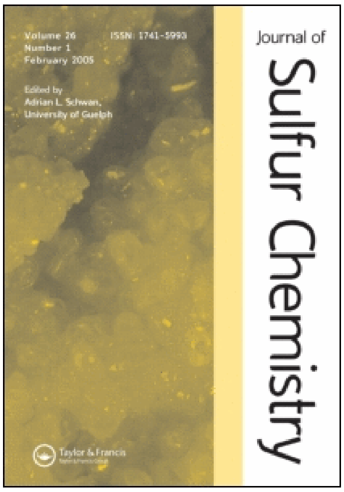

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1,2-Dithiole-3-Thiones and 1,2-Dithiol-3-Ones

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1,2-DITHIOLE-3-THIONES AND 1,2-DITHIOL-3-ONES

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Available data concerning synthesis, reactions and physical properties of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones published in the period 1980–1993 has been summarized in the present review. Selected topics concerning medicinal and industrial uses have been included.

Key words: 1,2-Dithiole-3-thiones, 1,2-dithiol-3-ones, synthesis, reactions, practical applications.

CONTENTS

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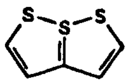
1. INTRODUCTION

1,2-Dithiole-3-thiones and 1,2-dithiol-3-ones are useful synthons for the synthesis of other 1,2-dithiole compounds such as 1,6,6aλ^4-trithiapentalenes **1** as well as for other cyclic sulfur compounds *e.g.* **2**, **3** and **4** and compounds where one or two of the ring sulfur atoms are lost, such as **5** and **6**.



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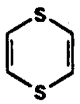

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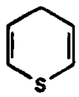

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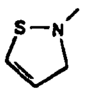

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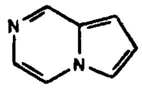


6

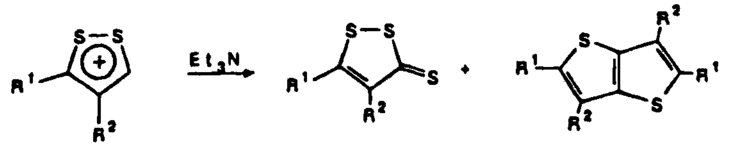
This review will deal with the literature published in the period 1980 to 1993 and covered in Chemical Abstracts Vols. 94–118. Earlier literature can be found in a series of older reviews.[1-5] As very few papers are dealing only with 1,2-dithiol-3-ones these will not be treated separately. Since 1980 there has been a growing pharmacological interest in 1,2-dithiole-3-thiones after the observation that 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione, Oltipraz, is active against bilharziosis, a tropical worm disease. Examples from the medicinal literature published on these compounds are therefore included. There has also been a growing industrial interest in these compounds, in particular 4,5-dichloro-1,2-dithiol-3-one as a microbiocide for slime control in paper production. Examples from the patent literature covering the industrial use of these compounds are for this reason also mentioned.

The treatment of the medicinal and industrial use is, however, not exhaustive.

2. SYNTHESIS

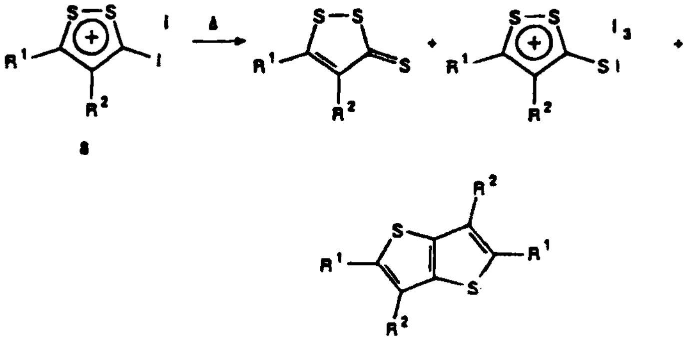
2.1. *From Compounds with the 1,2-Dithiole System Present*

The trivial transformation of 1,2-dithiol-3-ones into 1,2-dithiole-3-thiones by means of various sulfurating agents will not be treated in this section. A general review concerning sulfuration reagents and their use was recently published.[6] It is a well established synthesis of 1,3-TTF to treat 1,3-dithiolylium salts with weak bases such as Et_3N.[7] Attempts to carry out similar reactions in the 1,2-dithiole series, however, have not resulted in the formation of 1,2-TTF but have led to the formation of 1,2-dithiole-3-thiones and thieno[3,2-*b*]thiophenes.[8] Scheme 1:



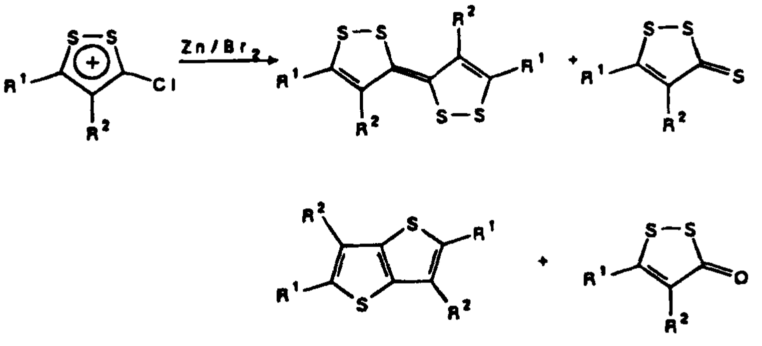
SCHEME 1

Similar results were obtained upon pyrolysis of 3-iodo-1,2-dithiolylium iodides.[8] Scheme 2:



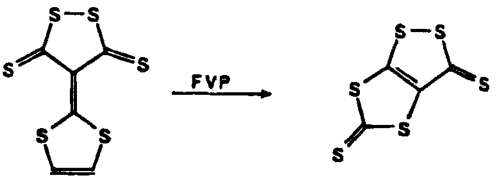
SCHEME 2

Reduction of 3-chloro-1,2-dithiolylium salts with Zn gave rise to 1,2-TTF in low yields in some cases but the formation of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones was also observed.[9] Scheme 3:



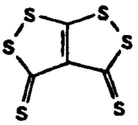
SCHEME 3

Flash vacuum pyrolysis of **10** gives rise to [1,3]dithiolo[4,5-*c*]1,2-dithiole-3,5-dithione **11**.[10]



10 **11**

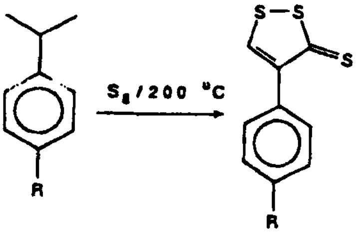
The structure was determined by X-ray determination of an iodine complex. The compound has earlier erroneously been ascribed the structure **12**.[11]



12

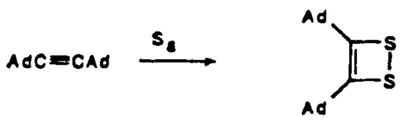
2.2. *From Compounds not Containing the 1,2-Dithiole System*

2.2.1. *From hydrocarbons.* The reaction of isopropyl- or isopropenylbenzenes with elemental sulfur has been a well established synthesis for 4-substituted 1,2-dithiole-3-thiones, the hydrocarbon itself or mesitylene is used as a solvent. The yield, however, is not always satisfactory and the method may fail if functional groups are present in the benzene ring. It has been shown that if the hydrocarbon is added to molten sulfur at 200–200 °C the yields are improved and the method can be used for hydrocarbons containing functional groups.[12] Scheme 4:



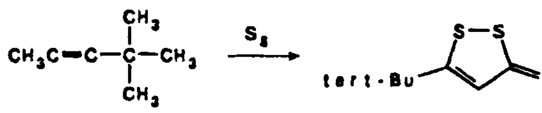
SCHEME 4

The reaction of sterically hindered alkynes such as 1,2-diadamantyl ethyne gives rise to 1,2-dithietes in fairly good yields.



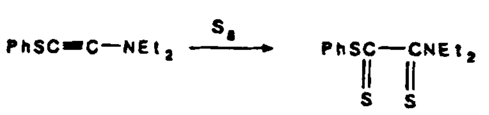
13

However, the reaction of 1-methyl-2-*tert*-butylethyne gave no dithiete but 5-*tert*-butyl-1,2-dithiole-3-thione **14** in 20% yield.[13]



14

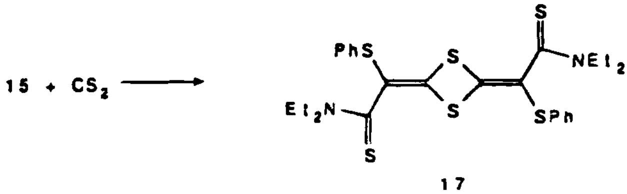
In the case of the alkyne **15** the product formed was the trithio-oxalic acid derivative **16**.[13]



15

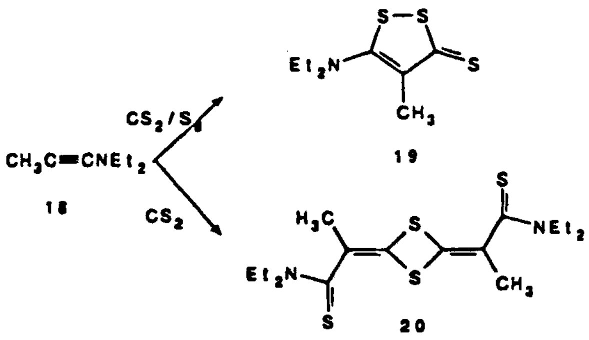
16

If **15** was treated with CS_2 at 800 MPa, however, a dithiete **17** was isolated as the reaction product.[14]

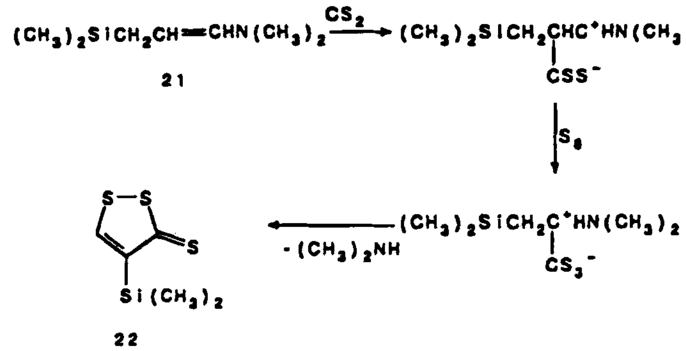


17

It has further been shown that the reaction of 1-methyl-2-(*N*,*N*-diethyl-amino)ethyne **18** with sulfur and CS_2 gave the 1,2-dithiole-3-thione **19**.[15] In the absence of sulfur this alkyne too gave a dithiete derivative **20** for which the x-ray structure is given.[15]

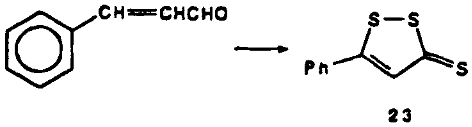


During a general study of the reactivity of silylene amines **21**,[16] it was found that the addition of CS_2 to a silylene amine with subsequent reaction with elemental sulfur resulted in the formation of 4-(trimethylsilyl)-1,2-dithiole-3-thione **22** in 40% yield. Scheme 5:

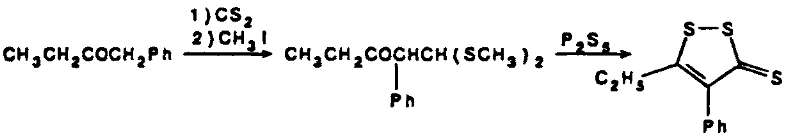


SCHEME 5

2.2.2. *From ketones and aldehydes.* The sulfur-carbon electrode used as a cathode is an excellent source of nucleophilic sulfur,[17] which is a good sulfurating agent. If cinnamaldehyde is electrolysed in DMF with a carbon-sulfur electrode, 5-phenyl-1,2-dithiole-3-thione **23** is obtained in 36% yield.[18]

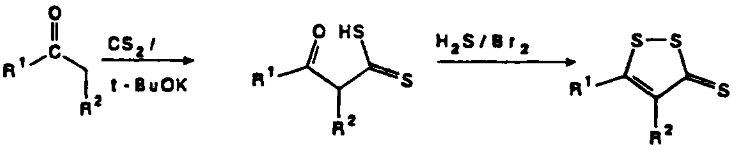


The reaction with base and CS_2 of ketones having a methyl or methylene group next to the carbonyl group, methylation of the anion formed and subsequent reaction with P_2S_5 or another sulfurating agent is one of the most general methods for preparing 1,2-dithiole-3-thiones.[19] 4-Phenyl-5-methyl-1,-2-dithiole-3-thione **24** has been prepared in this way.[20]



24

The reaction can also be carried out with polysulfanes in liquid hydrogen sulfide for the thionation of the 3-oxo-dithioic acids primarily formed.[21] Scheme 6:

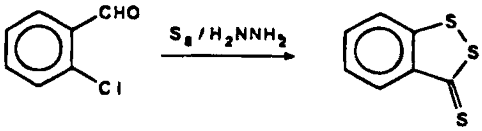


SCHEME 6

The hydrogen sulfide is oxidized by the bromine to give a complex mixture of higher sulfanes, which probably disproportionates to give disulfane.

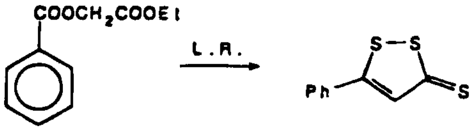
High yields are obtained in this way also with ketones with functional groups such as ester groups. The isolation is easy as few by-products are formed. The disadvantage of the method is the use of large amounts of the highly toxic liquid hydrogen sulfide. The method is therefore most suitable for preparations on the 1–100 mmole scale.

The reaction of aromatic aldehydes with a mixture of hydrazine and elemental sulfur normally leads to the formation of 1,3,4-thiadiazoles; however, if 2-chlorobenzaldehyde is used for the reaction benzo-1,2-dithiole-3-thione 24 is formed.[22]



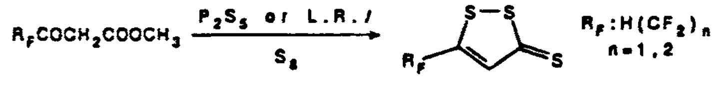
24

2.2.3. *From β-keto esters.* β-Keto esters react with P_2S_5. Lawesson's reagent (L.R.) or other sulfurating agents to give directly 5-substituted 1,2-dithiole-3-thiones. A series of phenyl substituted 1,2-dithiole-3-thiones **25** have been prepared by this method.[23]



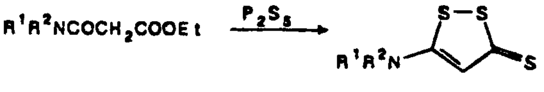
25

A series of 1,2-dithiole-3-thiones with perfluorinated aliphatic side chains in the 5-position **26** has also been prepared in this way.[24,25]



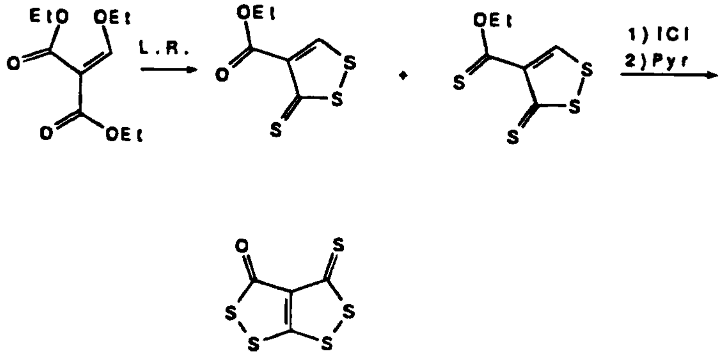
26

Such perfluorinated 1,2-dithiole-3-thiones can also be prepared with basic sulfurating agents such as P_2S_5/K_2CO_3.[26] A series of 5-amino substituted 1,2-dithiole-3-thiones **27** has been obtained with P_2S_5 as sulfurating agent.[27]



27

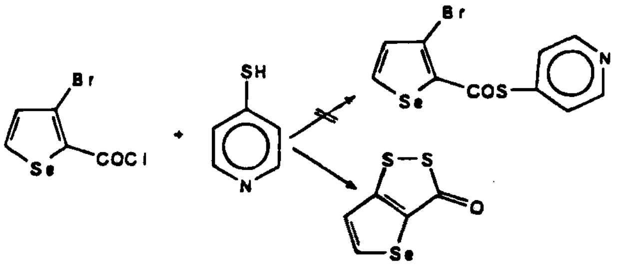
3-Oxo-4-thioxo-1,5,6-tetrathiapentalene **28** can be prepared by the reaction sequence shown in Scheme 7.[28]



28

SCHEME 7

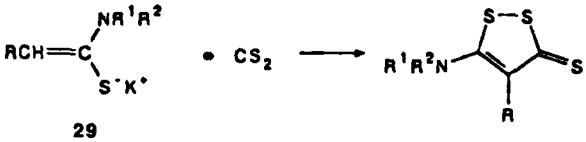
2.2.4. *From acids and acid derivatives.* The reaction of 3-bromoselenophene-2-carboxylic acid chloride with 4-pyridinethiol did not result in the formation of the expected thiocarboxylic acid *S*-ester but the condensed 1,2-dithiol-3-one.[29] Scheme 8:



SCHEME 8

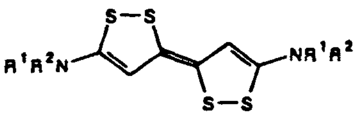
Aliphatic dithioacids are oxidized by $Na_2S_2O^8$ in the presence of $CuCl_2$ to give 1,2-dithiole-3-thiones and hexathiaadamantanes.[30]

The reaction of potassium salts of *N,N*-disubstituted 1-amino-1-propenethiolates **29** with CS_2 resulted in the formation of 1,2-dithiole-3-thiones.[30,35]



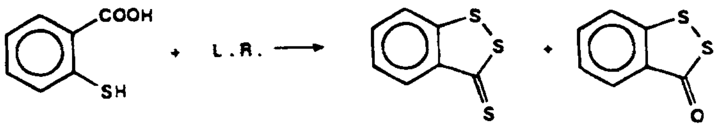
29

If R = H the formation of 1,2-tetrathiafulvalenes **30** is also observed.[31]



30

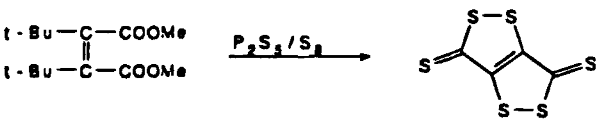
2-Mercaptobenzoic acid reacts with Lawesson's reagent to give a mixture of 52% benzo-1,2-dithiole-3-thione and 15% benzo-1,2-dithiol-3-one.[32] Scheme 9:



SCHEME 9

If 2-mercaptobenzoic acid is condensed with thioacetic acid benzo-1,2-dithiol-3-one is formed.[33,34]

Substituted butenedioates give rise to [1,2]dithiolo[4,3-*c*]1,2-dithiole-3,6-dithione **31** when treated with various sulfurating agents in the presence of elemental sulfur.[36]

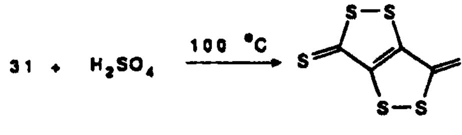


31

Compound **31** is also formed from perchloro-1,3-butadiene and sodium sulfides.[37,38,39,40]

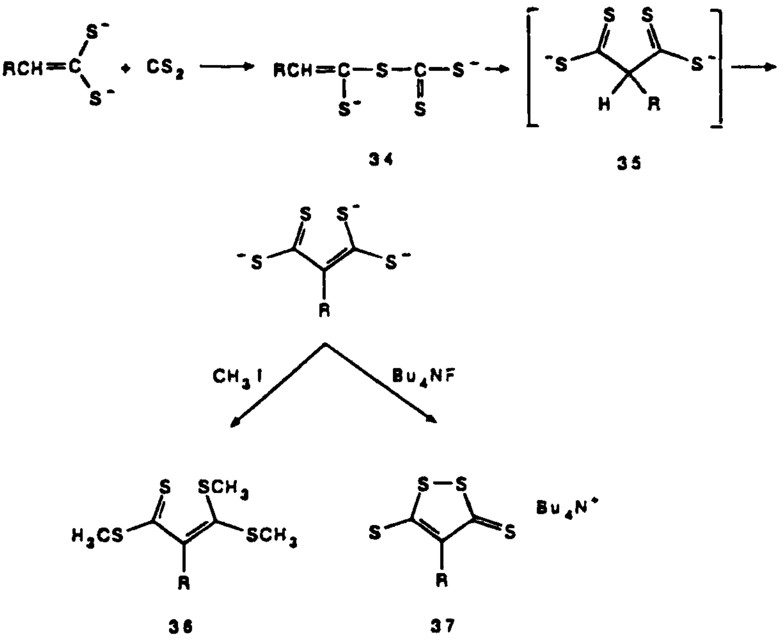
$$Cl_2C{=}CCl{-}CCl{=}CCl_2 + Na_2S_2 \longrightarrow 31$$

The monothione **32** could be prepared by dissolution in concentrated sulfuric acid at 100 °C.[38]



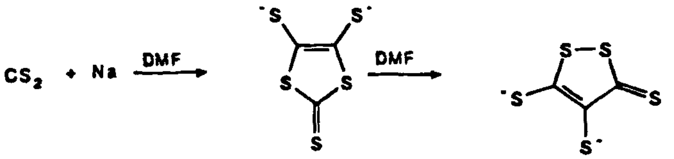
32

The dianions of dithiocarboxylic acids **33** react with CS_2 at −78 °C to give the adduct **34**,[41] Scheme 10. This rearranges at room temperature to give the thermodynamically more stable C-adduct **35** which is a tetrathiomalonic acid dianion, which can be isolated after methylation as the 3,3-bis(methylthio)dithioacrylic acid methyl ester **36**. If, however, **35** is oxidized by iodine with subsequent treatment with tetrabutylammonium fluoride the tetrabutylammonium salt **37** can be isolated.



SCHEME 10

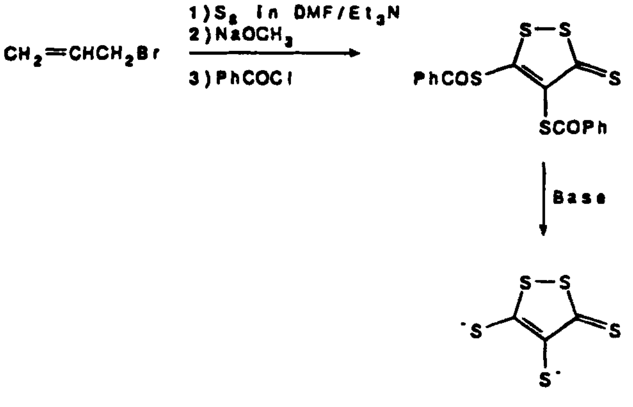
2.2.5. *Miscellaneous.* 1,2-Dithiole-3-thiones have been prepared by rearrangement of 1,3-dithiole derivatives.[42,43] Scheme 11:



SCHEME 11

The mechanism of this thermal transformation, the "Steimecke rearrangement," has been discussed.[44]

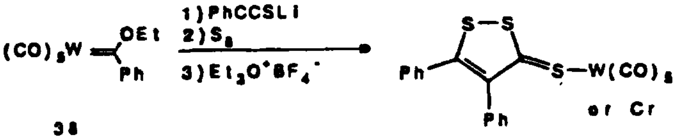
Derivatives of the dimercapto compound have been synthesized from allyl bromide.[45] Scheme 12:



SCHEME 12

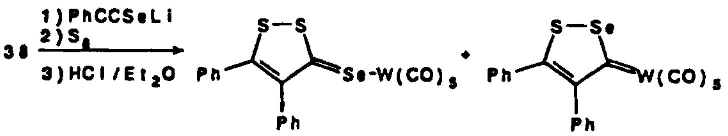
The benzoyl derivative isolated could be saponified to give the free dithiol.

1,2-Dithiole-3-thiones have been prepared in the form of their metal complexes with chromium and tungsten.[46,47] The starting material is the Fischer carbene complex {M(CO)$_5$ [C(OEt)Ph]} **38**. No attempts were made to prepare the free thione from the complexes.



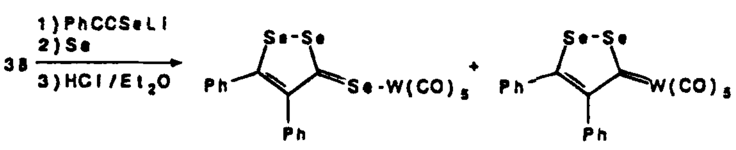
38

By the use of PhCCSeLi instead of the sulfur compound the two monoselenium compounds **39** and **40** could be isolated.[47]



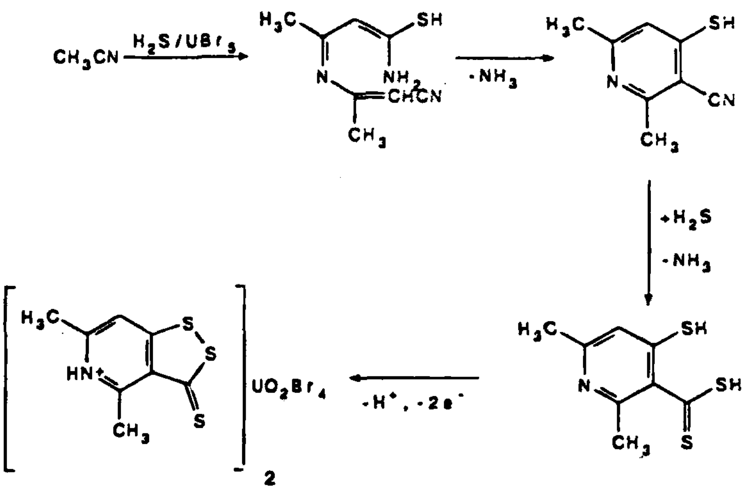
39 40

If PhCCSeLi and Se is used the tri- **41** and diselenium **42** compounds could be isolated.[47]



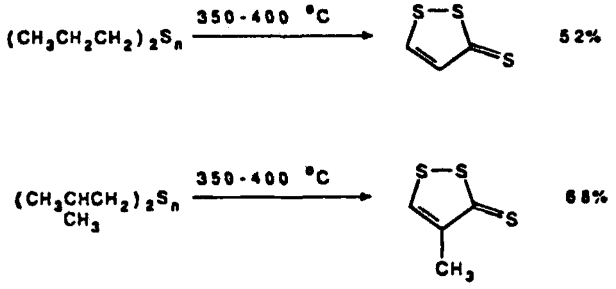
41 42

A condensed 1,2-dithiole-3-thione is formed as a complex salt if uranium pentabromide is treated with hydrogen sulfide in acetonitrile.[48] Scheme 13:

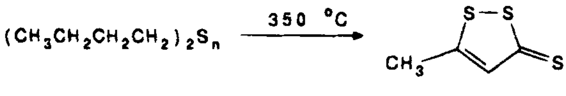


SCHEME 13

1,2-Dithiole-3-thiones are formed by high temperature pyrolysis of alkyl polysulfides. When propyl and 2-methylpropyl polysulfide were pyrolysed at 350–400 °C the parent 1,2-dithiole-3-thione and 4-methyl-1,2-dithiole-3-thione were formed, respectively,[49] Scheme 14, whereas the pyrolysis of dibutyl tetrasulfide afforded 5-methyl-1,2-dithiole-3-thione **43** in low yield, thiophene being the main product.[50]

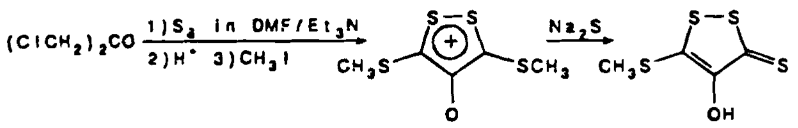


SCHEME 14



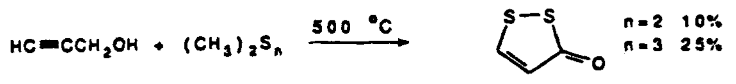
43

3-Hydroxy-5-methylthio-1,2-dithiole-3-thione is formed from 1,3-dichloro-2-propanone and elemental sulfur.[51,52] Scheme 15:



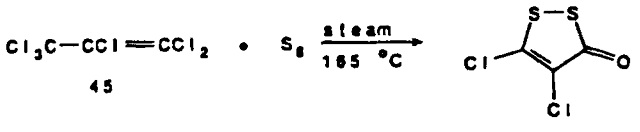
SCHEME 15

High temperature reaction of 2-propynol with polysulfides gave rise to the parent 1,2-dithiol-3-one **44** in yields dependent on the sulfide used.[44]

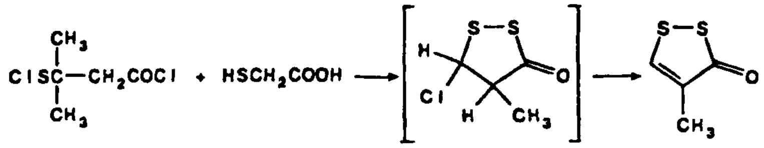


44

4,5-Dichloro-1,2-dithiol-3-one could be prepared on a large scale, 50 kg, by reaction of 1,1,2,3,3,3-hexachloropropene **45** with elemental sulfur and water at 165 °C.[53]

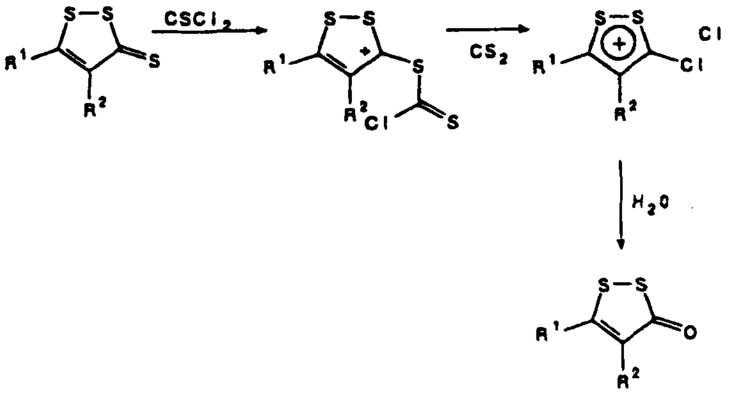


During an attempt to synthesise 5-halo substituted 1,2-dithiolan-3-ones it was observed that compounds with hydrogen in the 4 position were unstable and underwent dehydrohalogenation with formation of 1,2-dithiol-3-ones for example.[55] Scheme 16:



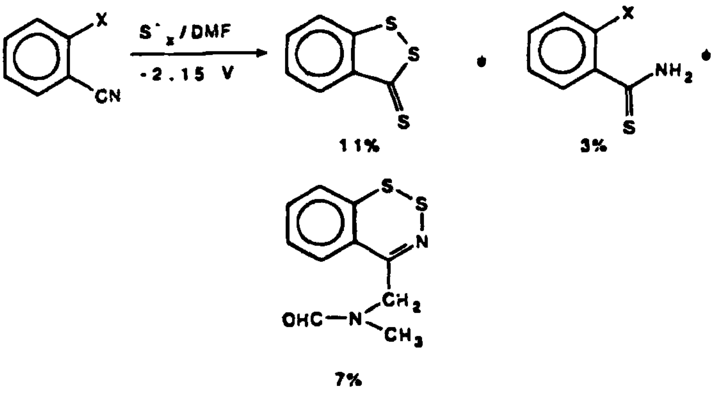
SCHEME 16

1,2-Dithiole-3-thiones can be converted to 1,2-dithiol-3-ones by reaction with $CSCl_2$.[56] Scheme 17:



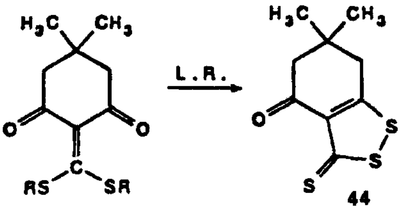
SCHEME 17

2-Chloro- and 2-bromobenzonitrile have been electrolysed at a carbon-sulfur electrode.[57] At a working potential at −2.15 V benzo-1,2-dithiole-3-thione was formed among other products. Scheme 18:



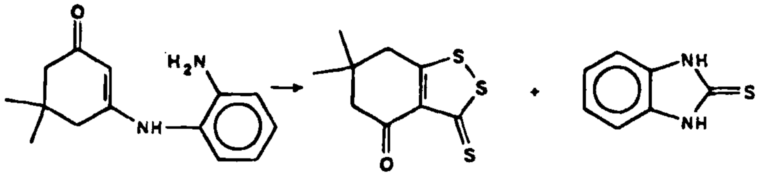
SCHEME 18

It has been reported that thionation of diacylketene dithioacetals derived from dimedone with Lawesson's reagent leads to the formation of 1,2-dithiole-3-thiones **44**.[58,59]



44

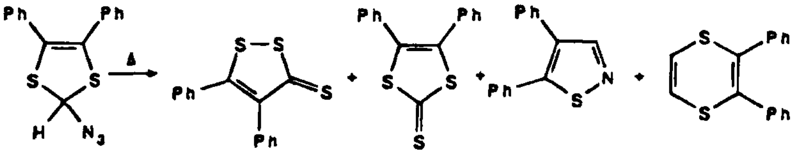
Enamino ketones such as **45** have been reported to react with carbon disulfide to form 1,2-dithiole-3-thiones.[60]



45

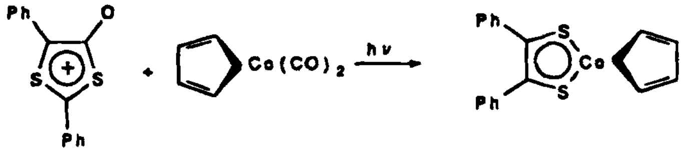
The reaction of substituted 2-chlorobenzyl chlorides with elemental sulfur in methanol in the presence of sodium methoxide is reported to give substituted benzo-1,2-dithiole-3-thiones in high yields.[61]

Thermolysis of 2-azido-4,5-diphenyl-1,3-dithiole resulted in a complex mixture of products[62] one of these being 4,5-diphenyl-1,2-dithiole-3-thione, Scheme 19. The complex reaction mixture was explained by assuming different reaction pathways.



SCHEME 19

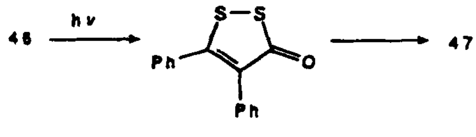
The photolysis of 2,5-diaryl-1,3-dithiolylium-4-olates **46** in the presence of a source of [Co(cp)] groups gives dithiolatocobalt complexes such as **47**.[63]



46 **47**

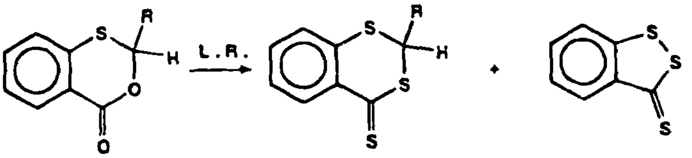
It is proposed that these complexes are produced from primarily formed 4,5-diaryl-1,2-dithiol-3-ones.

This assumption is in agreement with the observation that 4,5-diaryl-1,2-dithiol-3-ones can be isolated if **46** is photolysed in the absence of complexing agents.[64] Scheme 20:



SCHEME 20

3,1-Benzoxathian-4-ones reacts with Lawesson's reagent to give a mixture of 3,1-benzoxathiane-4-thiones and benzo-1,2-dithiole-3-thione.[65] Scheme 21.



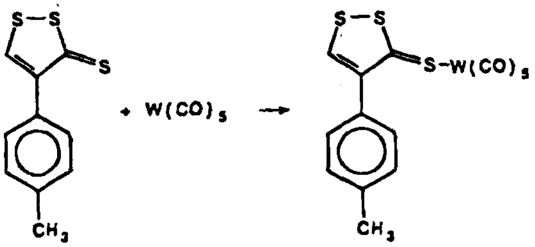
SCHEME 21

4-Methyl- and 5-methyl-1,2-dithiole-3-thione have been identified as products of the degradation of cysteine in water at 160 °C at pH 5.5.[66]

3. REACTIONS

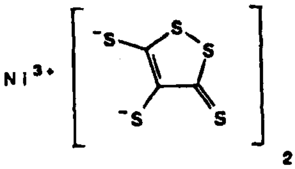
3.1. *Metal Complexes*

Most metal complexes reported involve coordination to the exocyclic sulfur atom of 1,2-dithiole-3-thiones. It has been reported that metal complexes are formed *in situ* during the synthesis of 1,2-dithiole-3-thiones.[46,47] The same type of complexes with CO as the other ligand, *e.g.* **48**, can also be formed from 1,2-dithiole-3-thiones and metal carbonyl complexes.[67]

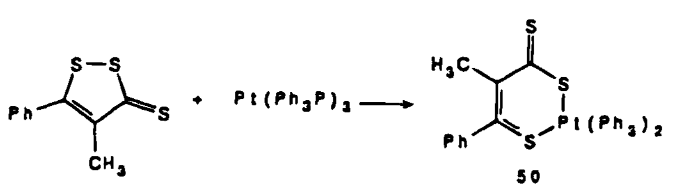


48

Several examples of complexes formed from 4,5-dimercapto-1,2-dithiole-3-thione **49** have been reported.[43,68,69,70] and crystal structures are given in some cases. It has been shown that such complexes undergo photooxidation to the metal (III) bis-chelates when irradiated at 313 nm.[71]



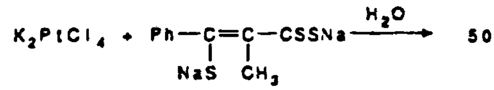
Insertion of the metal in the S-S bond has also been reported.[72] Scheme 22:



50

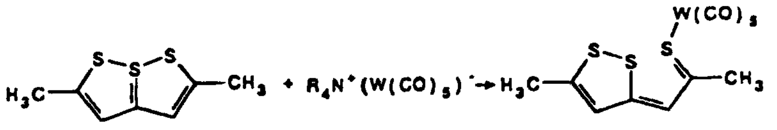
SCHEME 22

This complex can also be formed in aqueous solution from open chain compounds.



$$K_2PtCl_4 + Ph-\underset{NaS}{C}=\underset{CH_3}{C}-CSSNa \xrightarrow{H_2O} 50$$

It has been reported that 1,6,6aλ^4-trithiapentalenes can form coordination compounds which can be considered as complexes of vinylogs of 1,2-dithiole-3-thiones. It has never been possible to show the existence of valence tautomers in the free 1,6,6aλ^4-trithiapentalenes **51**.[73,74]



51 52

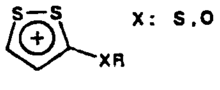
However, if 1,6,6aλ^4-trithiapentalenes are treated with $\{R_4N^+[W(CO)_5]^-\}$ compounds with one short and one long sulfur-sulfur bond **52** can be isolated.[75] Such compounds can be considered as derived from vinylogs of 1,2,-dithiole-3-thiones.

It has also been described that 1,6,6aλ^4-trithiapentalenes react with {Au[(tetrahydrothiophene)Cl]} to form analogous complexes with one long and one short sulfur-sulfur distance.[76] A theoretical discussion of such complexes has been given.[77]

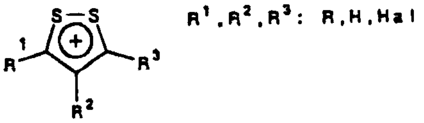
It has been reported that 1,2-dithiole-3-thiones react with lithium to give complexes with 2 to 7 lithium atoms per molecule. The parent 1,2-dithiole-3-thione reacts with two atoms whereas the benzo-condensed and the 5-phenyl substituted compound react with 6–7 lithium atoms per mole.[78] The structure of these complexes was not given.

3.2. *Salts*

Two fundamentally different types of salts can be formed from 1,2-dithiole-3-thiones and 1,2-dithiol-3-one; in the one type the exocyclic sulfur or oxygen atom is still present (**53**), in the other type (**54**) this is lost and substituted by hydrogen or halogen.



53

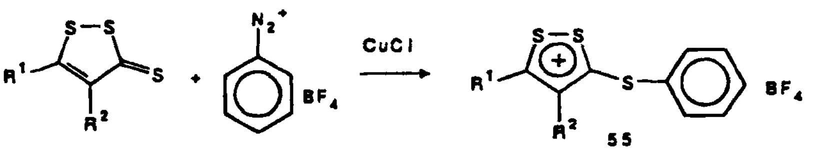


54

1,2-Dithiole-3-thiones can be alkylated with mild alkylating agents such as alkyl iodides.[8,27,42,43,79,80] Stronger alkylating agents, however, such as methyl triflate have also been used.[81]

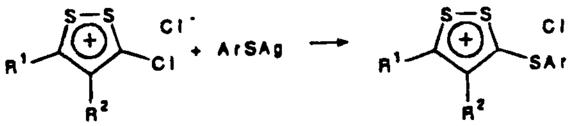
One of the thione sulfur atoms in [1,2]dithiolo[4,3-*c*]1,2-dithiole-3,6-dithione could be methylated by use of trimethyloxonium tetrafluoroborate, but it was not possible to methylate both with this reagent. Only by the use of bis(ethoxy) carbonium hexachloroantimonate the dication could be formed.[40,82]

Arylation of the exocyclic sulfur is not possible by means of aryl halides but 3-arylthio-1,2-dithiolylium salts **55** can be prepared by allowing 1,2-dithiole-3-thiones to react with aryl diazonium salts in the presence of copper(I) chloride.[83,84]

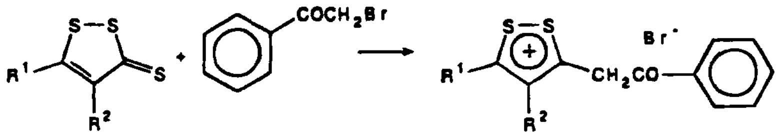


SCHEME 23

Such arylthio-1,2-dithiolylium salts have earlier been prepared by treatment of 3-chloro-1,2-dithiolylium salts with silver thiolates.[85]



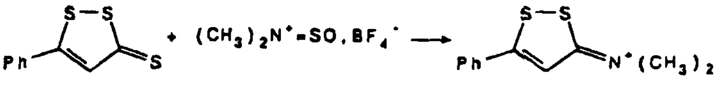
1,2-Dithiole-3-thiones react with halides of the phenacyl halide type to give *S*-alkylated salts **56**.[86]



56

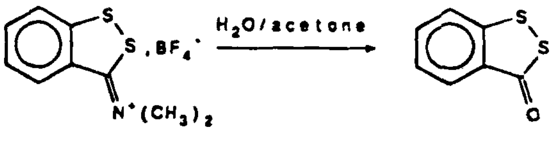
These reactions have earlier been discussed in detail *cf.* ref. 5.

1,2-Dithiole-3-thiones react with *N*-methyl-*N*-sulfinyl-methanaminium tetrafluoroborate to form iminium salts **57**.[87]

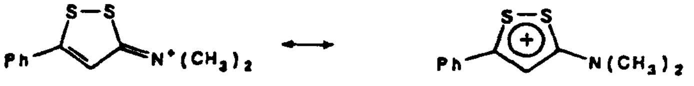


57

Such salts can be hydrolysed in aqueous acetone solution to give the corresponding 1,2-dithiol-3-ones.

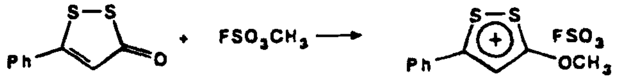


In the ^1H NMR spectrum two methyl signals are found indicating hindered rotation around the C-N bond. However, the coalescence temperature of 52 °C for the benzo condensed compound and of 79 °C for the 5-phenyl substituted compound is lower than usual for this type of compounds indicating contribution of 1,2-dithiolylium structures **58**.



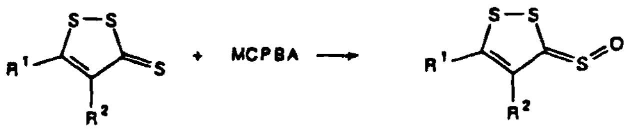
58

1,2-Dithiol-3-ones can only be *O*-alkylated by strong alkylating agents such as Meerwein salts or fluorosulfonic acid esters.[88]



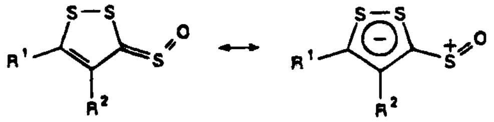
3.3. *Oxidations*

Oxidation of 1,2-dithiole-3-thiones by peracids or hydrogen peroxide usually leads to the formation of 1,2-dithiolylium salts.[71] If, however, the oxidation is carried out with caution in methylene chloride and with *m*-chloroperbenzoic acid (MCPBA) thione *S*-oxides **59** are obtained.[23,90,91]

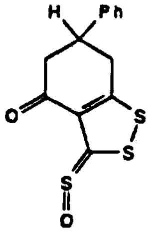


59

Only the Z-form could be isolated. Both ^{1}H and ^{13}C NMR spectra show upfield shifts compared to the thiones indicating that the sulfinyl group functions as an electro donating group with respect to the ring.



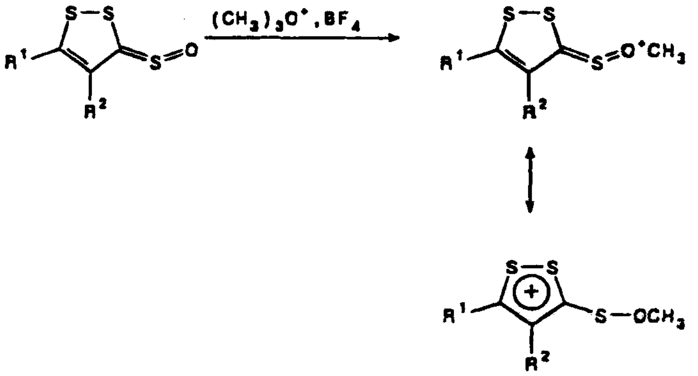
6-Phenyl-3-thioxo-6,7-dihydro-3*H*-1,2-benzodithiol-4(5*H*)-one *S*-oxide **60** has been prepared by oxidation of the corresponding thione with MCPBA.[59]



60

The x-ray structure has been reported. The *S*-oxide displays a very short intermolecular distance (2.81 Å), between the S=O oxygen and the S(2) atom in the dithiole ring.

The 1,2-dithiole-3-thione *S*-oxides could be *O*-alkylated with Meerwein salts in nitromethane.[92] Such *O*-alkylated salts are unusually stable, which indicates a contribution of 1,2-dithiolylium structures. Scheme 24:



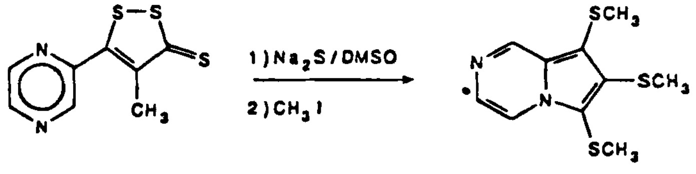
SCHEME 24

3.4. *Reductions*

This section will only deal with chemical reductions. Electrochemical reductions will be treated in Section 3.6.

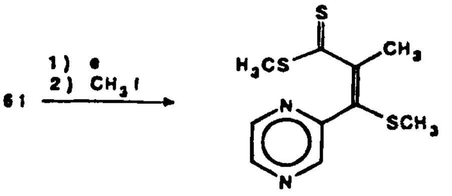
The reduction of Oltipraz, 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione, both by chemical and electrochemical methods, has attracted great interest as such reductions give rise to derivatives of pyrrolo[1,2-*a*]pyrazines. Derivatives of the same system are found as metabolites from Oltipraz in living organisms.

If Oltipraz **61** is reduced with sodium sulfide in the presence of halides the condensed 1,4-pyrazine **62** is formed.[93]



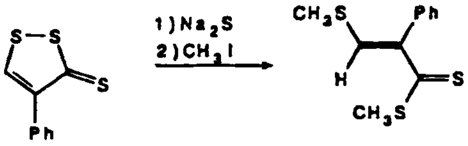
61 62

It is assumed that the reaction proceeds via an attack on the disulfide bond with ring opening and subsequent alkylation, Scheme 25, as shown earlier for simple 1,2-dithiole-3-thiones.[94]



SCHEME 25

Simple 1,2-dithiole-3-thiones such as 4-phenyl-1,2-dithiole-3-thione have also been reduced with sodium sulfide.[95]



63

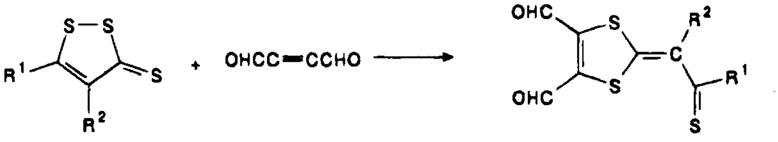
The reduction has been shown to give exclusively the *E*-isomer **63** in contrast to the corresponding reduction of 5-phenyl-1,2-dithiole-3-thione[94] which gives the *Z*-isomer.

3.5. *Ring Transformations*

This Section will only deal with transformations of the 1,2-dithiole ring to other ring systems. Transformations to open chain compounds will be treated in another Section. Electrochemically induced transformations will be discussed in Section 3.6.

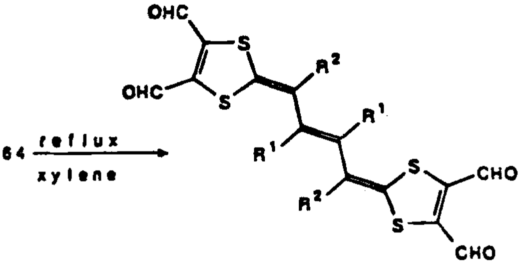
It is a well established observation that 1,2-dithiole derivatives can be transformed into 1,3-dithiole derivatives *cf.* ref. 5.

Butynedial and its acetals react with 1,2-dithiole-3-thiones to give compounds of type **64**.[96,97]



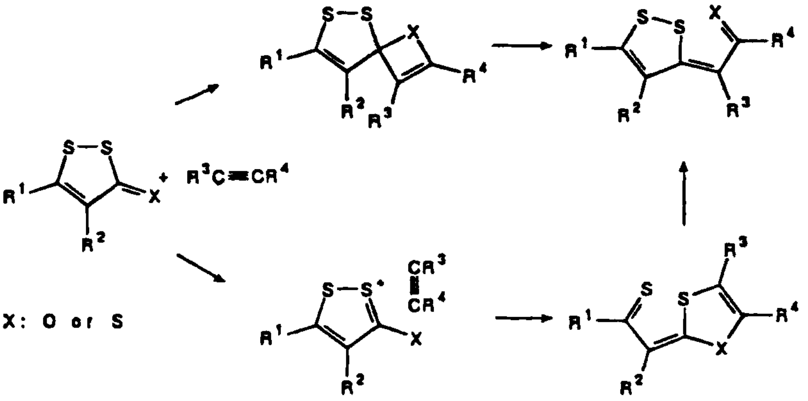
64

These compounds are of interest as models for one-dimensional metals as they can easily be transformed into vinylogs of TTF **65**.



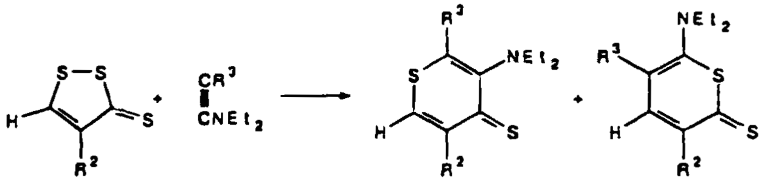
65

1,3-Dithiole derivatives are also formed from ynamines and 1,2-dithiole-3-thiones[98] following the general Scheme 26.



SCHEME 26

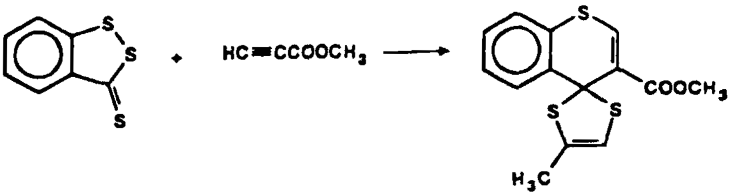
However, if a proton is present in position 5 the resulting compound is a thiopyran derivative.[98]



SCHEME 27

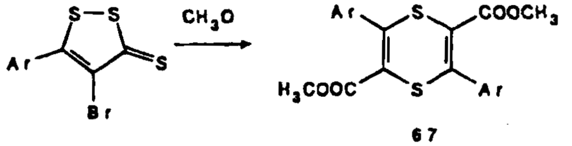
The photochemical addition of alkenes to 5-aryl-1,2-dithiole-3-thiones to give 1,3-dithiole derivatives has been studied.[100]

3*H*-Benzo-1,2-dithiole-3-thione reacts with ethyl propiolate in a double condensation to give **66**.[99]



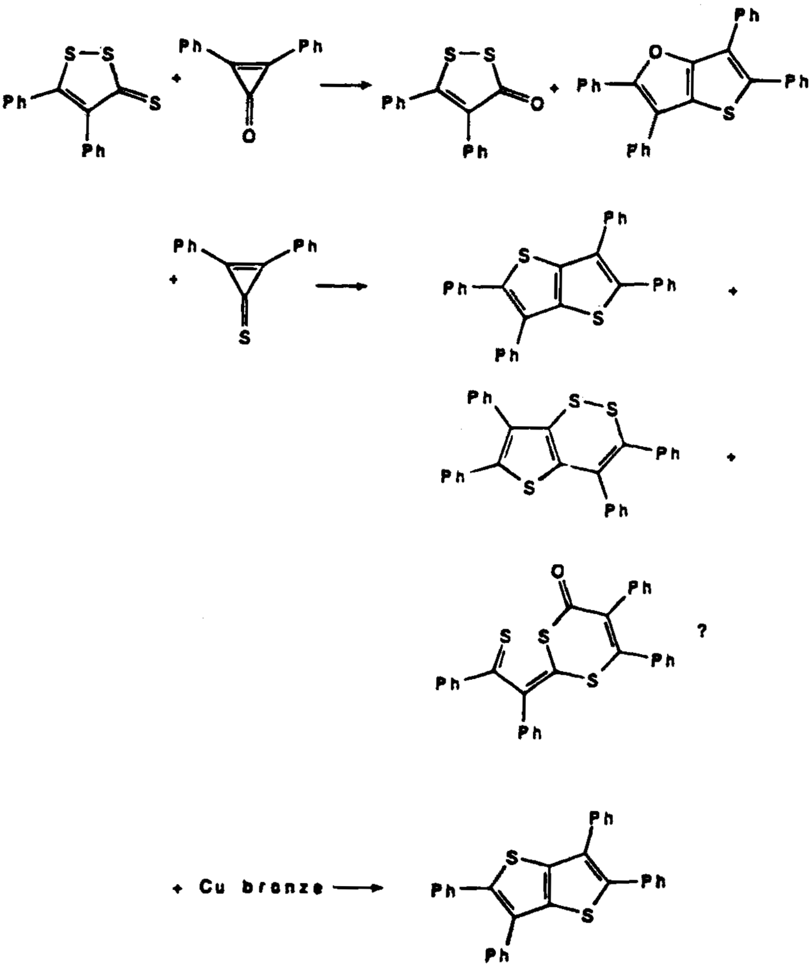
66

1,4-Dithiins **67** are formed from 4-bromo-1,2-dithiol-3-ones and methoxide ions.[101]



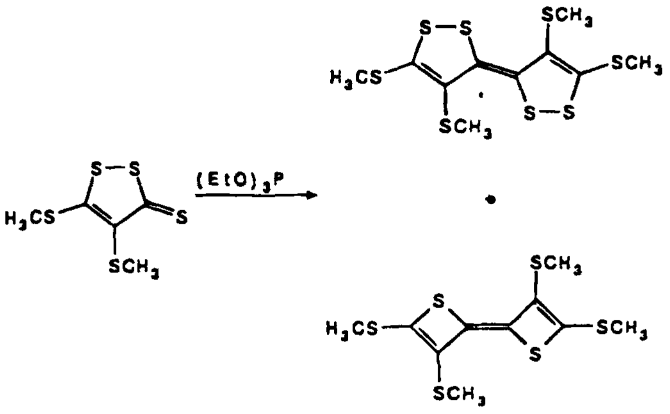
67

Numerous unsuccessful attempts have been made to transform 1,2-dithiole-3-thiones into 1,2-tetrathiafulvalenes. During these studies[8,9,102] various other sulfur-containing ring systems have been found. Scheme 28:



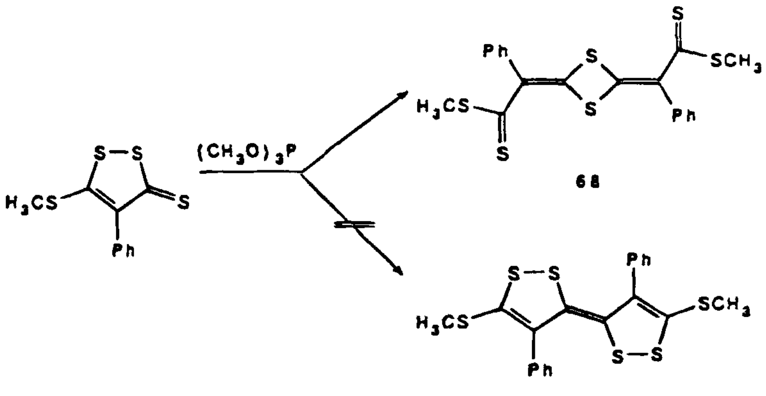
SCHEME 28

Although previous attempts to convert 1,2-dithiole-3-thiones into 1,2-tetrathiafulvalenes by reaction with trivalent phosphorus compounds such as phosphines and phosphites have been unsuccessful[103] it has been reported that the desulfurization of 1,2-dithiole-3-thiones with a methylthio substituent in the 5-position gives rise to 1,2-tetrathiafulvalenes in good yield with concomitant formation of thiete derivatives.[80] Scheme 29:

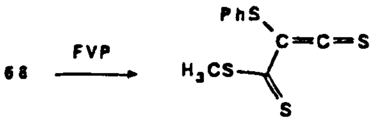


SCHEME 29

It was, however, later shown by UV-VIS and ESCA studies that the compounds formed were not 1,2-tetrathiafulvalenes but the isomeric thioxo desaurines **68**.[104]

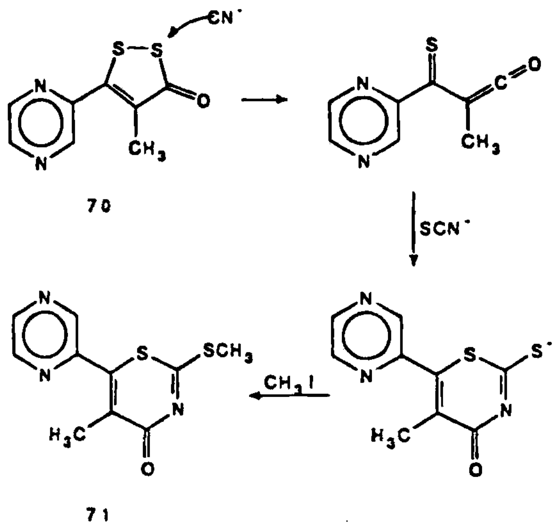


This was further confirmed by the formation of monomeric thioacyl thioketenes **69** by flash vacuum pyrolysis of the thioxo desaurines,[105] which are the dimers of such thioacyl thioketenes.

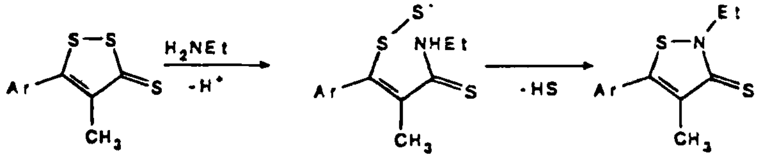


69

The reaction of the oxygen analog of Oltipraz **70** with cyanide ions gives a 1,3-thiazine derivative **71**.[106]

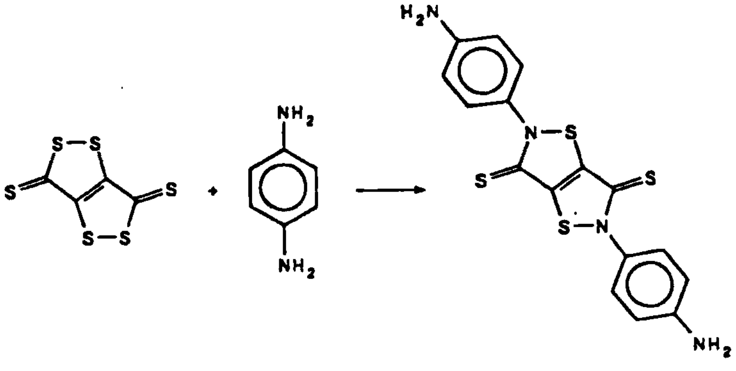


Rings where one of the sulfur atoms from the original 1,2-dithiole system is preserved can also be formed by reaction with *e.g.* amines.[107] Scheme 30:



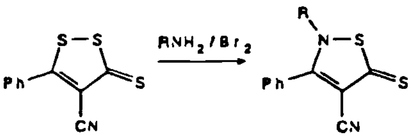
SCHEME 30

[1,2]Dithiolo[4,3-*c*]1,2-dithiole-3,6-dithione may react with aromatic amines forming imines; however, the amine nitrogen may also be incorporated in the ring forming 1,2-thiazole derivatives **72**.[108,109,110]



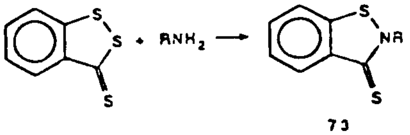
72

1,2-Dithiole-3-thiones react via their bromine complexes with amines to form isothiazole derivatives.[111]



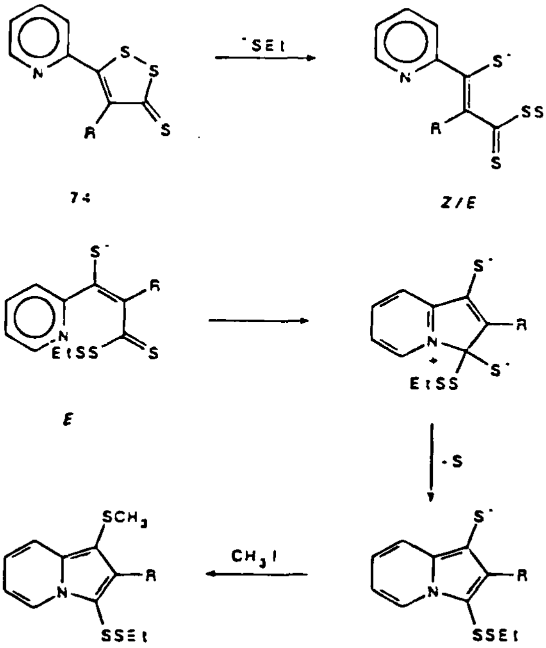
It has been unexpectedly observed that 5-aryl substituted 1,2-dithiole-3-thiones react too. An aryl substituent in the 5-position normally prevents the reaction with amines.

3*H*-Benzo-1,2-dithiole-3-thione reacts with amines to give **73**.[112]



1,2-Dithiole-3-thiones have been reported to react with diazonium salts to form 1,2-diaza-6,6aλ^4-dithiapentalenes.[113]

Both endocyclic sulfur atoms may also be removed from the 1,2-dithiole systems which then form rings not containing sulfur. The reaction of 5-pyridyl substituted 1,2-dithiole-3-thiones with ethanethiolate ions gives products where a cyclisation to the pyridine nitrogen atom has occurred.[114] Scheme 31:



SCHEME 31

The reaction of 1,2-dithiole-3-thiones with various nucleophiles such as alkoxide and thiolate anions has been studied in detail.[115] The reaction products are strongly dependent on the substitution pattern of the 1,2-dithiole-3-thione and the presence of substituents in the 5-position which allows new cyclisations to occur, which is the case for Oltipraz.

It has also been observed that Oltipraz by reaction with sodium sufide gives derivatives of pyrolo[1,2-*c*]pyrazine.[93]

Such compounds are also formed by electrochemical reduction of Oltipraz, *cf.* Section 3.6.

3.6. *Electrochemistry*

The carbon-sulfur electrode[17] has been used for the synthesis of 1,2-dithiole-3-thiones,[18] *cf.* Section 2.2.2.

The electrochemical reduction of Oltipraz, 4-methyl-5-(pyrazin-2-yl)-1,2-dithiole-3-thione, an antischistosomal drug, has been studied in detail since the electrochemical reduction products are identical with metabolites formed when Oltipraz is used as a drug in humans.[116]

The electrochemical reduction of Oltipraz at a glossy carbon electrode in DMF leads, after methylation, to the pyrrolo[1,2-*a*]pyrazine derivative **62**.[117]

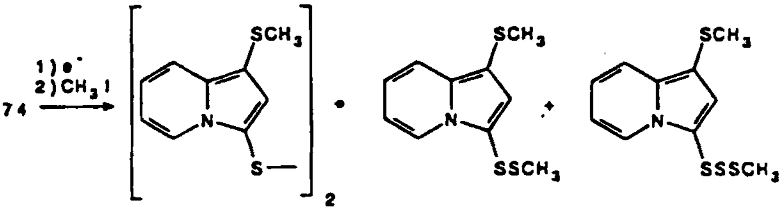
$$61 \xrightarrow[2)\,CH_3I]{1)\,e^-} 62$$

Analogous results are obtained upon reduction in acetonitrile solution.[118]

The electrochemical reduction of Oltipraz has been further discussed.[119] The electrochemistry of analogs of Oltipraz has been discussed.[120] Open chain thiyl radicals formed during the reduction are proposed. They give rise to ring closed products if a nitrogen is present in the 2-position of the 5-substituent on the dithiole ring.

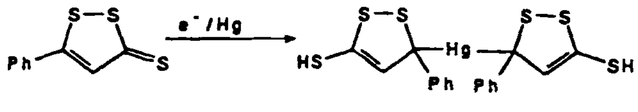
The reduction of 1,2-dithiole-3-thiones with a 2-pyridyl substituent in the 5-position of the dithiole ring gives rise to ring closure of this type with formation of pyrrolopyridine systems.[121] Such systems have also been observed in the reaction of **74** with ethanethiolate ions.[114]

In the electrochemical reduction both mono-, di- and trisulfides are formed. Scheme 32:



SCHEME 32

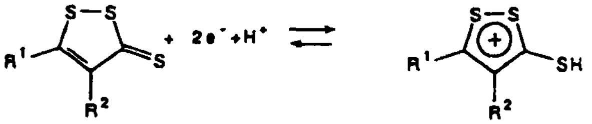
In a study of the electrochemistry of 1,2-dithiole-3-thiones in water/ethanol mixtures at a mercury electrode[122] the formation of organomercurials such as **76** was observed.



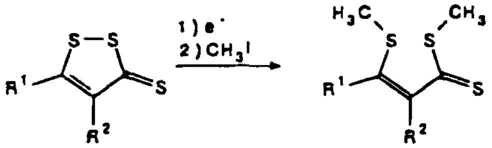
76

This is in accordance with polarographic studies of 1,2-dithiole-3-thiones in DMF, where the formation of organomercurials is also proposed.[123]

When the reduction was essentially diffusion controlled a reversible 2e reduction at pH 7 was observed.[122]



By preparative electrochemistry of a series of substituted 1,2-dithiole-3-thiones and subsequent methylation mixtures of *E* and *Z* isomers of propenedithioates 77 could be isolated.[124]

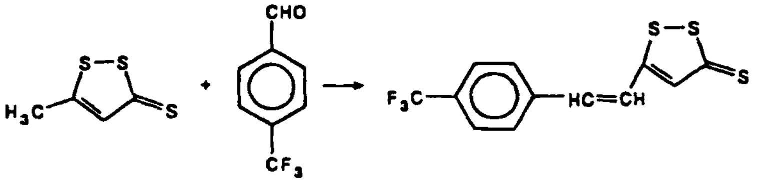


77

3.7. *Reactions Involving Side Chains*

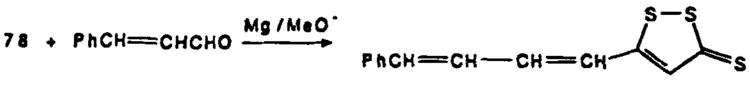
Most side chain reactions described for 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones involve reactions of a methyl or methylene group in the 5-position.

Reactions with substituted benzaldehydes such as 79 have been described.[125,126,127]

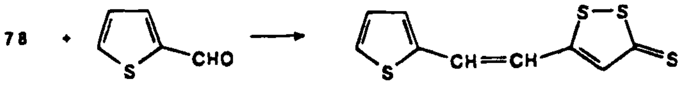


78 79

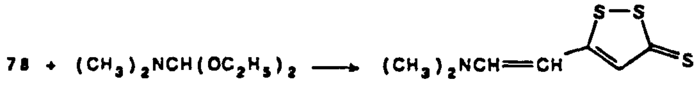
Unsaturated aldehydes where the double bond is conjugated with the carbonyl group react in the same way.[128]



Reaction with heterocyclic aldehydes proceeds in the same manner.[129]



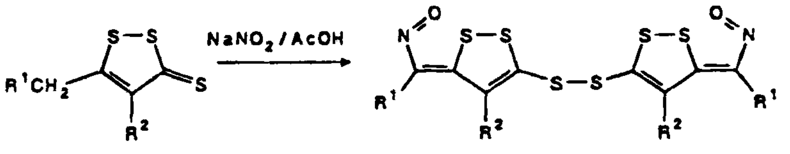
Acetals can also be used in the reaction.[130] Scheme 33:



SCHEME 33

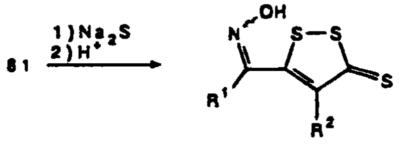
Reactions in the side chain can in this way be used to introduce functional groups in the 5-position, for instance hydroxyimino and carbonyl groups.[20,131]

When 1,2-dithiole-3-thiones **80** are treated with sodium nitrite in anhydrous acetic acid disulfides **81** are obtained.



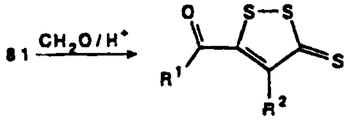
80 **81**

These can be reduced with sodium sulfide in DMSO to give 5-(1-hydroxyiminoalkyl)-1,2-dithiole-3-thiones **82**.[131]



82

If these disulfides are treated with formaldehyde under solvolytic conditions 5-acyl-1,2-dithiole-3-thiones are obtained.[131]



83

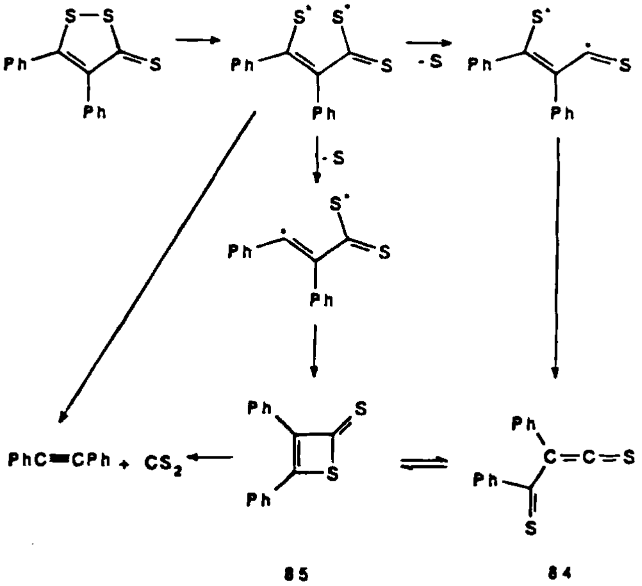
Compound **83** can be formed directly from the 1,2-dithiole-3-thiones by reaction with isoamyl nitrite in the presence of sodium ethoxide in ethanolic solution.

$$80 \xrightarrow[\text{EtO}^-]{\text{Isoamyl nitrite}} 83$$

3.8. *Formation of Open Chain Compounds*

Examples of the formation of compounds where the 1,2-dithiole ring is opened have already been given in previous Sections.[95,115,124]

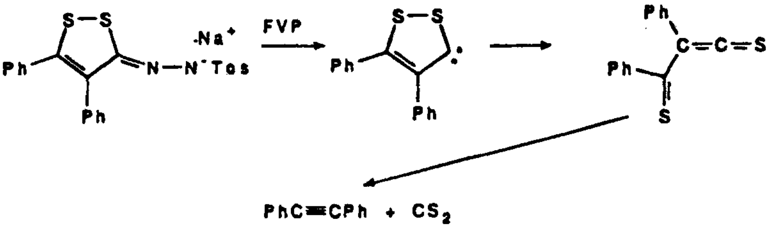
If 1,2-dithiole-3-thiones are subjected to flash vacuum pyrolysis the formation of thioacyl thioketenes is observed.[105] It was found that the thioacyl thioketenes **84** rearrange to thiete-2-thiones **85** which further decompose to acetylenes and carbon disulfide according to Scheme 34.



SCHEME 34

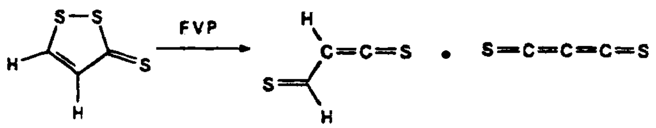
These observations are in accordance with earlier CNDO calculations of the stability of 1,2-dithiole carbenes and thioacyl thioketenes.[132,133]

It has been found that 4- and 5-phenyl-1,2-dithiole-3-thione behave in the same manner. If the sodium salt of 4,5-diphenyl-1,2-dithiole-3-thione tosylhydrazone, a known carbene precursor, is pyrolysed the same result is obtained, Scheme 35.



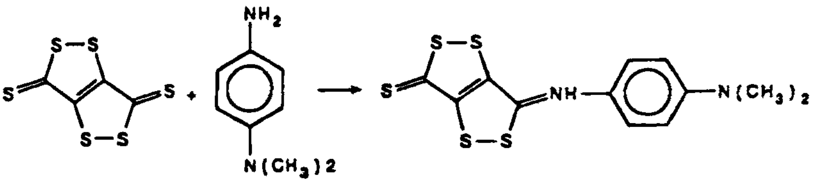
SCHEME 35

In the pyrolysis of the unsubstituted 1,2-dithiole-3-thione thioformyl thioketene was formed, but substantial amounts of C_3S_2, propadiene-1,3-dithione were observed, too, Scheme 36.



SCHEME 36

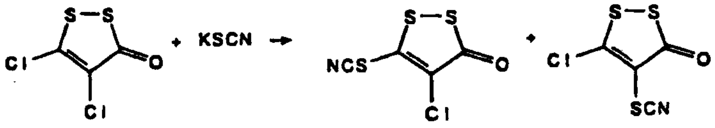
The dithiole ring of 3*H*-benzo-1,2-dithiole-3-thione is opened by chlorine,[134] Scheme 37.



SCHEME 37

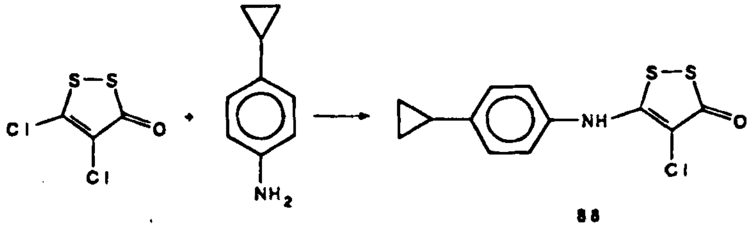
3.9. *Miscellaneous*

Substitution reactions of halogen atoms in the 4- or 5-position of 1,2-dithiol-3-ones have been observed. Reaction of 4,5-dichloro-1,2-dithiol-3-one with KSCN gives rise to a mixture of the two thiocyanates **86** and **87**.[135]



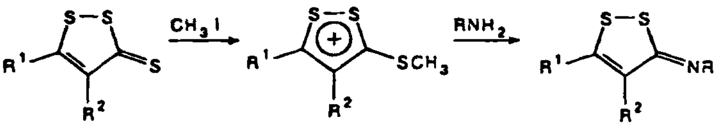
86 **87**

Reaction of 4,5-dichloro-1,2-dithiol-3-one with aromatic amines and phenoxide ions gives the corresponding amino **88** or phenoxy substituted compounds.[136]

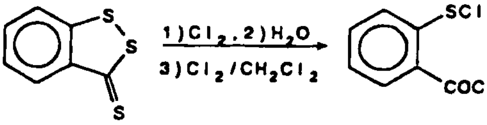


88

Reactions involving the C=S bond have also been described. 1,2-Dithiole-3-thiones can, via the corresponding methylthiodithiolylium salts, be converted into 3-arylimino-1,2-dithioles.[137]

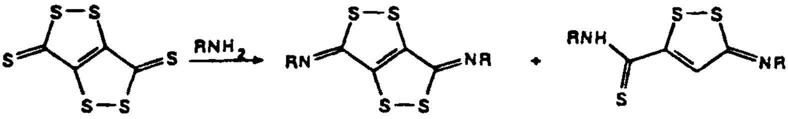


Such reactions are also observed with the more complex [1,2]dithiolo[4,3-*c*]1,2-dithiole-3,6-dithione.[82,108] It has been found that the free dithione is also able to react with aromatic amines, which may give the monosubstituted product. Scheme 37:[109]



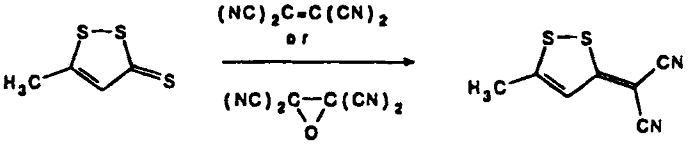
SCHEME 37

With aliphatic amines it has been observed that one of the dithiole rings is opened due to the greater nucleophilicity of the amine. Scheme 38:[110]



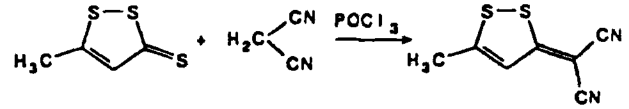
SCHEME 38

1,2-Dithiole-3-thiones react with tetracyanoethene or the corresponding epoxide to form 3-substituted dicyanoalkylidene compounds.[129] Scheme 39:

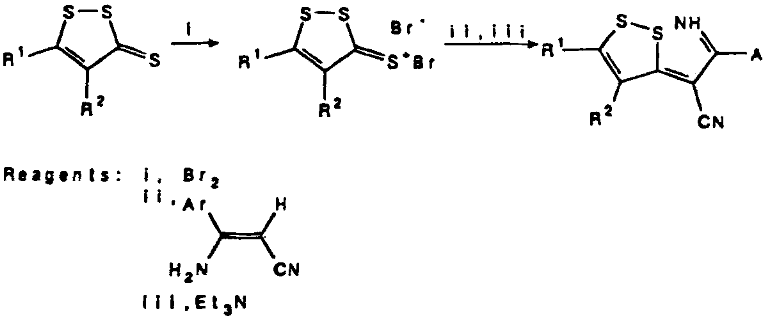


SCHEME 39

These compounds can also be formed directly from 1,2-dithiol-3-ones and malononitrile.[129]

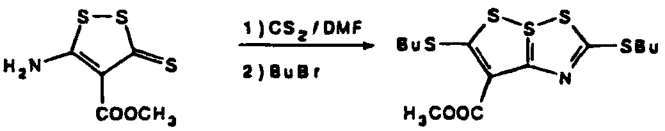


1,2-Dithiole-3-thiones can, via their bromine complexes, react with enamino nitriles.[138] Scheme 40:



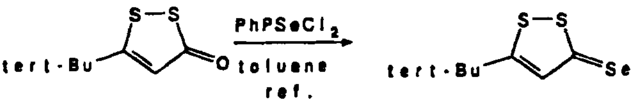
SCHEME 40

5-Amino-1,2-dithiole-3-thiones can be condensed with carbon disulfide to form bicyclic systems **89**.[139]



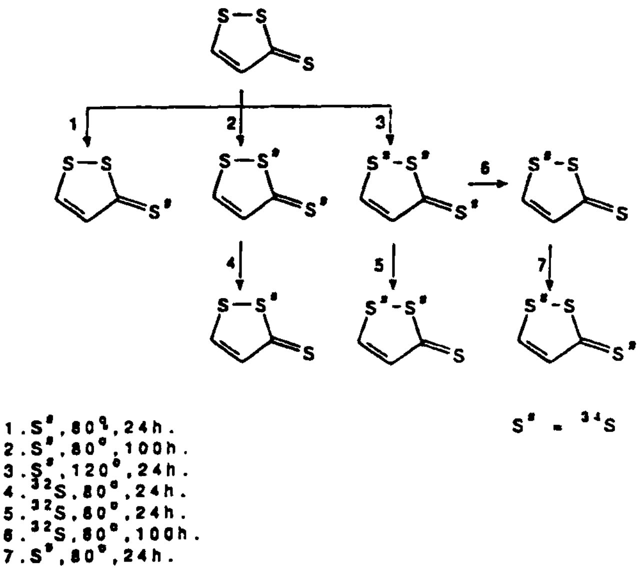
89

1,2-Dithiol-3-ones can be converted to the corresponding selenones by reaction with phenylselenophosphorus dichloride.[140]



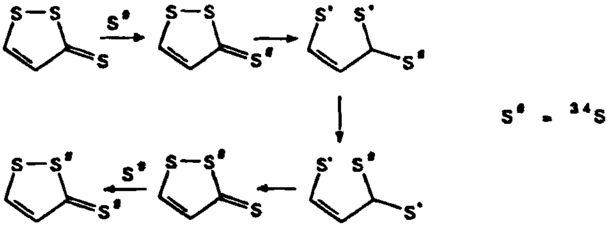
The selenones can also be prepared from 3-chloro-1,2-dithiolylium salts and sodium diselenide.[104]

Thermolysis of 1,2-dithiole-3-thione is shown by mass spectrometry to give rise to scrambling among the sulfur atoms if ^{34}S is introduced.[141] This method can be used for preparation of all eight ^{34}S-isotopomers of 1,2-dithiole-3-thione. Scheme 41:



SCHEME 41

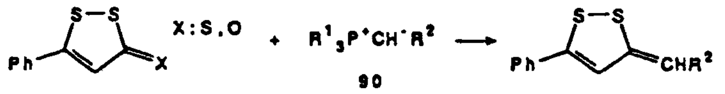
It is assumed that the two ^{34}S atoms are introduced via an open biradical. Scheme 42:



SCHEME 42

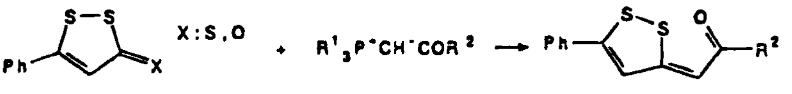
The third labeled sulfur may be introduced by reaction between the dithiole biradicals and ·S-S_6-S· biradicals.

Both 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones react with Wittig reagents **90** to form 3-alkylidene substituted derivatives.[142]



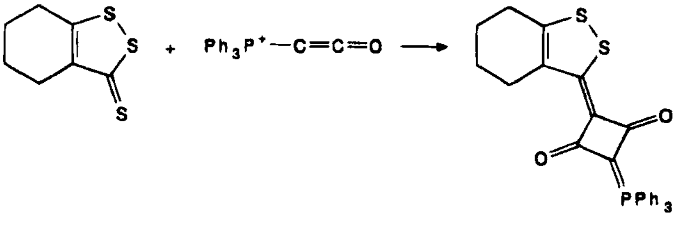
90

The vinylogs of 1,2-dithiol-3-ones, 3-(1,2-dithiolylidene) ketones **91** can be synthesized in the same way.



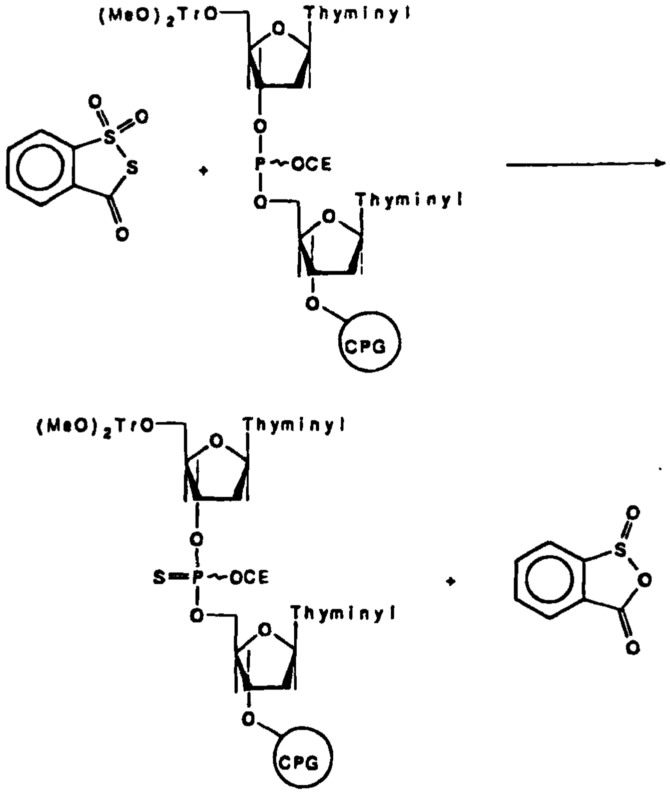
91

Reaction of 4,5-tetramethylene-1,2-dithiole-3-thione with triphenylphosphoranylideneketene has been reported to give the most unusual phosphorus compound **92**.[143]



92

3*H*-1,2-Benzodithiol-3-one 1,1-dioxide has been used as a sulfur-transfer reagent in the synthesis of sulfur-containing oligodeoxyribonucleotides.[34,144,145] Scheme 43:



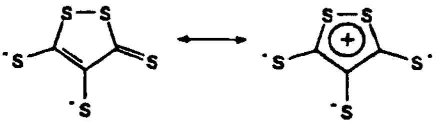
(MeO)$_2$Tr : di(p-anisyl)phenylmethyl
CE : β-cyanoethyl
CPG : controlled-pore glass

SCHEME 43

4. PHYSICAL PROPERTIES

4.1 *Structural Studies*

The structures of various 1,2-dithiole-3-thiones have been determined by means of X-ray crystallography: unsubstituted 1,2-dithiole-3-thione,[146] 4- and 5-phenyl-1,2-dithiole-3-thione,[147] 5-(*p*-methoxyphenyl)-1,2-dithiole-3-thione,[148] 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione, Oltipraz.[149] The structure of the vinylog of Oltipraz, 4-methyl-5-(2-pyrazinylvinyl)-3*H*-1,2-dithiole-3-thione, which does not show any antischistosomal activity, has also been recorded.[150] The structure of the condensed 6-chlorobenzo-1,2-dithiole-3-thione has been reported.[151] The structures of 4,5-bis(methylthio)-1,2-dithiole-3-thione and 1,2-dithiole-3-thione-[4,5-*b*]-5,6-dihydro-1,4-dithiin have been determined.[152] The structure of 6,6-dimethyl-3-thioxo-6,7-dihydro-3*H*-1,2-benzodithiol-4(5*H*)-one has been determined.[59] The structure of the dianion **93** shows this ion to have C_{2v} symmetry.[153]

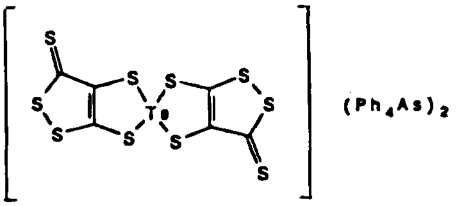


93

The oxygen analog of Oltipraz, 4-methyl-5-(2-pyrazinyl)-1,2-dithiol-3-one has a structure which is not principally different from that of Oltipraz.[154]

4.2. *NMR and EPR Studies*

^{1}H and ^{13}C NMR spectra have been reported for some 1,2-dithiole-3-thiones of pharmaceutical interest.[155] In a study of ^{125}Te NMR spectra of coordination compounds of Te(II) and thio and seleno ligands the ^{125}Te chemical shift of **94** was reported.[156]



94

^{13}C-NMR chemical shifts have also been reported for other chelates with 1,2-dithiole-3-thione-4,5-dithiolate as ligand.[157] Analogous studies of ^{77}Se NMR spectra have been reported.[158] ^{1}H and ^{13}C NMR spectra of 1,2-dithiole-3-thione have been discussed in a study of sulfur and selenium containing 6π cations.[159] ^{13}C Chemical shifts of tropone/thiotropone have been compared with the shifts in a series of 1,2-dithiol-3-ones/1,2-dithiole-3-thiones.[160]

EPR studies of oxovanadium(IV) bis-complexes of 1,2-dithiole-3-thione-4,5-dithiolate have been reported.[161]

4.3. *Mass Spectrometric Studies*

Mass spectra have been used for the characterisation and identification of 1,2-dithiole-3-thiones and 1,2-dithiol-3-ones in many cases. However, unless more fundamental studies have been carried out, such studies will not be mentioned in this Section.

The thermally induced sulfur scrambling in 1,2-dithiole-3-thione has been studied by mass spectrometry.[141] The scrambling is followed by comparison of the molecular-ion pattern of 1,2-dithiole-3-thione with that of 1,2-dithiole-3-thione heated together with ^{34}S. Further MS-MS technique using pure isotopomers has been used to elucidate this thermal scrambling further. The MIKE spectrum of the *m*/*z* 134 molecular ion of 1,2-dithiole-3-thione has been recorded.

The electron impact ionization mass spectrum of 1,2-dithiolo[4,3-*c*]1,2-dithiole-3,6-dithione shows an intense peak at *m*/*z* 112, which corresponds to the elemental composition C_4S_2.[37] Based on collisional activation (CA) mass spectrometry it is proposed that this ion corresponds to the linear species **95**.[162]

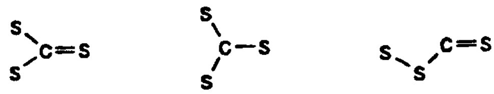
$$S{=}C{=}C{=}C{=}C{=}S$$

95

By use of neutralization-reionization mass spectrometry the neutral molecule is shown to exist with a life-time > 1 microsec. The NR spectrum obtained is also best compatible with a linear structure.

In a study of the possible isomers of CS_3 such species were generated from 1,2-dithiole-3-thione as well as from 1,3-dithiole-2-thione.[163]

Based on the CA mass spectra of singly and doubly ^{34}S labeled cation radicals it is proposed that three different species of CS_3 exist in the dilute gas phase. Scheme 44:



SCHEME 44

Two of them are also formed from the 1,3 derivative while one is only observed in 1,2-dithiole-3-thione and this isomer has tentatively been ascribed the structure of a carbon disulfide *S*-sulfide

$$S{=}C{=}S^{+}\text{-}S^{\cdot}$$

4.4. *Analytical*

1,2-Dithiole-3-thiones have been determined by various chromatographic methods. Sixteen 1,2-dithiole-3-thiones have been detected on the nanogram scale by HPLC and retention characteristics given.[164] Methods combining TLC and GC have been used to isolate and identify 1,2-dithiole-3-thiones in sandy materials.[165] HPLC has been used to identify Oltipraz and its metabolites in serum and urine on the nanogram scale.[166] Urine from mice fed with 5-(*p*-methoxyphenyl)-1,2-dithiole-3-thione (trithioanethole) has been analyzed by reverse phase HPLC.[167]

5. ASPECTS OF PRACTICAL APPLICATIONS

5.1. *Medicinal Uses*

It was found 15 years ago that Oltipraz (4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione) was active against a tropical worm disease, bilharziosis, caused by the worm *Schistosoma* *mansoni.* This schistosomicidal effect is closely related to the structure of Oltipraz, the oxygen analog *e.g.* had no effect.[168]

The mechanism of the schistosomicidal effect of Oltipraz has been studied by chemical, electrochemical and enzymatic methods.[169]

The anticarcinogenic effect of Oltipraz has also been studied. It has an effect on mice treated with aflatoxin B_1.[170,171] The effect on neoplasia caused by administration of benzo[*c*]pyrene has been studied.[172] The effect of 1,2-dithiole-3-thiones on hepatoma cells has been investigated.[173]

Treatment of mice with Oltipraz gave significant increase in hepatic glutathione and decreased the hepatic liver DNA damage and may have a retarding effect on the radical processes associated with aging.[174,175] The effect of Oltipraz on DNA damage in aging mice has been compared to that of the well known antioxidant BHA (a mixture of 2- and 3-*tert*-butyl-4-methoxyphenol).[176]

It has been found that chronic treatment with 5-(methoxyphenyl)-1,2-dithiole-3-thione (trithioanethole) enhances the salivary secretion.[177,178]

4-Chloro-1,2-dithiol-3-ones[179] and 5-amino-1,2-dithiol-3-ones[180] have been examined for antirheumatic activity.

5.2. *Industrial Uses*

It has been shown that 4,5-dichloro-1,2-dithiol-3-one can control the growth of *Klebsiella pneumoniae* in aqueous systems.[181] It has been used as an industrial microbicide in paper manufacturing and has effect against *Pseudomonas, Alcaligenes, Flavobacterium* and *Micrococcus.*[182] It has been found to kill *Pseudomonas fluorescens* in a concentration of 10–50 ppm.[183] 4,5-Dichloro-1,2-dithiol-3-one is decomposed in aqueous food, therefore migration from paper into the food is unlikely in cases where the compound has been used in the manufacture as a slimicide.[184]

[1,2]Dithiolo[4,3-*c*]1,2-dithiole-3,6-dithione has, in combination with other 1,2-dithiole-3-thione derivatives, been tested as electrode material in batteries.[185,186] Metal complexes derived from 4,5-dimercapto-1,2-dithiole-3-thione have been used for IR-sensitive silver halide photosensitive materials.[187]

1,2-Dithiole-3-thiones, in particular 4-*tert*-butyl-5-neopentyl-1,2-dithiole-3-thione, have been used as inhibitors of carbon dioxide corrosion in petroleum service.[188,189]

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