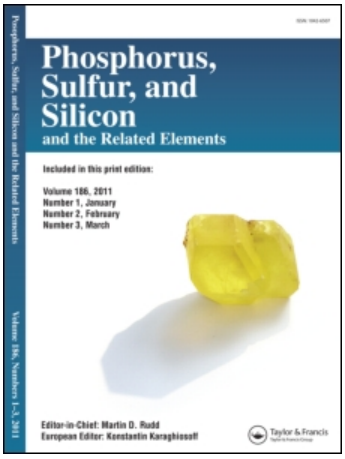

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New Aspects of Dithio and Thiono Esters

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NEW ASPECTS OF DITHIO AND THIONO ESTERS

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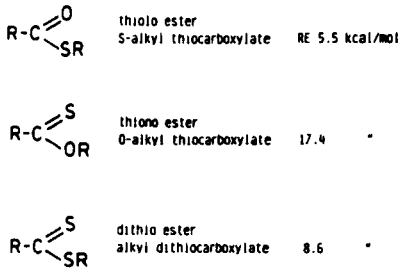
Abstract The field of dithio and thiono esters is expanding rapidly. Therefore emphasis is layed mainly on results obtained by the research group of the author. In agreement with theoretical considerations thiono esters are always more stable than dithio esters. In the preparation of dithio and thiono esters by thiolysis slightly acidic conditions were found to be essential. The CH-acidity at the α-carbon of dithio and thiono esters with pK_a values about 12 is comparable to that of classical CH-acidic compounds such as acetoacetic ester. Dithiono and tetrathio malonates do not show the expected chemistry of malonic esters; the electrophile reacts preferentially at the sulfur atom. α,β-Unsaturated dithio and thiono esters have been prepared by Wittig-Horner reactions, by Peterson synthesis, and by aldol condensations. α,β-Acetylenic dithio and thiono esters were obtained for the first time. In the formation of thiopeptide bonds from α-amino dithio esters the racemization observed seems to be of fundamental importance. Dianions of dithio acids were found to condense with different electrophiles.

INTRODUCTION

The first thioesters were prepared at the beginning of this century. These papers, however, did not find the interest of the chemical community at that time. Therefore thioesters remained a rather exotic class of compounds, unknown to most chemists. This situation has changed gradually during the last 25 years. But even now our knowledge of thioesters is rather limited in comparison with the wealth of information published on normal esters.

A replacement of oxygen in an ester group by sulfur may lead to 3 different types of thio esters, which I would like to call thiolo esters, thiono esters and dithio esters. Thiolo esters show a C=O double bond and behave as typical acylating agents. A well known and very characteristic example of a thiolo ester is the acyl coenzym A, which transfers

acyl groups to nucleophilic substrates in every living cell.



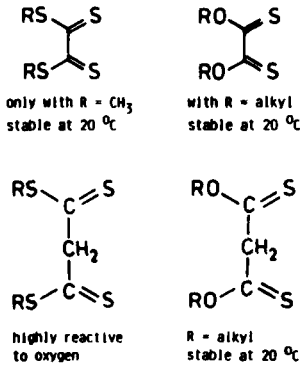
Scheme 1

The chemical properties of thiono and dithio esters are determined by a C=S double bond, formed by lateral overlap of a 3p orbital of sulfur with a 2p orbital of carbon. Sometime ago the resonance energy has been calculated for thiono esters with about 17,4 kcal/mol and for dithio esters with about 8,6 kcal/mol[1]. In agreement with these figures we have always found that the dithio esters are less stable and chemically more reactive than the corresponding thiono esters. This may be illustrated with some typical examples.

STABILITY OF DITHIO AND THIONO ESTERS

From all tetrathio oxalates we have tried to study so far, only the dimethylester was found to be stable at room temperature. Other esters decompose completely even at temperatures of -100°C or less. On the other hand dialkyl dithiono oxalates may be stored at room temperature for years without any decomposition.

Tetrathio malonates are highly sensitive, especially against oxygen. Chemical reactions with tetrathio malonates normally lead to a broad spectrum of products. Therefore the application of tetrathio malonates in synthesis is rather limited. In contrast dithiono malonates are prepared more easily and show a variety of very useful transformations.

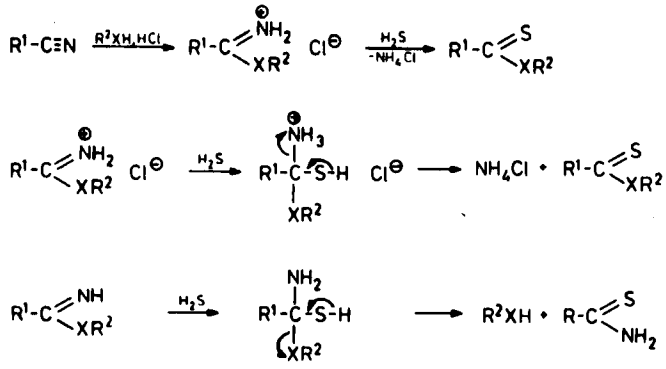


Scheme 2

PREPARATION BY THIOLYSIS

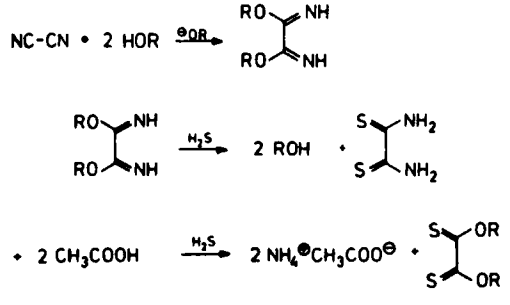
During the last 25 years a considerable number of different approaches for the preparation of dithio and thiono esters have been published. According to our experience the thiolysis of imidoesters or thioloimidoesters with hydrogen sulfide is by far the most versatile procedure for larger quantities of dithio and thiono esters. Going through the recent literature there seem to exist some misconceptions as far as experimental conditions are concerned. In the most simple case the starting material is a nitrile group that is first converted into the imidoester hydrochloride or the thioloimidoester hydrochloride in a Pinner reaction. It is essential to subject the hydrochloride and not the deprotonated imidate itself to a treatment with hydrogen sulfide. Only in this way good yields of thiono or dithio esters are obtained by elimination of ammonium chloride. In the first step hydrogen sulfide adds to the C=N double bond with the formation of a tetrahedral intermediate. In this intermediate the amino group must retain its positive charge, in order to be eliminated in the next step. Starting with the imidate base the tetrahedral intermediate is uncharged. In this case alcohol or mercaptane is eliminated with preference and our product is not the desired thioester but rather

the thioamide.



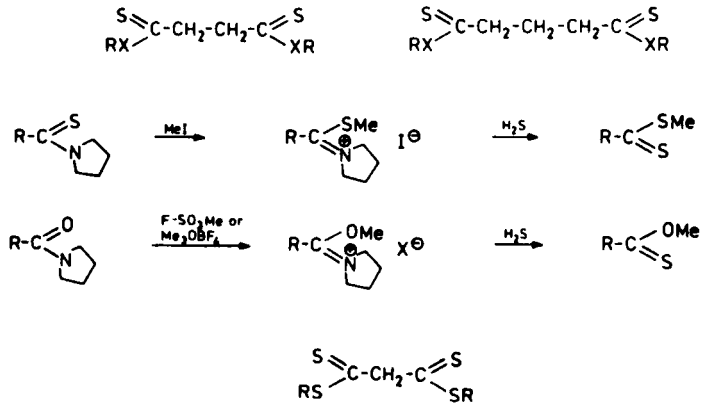
Scheme 3

This fundamental principle is best illustrated by the preparation of the dithiono oxalates. Base catalysed addition of alcohols to cyanogen gives high yields of oxaloimidates. When these imidoesters are dissolved in ether and treated with hydrogen sulfide, the only product is dithio oxamide. Addition of 2 equivalents of glacial acetic acid changes the result completely. Now solid ammonium acetate separates from the reaction mixture and the desired dithiono oxalates are isolated in about 90% yield[2].



Scheme 4

In a number of cases the imidoesters or thioloimido esters are not accessible by a Pinner reaction; in some others the thiolysis step is accompanied by extensive decomposition. These difficulties very often can be overcome by using tertiary amides or thioamides as starting material. Typical examples in this respect are tetrathio malonates and the dithiono or tetrathio esters of succinic and glutaric acid[3]. Pyrrolidine as an amine component is especially useful in obtaining crystalline compounds and in accelerating the alkylation step. For tertiary thioamides the alkylation potential of methyl iodide is normally sufficient. For the oxygen analogs stronger alkylating agents such as magic methyl or oxonium salts are required[3].

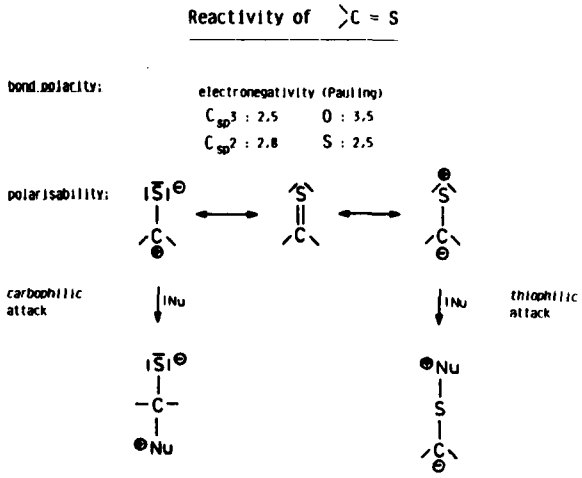


Scheme 5

THIOPHILIC VERSUS CARBOPHILIC ATTACK

The chemistry of thiono and dithio esters is in general fundamentally different from that of the oxygen esters. Thus the thiocarbonyl group in dithio and thiono esters shows a twofold reactivity not observed with the carbonyl group in normal oxygen esters. According to the electronegativity table of Pauling the bond polarity of a thiocarbonyl group should be very low. The corresponding figures are 2,8 for an sp^2 carbon atom and 2,5 for the sulfur atom. Therefore

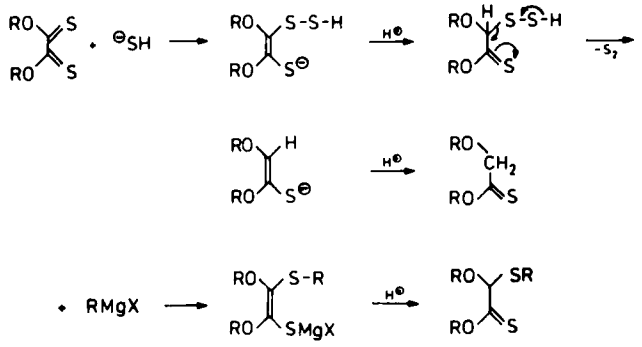
the thiocarbonyl group may be described as a resonance hybrid of the 3 structures. One polar structure shows a negative charge on the sulfur atom and the other one a negative charge on the carbon atom. As a consequence an incomming nucleophile may either attack the carbon atom or the sulfur atom. Both types of reactions are indeed observed. According to our experience the normal reaction pathway is the carbophilic attack by the nucleophile. Numerous examples, however, are also known for a thiophilic attack. This way is obviously favoured in thioesters where the developing negative charge on the thiocarbonyl carbon can be taken over by adjacent groups.



Scheme 6

The structural features of thiono and tetrathio oxalates are such that they favour strongly a thiophilic attack. The developing negative charge on the thiocarbonyl carbon can be stabilized by the adjacent thiocarbonyl group. Therefore no species of higher energy blocks this reaction pathway. According to our experience soft nucleophiles such as negative sulfur or carbanions show predominantly thiophilic attack on dithiono and tetrathio oxalates.

To illustrate this statement I would like to discuss two typical examples. Dithiono oxalates are reduced by potassium hydrogen sulfide to α-alkoxy thiono acetates. Hydrogen sulfide ion presumably adds to the double bonded sulfur. Proton shifts combined with the loss of elemental sulfur finally lead to the reduced product[4]. In a similar way carbanionic reagents such as Grignard solutions or organo lithium compounds attack the thiocarbonyl sulfur to form an intermediate that is hydrolysed to a new thiono ester with an acetalic α-carbon atom[5].

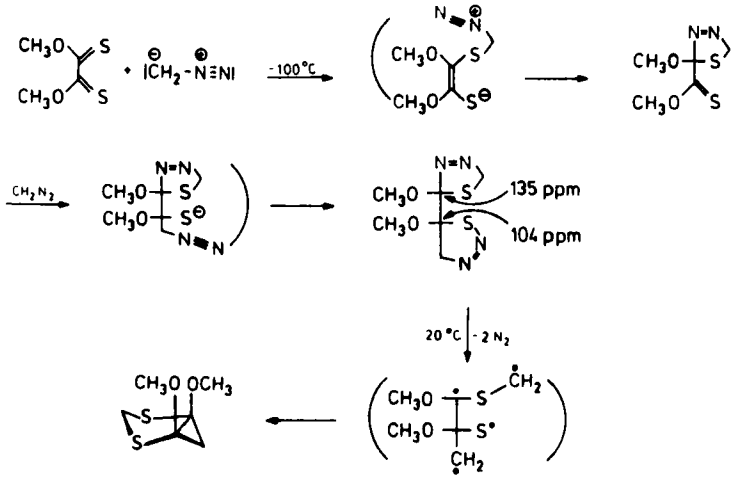


Scheme 7

A very interesting example for thiophilic versus carbophilic attack in the same molecule is the reaction of dithiono oxalates with an excess of diazomethane at -100°C. Under these conditions a crystalline bis-thiadiazoline is formed where both thiocarbonyl groups have added diazomethane. According to the ^{13}C spectral data, however, the bis-thiadiazoline has an unsymmetric structure. The quarternary carbon atoms C-5 and C-5' show a shift difference of 30ppm. This is best explained by a 1,2,3-thiadiazoline ring and a 1,3,4-thiadiazoline ring. We suppose that the first diazomethane reacts by a thiophilic attack, as the negative charge formed can be stabilized by the adjacent thiocarbonyl group. This gives rise to a 1,3,4-thiadiazoline ring. The second diazomethane reacts by a carbophilic attack as a

charge stabilization is no longer possible[6].

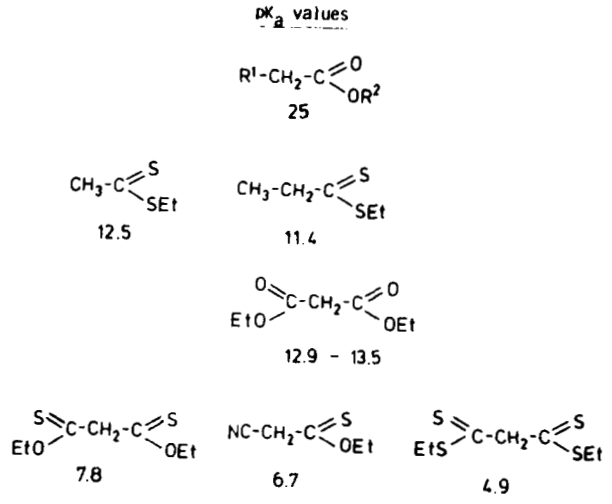
At room temperature the bis-thiadiazoline decomposes to form a bicyclohexane derivative.



Scheme 8

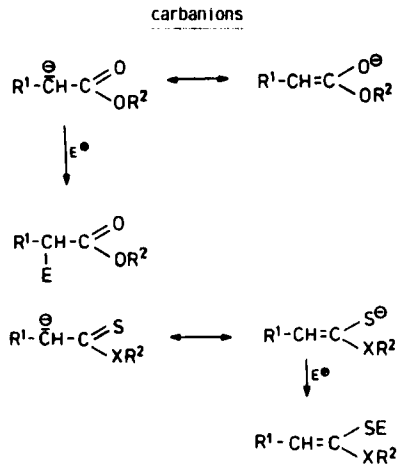
CH-ACIDITY

Apart from the different polarity of the thiocarbonyl and the carbonyl group a second point of fundamental difference between dithio and thiono esters on the one hand and oxygen esters on the other hand is the CH-acidity at the α-carbon atom. The acidity of oxygen esters is normally about pK_a = 25. Simple dithio esters, however, such as dithio acetate and dithio propionate show pK_a values of about 12[7]. This means that dithio and thiono esters are about 13 powers of ten more acidic than their oxygen analogs. The CH-acidity of simple dithio and thiono esters is therefore better comparable to that of malonic esters, which are considered as prototypes of CH-acidic compounds in organic chemistry. In dithiono malonates the CH-acidity goes up to 7.8 and in tetrathio malonates even to 4.9[8]. This means that tetrathio malonates show nearly the same acidity as acetic acid.



Scheme 9

Carbanions of oxygen esters are normally attacked by electrophiles at the α-carbon atom. Attack at the oxygen atom is the exception. With dithio and thiono esters just the reverse is true. Carbanions of sulfur esters are normally attacked by electrophiles at the sulfur atom; attack at carbon is the exception. In other words the carbanion chemistry of thioesters is determined by the exceptionally high nucleophilicity of the negative charge on sulfur.



Scheme 10

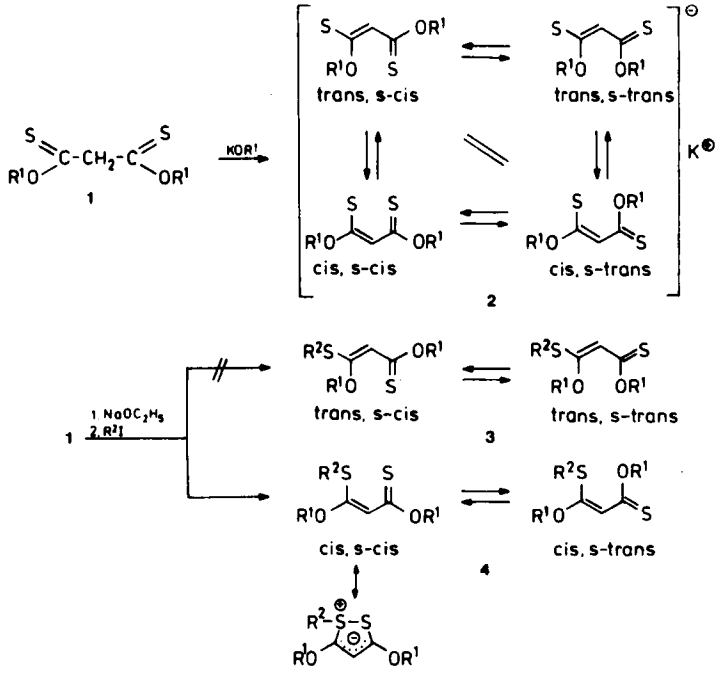
INDIVIDUAL DITHIO AND THIONO ESTERS

After these general remarks on dithio and thiono esters, I would like to come to some individual compounds. Dithiono malonates are readily available from malononitrile and can be stored in the refrigerator for months without any decomposition. They show a rich chemistry that is fundamentally different form classical malonoester chemistry[8-11].

DITHIONO AND TETRATHIO MALONATES

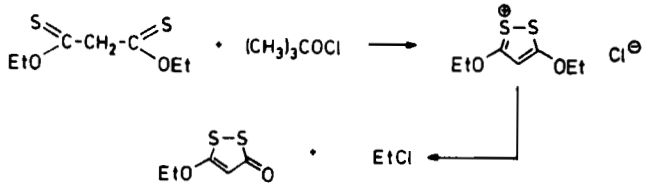
Due to the relatively high acidity of dithiono malonates, their alkali salts are perfectly stable compounds that can be obtained in an analytically pure form by simple recrystallization. These salts show the trans,s-trans configuration in the crystalline state and in solution according to X-ray analysis and Nuclear-Overhauser experiments. Alkylation of these salts lead exclusively to S-alkyl thioenol ethers. The trans,s-trans configuration of the anion is not retained during the alkylation process. The thioenol ether instead has a cis,s-cis or a cis,s-trans configuration, according to Nuclear-Overhauser results. We suppose that

the cis,s-cis arrangement is stabilized by some sort of sulfur-sulfur interaction. To clarify this point an X-ray analysis is desirable[9].



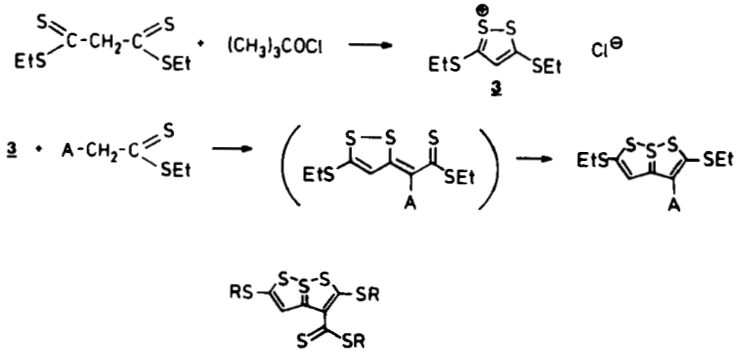
Scheme 11

Dithiono malonates and tetrathio malonates are easily oxidized to 1,2-dithiolium salts by a variety of oxidizing agents. Tert.butyl hypochlorite proved to be especially suitable. The 3,5-bisethoxy derivative obtained from diethyl dithiono malonate is rather unstable at room temperature and alkylates its own anion to yield 5-ethoxy-1,2-dithiol-3-on together with ethyl chloride[10].



Scheme 12

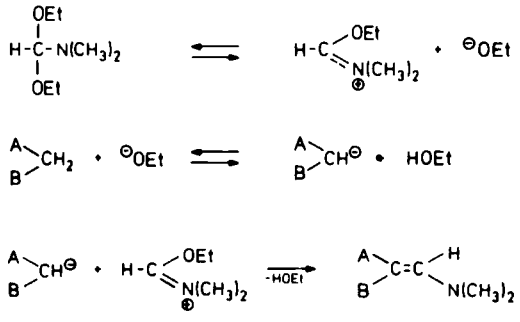
The 3,5-bisethylthio dithiolium salts, obtained by oxidation of diethyl tetrathio malonate, show a higher stability and may be handled at room temperature without any decomposition. A condensation with derivatives of thioacetates leads to the trithiapentalene ring system. Such a condensation is also observed with tetrathio malonate itself. In this way the structure of a red crystalline byproduct in the synthesis of tetrathio malonates could be elucidated. These trithiapentalenes always separate from the red, liquid tetrathio malonates on storage in the refrigerator[11].



Scheme 13

The condensation of amide acetals or aminal esters with acidic methylene compounds leads to aminomethylene derivatives. These compounds are especially useful building blocks in the synthesis of numerous heterocyclic ring systems. The

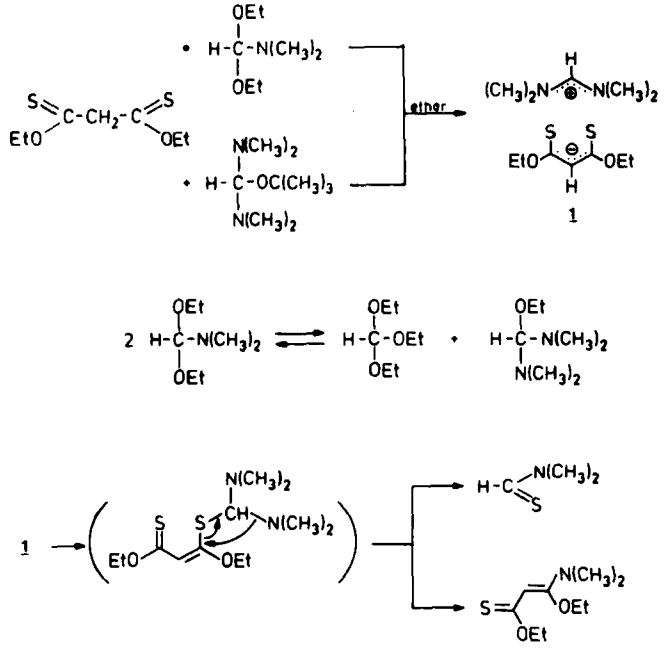
reaction is initiated by an ionic cleavage of the amide acetal. The alkoxide formed generates an anion at the methylenic carbon atom which in turn condenses with the iminium salt to give the endproduct.



Scheme 14

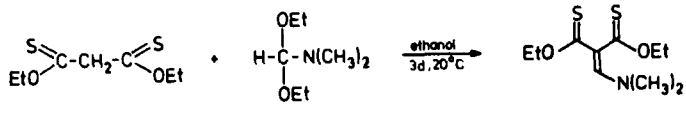
By applying this reaction to diethyl dithiono malonate we made some interesting observations. In ether as a solvent a yellow crystalline precipitate is formed, which was identified as the formamidinium salt of diethyl dithiono malonate. This can be explained by assuming that a dismutation takes place with the amide acetal yielding on ortho ester and an aminal ester. The aminal ester may generate the formamidinium cation and the alkoxide, capable of deprotonating the dithiono malonate. The precipitation of the yellow salt is accelerated and the yield increased considerably by using directly an aminal ester instead of an amide acetal[9].

The yellow salt is rather unstable, especially in solution and decomposes to an orange oil consisting of N,N-dimethyl thioformamide and a thiono acrylic ester. These products are formed by an electrophilic attack of the formamidinium cation at one of the sulfur atoms leading to a covalent intermediate that collapses to the final products[9].



Scheme 15

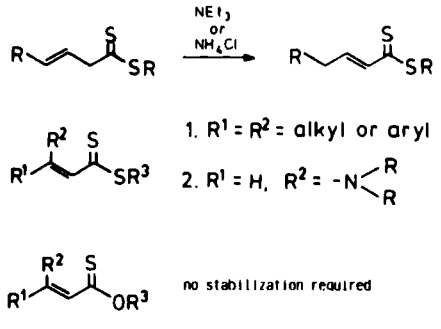
In ethanol as a solvent the reaction between diethyl dithiono malonate and amide acetals takes a different course. After 3 days at room temperature a 55% yield of the desired aminomethylene compound could be isolated. This is the only example so far, where the attack of an electrophile at the central carbon atom of a dithiono malonate has been observed[9].



Scheme 16

α,β-UNSATURATED DITHIO AND THIONO ESTERS

α,β-Unsaturated dithio and thiono esters were first prepared some 10 years ago by the research group of Prof.Thuillier rearranging the double bond from the β,γ-position into the α,β-position[12]. This can be achieved by aliphatic amines or aqueous ammonium chloride solution[13]. In the meantime a number of additional synthetic approaches for α,β-unsaturated dithio and thiono esters have been reported. From these activities it has become clear that α,β-unsaturated dithio esters are prone to dimerize to Diels-Alder-adducts at room temperature. This dimerization is retarded by electronic or steric interactions. In general two alkyl groups in the β-position or one dialkylamino group as potent electron donator will stabilize the monomeric form. In contrast α,β-unsaturated thiono esters do not need any stabilizing substituents.

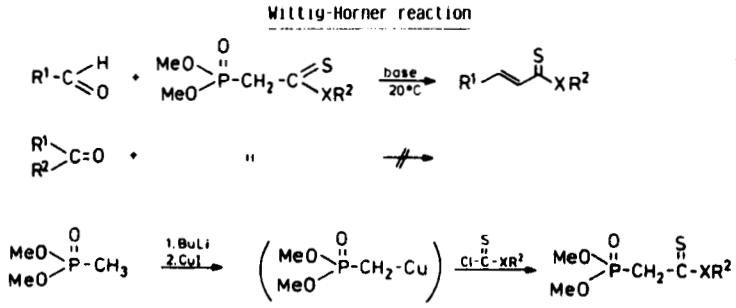


Scheme 17

We have shown recently, that α,β-unsaturated thiono and dithio esters may be prepared in good yield by condensation reactions such as the Horner-Wittig reaction, the Peterson synthesis and the aldol addition[14]. Starting material for the Horner-Wittig reaction are (dimethoxyphosphinyl)thioacetates, which condense with aldehydes in the presence of base. Best results were obtained with mild bases in aqueous medium such as potassium carbonate or potassium hydrogencarbonate. Aqueous conditions also facilitate work up

procedures considerably. Ketones as carbonyl components do not react in the Wittig-Horner condensation. This is probably due to the relatively high acidity of the (dimethoxyphosphinyl)thioacetates compared to their oxygen analogs. High acidity means at the same time low nucleophilicity of the conjugated anion, that is not capable of attacking ketones.

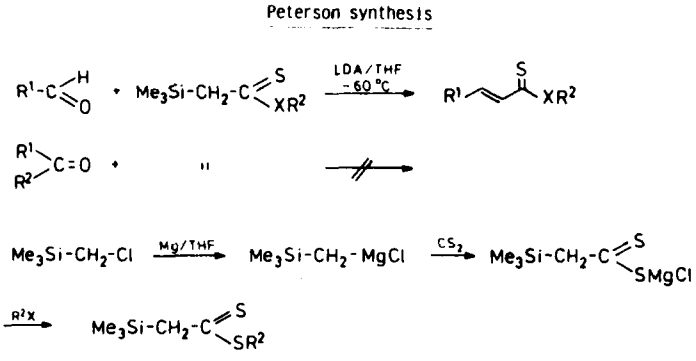
The (dimethoxyphosphinyl)thioacetates may be obtained from methanephosphonic esters. The copper salt, available with butyl lithium and copper(I)iodide, is easily thioacylated with chloro thiocarbonates.



Scheme 18

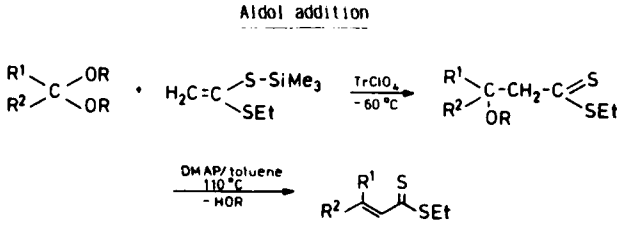
A procedure related to the Wittig-Horner reaction is the Peterson synthesis utilizing silicon instead of phosphorus as an oxophilic element. The condensation with the carbonyl group of an aldehyde is effected at -60°C with a strong base such as lithium diisopropylamide. The reaction conditions at -60°C indicate, that the carbanion formed in the 1.step is more reactive than that formed in the Wittig-Horner synthesis. Its nucleophilicity, however, is again unsufficient to attack also ketones[14].

The trimethylsilyl dithioacetate is best prepared from chloromethyl trimethylsilane via the Grignard reagent followed by addition of carbon disulfide and subsequent alkylation[14].



Scheme 19

The aldol addition for the preparation of α,ß-unsaturated thioesters works best with ketones, used in form of their aliphatic ketals. The second reaction partner, the dithioacetate, is first silylated to give the trimethylsilyl ketenedithioacetal. An excellent catalyst for this type of an aldol addition is trityl perchlorate, first introduced by Mukaiyama and his group[15]. The product obtained in high yield at -60°C is the ß-alkoxy dithio ester. This can be converted into an α,ß-unsaturated dithio ester by heating with 4-dimethylamino pyridine in toluene[14].

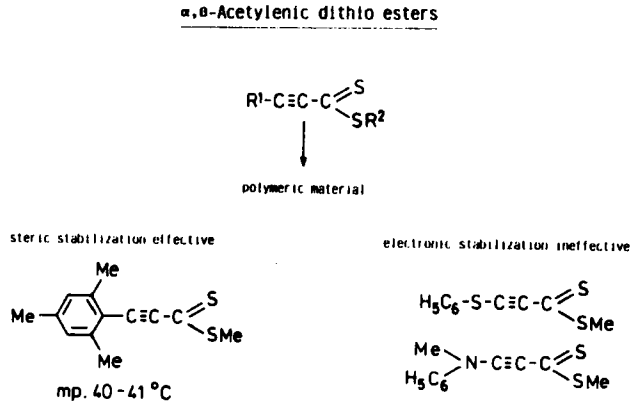


Scheme 20

α,β-ACETYLENIC DITHIO AND THIONO ESTERS

α,β-acetylenic dithio and thiono esters were first investigated by our group in Marburg. According to our experience gathered during the last few years acetylenic dithio esters are a rather unstable class of compounds[16]. They tend to decompose into a complex mixture of mainly polymeric material. The polymerization probably starts with the attack of a nucleophile at the β-position. Therefore bulky groups, protecting the β-carbon atom, will also stabilize the dithio ester function. A typical example is the mesityl group. The corresponding methyl dithio ester is a crystalline compound, perfectly stable at room temperature.

An electronic stabilization by an electron donating group at the β-carbon was found to be ineffective. Typical substituents we tried were phenylthio and methylphenyl-amino[16].

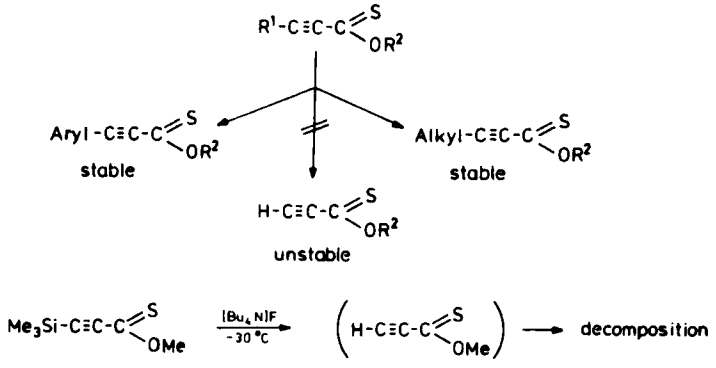


Scheme 21

In contrast to α,β-acetylenic dithio esters the corresponding thiono esters are in general stable compounds, independent whether the substituent R^1 is an aryl or alkyl group. Only the most simple representatives, the thiono propiolates, could not be isolated. Even very smooth methods for their synthesis failed. Desilylation of the trimethylsilyl derivative with tetrabutylammonium fluoride at -30°C

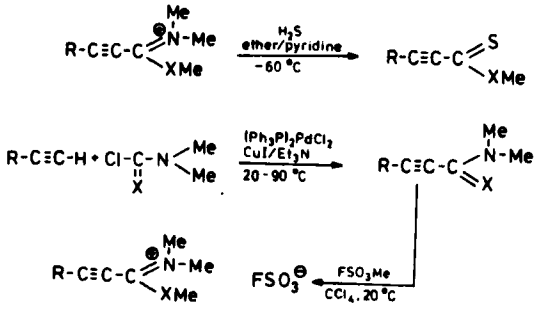
lead to an yellow oil consisting mainly of the desired thiono ester, according to spectroscopic data. A purification, however, was unsuccessful due to rapid decomposition reactions[16].

α,β-Acetylenic thiono esters



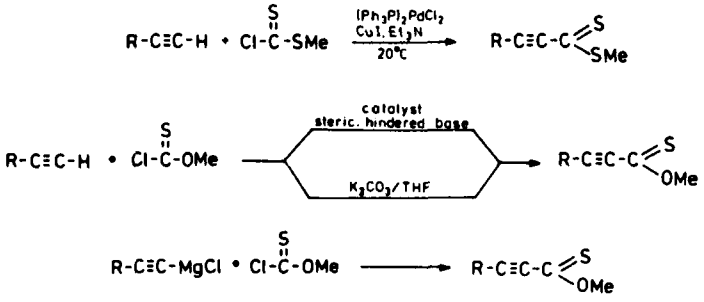
Scheme 22

The most general preparation of α,β-acetylenic dithio and thiono esters is the thiolysis of suitable iminium salts. This reaction must be carried out at low temperatures of -50 to -60°C in order to avoid addition of H_2S to the triple bond. The tertiary amides or thioamides, required as starting material, were obtained in a straight forward procedure from the acetylene and a carbamoyl or thiocarbamoyl chloride. An effective catalyst for this conversion proved to be the complex of palladium(II)chloride and triphenyl phosphine together with copper(I)iodide in an aliphatic amine as a solvent. For tertiary thioamides the yields are nearly quantitative[17].



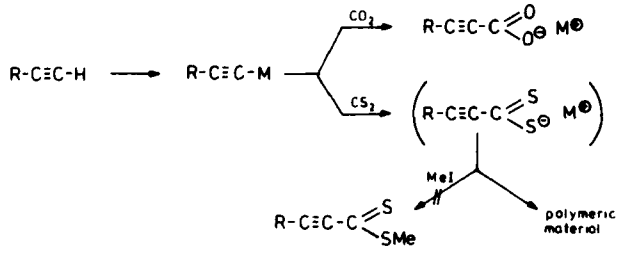
Scheme 23

As far as α,β-acetylenic dithio esters are stable compounds, they have also been obtained directly form the acetylene and a chloro dithiocarbonate. This reaction is catalyzed once again by the complex of palladium(II)chloride and triphenyl phosphine. The same approach, however, gives markedly lower yield in the preparation of the α,β-acetylenic thiono esters. As triethylamine reacts vigorously with the chloro thionocarbonate a more hindered tertiary amine is required. Medium yields were observed with 1,2,2,6,6-pentamethyl piperidine. Other alternatives are potassium carbonate in tetrahydrofurane or an acetylenic Grignard reagent[16.17].



Scheme 24

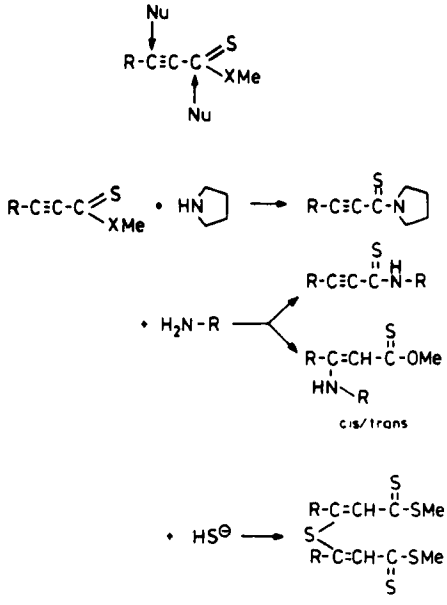
In the oxygen series the most elegant way in preparing α,ß-acetylenic carboxylic acids is the reaction of a metal acetylide with solid carbon dioxide. This reaction fails completely with carbon disulfide instead of carbon dioxide; only polymeric material is obtained. We suppose, that the α,ß-acetylenic dithio carboxylate is indeed formed in the first step. Such dithiocarboxylates, however, are even more unstable than the corresponding dithio esters. Nucleophilic attack at the ß-carbon atom probably initiates polymerization[17].



Scheme 25

α,ß-acetylenic dithio and thiono esters show two centres for nucleophilic attack: the thiocarbonyl carbon and the ß-carbon. The site of attack depends on individual factors. Cyclic secondary amines such as pyrrolidine reacted at room temperature with thiono and dithio esters to form the corresponding thioamides exclusively. Primary aliphatic amines

very often lead to mixtures of products resulting from attack on both sites. With n-propyl amine and a thiono ester only addition at the ß-carbon was observed resulting in a cis/trans mixture at the new double bond. Such mixtures were also obtained in base catalyzed reactions with thioles or hydrogen sulfide[18].

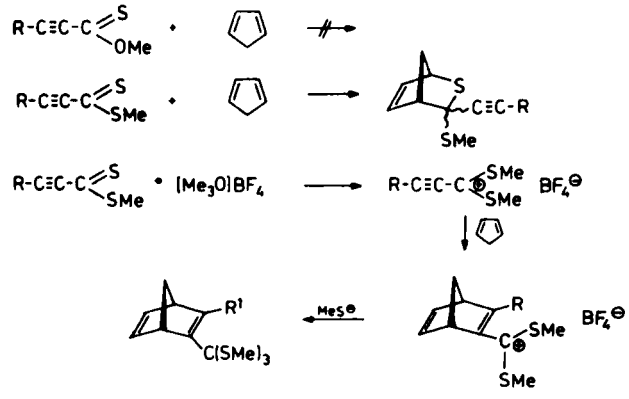


Scheme 26

α,ß-acetylenic thiono esters were found to be poor dienophiles in Diels-Alder reactions. No addition, neither at the triple bond nor at the thiocarbonyl group, was observed with cyclopentadiene. In contrast to this observation α,ß-acetylenic dithio esters react readily with cyclopentadiene to form thia-norbornene derivatives as a mixture of endo/exo isomers[16,17].

Alkylation of the thiocarbonyl group with oxonium salts leads to a stable cationic species with strong dienophilic properties. It readily adds cyclopentadiene, this time at

the triple bond, yielding a cationic norbornadiene derivative. Trapping with thiols leads to stable orthoesters with sulfur[18].

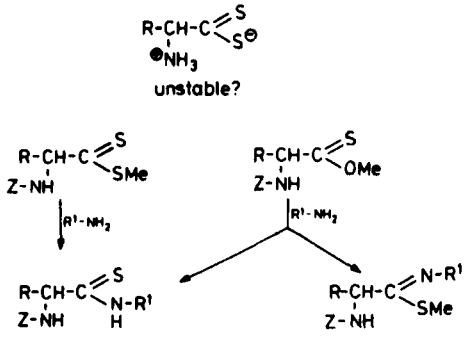


Scheme 27

α-AMINO DITHIO AND THIONO ESTERS

For everyone working on dithio and thiono esters, the preparation of α-amino thioacid derivatives, suitable for peptide synthesis, is a special challenge. As far as I know a sulfur analog of an α-amino acid has never been prepared; such a species is supposed to be unstable. Condensing the amino function with a good protecting group and converting the dithio acid into a dithio or thiono ester should lead to suitable building blocks for thiopeptide bond formation.

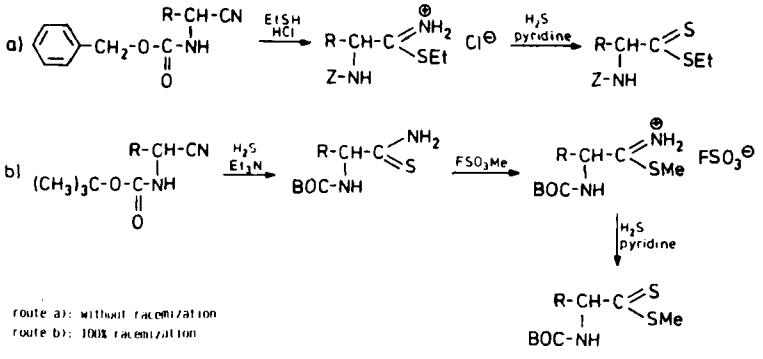
It is well known that the dithio ester function reacts readily at room temperature with primary amines to form thioamides. Therefore no special activation of the dithio ester is required for the formation of a thiopeptide bond. With thiono esters the aminolysis occurs less readily and may lead to an thioloimido ester as a byproduct due to the elimination of hydrogen sulfide. Such a side reaction was indeed observed by Lawesson and his group and since then efforts have concentrated on the corresponding N-protected dithio esters[19].



Schema 28

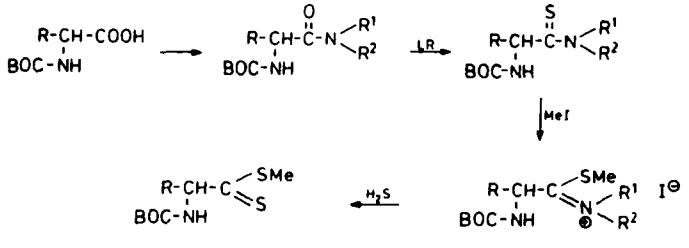
According to our experience the best starting material for N-protected, α-amino dithio esters are α-amino nitriles. The method of their conversion into the dithio ester function depends on the protecting group. The carbobenzoxy group for example survives Pinner conditions and α-amino nitriles with this group are therefore readily converted into dithio esters by the classical route[20].

BOC-protected α-amino nitriles are cleaved in the Pinner reaction. Therefore their nitrile group is first converted into a primary thioamide by a base catalyzed addition of hydrogen sulfide. Subsequent alkylation with magic methyl leads to the thioloimidate which is then thiolysed with preservation of the protecting group[20].



Scheme 29

A central question in peptide chemistry is racemization at the α-carbon atom of amino acids. This question has not been addressed extensively for α-amino dithioesters and endothio peptides. The first problem to be solved is therefore the synthesis of chiral α-amino dithio esters. Some examples have been reported in the literature, based on the same reaction principle. A natural, N-protected, α-amino acid is converted into its amide, sulfurated with Lawessons reagent, S-methylated with methyl iodide and thiolysed with hydrogen sulfide. In this reaction sequence the chiral centre survives[21]. An unambigous proof, however, is still missing.

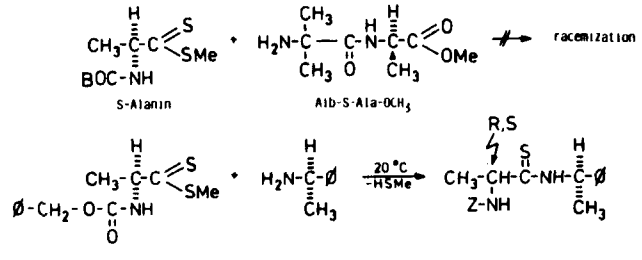


Scheme 30

When we started with an optically active α-amino nitrile and converted it via the Pinner conditions into a dithio ester, the optical activity was also preserved. This is not true for our second approach passing through the thioamide. Here the result was 100% racemization. We suppose that this occurs during the amine catalyzed conversion of the nitrile function into the thioamide, as the following steps are similar to the first reaction sequence[20].

The second question to be answered concerns the preservation of optical activity during the coupling step. Is optical activity retained when an N-protected, α-amino dithio ester reacts with the amino group of a second amino acid to form the thiopeptide bond? This question is still open. There are, however, some preliminary observations. Jensen and Senning reported that an Aib-S-Alanin-methylester did not react with a BOC-protected α-amino-S-alanin-dithioester. The starting materials could be recovered; the dithioester, however, was completely racemized[22].

We have tried to study the coupling of N-protected α-amino dithio esters with primary amines in a model reaction. With this aim we condensed the S-configurated N-carbobenzoxy-S-alanin dithioester with the optically active, R-configurated phenylethyl amine at room temperature in ether. The reaction was complete after 48 hours. The chiral centre in the alanine residue, however, was totally racemized. This was confirmed by running the same reaction with the D,L-Alanin dithioester, leading to the same product[20].



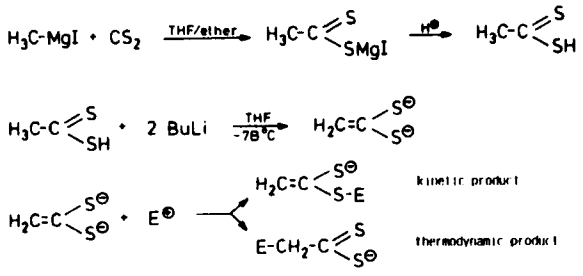
Scheme 31

According to our experience these results are not surprising. The CH-acidity at the α-carbon of N-protected, α-amino dithio esters should be in the same range as those in ordinary dithio esters. This means that for N-protected, α-amino dithio esters pK_a-values of about 9-10 are to be expected. Compounds of such a CH-acidity are not inert in the presence of aliphatic amines. They are deprotonated to a very small extent and racemization will be the consequence.

Therefore the highly attractive approach of forming endothio peptide bonds by the condensation of α-amino dithio esters with amino acids will most probably end in a dead street.

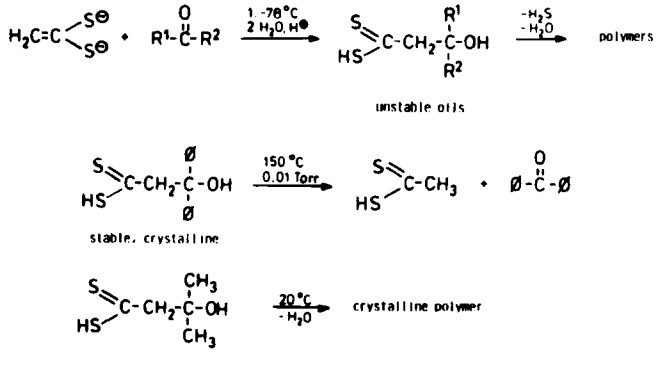
DIANIONS OF DITHIO ACIDS

During the last few minutes of my lecture I would like to turn your attention to the chemistry of dithio acids. This is really unexplored territory. Only Beslin and Houtteville a few months ago have reported studies concerning the addition of dilithio dithiopropionate to aldehydes[23]. Dithio acids are most conveniently prepared from Grignard reagents and carbon disulfide in tetrahydrofurane and can be kept in the refrigerator for a few weeks without serious decomposition. With strong bases, such as butyl lithium, their dianions are formed. These are rather potent ambident nucleophiles. An electrophilic species will either attack the sulfur atom or the α-carbon atom. The attack on sulfur gives rise to the kinetic product whereas attack on carbon leads to the thermodynamic product. This different behaviour may be illustrated by a few examples.



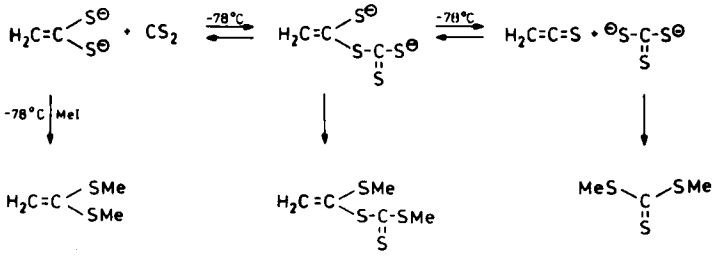
Scheme 32

The dianion of dithio acetic acid adds readily to aldehydes or ketones. Even at -78°C we observe C-addition exclusively. On acidification ß-hydroxy dithio acids are isolated in quantitative yield. They are, however, unstable at room temperature condensing to mixtures of polymers by elimination of both, hydrogen sulfide and water. A few exceptions could be found. Two aryl groups at the ß-carbon atom will stabilize the monomeric form. Thus the adduct with benzophenone is a stable, crystalline compound showing a retro aldol reaction on heating. The liquid adduct with acetone on the other hand solidifies slowly at room temperature. Thereby water is eliminated exclusively and a crystalline polymer is formed[24].



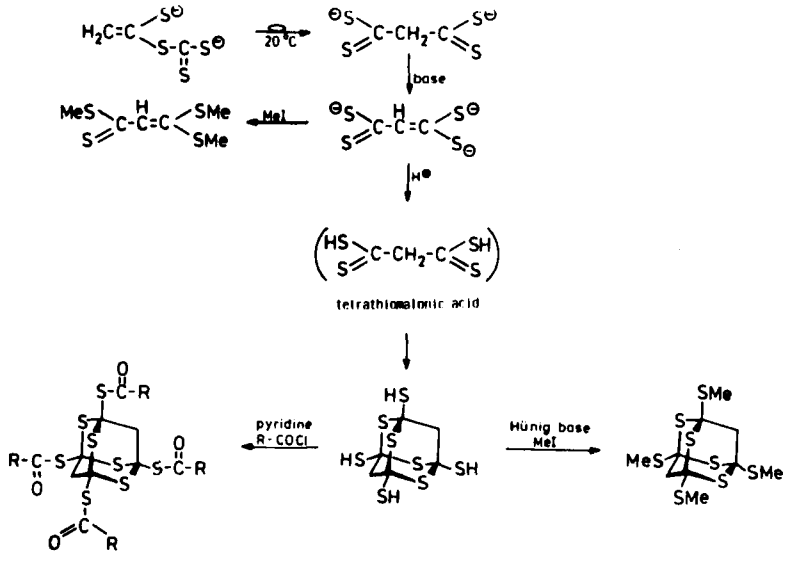
Scheme 33

At -78°C the dianion of dithio acetic acid shows S-addition to carbon disulfide. This is demonstrated by alkylation with methyl iodide, giving rise to methylvinyltrithiocarbonate. This main product, however, is accompanied by two more compounds, namely dimethyl dithioketene acetal and dimethyl trithiocarbonate. Such a result may be explained by an equilibrium between the starting material, the S-addition product and an elimination reaction leading to thioketene and trithiocarbonate[24].



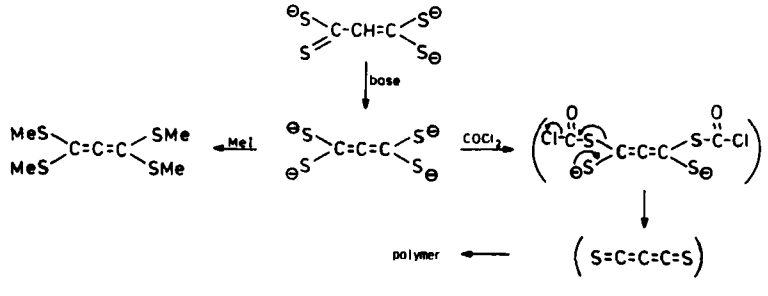
Scheme 34

When the reaction mixture with the S-addition product is allowed to warm up to room temperature, the thermodynamically more stable C-addition product is formed, which is the dianion of tetrathiomalonic acid. This rearrangement can be completed by addition of base, e.g. lithium hexamethyldisilazane, to form the more stable trianion. Alkylation at this stage leads to a well known dithio acrylic ester. By acidification the unknown tetrathiomalonic acid is to be expected. This acid, however, seems to be an unstable product, that readily forms a stable dimer. We would like to propose for this dimer a tetrathiaadamantane skeleton. This dimer can be alkylated or acylated without difficulty; it does, however, not revert to the trianion with excess base. The dimeric structures are supported by mass spectroscopy and other spectroscopic data[24].



Scheme 35

The trianion has one hydrogen left in the molecule. This can be abstracted with another mole of lithium hexamethyldisilazane leading to the tetraanion of tetrathio malonic acid, which is at the same time the tetraanion of tetramercapto allene. Its structure is established by a simple methylation to form a known compound, tetrakis(methylthio)allene. The further chemistry of the tetraanion is right now under investigation. With some reagents, e.g. phosgene, elimination reactions are prevailing yielding polymeric material, probably via the unstable carbon subsulfide[24].



Scheme 36

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