIONS OF SULFUR OXIDES

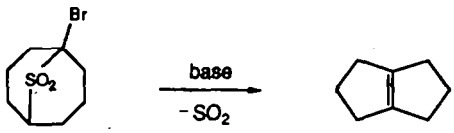
2.1 Alkene Preparations: The Ramberg-Backlund and Related Reactions

Probably the most synthetically useful sulfur-based extrusion reaction is the Ramberg-Backlund reaction. This involves the treatment of an α-halo sulfone with base to afford an olefin. The mechanism of this reaction involves the formation of an episulfone intermediate followed by elimination of sulfur dioxide (**Scheme 2**). The standard procedure has been used in the preparation of a variety of strained organic molecules, for example in the synthesis of the bicyclooctene **1** (**Scheme 3**).[5] This reaction has been extensively reviewed [6,7] and some recent applications of these reactions have been collected.[8,9]

Scheme 2



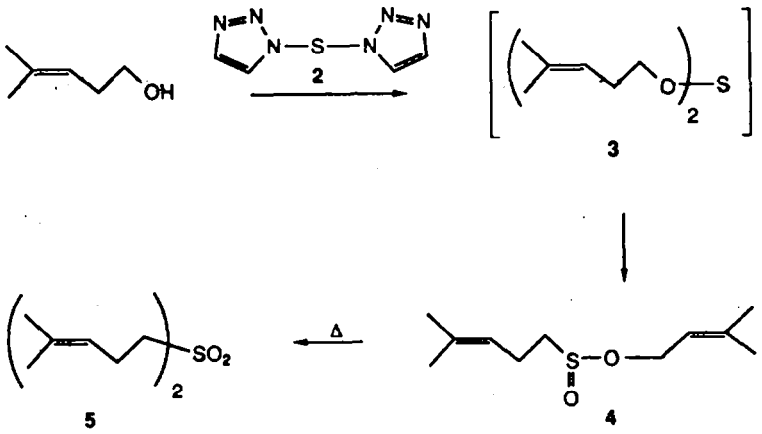
Scheme 3



1

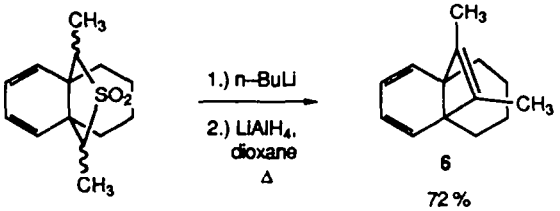
There are a number of interesting variants on the standard Ramberg-Backlund procedure. One such method has been utilized by Büchi for the synthesis of polyolefins from allylic alcohols.[10] Treatment of an allylic alcohol with sulfide **2** affords sulfinate derivative **4** which can be converted to the corresponding sulfone **5** thermally or via catalysis. The diallylic sulfoxylate **3** is a probable intermediate in this reaction (**Scheme 4**). Treatment of the resulting sulfone with carbon tetrachloride - potassium hydroxide[11] led to the desired Ramberg-Backlund transformation affording the polyene. Vitamin A has also been converted to β-carotene using this reaction sequence.

Scheme 4



Treatment of cyclic sulfones with n-butyl lithium followed by addition of lithium aluminum hydride leads to a ring contraction with concomitant formation of a carbon-carbon double bond. This process may involve rearrangement to an intermediate sulfinate followed by reductive elimination affording the olefin. In non-hindered cases reduction to the sulfide is a competing side-reaction. This method has been utilized for the efficient synthesis of a variety of complex cyclobutene derivatives such as **6** (**Scheme 5**).[12-14] In a related reaction oxidation of sulfonyl 1,3-dianions with Cu(II) salts also affords alkenes, presumably via a thiirane dioxide intermediate.[15]

Scheme 5



6

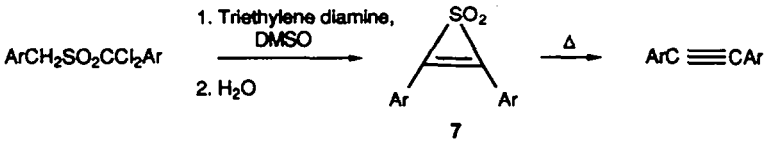
72%

Other preparations of alkenes via loss of sulfur dioxide are reported in Section 4.2.

2.2 Alkyne Preparations:

The reaction of α, α-dihalo sulfones with excess base affords isolable thiirene-1,1-dioxides **7** which can be thermally decomposed to the corresponding acetylenes (**Scheme 6**).[16] In a related reaction α, α-dichlorobenzyl sulfides can be converted to acetylenes upon treatment with base and triphenylphosphine, again presumably via a thiirene intermediate.[17,18]

Scheme 6

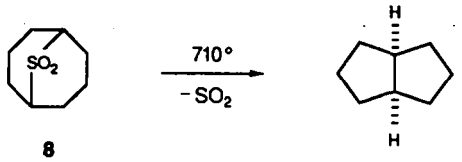


7

2.3 Carbon-Carbon Single Bond Formation and Cyclophane Synthesis:

Thermal and photochemical extrusions of sulfur dioxide have proved to be very useful in a variety of carbon - carbon single bond forming reactions. The thermal extrusion of sulfur dioxide from the bicyclic sulfone **8**, essentially under flash vacuum thermolysis conditions, provided a convenient route to bicyclooctane **9** (**Scheme 7**).[5] Similarly pyrolysis of the thietane S,S-dioxide **10** led to efficient formation of the cyclopropane mixture **11** and **12** (**Scheme 8**).[19]

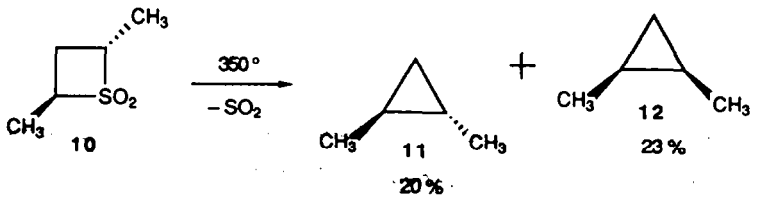
Scheme 7



8 **9**

50 %

Scheme 8

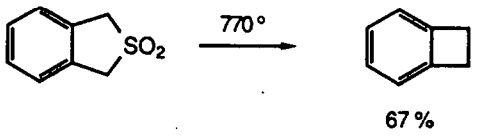


10 **11** **12**

20 % 23 %

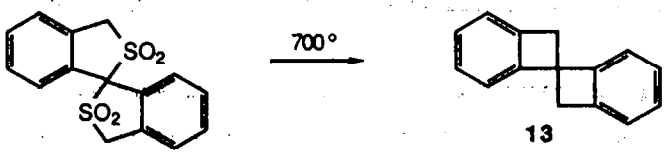
The thermal extrusion of benzylic substituted sulfur dioxide was initially developed by Cava as a synthetic route to a variety of benzocyclobutene derivatives (**Scheme 9**).[20] Flash vacuum thermolysis of these derivatives provided a powerful method for the preparation of extremely strained benzocyclobutenes such as **13** (**Scheme 10**).[21] This method subsequently found wide application in cyclophane and related syntheses.[22-24]

Scheme 9



67 %

Scheme 10

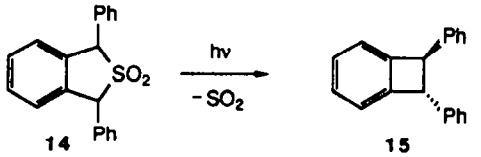


13

47 %

Photoextrusion of sulfur dioxide as a synthetically useful route to carbon-carbon single bonds was also pioneered by Cava and coworkers.[25] Irradiation of sulfone **14** afforded the benzocyclobutene **15** (**Scheme 11**). Under the attempted conditions required for thermal sulfur dioxide extrusion, the desired benzocyclobutene underwent further thermal reactions preventing its isolation.

Scheme 11

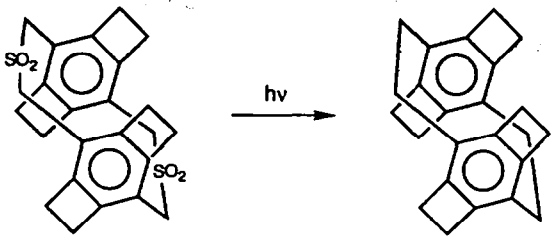


14 **15**

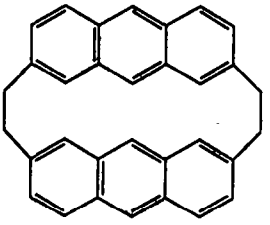
13 %

Photoextrusion in many cases is milder than thermal extrusion and has found wide applicability in [2.2]cyclophane synthesis (**Scheme 12**) [26-32] As expected, only dibenzylic sulfones undergo this reaction.[32] Some recent applications of this reaction include the preparation

Scheme 12



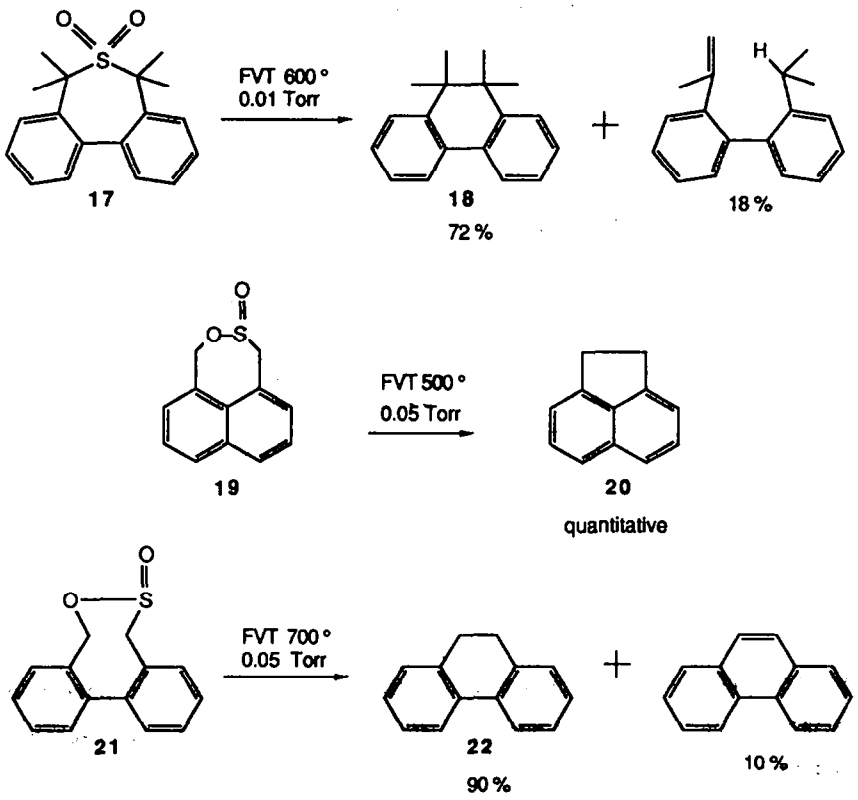
of [2.2] (2,7) anthracenophan **16** [33] and the preparation of a key intermediate in the synthesis of "kekulene."[34]



16

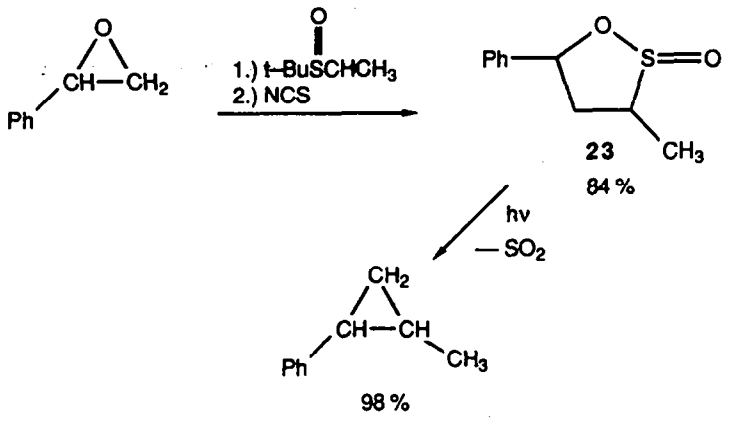
Flash vacuum pyrolysis of the cyclic sulfone **17** and cyclic sulfinates **19** and **21** afforded excellent yields of the corresponding extrusion products **18**, **20** and **22** (**Scheme13**).[35]

Scheme 13



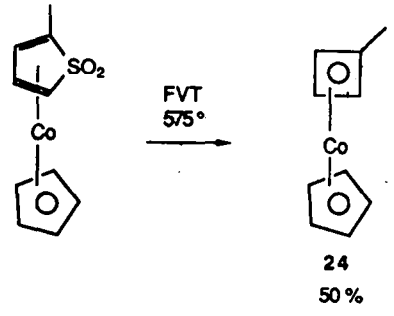
Photochemical extrusion of sulfur dioxide from a γ-sultine **23** is also a key step in the conversion of epoxides to cyclopropanes (**Scheme 14**).[36] Only those sultines with an aryl group α to the ring oxygen undergo the desired extrusion.

Scheme 14



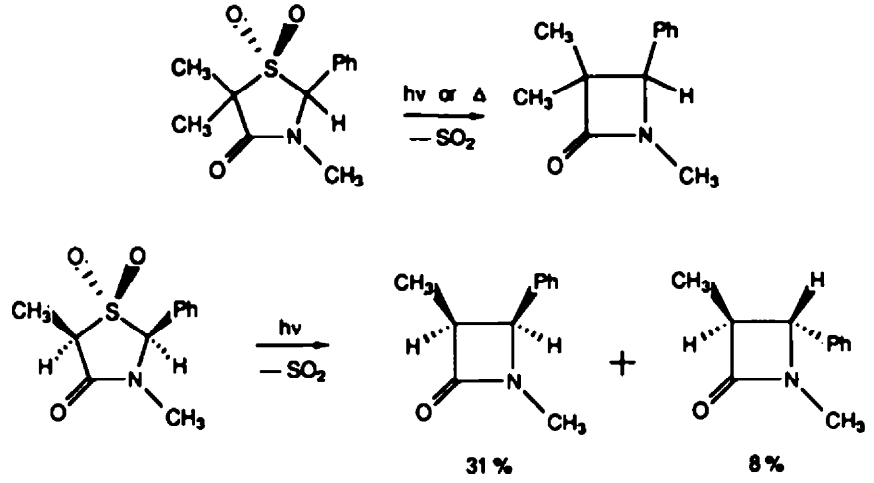
Sulfur dioxide extrusion via flash vacuum thermolysis was a key step in the preparation of metal-complexed cyclobutadiene **24** (**Scheme 15**).[37]

Scheme 15

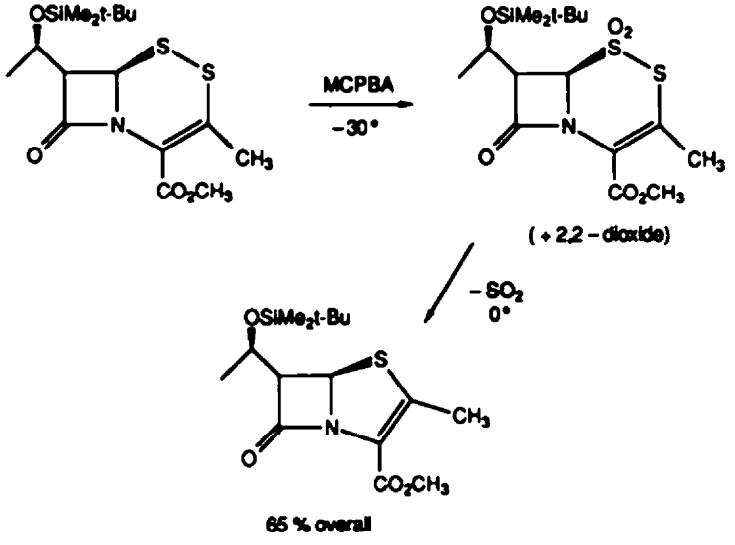


Thermal and photochemical sulfur dioxide extrusions have also been used in the preparations of β-lactams (**Scheme 16**) [38] and also in the stereospecific conversion of 2-thiacephems to penems (**Scheme 17**).[39]

Scheme 16



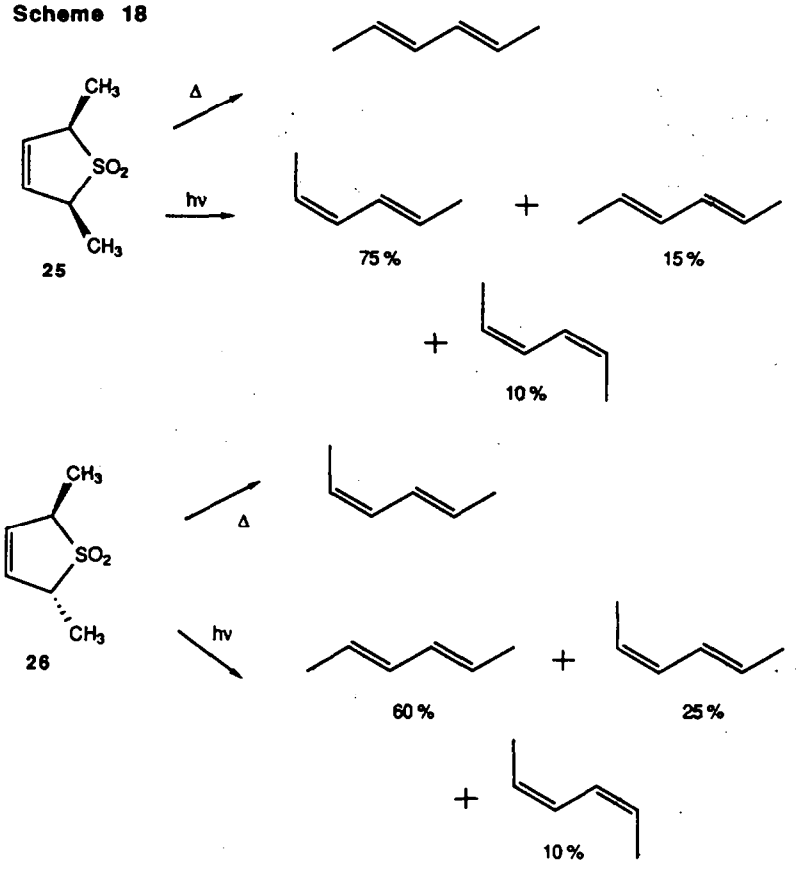
Scheme 17



2.4 Synthetically Useful Cheletropic Extrusions of Sulfur Dioxide

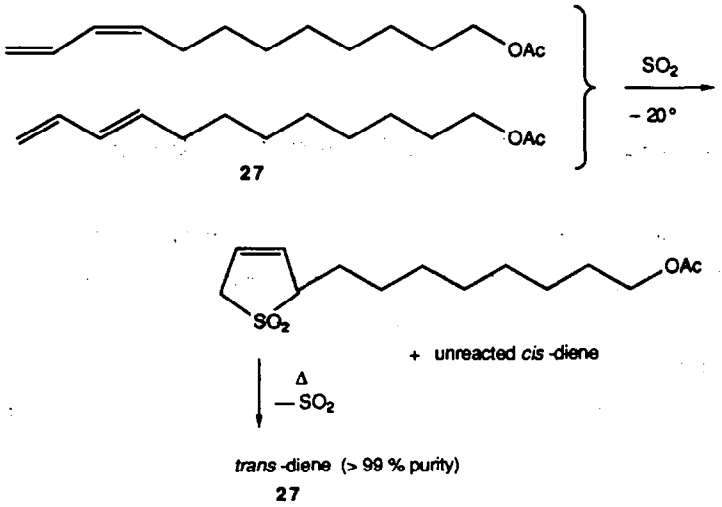
The thermal and photochemical extrusions of sulfur dioxide from cyclic systems leading to polyenes have proved to be a synthetically useful reaction in many cases. For example, the thermolyses of the sulfolenes 25 and 26 proceeds in a stereospecific manner, affording products of disrotatory ring opening in greater than 99.9% stereochemical purity.[40,41] The photochemical process is not completely stereospecific, but favors a conrotatory ring opening as predicted by Woodward-Hoffmann rules (**Scheme 18**).[42]

Scheme 18



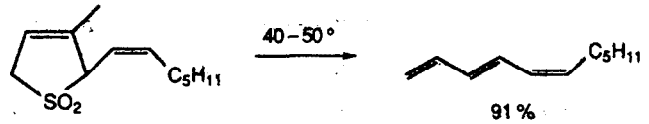
A number of excellent applications for this reaction in synthesis have been reported, including the separation of the 9-*cis* and *trans* isomers of the red bollworm moth pheromone. Sulfur dioxide adds only to the *trans* diene **27** which can then be separated and regenerated upon pyrolysis **(Scheme 19)**.[43]

Scheme 19

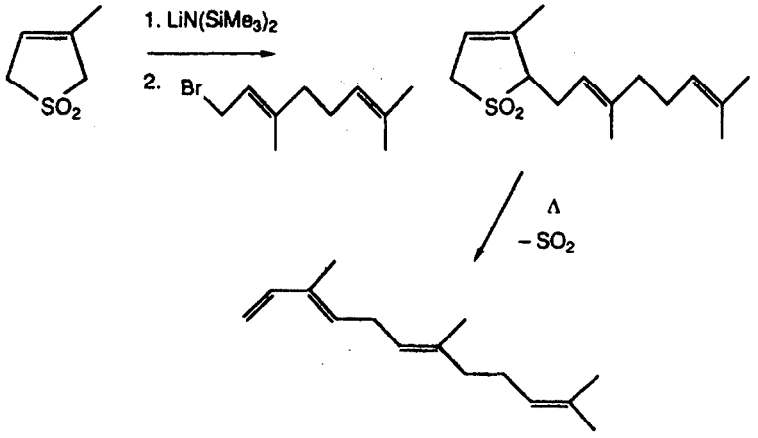


Alkylations of sulfolenes followed by thermal extrusion of sulfur dioxide provided convenient routes to 1,3,5-trienes (**Scheme 20**) [44] and polyenes (**Scheme 21**).[45] These extrusion reactions are reported to be promoted by lithium aluminum hydride.[46]

Scheme 20

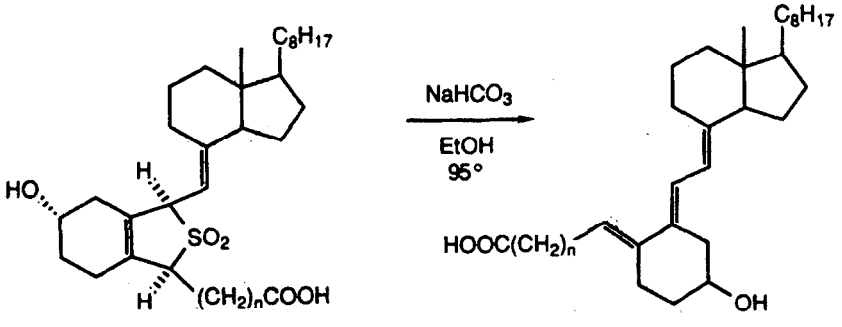


Scheme 21



Sulfolene formation has also been used as a method for the protection of the *s*-cis diene portion of vitamin D derivatives. It should be noted however that thermolysis of **28** afforded **29** in high yield in apparent violation of orbital symmetry rules (**Scheme 22**).[47,48] Block has summarized a variety of related cheletropic reactions.[49]

Scheme 22

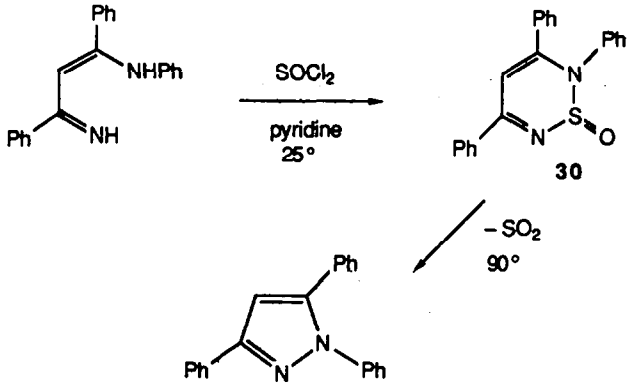


28 **29**
77 %

2.5. Sulfur Monoxide Extrusions

Although synthetically useful extrusion reactions of sulfur dioxide are quite common, the direct loss of sulfur monoxide in an extrusion is much less common.[50] This is perhaps surprising in view of the previously mentioned extrudability scales for sulfur species. One interesting synthetic application of sulfur monoxide extrusion involves the conversion of 1,2,6-thiadiazene S-oxides **30** to pyrazoles **31** (**Scheme 23**).[51] The procedure can also be carried out using sulfur dichloride, with sulfur extrusion, however no extrusion of sulfur dioxide was noted upon thermolysis of the corresponding thiadiazene S-dioxides even under forcing conditions.[52]

Scheme 23



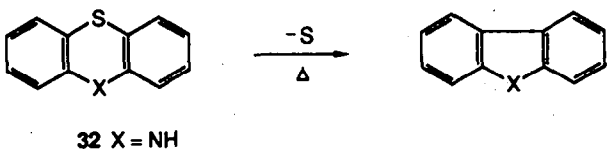
31

3. Direct Extrusions of Elemental Sulfur, Selenium and Tellurium:

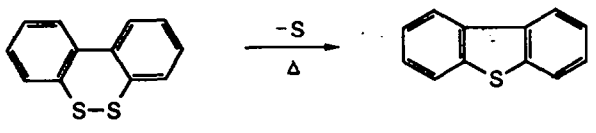
3.1. Heterocyclic Synthesis via Sulfur Extrusions

The pyrolytic extrusions of elemental sulfur from phenothiazine **32**, thianthrene **33** and cyclic disulfide **34** are some early examples of the preparative use of extrusion reactions (**Scheme 24**). The driving force for such reactions is the increase in the aromatic character of the product heterocycles.[53-58] Much of the early work in this area has been reviewed by Stark and Duke.[59]

Scheme 24



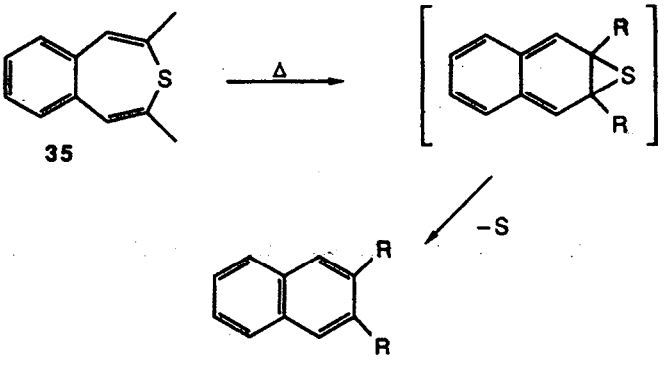
32 X = NH
33 X = S



34

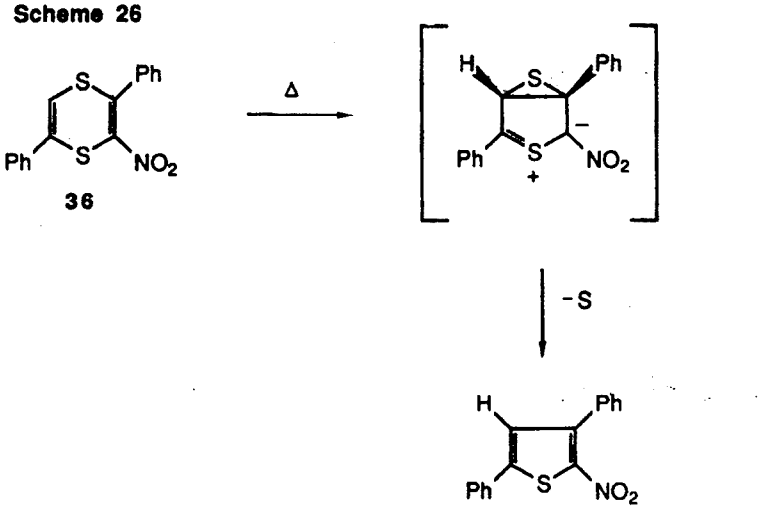
In many other direct sulfur extrusions episulfides have been postulated as intermediates. For example, 4,5-benzothiepin derivatives **35** rapidly extrude sulfur under mild conditions (**Scheme 25**).[60-62] The dibenzothiepins also extrude sulfur affording the corresponding phenanthrenes, although at significantly higher temperatures.[63] The extrusion of sulfur from the thiazepin system has been studied in detail, and the results were also consistent with an episulfide intermediate in this reaction.[64]

Scheme 25

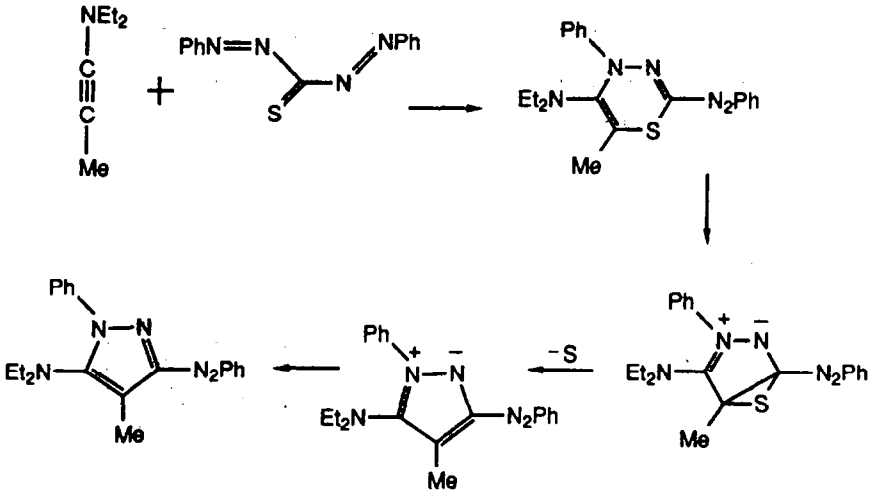


Extrusion of sulfur from the 1,4-dithiin system **36** has been extensively studied (**Scheme 26**).[65] The regiochemical preferences in this reaction have also been recently reported.[66] This and related chemistry have also been adequately reviewed.[59] A number of other interesting applications of sulfur extrusion in ring contraction leading to novel heterocycles have also been recently reported,[67,68] including, for example, that indicated in **Scheme 27**.[69]

Scheme 26



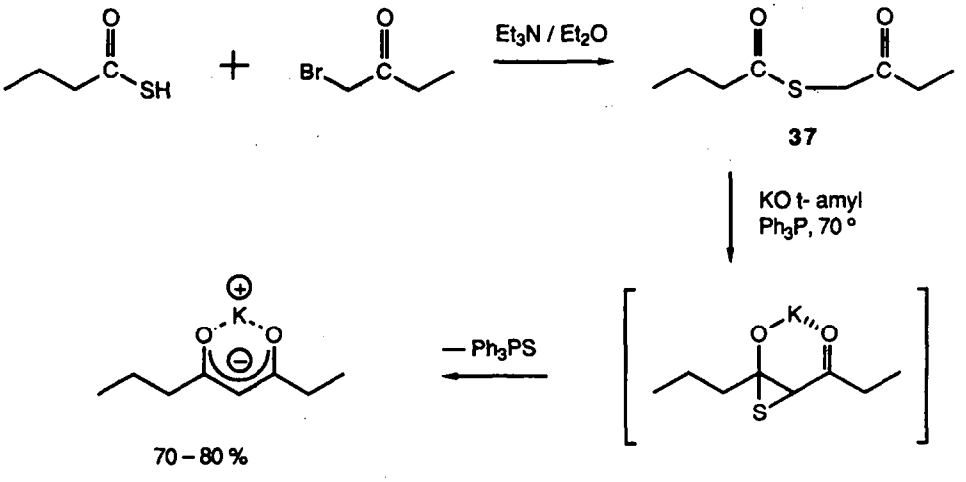
Scheme 27



3.2 Thermal Sulfur Extrusions in Carbon-Carbon Single Bond Formation

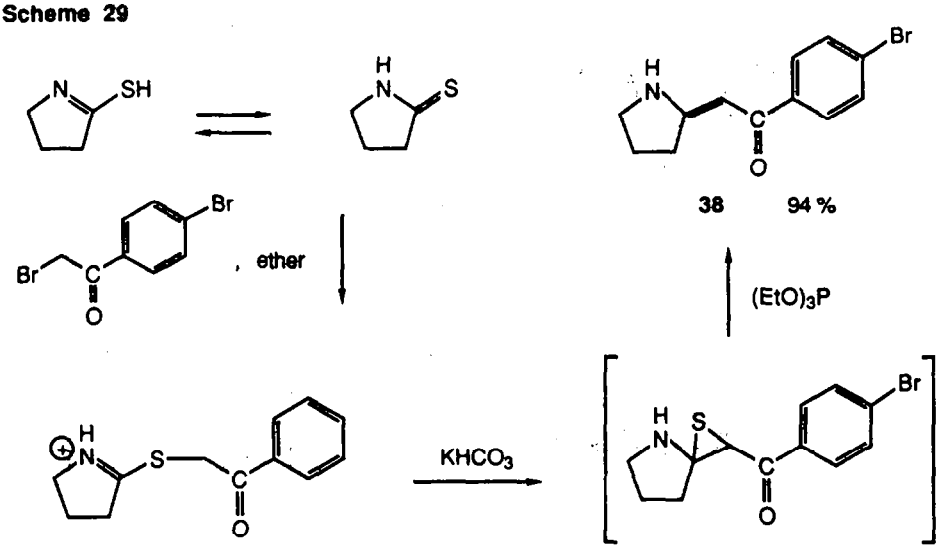
A number of clever synthetic procedures have been devised in which *in situ* generated episulfides are desulfurized generating carbon-carbon bonds. Eschenmoser has used sulfur extrusion from *in situ* generated episulfides in a number of particularly useful transformations. Enolizable β-dicarbonyl systems can be prepared in a two step alkylative-extrusion procedure. Treatment of the thiocarboxylate with an α-haloketone affords a β-keto thioester **37**. Treatment of this compound with a tertiary phosphine at elevated temperatures affords the corresponding β-diketone in excellent yield (**Scheme 28**). [70] A similar reaction has been reported using the corresponding selenocarboxylates.[71]

Scheme 28



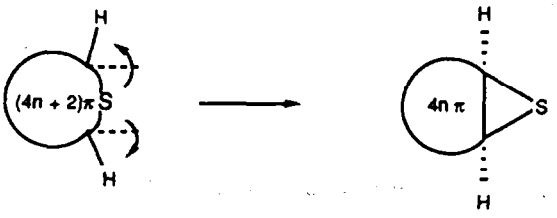
A related sulfur extrusion could be utilized for the preparation of secondary vinylogous amides **38** (**Scheme 29**).[72] This procedure was used by Eschenmoser as a key step in the synthesis of corrins, including the cobyrinic acid portion of vitamin B_{12}.[72,73] Ketamidines have been prepared using an analogous extrusion.[74]

Scheme 29



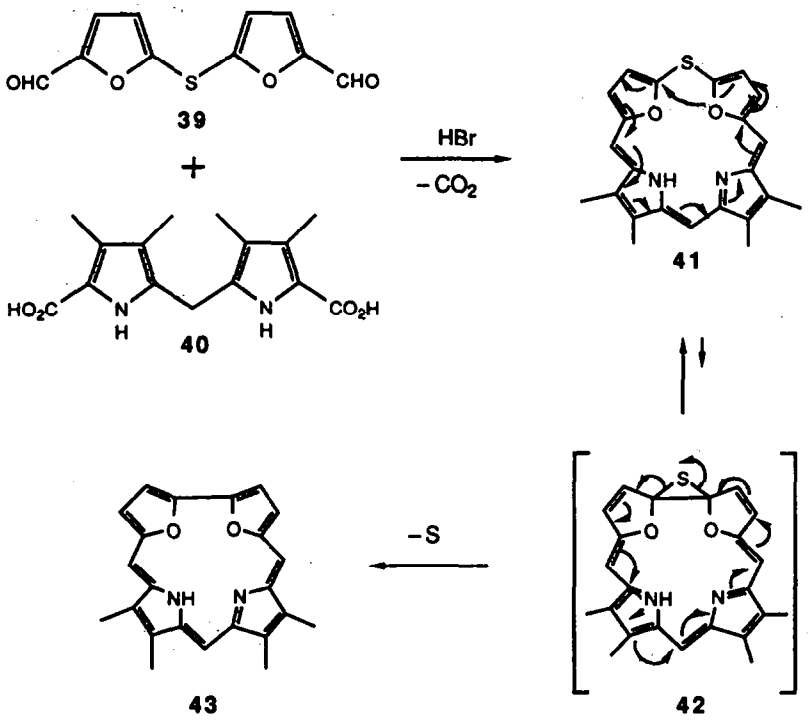
Another type of direct sulfur extrusion reaction has been applied in an elegant synthesis of corroles and related compounds. Grigg and coworkers recognized that a disrotatory electrocyclic reaction of a cyclic sulfide with (4n+2) π electrons could be used in complex macrocycle formation (**Scheme 30**).

Scheme 30

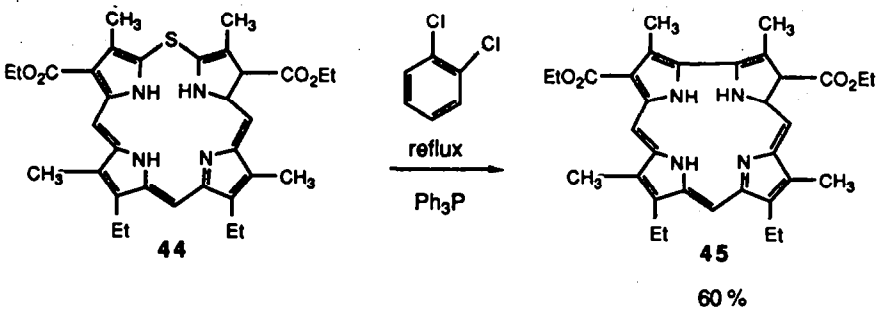


Treatment of sulfide **39** with diacid **40** in the presence of hydrogen bromide directly afforded macrocycle **43**. Presumably the initially formed thiamacrocycle **41** is converted to episulfide **42** in the pericyclic process. Direct thermal loss of sulfur then leads to the desired macrocycles (**Scheme 31**). Heating the isolated *meso*-thiaphlorin **44** with triphenylphosphine also afforded corrole **45** in good yield (**Scheme 32**).[75]

Scheme 31



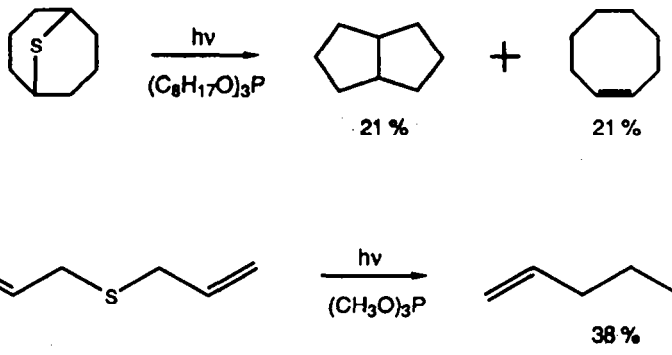
Scheme 32



3.3. Photoextrusion of Elemental Sulfur and Selenium — Cyclophane Synthesis

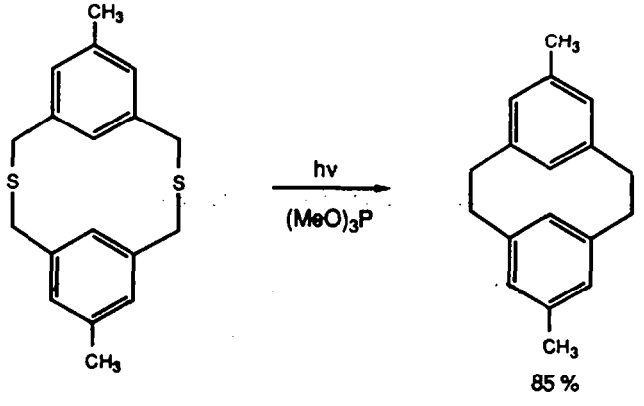
Photolysis of dialkylsulfides in the presence of a tertiary phosphine was shown by Corey and Block to lead to sulfur extrusion and carbon-carbon bond formation (**Scheme 33**). The mechanism for this transformation involves cleavage of a carbon sulfur bond and formation of alkyl and thiyl radicals. The latter are desulfurized with the phosphine and radical recombination affords the desired carbon-carbon bond.[5]

Scheme 33



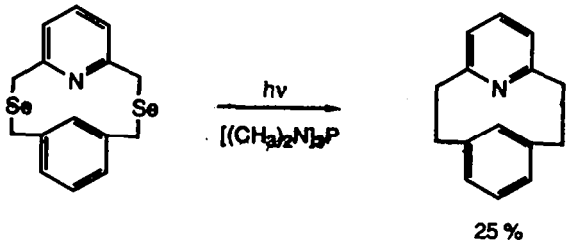
The method has proved to be quite useful in the preparation of cyclophane derivatives, especially in cases where oxidation to the sulfone would be difficult (**Scheme 34**).[76] A great variety of related transformations have been reported.[77-80]

Scheme 34

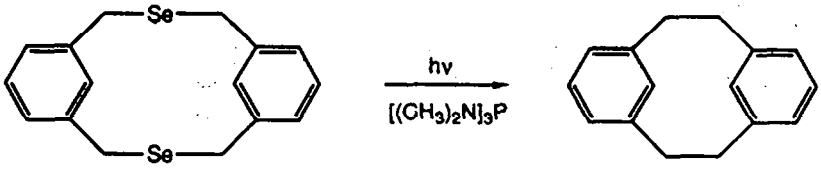


Thermal and photochemical extrusions of selenium from selenides have also been used in cyclophane synthesis (**Scheme 35**).[81,82] It is claimed that photodeselenation is the method of choice for extrusion based synthesis of cyclophanes. The metacyclophane **46** could be obtained in excellent yield using the photodeselenenation (**Scheme 36**).[82] Flash vacuum thermolysis afforded **46** in only 8% yield while Stevens rearrangement followed by Raney nickel treatment led to a 49% yield of the cyclophane.[81]

Scheme 35



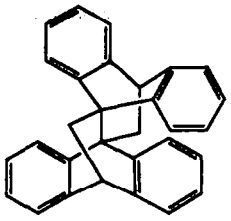
Scheme 36



46

93 %

Photochemical extrusion of selenium or sulfur from bis-9-anthryl selenide and also from the corresponding sulfide afforded the interesting lepidopterene **47**.[83]

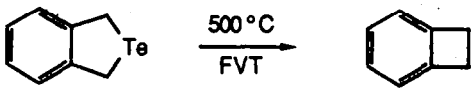


47

3.4 Thermal Extrusions of Selenium and Tellurium

While benzylic sulfides are moderately stable thermally, benzylic selenides and tellurides upon thermolysis afford 1,2-diarylethanes with extrusion of selenium or tellurium.[83-86] Similar extrusions have been noted for the corresponding diselenides and ditellurides.[83,84,87] Thermal tellurium extrusion has been used in a convenient preparation of benzocyclobutenes **48** (**Scheme 37**).[88]

Scheme 37

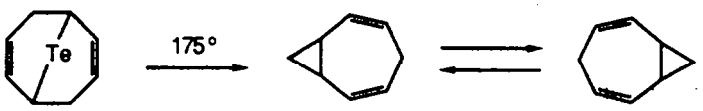


48

74 %

Thermal extrusion of elemental tellurium from the cyclic telluride **49** has also been reported to yield the fluxionally mobile bicyclic diene **50** (**Scheme 38**).[89] The corresponding sulfide is stable at 200 °C. for 16 hrs. The selenium analogue upon prolonged heating decomposes to ethylbenzene and *o*-xylene.[90]

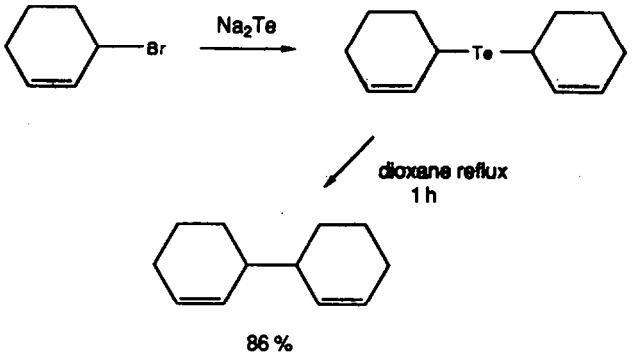
Scheme 38



49 **50**

Coupling of allylic halides via thermal tellurium extrusion from *in situ* generated tellurides is reported to proceed in high yield (**Scheme 39**).[91] The reaction appears to proceed via radical coupling. The corresponding selenides are reported to be stable under the required reaction conditions.

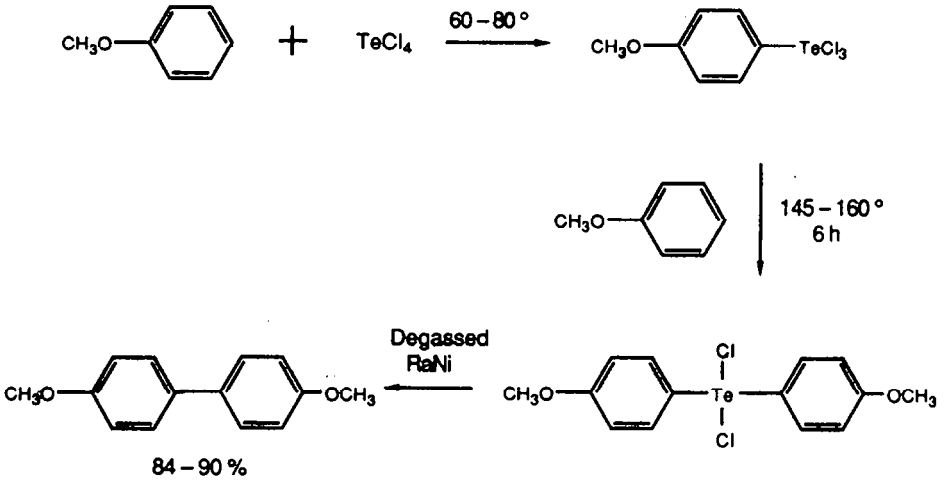
Scheme 39



3.5 Metal and Organometallic Promoted Extrusions

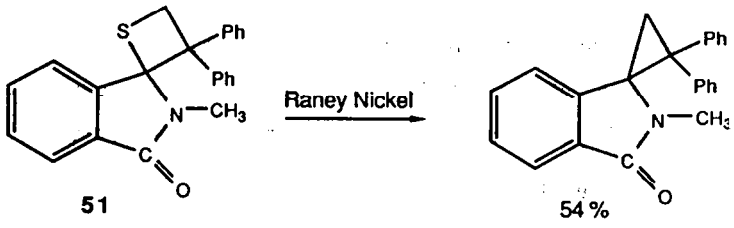
Another synthetically useful selenium and tellurium based extrusion reaction involves conversion of diaryl selenides and diaryl tellurides to the corresponding biaryls by their treatment with Raney nickel.[92,93] The tellurium reaction is especially useful since the desired telluride intermediates can be generated *in situ* by reduction of the corresponding readily available tellurium halides (**Scheme 40**).[94]

Scheme 40



Raney Nickel is reported to convert the spirothietanes such as **51** to the corresponding cyclopropanes in moderate yield **(Scheme 41)**.[95]

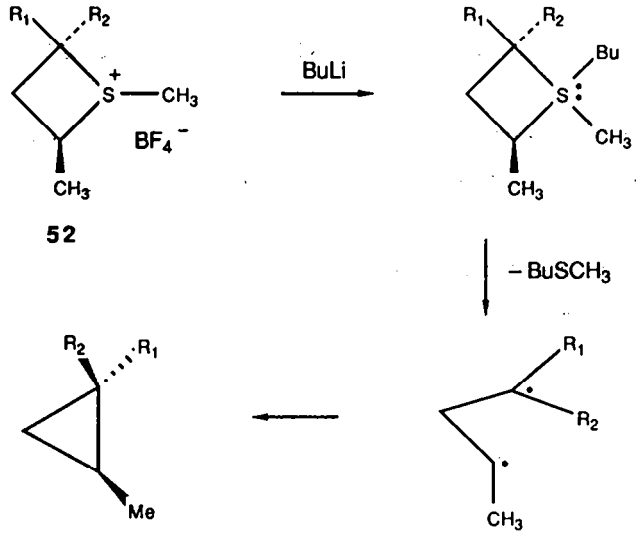
Scheme 41



51 54 %

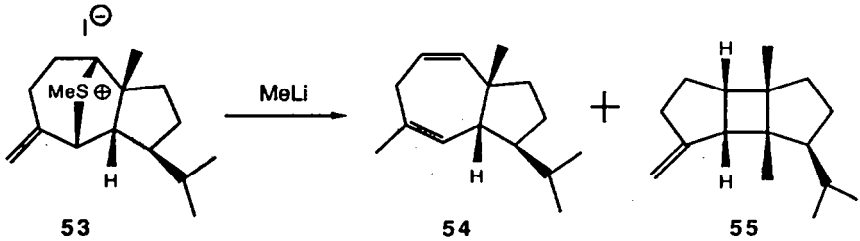
Trost and coworkers reported that treatment of thietanonium salt **52** with *n*-butyl lithium leads to extrusion of a sulfide affording the cyclopropane ring stereospecifically **(Scheme 42)**.[96] A related sulfide extrusion has been used to convert mintsulfide **53** and its isomer to a mixture of **54** and tricyclic cyclobutane **55** stereoselectively **(Scheme 43)**.[97]

Scheme 42



52

Scheme 43

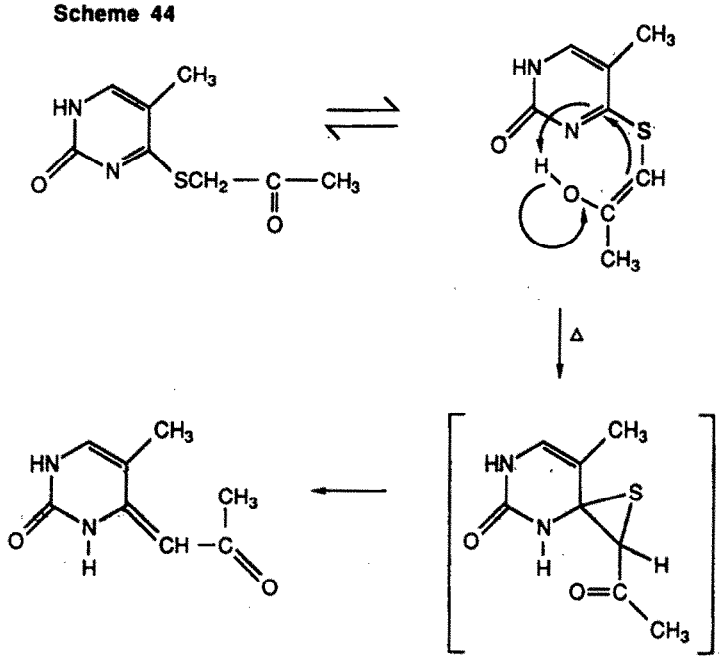


53 **54** 43 % **55** 29 %

3.6. Multiple Bond Formation

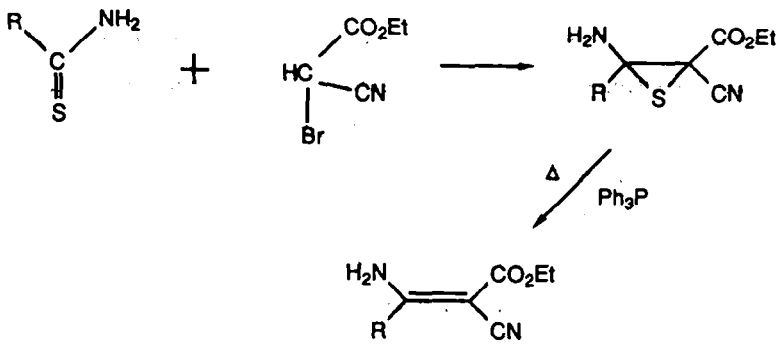
Desulfurization of episulfides provides a convenient route to carbon-carbon double bonds. A number of previously described synthetic methods utilized sulfur nucleophilicity as a route to carbon-carbon single bond formation (see **Schemes 28, 29**). In a number of other cases thiocarbonyl nucleophilicity has been utilized in carbon-carbon double bond formation. Thiocarbonyl groups can be easily alkylated using α-halocarbonyl compounds. Intramolecular episulfide formation followed by sulfur extrusion provides a convenient route to carbon-carbon double bond formation **(Scheme 44)**[98], **(Scheme 45)**[99], **(Scheme 46)**[100]. A variety of similar transformations using alkylation-extrusion procedures have also been reported,[101-103] including introduction of carbon substituents into nucleosides using this method.[104]

Scheme 44



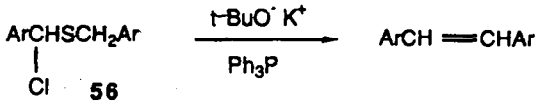
Scheme 45

Scheme 46



A variant of the Ramberg-Backlund reaction involves using α-halo sulfides **56** as intermediates. Treatment with base and triphenylphosphine in refluxing tetrahydrofuran affords alkenes, presumably via a thiirane intermediate **(Scheme 47)**.[105]

Scheme 47



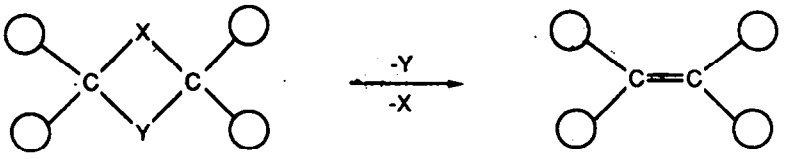
4. Twofold Extrusion Reactions

4.1 Sterically Hindered Alkenes via 1,3,4-Thiadiazolines

There are a great variety of methods for the preparation of olefins, however most of these methods fail in the attempted preparation of sterically hindered carbon-carbon double bonds. The Wittig reaction is especially limited in this respect. While yields of disubstituted olefins via the Wittig reaction are quite acceptable, yields of trisubstituted olefins are lower. Yields of tetrasubstituted olefins are very low or often go unreported. While elimination reactions often provide high yields of sterically hindered alkenes, the highly substituted substrates for such eliminations are often difficult to prepare. A new strategy, that of twofold extrusion, was developed in order to prepare and investigate the properties of extremely hindered alkenes.

The twofold extrusion reaction has been extensively utilized in the preparation of sterically hindered olefins. This method was independently developed by Barton and Kellogg and involves preparation of species such as **A**. The rationale for the process is the fact that intermolecular reactions are much more influenced by steric hindrance than intramolecular processes. Construction of a molecule such as **A** would keep steric interactions to a minimum in the intermolecular step. Consecutive extrusions of **X** and **Y** in subsequent reactions would lead to the introduction of the sterically strained double bond into **B (Scheme 48)**.

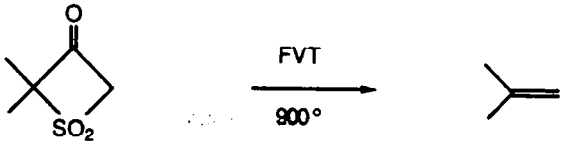
Scheme 48



A **B**

An example of an early twofold extrusion process involves the flash vacuum thermolysis of thietan-3-one-1,1-dioxide **57** which extrudes sulfur dioxide and carbon monoxide at over 900 °C to afford 2-methylpropene (**Scheme 49**).[106] Similarly, the 1,3-dithietan-1,1-dioxide derivative **58** extrudes sulfur dioxide at 600 °C to afford the corresponding thiirane (**Scheme 50**),[107] which in theory could be desulfurized to the corresponding alkene, for example by using a tertiary phosphine.

Scheme 49



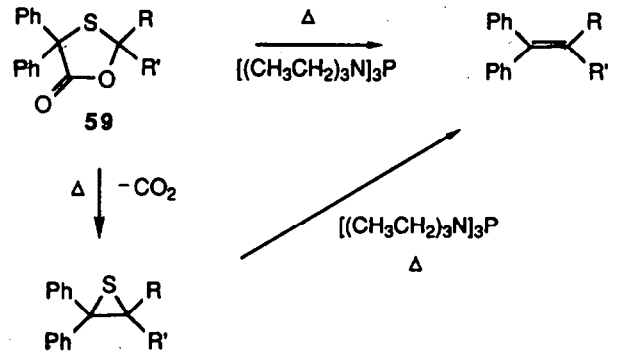
57

Scheme 50

58

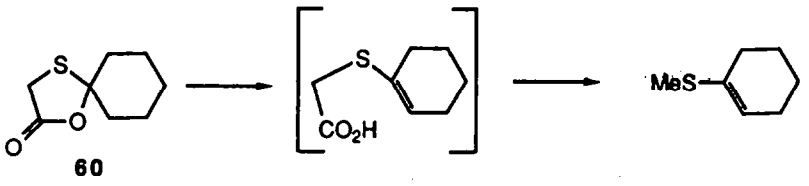
Barton and coworkers initially investigated oxathiolan-5-ones **59** as potential substrates for the twofold extrusion reaction.[108,109] Aryl substituted oxathiolanones could be easily prepared by the acid-catalyzed condensation of thiobenzilic acid with aldehydes and ketones. Pyrolysis of these compounds in the presence of a tertiary phosphine led to extrusion of carbon dioxide followed by desulfurization affording the corresponding alkenes (**Scheme 51**). In the absence of tertiary

Scheme 51



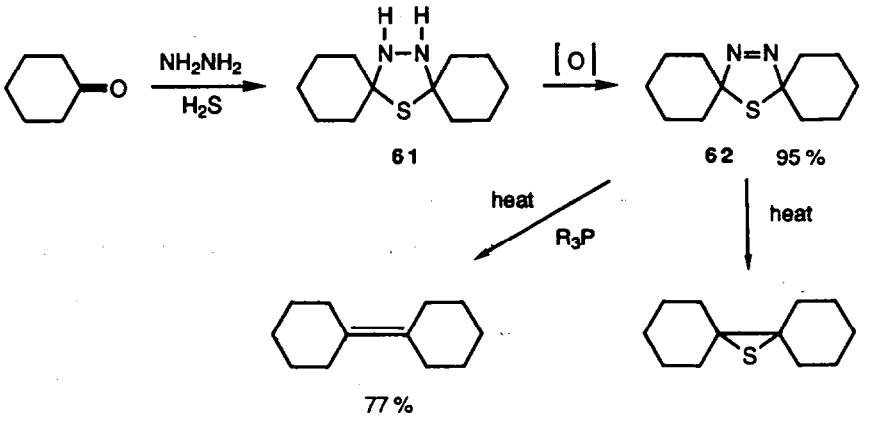
phosphine, thiiranes were obtained. The reaction could be used to prepare highly hindered alkenes, however aryl substitution was necessary for efficient extrusion of carbon dioxide. Pyrolysis of oxathiolanone **60** without aryl substitution led only to decarboxylative elimination (**Scheme 52**). Increased aryl substitution on the oxathiolanone led to extrusion of carbon dioxide at a lowered temperature.

Scheme 52



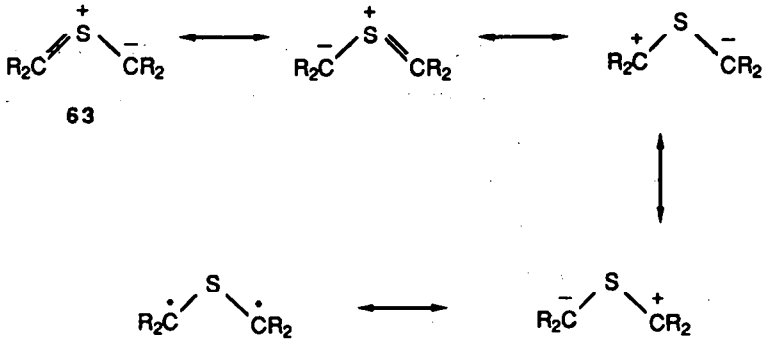
The 1,3,4-thiadiazoline system independently investigated by Barton[108,109] and Kellogg[110,111] proved to be particularly useful for the synthesis of a variety of sterically hindered alkenes. Treatment of cyclohexanone with hydrazine hydrate and hydrogen sulfide followed by oxidation of the intermediate thiadiazolidine **61** afforded the desired thiadiazoline **62**. Pyrolysis of this compound at 100 °C afforded the thiirane. If the pyrolysis was carried out in the presence of a tertiary phosphine, bis-cyclohexylidene was obtained in high yield (**Scheme 53**).[109,110]

Scheme 53



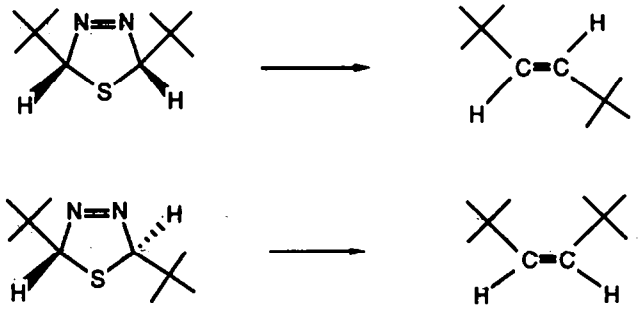
Similar results were obtained by Kellogg and coworkers who also investigated the mechanism of this reaction. They showed that the thermolysis of thiadiazolines involved a stereospecific conrotatory ring closure of a resonance stabilized thiocarbonyl ylide intermediate **63** formed upon extrusion of molecular nitrogen (**Scheme 54**).[111,112] The resulting thiiranes could be desulfurized to the corresponding olefins upon treatment with phenyllithium. Using this method both cis- and trans 1,2-di-*tert*-butylethylene could be readily prepared (**Scheme 55**).[111] A variety of other sterically hindered alkenes could be prepared using this method including compounds **64**-**67**.[113-117]

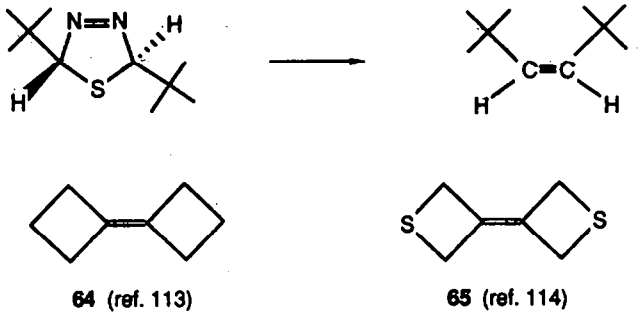
Scheme 54



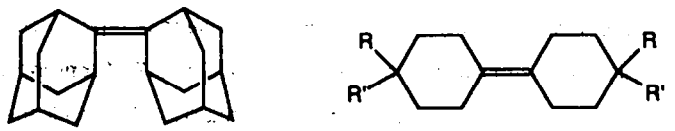
63

Scheme 55



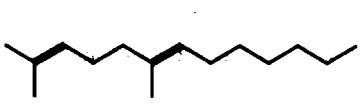


64 (ref. 113) **65** (ref. 114)

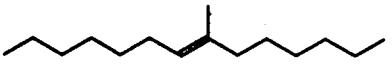


66 (ref. 117) **67** (ref. 116, 117)

It should be noted that thermolysis of relatively non-hindered thiadiazolines leads to low yields of thiiranes or olefins. For example, tri-substituted olefins **68** and **69** could be obtained from the corresponding thiadiazolines in yields of only 10 and 13% respectively.[118]



68

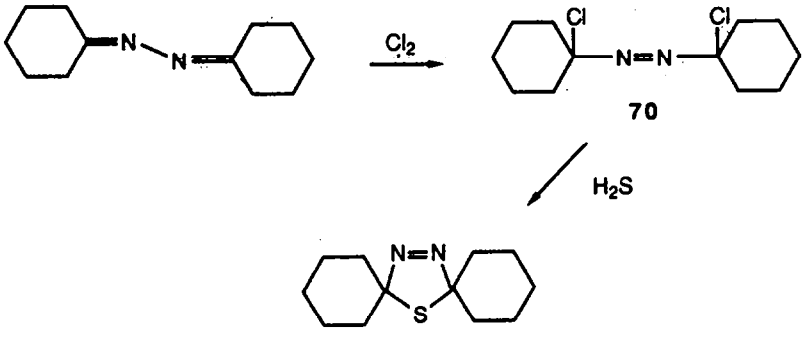


69

Relatively non-hindered 1,3,4-thiadiazolines such as the spiro-*bis*-cyclohexyl derivative can be readily prepared by the direct addition of hydrogen sulfide to an azine. Oxidation of the resulting thiadiazolidine using lead tetraacetate or diethyl azodicarboxylate affords the desired thiadiazoline. With increased steric hindrance the thiadiazolidine is unstable relative to hydrogen sulfide and azine. In cases such as the di-*tert*-butyl derivatives addition of hydrogen sulfide to the azine had to be carried out under pressure. The resulting extremely unstable thiadiazolidines also had to be quickly oxidized to the more stable thiadiazolines.[110]

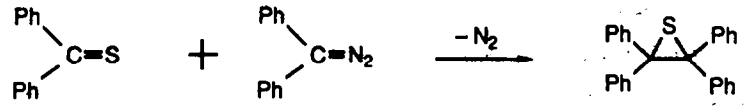
An alternative route for converting azines to the required thiadiazolines without the intermediacy of thiadiazolidines was subsequently devised by Kellogg and involved "oxidizing" the azine with chlorine to the dichloroazoalkane **70** prior to hydrogen sulfide addition. The desired thiadiazolines were obtained in 60-100% yield using this method (**Scheme 56**).[119]

Scheme 56



An alternative route to the thiadiazoline ring system had long been known.[120,121] Staudinger showed that addition of diphenyldiazomethane to thiobenzophenone rapidly occurred at low temperatures with nitrogen extrusion affording tetraphenylthiirane **71** (**Scheme 57**). He proposed a 1,2,3-thiadiazoline intermediate for this reaction.[120] The reaction of diazoalkanes with sulfur was also known to afford episulfides, presumably through thione and thiadiazoline intermediates.[122]

Scheme 57

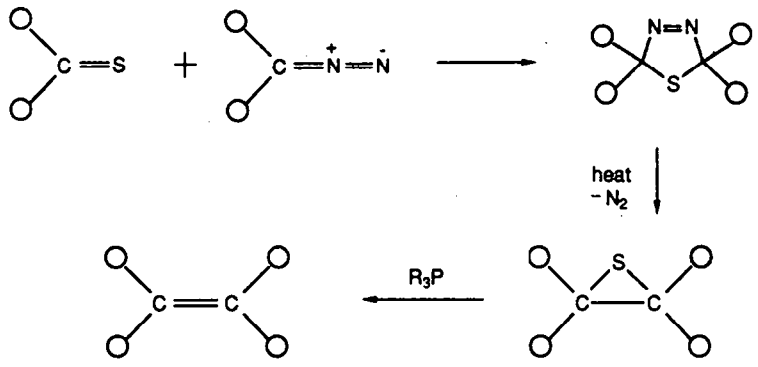


71

A number of other investigators indicated that the reactions of thiones with diazo compounds could lead to both 1,2,3- and 1,3,4-thiadiazoline intermediates.[123-126] Thermolysis of these compounds afforded episulfides which could be desulfurized to the corresponding olefins using triphenylphosphine. They however failed to adapt this reaction to the synthesis of extremely sterically hindered alkenes.

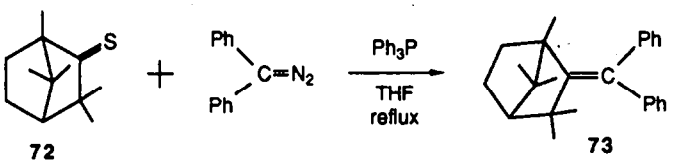
Barton and coworkers subsequently investigated the cycloadditions of sterically hindered thiones with sterically hindered diazoalkanes. This reaction provided a very facile method for the preparation of extremely sterically hindered thiadiazolines which could be easily converted to the corresponding alkenes (**Scheme 58**).[127] For example, treatment of thiocamphor **72** or thiofenchone **74** with diphenyldiazomethane followed by addition of triphenylphosphine in refluxing

Scheme 58

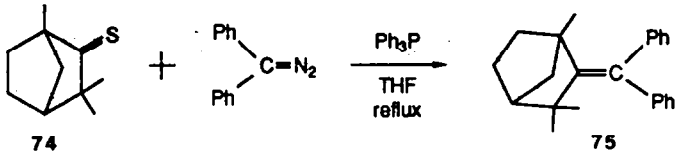


tetrahydrofuran afforded the corresponding diphenylmethylene derivatives **73** and **75** in excellent yield (**Scheme 59**).

Scheme 59



72 73

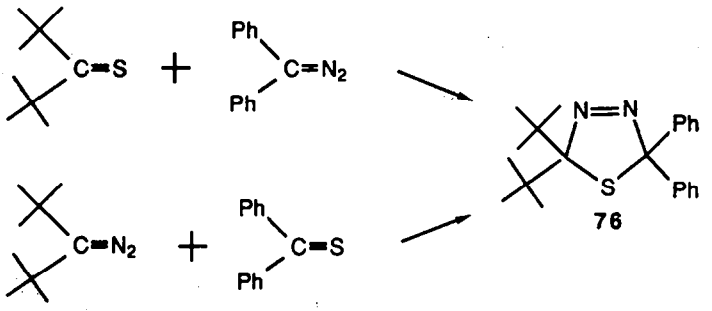


74 75

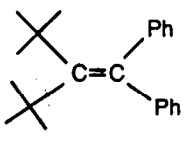
This method of thiadiazoline preparation can be especially useful because the stability of both the thiones and diazoalkanes increases with increasing steric hindrance.[128,129] The diazo component in the reaction could also be generated *in situ* from the corresponding tosyl hydrazone or upon thermolysis of the phosphoranylidene hydrazone derivative. In the latter reaction, the phosphoranylidene hydrazone reagent also generates the required tertiary phosphine necessary for episulfide desulfurization.[129]

As previously described, in the reactions of moderately hindered thiones with diazomethane, mixtures of 1,3,4-thiadiazolines and the corresponding 1,2,3-isomers were obtained.[124,130] The nature of the thiadiazoline intermediate involved in the twofold extrusion reaction was determined to be the less hindered 1,3,4-thiadiazoline. Treatment of di-*tert*-butyl thione with diphenyldiazomethane afforded the same thiadiazoline as that obtained upon treatment of thiobenzophenone with di-*tert*-butyldiazomethane (**Scheme 60**). This could only be possible if the intermediate was in fact the symmetrical 1,3,4-thiadiazoline **76**.[127]

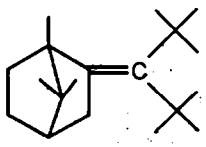
Scheme 60



The conversion of thiadiazoline to olefin proceeded without difficulty in most cases. Nitrogen and sulfur extrusion via thermolysis of **76** in the presence of triphenylphosphine afforded the extremely hindered 1,1-di-*tert*-butyl-2,2-diphenylethylene **77** in good yield. The even more hindered di-*tert*-butylmethylene camphane **78** could similarly be prepared from di-*tert*-butyldiazomethane and thiocamphor, however the more reactive tri-*n*-butylphosphine was necessary for desulfurization.[127]

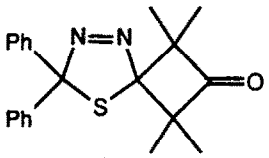


77

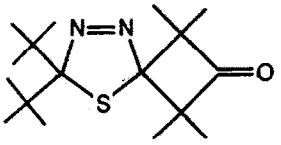


78

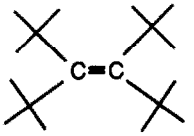
As expected phenyl substitution of the thiadiazoline ring greatly increases the ease with which nitrogen can be thermally extruded. The diphenyl substituted thiadiazoline **79** rapidly loses nitrogen in refluxing tetrahydrofuran to afford the desired episulfide. Hindered alkyl substituted thiadiazolines are significantly more thermally stable than the aryl derivatives. For example the di-*tert*-butyl derivative **80** is thermally stable up to its melting point,141 °C.[134]



79



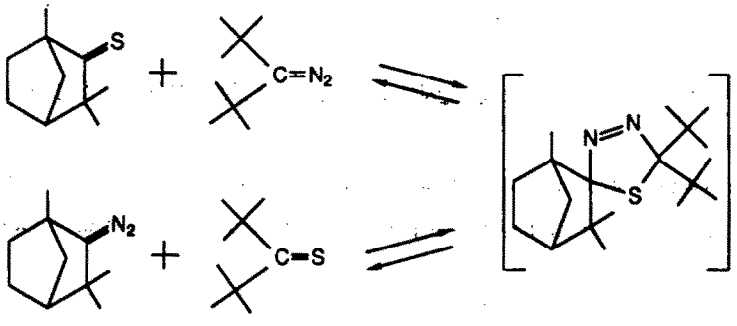
80



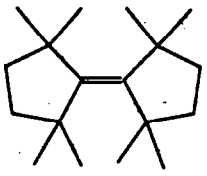
81

There are some significant steric limitations to the thiadiazoline method. The attempted synthesis of the extremely sterically hindered tetra-*tert*-butylethylene **81** failed. No reaction between di-*tert*-butyl thione and di-*tert*-butyldiazomethane was observed even under forcing conditions of temperature or pressure.[127] This suggests that either the desired thiadiazoline failed to form or that retrocyclization of the thiadiazoline occured in preference to nitrogen extrusion. Retrocyclization can be a major limitation in thiadiazoline thermolyses. In contrast to the previously mentioned successful preparation of di-*tert*-butylmethylene camphane **81**, when thiofenchone was treated with di-*tert*-butyldiazomethane and the mixture heated to reflux in tetrahydrofuran, the only identifiable product was di-*tert*-butyl thione **(Scheme 61)**. Apparently retrocyclization of the intermediate thiadiazoline is favored over nitrogen extrusion in this extremely hindered case.[127]

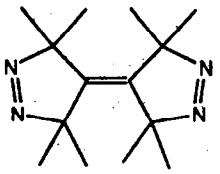
Scheme 61



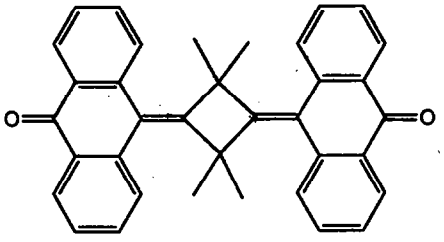
Despite these limitations the reactions of sterically hindered diazoalkanes with thiones have proved to be very useful in the synthesis of a variety of extremely sterically hindered olefins, among them, compounds **82 - 87**.



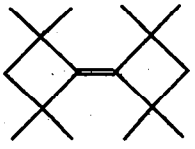
82 (ref. 132)



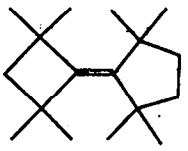
83 (ref. 133)



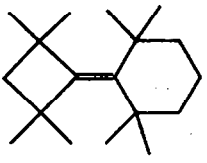
84 (ref. 134)



85 (ref. 135)



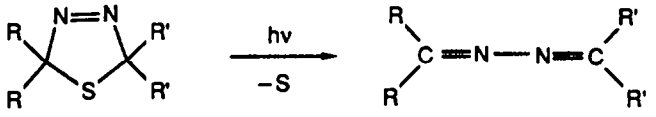
86 (ref. 135)



87 (ref. 135)

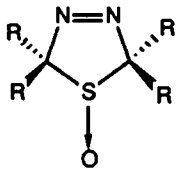
Photolysis of the sterically hindered thiadiazolines led to extrusion of sulfur with formation of the corresponding azine (**Scheme 62**).[109,110] While this result would seem at first surprising, it appears that the sulfur extrusion occurs because no symmetry allowed pathway for nitrogen extrusion exists in the case of the thiadiazoline ring system.[110]

Scheme 62

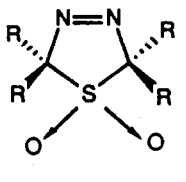


4.2 Reactions of Thiadiazoline S-oxides and Thiadiazoline S,S-dioxides

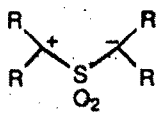
The 1,3,4-thiadiazoline system could be oxidized to the corresponding S-oxide or S,S-dioxide derivatives **88** and **89**, however pyrolysis of these materials led to only poor yields of the olefin.[109]



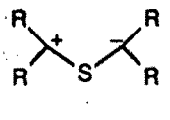
88



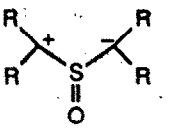
89



91



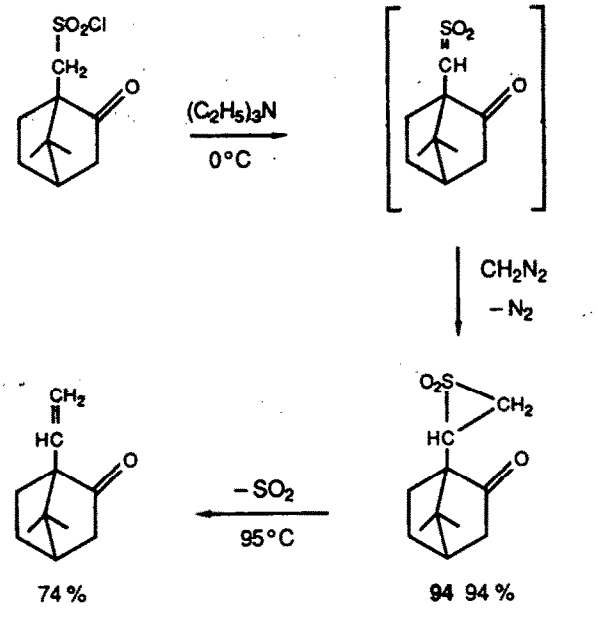
92



93

The reactions of *in situ* generated sulfenes have been utilized much more successfully in the synthesis of unhindered alkenes. Treatment of an alkylsulfonyl chloride with triethylamine in the presence of a diazoalkane affords the corresponding episulfone **94**. Thermal extrusion of sulfur dioxide then affords the desired alkene.[147] Both reactions proceed in high yields (**Scheme 67**). In no case was formation of an intermediate thiadiazoline S,S-dioxide observed. It is likely that a dipolar intermediate is involved in this reaction. Similar dipolar intermediates have been proposed both in the successful Staudinger-Pfenninger reactions [142-144] as well as in the formation of an episulfoxide from the reaction of sulfine with diazomethane (see **Scheme 64**).

Scheme 67



74 %

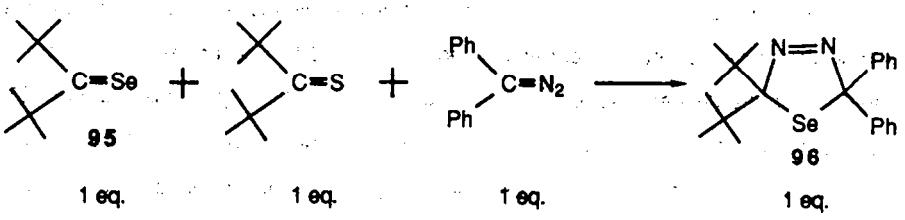
94 94 %

4.3 Sterically Hindered Alkenes via 1,3,4-Selenadiazolines

To extend the twofold extrusion procedure of thiadiazolines to the preparation of even more sterically hindered olefins, Barton and co-workers attempted to prepare the corresponding selenium analogues of thiadiazolines. They developed the first method for the preparation of selones, selenium analogues of ketones, and investigated the reactions of these compounds with hindered diazoalkanes.[148,149]

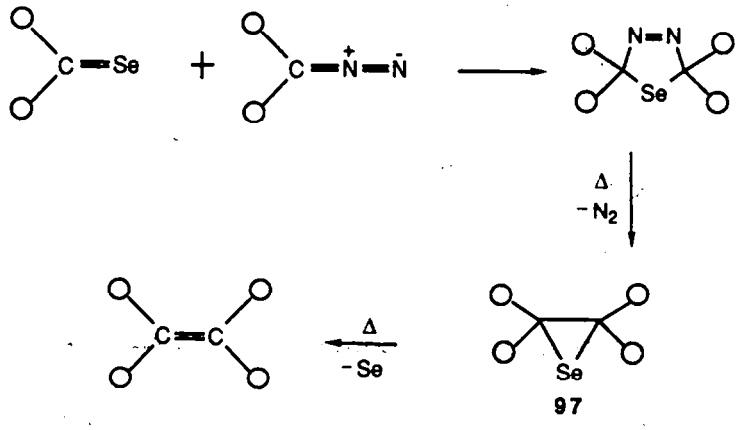
The selones reacted cleanly with diazoalkanes to afford 1,3,4-selenadiazolines. They proved to be significantly more reactive than the corresponding thiones in these cycloadditions. For example, treatment of an equimolar mixture of di-*tert*-butyl selone **95** and di-*tert*-butyl thione with one equivalent of diphenyldiazomethane afforded only the 1,3,4-selenadiazoline **96** (**Scheme 68**). None of the corresponding thiadiazoline was observed.[149]

Scheme 68



Another advantage of the selenadiazoline procedure was that it allowed for the direct thermal extrusion of both nitrogen and selenium. Pyrolysis of the selenadiazoline in moderately hindered cases led to rapid nitrogen evolution, followed by direct extrusion of selenium from the presumed thermally unstable episelenide intermediate **97**, affording the desired hindered alkene (**Scheme 69**). This eliminated the need for a phosphine-mediated removal of the thiirane sulfur as was necessary in the case of the thiadiazoline reactions.[149]

Scheme 69



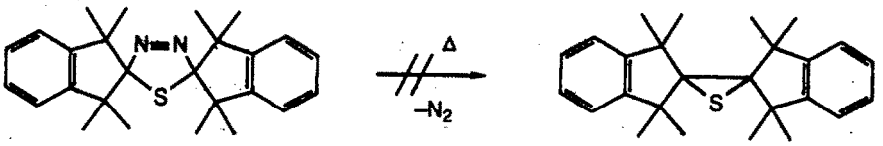
Use of the selenadiazoline route allowed for the ready preparation of a variety of sterically hindered alkenes, in our experience, more conveniently than the thiadiazoline procedure. The overall procedure was significantly improved with the advent of an improved method for the preparation of the starting selones.[150]

In a number of applications the selenadiazoline procedure proved to be successful in cases where the thiadiazoline procedure failed. Pyrolysis of the symmetrical bis-tetramethylindane derived selenadiazoline **98** directly affords the desired sterically hindered alkene **99** in good yield (Scheme 70).[129,151] Krebs reported that upon pyrolysis, the corresponding thiadiazoline **100** does not afford the desired thiirane **101**, but instead yields mainly retrocyclization products plus a thioether of structure **102** or **103** (Scheme 71).[135] No corresponding selenoether was detected

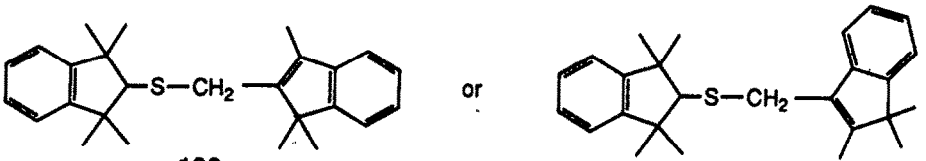
Scheme 70

98 **99** 71 %

Scheme 71

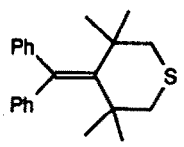


100 **101**

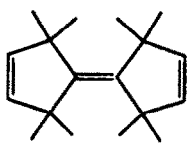


102 **103**

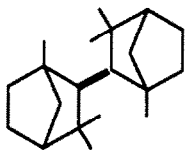
in the selenadiazoline pyrolyses. Aside from the previously mentioned compounds, extremely sterically hindered alkenes **104-109** could be readily prepared using selenadiazoline intermediates.[129,149,152]



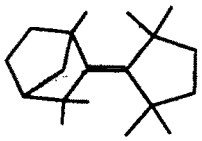
104



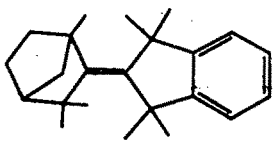
105



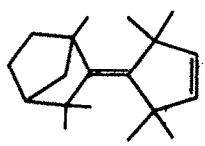
106



107



108

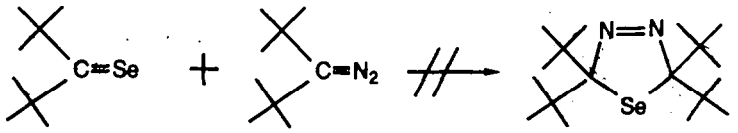


109

4.4 Steric Limitations of Twofold Extrusion Reactions

The steric limitations of both the selenadiazoline and thiadiazoline based twofold extrusion reactions have been reported.[129,135] Similar to the previously mentioned case of di-*tert*-butyl thione, di-*tert*-butyl selone does not react with di-*tert*-butyldiazomethane to afford either tetra-*tert*-butylethylene **81** or the corresponding selenadiazoline **110** (**Scheme 72**).

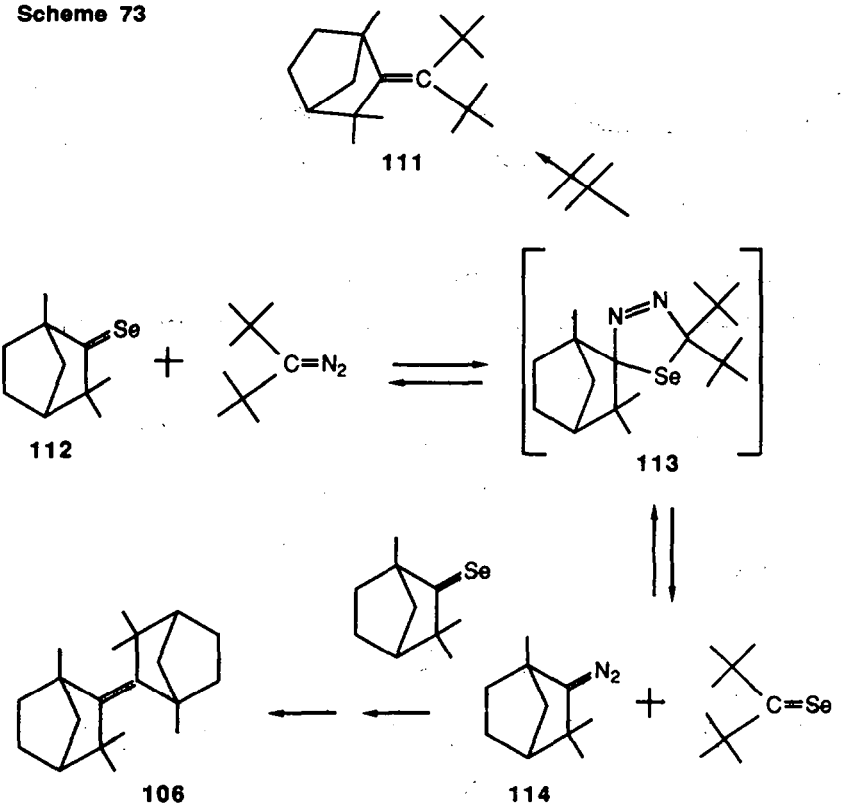
Scheme 72



110

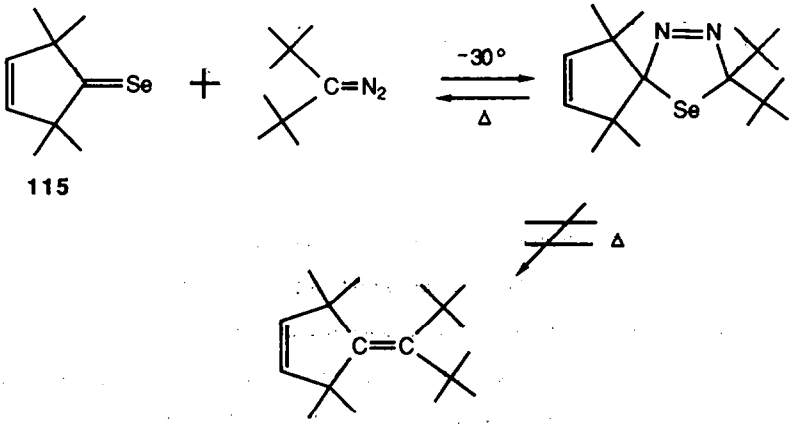
Attempts to prepare di-*tert*-butylmethylene fenchane **111** were also unsuccessful. Treatment of selenofenchone **112** with di-*tert*-butyldiazomethane led only to formation of the less hindered symmetrical olefin, bifenchylidene **106**. Presumably in this case the desired selenadiazoline **113** formed, however retrocyclization rather than nitrogen extrusion predominated. The resulting diazofenchane **114** reacted with selenofenchone to afford the observed alkene **106** (**Scheme 73**).[149]

Scheme 73



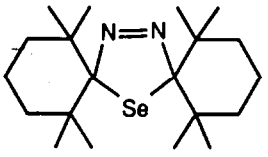
Addition of di-*tert*-butyldiazomethane to the neat sterically hindered selones such as **115** at -30 °C afforded crystalline di-*tert*-butylmethyl substituted selenadiazolines in good yield. These compounds were stable in crystalline form to their melting points, but retrocyclized in a matter of hours at room temperature upon dissolving in common solvents (**Scheme 74**). Pyrolysis of these materials led only to products derived from retrocyclization.[153]

Scheme 74



115

Treatment of the deep blue 2,2,6,6-tetramethylcyclohexane selone with the corresponding orange diazo compound at -30 °C led to complete decolorization of the mixture and formation of a colorless crystalline material, presumably the desired selenadiazoline **116**. Upon warming this material to room temperature or upon attempted dissolution of this material in deuterochloroform at -30 °C, only the starting selone and diazo compound could be detected. These observations indicate the steric limits of selenadiazoline thermal stability.[153]

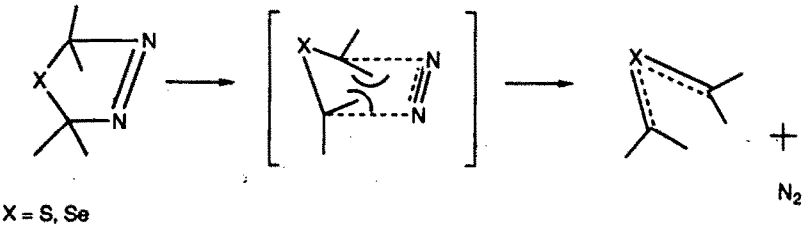


116

How can a thia- or selenadiazoline decide whether to extrude nitrogen or retrocyclize? At first glance steric interactions are kept to a minimum until a thio- or selenocarbonyl ylide forms. Perhaps the best explanation comes from the work of Kellogg on thiadiazoline decomposition and the geometry of thiocarbonyl ylides.[119] In the transition state leading to the ylide intermediate, a significant geometric change occurs simultaneously with nitrogen extrusion. The required conrotatory twisting may lead to severe steric interactions, raising the energy necessary for nitrogen evolution

(Scheme 75). If the steric interactions are great enough, this pathway is inhibited and retrocyclization predominates. The increased length of the carbon-selenium bond relative to a carbon-sulfur bond may decrease these steric interactions allowing for greater success in many selenadiazoline pyrolyses.

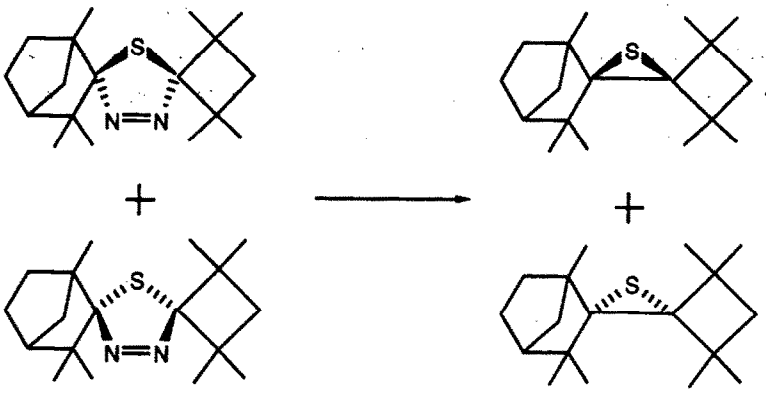
Scheme 75



X = S, Se

Even in cases where retrocyclizations were not complete, extreme steric hindrance could change the course of the reaction. Kellogg had showed that the initial nitrogen extrusion from the thiadiazolines was stereospecific. Since thiirane desulfurizations are also stereospecific, the overall twofold extrusion reaction should be stereospecific.[112] In contrast to these observations, Krebs noted that the pyrolyses of some sterically hindered thiadiazolines led to mixtures of products with loss of stereochemistry (**Scheme 76**).[135] This loss of stereochemistry may be explained by a twisting of the thiocarbonyl ylid intermediate due to extreme steric hindrance.[112,119]

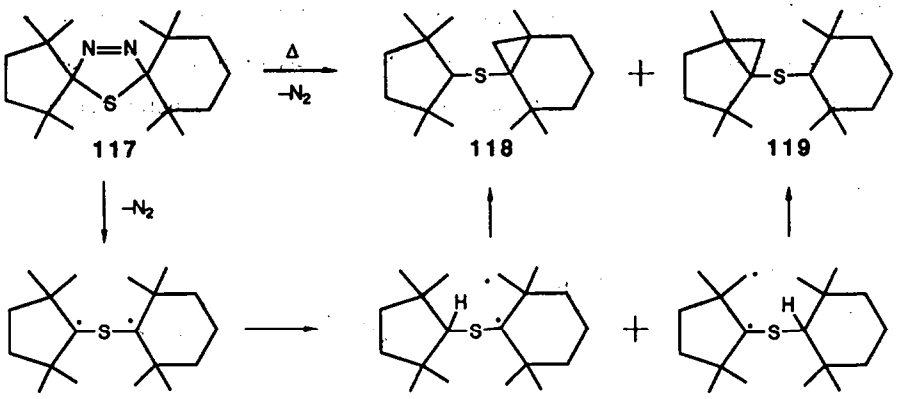
Scheme 76



various ratios ~ same ratio

In the extreme case such a twisting would lead to a singlet diradical intermediate. Consistent with this view is another observation of Krebs.[135] Pyrolysis of the extremely sterically hindered thiadiazoline **117** leads mainly to retrocyclization, but thioether by-products **118** and **119** are also obtained. These materials could arise from intramolecular radical abstraction - recombination reactions (**Scheme 77**). Similar diradical species may account for the products of the previously mentioned pyrolysis of thiadiazoline **101** (**Scheme 71**). While there are no other reports of the

Scheme 77

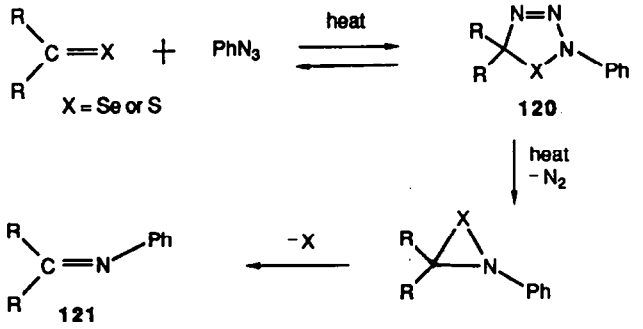


isolation and characterization of such radical-derived products, it is likely that such products do form in other sterically hindered thiadiazoline and selenadiazoline pyrolyses. In most cases such pyrolyses lead to complex mixtures of products even when the desired alkenes can be obtained.

4.5 Other Synthetic Applications of Twofold Extrusion Reactions

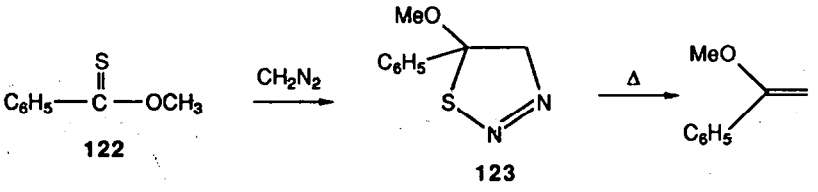
Sulfur and selenium-based twofold extrusion reactions have also proved to be extremely useful in the synthesis of other strained organic molecules. Schönberg reported that reaction of a thione with an aromatic azide afforded imines in undetermined yield.[154] We subsequently compared the reactions of thiones and selones with azides, and found that this reaction is a convenient method for the preparation of a variety of extremely sterically hindered imines.[155] The reaction presumably involves the formation of 2,5-dihydrothiatriazole **120** (and its selenium analogue), which upon heating can consecutively extrude nitrogen and sulfur (or selenium) affording the corresponding N-phenylimines **121**. As with the previously described reactions with diazoalkanes, selones proved to be more reactive than thiones. The selone reactions also allowed for easier isolation of pure hindered imines in comparison with the thione reactions (**Scheme 78**).

Scheme 78



The reactions of a number of thione esters and dithioesters with diazoalkanes have also been studied. The aromatic thioester **122** upon reaction with diazomethane affords an intermediate thiadiazoline which was thoroughly characterized as the 1,2,3-derivative **123**. This compound extrudes both nitrogen and sulfur upon heating yielding the enol ether **(Scheme 79)**.[156]

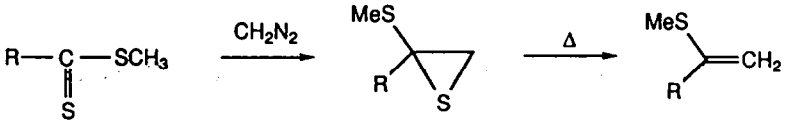
Scheme 79



122 **123**

Treatment of dithioester **124** with diazomethane afforded the episulfide **125** directly which could be thermally desulfurized to the enethiol ether **126 (Scheme 80)**.

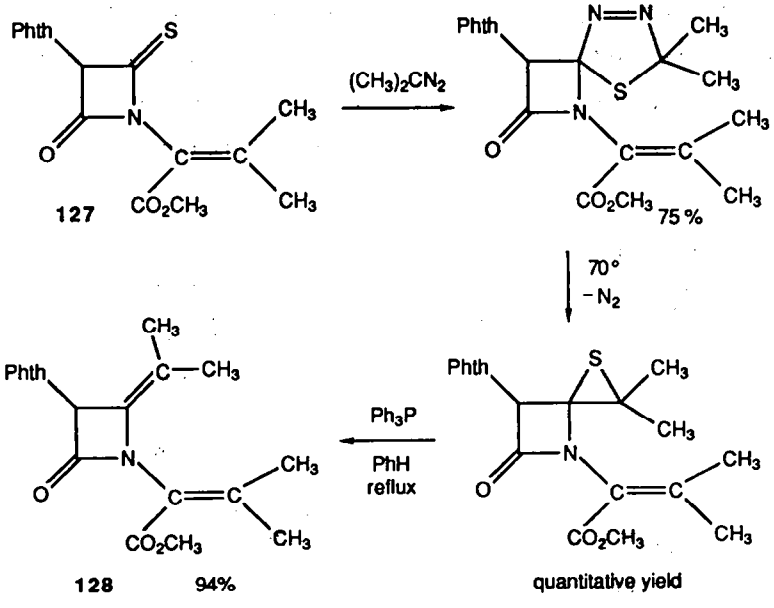
Scheme 80



124 **125** **126**

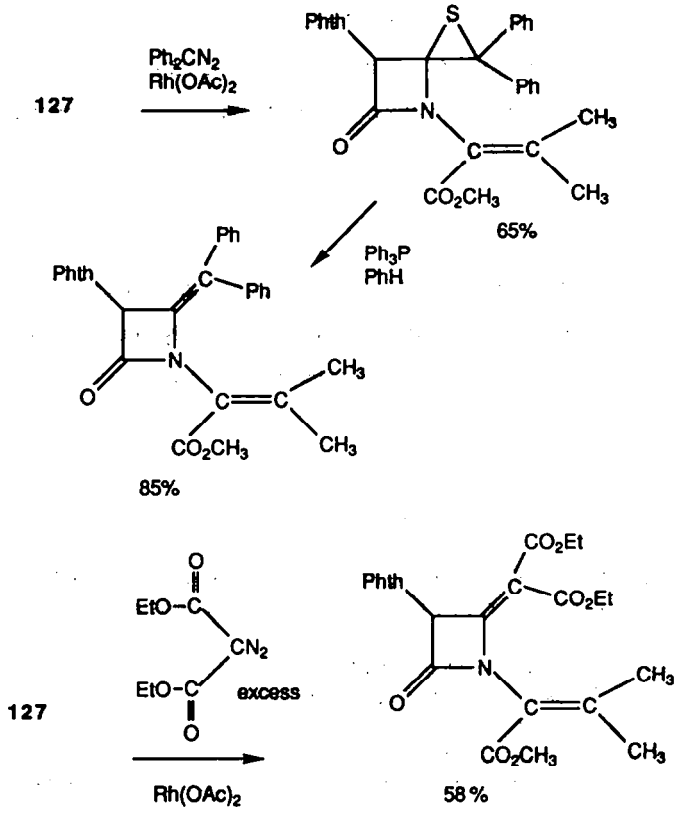
The twofold extrusion reaction also provided a route from the thioxo-azetidinone **127** to functionalized β-lactams such as **128 (Scheme 81)**. Related compounds have also been prepared using transition metal catalysis in this reaction **(Scheme 82)**.[157]

Scheme 81



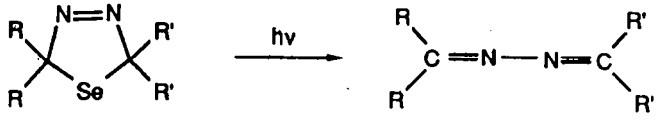
127 **128**

Scheme 82



Finally, photolytic selenium extrusion from symmetrical or unsymmetrical selenadiazolines provides a convenient route to the corresponding azines (**Scheme 83**).[155]

Scheme 83



5. Overview

From the previous descriptions, it should be clear that extrusion reactions have proved to be remarkably versatile methods for the synthesis of many strained organic molecules. Why then are extrusion reactions not more commonly used in the synthesis of less strained molecules? Fears about preparative scale pyrolytic and photolytic reactions necessary for some extrusions are not unfounded. There has been very little work investigating the effects of complex functionality on the course of extrusion reactions. It should be noted that even in the case of the thoroughly studied twofold extrusion reaction, attempts to prepare unhindered molecules such as **68** or **69** worked

poorly, if at all. One possible future course of investigation in this area involves determining the effects of organometallic catalysts on the course of extrusion reactions. Despite the recent advances in such catalysis in other areas, applications of organometallic catalysis to extrusion reactions have been largely untapped (although note **Scheme 82**). It is possible that such investigations may lead to a much wider application of extrusion reactions in complex organic synthesis.

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