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Author's Review

2-Thiazolin-5-thiones, a New Type of Sulfur Heterocycle Synthesis and Reactions

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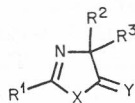
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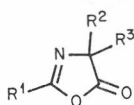
Simple syntheses of 4,4-disubstituted 2-thiazolin-5-thiones, which have so far been difficult to obtain, are described. These compounds are stable and undergo a number of different reactions. The first type of reaction discussed here are cyclosubstitutions, which occur on heating in the presence of electron-deficient acetylenes. 1,3-Dithiafulvenes are thus formed *via* nitrile elimination. Thiazolinthiones show different chemical behaviour in reactions with ynamines. On warming, thiazolinylidene-thioamides and -thioketones are formed *via* a [2+2] cycloaddition, followed by an electrocyclic ring opening reaction. The third reaction type has been observed in the conversion with 1,3-dipolar reagents. *In situ* generated benzonitriliumbetaines undergo 1,3-dipolar cycloaddition to the exocyclic C,S-double bond and form dithia-spiro[4.4]nonadienes.

1. INTRODUCTION

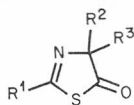
Five-membered heterocycles of type 1 have been known for quite some time and have been thoroughly investigated. Thus, 2-oxazolin-5-ones (azlactones) 2 have become the most important, as they are of special interest



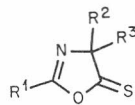
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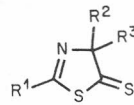
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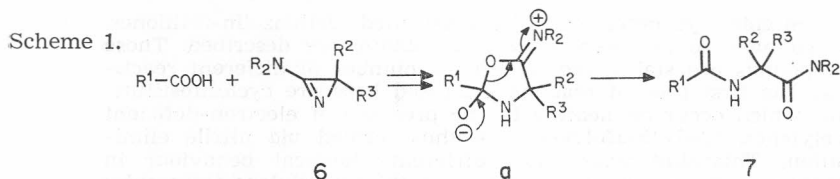
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for the synthesis and chemical behaviour of peptides (see ref.¹⁻³). Due to their wide-ranging reaction possibilities, they have also gained significance as reaction intermediates.⁴ The formal replacement of one or both oxygen atoms in formula 2 by sulfur gives 2-thiazolin-5-one 3, 2-oxazolin-5-thione 4 and 2-thiazolin-5-thione 5, respectively. 3 is by far the most important of these

three classes of compounds.⁵ 2-Thiazolin-5-ones **3** achieved special importance as intermediates in the Edman-degradation, an often used method for the determination of the amino acid sequence of peptides.⁶ For quite some time heterocycles of type **3** have also been known as useful synthetic intermediates.^{5,7} 4,4-Disubstituted 2-oxazolin-5-thiones of type **4**, however, seem to be practically unknown, in contrast to 4-methylene-2-oxazolin-5-thiones which have been described by several groups of authors.⁸

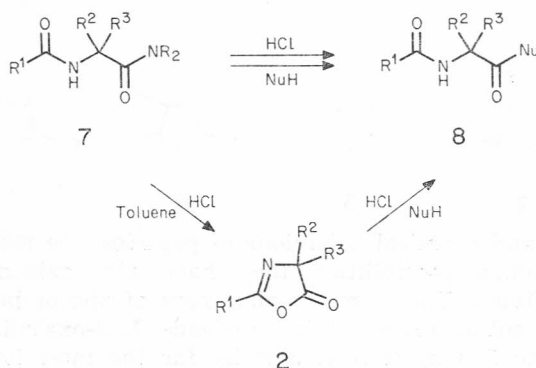
Only recently have some members of the class of 2-thiazolin-5-thiones **5**, the di-sulfur analogues of azlactones, been described. These compounds, hitherto rarely investigated are the subject of this article.

During the last couple of years we have been intensively engaged in investigating the reactions of 3-amino-2H-azirines (**6**).⁹⁻¹² Besides ring expansion reactions^{11,12}, we are mainly interested in the transformations with carboxylic acids.^{13,14} Under very mild conditions diamides of type **7** are thereby formed; intermediates are probably zwitterions **a**.



Scheme 1 shows that compounds **7** are *N*-acyl amino acid amides. Instead of carboxylic acids, amino acids and peptides can be transformed with aminoazirines **6**, which leads to dipeptides resp. polypeptides with *N,N*-disubstituted amide function at the carboxylic terminus.^{15,16} As the extension of peptide chains, according to the method in Scheme 1, is also successful with bulky substituents, aminoazirines (**6**) are obviously amino acid equivalents which could be of interest in the synthesis of peptides.^{17,18} This however, posed the problem of selectively converting the terminal disubstituted amide groups of the peptide derivative **7** to carboxylic acid derivatives suitable for further use in the synthesis of the peptide chain. We succeeded in doing so by treating compounds **7** with HCl-gas in the presence of an appropriate nucleophile¹⁵⁻¹⁷ (Scheme 2). This transformation, during which dimethylaminehydrochloride is formed as a by-product, takes place with a surprisingly high selectivity.^{15,19}

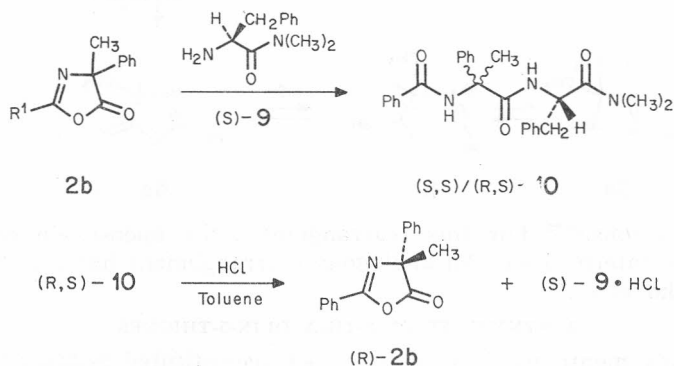
Scheme 2.



2-Oxazolin-5-ones **2** occur as intermediates of this selective amide cleavage¹⁵ and can be isolated in very good yields if the reaction is performed in the absence of nucleophiles.

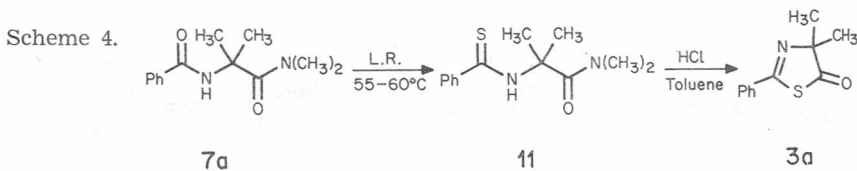
These observations were used to develop a new, easily performable synthesis of 2-oxazolin-5-ones.^{15,20} As an example, Scheme 3 outlines the synthesis of the optically active 2-oxazolin-5-one (*R*)-**2b** (resp. (*S*)-**2b**). This synthesis included the separation of the mixtures of diastereomers (*S,S*)/(*R,S*)-**10** obtained by the reaction of racemic **2b** with *L*-phenylalanine-dimethylamide ((*S*)-**9**) by flash-chromatography on silica gel and treating the suspension of e.g. (*R,S*)-**10** in toluene with HCl-gas.

Scheme 3.



The precipitate of (*S*)-**9**·HCl formed was filtered off and the filtrate reduced by evaporation. After recrystallization, the isolated (*R*)-**2b** (yield 39%) showed a $[\alpha]_D^{20}$ value of -127° .^{15,20,21}

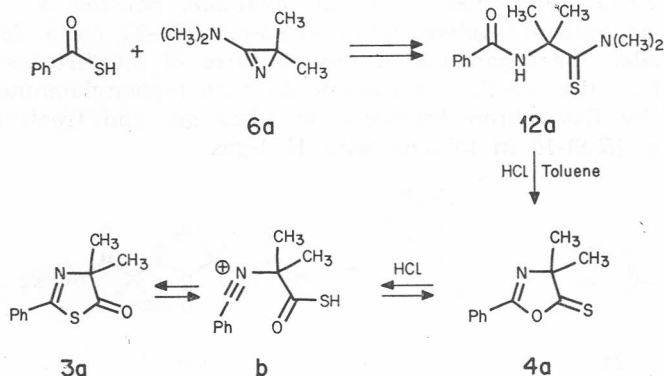
According to Scheme 2 it should be possible to obtain sulfur analogues of 2-oxazolin-5-ones **2** of type 3—5 by acid-catalyzed cyclization of the mono- and dithioamides derived from **7**. Sulfurization of diamide **7a** with Lawesson-reagent²² in toluene at 55—60 °C selectively leads to monothioamide **11** (not isolated) (Scheme 4), which, when HCl-gas was bubbled through the reaction solution, gave the 2-thiazolin-5-one **3a** in approx. 85% yield. This cyclization corresponds to the one for *N*-thio-benzoyl- α -amino amide described by Barrett.⁵



However, the cyclization of monothioamide **12**, isomer of **11**, gave a surprising result (Scheme 5). The reaction of thiobenzoic acid with aminoazirine **6a** afforded **12a** in approx. 90% yield. Treatment of a suspension of **12a** in toluene with HCl-gas at 80 °C, after the usual work-up procedure, gave the isomeric compound **3a** and not **4a**²⁰ as expected. With the aid of ¹H-NMR investigations it was shown that both heterocycles **4a** and **3a** were present after two minutes of reaction time in a ratio of 2:1, after five minutes, however, this ratio changed to 1:2. If after two minutes — at

this point no 12 can be detected in the reaction mixture — an excess of dimethylamine is added, then the thioamides 12 and 11 are isolated in a 2:1 ratio, *i.e.* the trapping products of 4a and 3a. It is observable that 2-oxazolin-5-thione 4a smoothly rearranges to 2-thiazolin-5-one in acidic

Scheme 5.

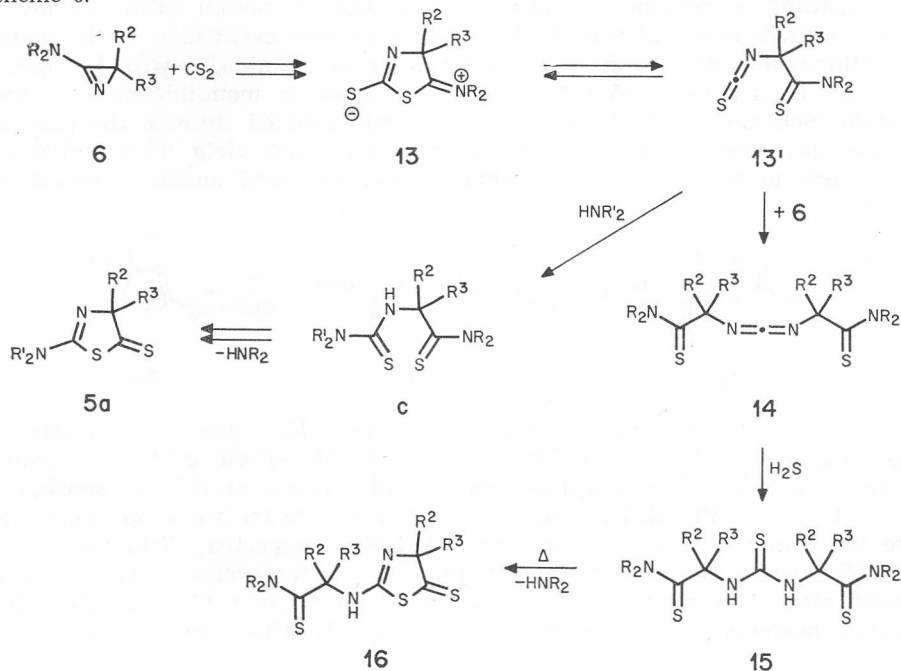


reaction conditions.^{20,23} For this rearrangement the open-chain compound *b* is a plausible intermediate. An analogous rearrangement has also been reported by Kvitko *et al.*²⁴

2. SYNTHESIS OF 2-THIAZOLIN-5-THIONES

As already mentioned in Chapter 1, 4,4-disubstituted 2-thiazolin-5-thiones 5 are a class of compounds which have hardly been investigated to date. Until now the only known representatives obtainable in reasonable yields have been synthesized according to the reaction shown in Scheme 6.²⁵⁻²⁷

Scheme 6.

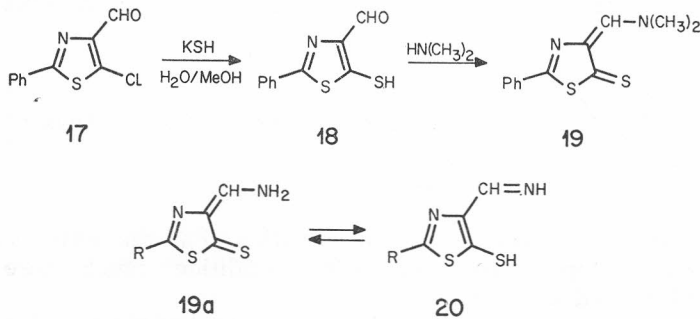


The (1:1)-adducts which are obtained from the reaction of aminoazirines **6** and CS_2 and which are present as valence polaromers **13** and **13'** thereby undergo, in the presence of primary or secondary amines, isomerization to 2-thiazolin-5-thiones **5a** which contain an amino group on C(2). During this reaction thiourea *c* could, for instance, occur as an intermediate. Similarly, the production of 2-thiazolin-5-thiones **16** can be explained (Scheme 6)^{25,27}: a second aminoazirine molecule reacts with the isothiocyanate form **13'** of the (1:1)-adduct to form carbodiimide **14**, a (2:1)-adduct. The latter reacts with hydrogen sulfide to give the symmetrical thiourea **15**, which on heating reacts to 2-thiazolin-5-thione **16** by elimination of the amine HNR_2 .

A 4,4-bis(trifluoromethyl)-2-thiazolin-5-thione of type **5** was isolated in a small yield by the cycloaddition of bis(trifluoromethyl)-substituted nitrile ylides to CS_2 .²⁸

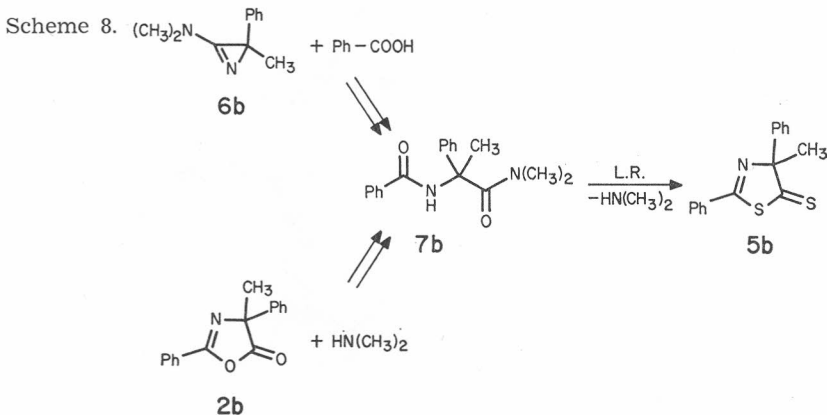
Some 4-methylen-2-thiazolin-5-thiones of type **19** are also described in the literature (Scheme 7). Rout *et al.*²⁹ for instance, synthesized merocyanines containing this heterocycle. So far, the only synthesis with good yields has been described by Kvitko *et al.*²⁴ (Scheme 7). In both groups of Kvitko and

Scheme 7.

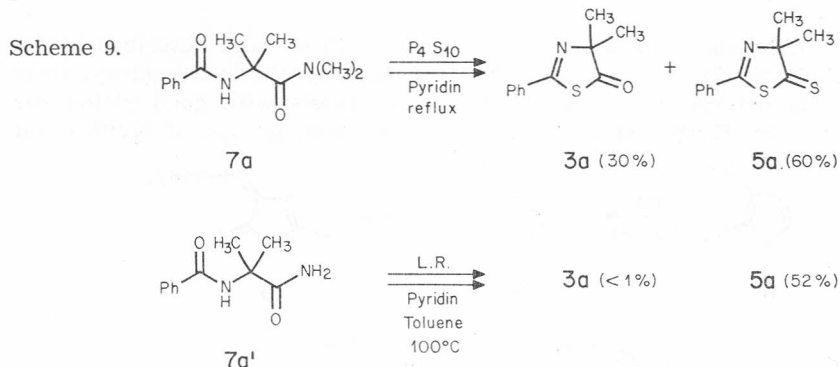


Minkin⁸ detailed calculations were carried out to determine the tautomeric equilibrium $19a \rightleftharpoons 20$. The heats of atomization calculated according to PPP-method show that **19a** is the more stable tautomer. Recently, Drach *et al.*³⁰ have described the synthesis of 4-phosphorylen-2-aryl-thiazolin-5-thiones.

Based on the reactions shown in Scheme 6, the cyclization of *N*-thioacyl amino acid thioamides of type *c* seemed to be a generally applicable synthetic pathway for 2-thiazolin-5-thiones **5**. Several of the realised examples are listed below.

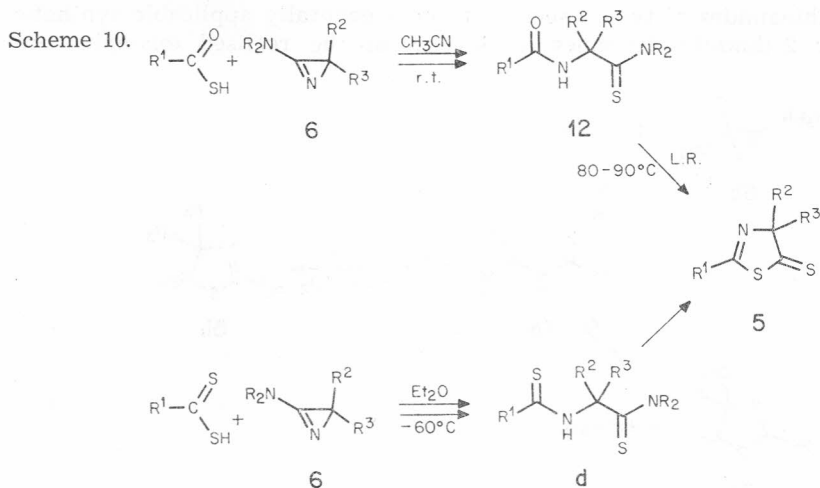


In the case of diamide **7b** (Scheme 8), which was obtained by the reaction of aminoazirine **6b** with benzoic acid or by ring opening of 2-oxazolin-5-one **2b** with dimethylamine, the sulfurization with Lawesson-reagent leads in a modest yield to **5b**, which is difficult to purify. During the treatment of the analogous diamide **7a** with Lawesson-reagent (cf. Scheme 4) partial cyclization to 2-thiazolin-5-one **3a** occurs before the second amide group is sulfurized. The sulfurization of **7a** with P_4S_{10} also proved to be unsatisfactory as a mixture of **3a** and **5a** (Scheme 9) was obtained, separable only by chromatography and with great losses.¹⁷ If, however, diamide **7a'**, instead of *N,N*-dimethylamide **7a**, was treated in a mixture of toluene and pyridine at 100 °C with 2.5 equivalents of Lawesson-reagent, then practically only **5a** was produced.¹⁷



This result reflects the general observation that the conversion of the terminal amide group occurs under acidic conditions much more easily in the *N,N*-disubstituted case.^{15,17}

The preparatively most efficient and elegant pathway to 2-thiazolin-5-thiones proved to be the reaction shown in Scheme 10.^{20,31} The reaction of aminoazirine **6** with thiocarboxylic acids leads in good yields to *N*-acyl amino acid thioamides **12** which, when treated with Lawesson-reagent at 80–90 °C, convert directly to heterocycles **5**. The transformations of aminoazirines **6**



with dithiocarboxylic acids proceeded with smaller yields. In these reactions dithioamides *d*, which occur as intermediates, could not be detected. On the contrary, under these reaction conditions or during work-up a spontaneous cyclization to **5** took place.

TABLE I
2-Thiazolin-5-thiones **5**, Synthesized According to Scheme 10

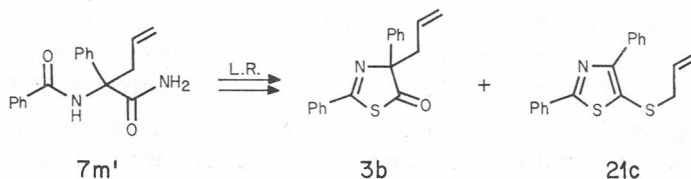
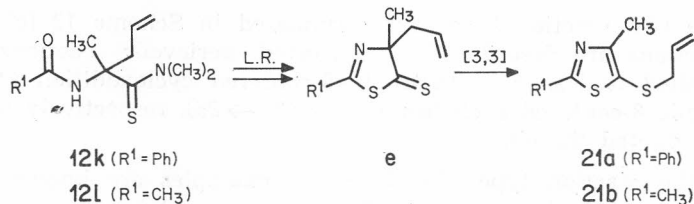
5	R ¹	R ²	R ³	m. p./°C	Yield/%
<i>a</i>	Ph	CH ₃	CH ₃	43—44	85
<i>b</i>	Ph	Ph	CH ₃	61—63	50
<i>c</i>	Ph	CH(CH ₃) ₂	CH ₃	49—50	90
<i>d</i>	Ph	CH=CH ₂	CH ₃	oil	70
<i>e</i>	Ph	Ph	Ph	129—130	60
<i>f</i>	C ₆ H ₄ NO ₂	CH ₃	CH ₃	112—114	50 ^a
<i>g</i>	C ₆ H ₄ OCH ₃	CH ₃	CH ₃	119—120	30 ^a
<i>h</i>	C(CH ₃) ₃	CH ₃	CH ₃	oil	55
<i>i</i>	CH ₃	CH(CH ₃) ₂	CH ₃	oil	85
<i>k</i>	CH ₃	CH=CH ₂	CH ₃	oil	65
<i>l</i>	CH ₃	CH ₃	CH ₃	oil	75

^a The monothiodiamide of type **12** has been synthesized by reacting the corresponding benzoic acid chloride with aminoisobutyric acid dimethylthioamide.

In Table I all the so far synthesized 2-thiazolin-5-thiones of type **5** are collected. They are mostly red crystalline compounds with characteristic spectroscopic properties. The UV-spectrum of **5a** (hexane), for instance, shows, besides intensive ($\epsilon \geq 10000$) absorption peaks at 316, 258 and 241 nm, two very weak ($\epsilon \approx 35$) long wavelength absorptions at 509 and 486 nm. Especially useful for the characterization is the ¹³C-NMR spectrum (CDCl₃): C(5) of **5a** appears as a singlet at 250.1 ppm, C(2) at 161.6 ppm and C(4) at 96.7 ppm.

The attempt to produce the 4-allyl-4-methyl-derivative (**5**, R² = CH₂CH=CH₂, R³ = CH₃) is particularly worth mentioning (Scheme 11).

Scheme 11.

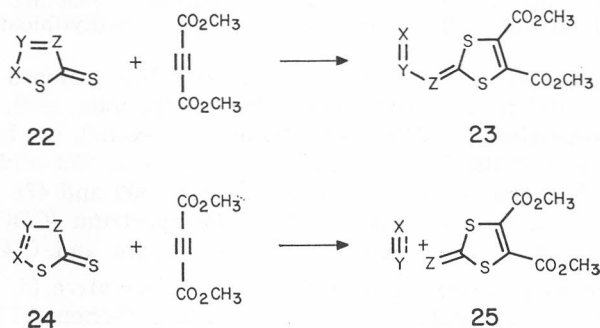


In this reaction, thiobenzoic acid was reacted with 2-allyl-3-dimethyl-2-amino-2-methyl-2H-azirine (6, $R = R^2 = \text{CH}_3$, $R^3 = \text{CH}_2\text{CH} = \text{CH}_2$) to give thioamide 12k, which was subsequently treated with Lawesson's reagent. Contrary to expectation, only the thiazole derivative 21a, and not 2-thiazoline-5-thione e, was isolated in approx. 75% yield. Apparently, the primary product e undergoes a fast Thio-Claisen rearrangement at the reaction temperature of 80–90 °C to form the thermodynamically more stable thiazole. The reaction of thioamide 12l with Lawesson's reagent showed comparable results. During the treatment of diamide 7m' with Lawesson's reagent a (1:1)-mixture of both products 3b and 21c was obtained in the total yield of approx. 70%. The formation of thiazole 21c again has to be explained by the [3,3]-rearrangement of a primary product of type e, whereby amide-cyclization, after monosulfurization of the benzamide function, is necessary for the production of 3b (cf. Scheme 4).

3. REACTIONS OF 2-THIAZOLIN-5-THIONES WITH ACETYLENE-CARBOXYLIC-ESTERS AND NITRILES

Recently, Drodz and Zefirov have comprehensively covered sigmatropic additions (e. g. 22 \rightarrow 23) and cyclosubstitutions (24 \rightarrow 25) of five-membered heterocycles with an exocyclic double bond, in particular a C,S-double bond, in an excellent review article.³²

Scheme 12.

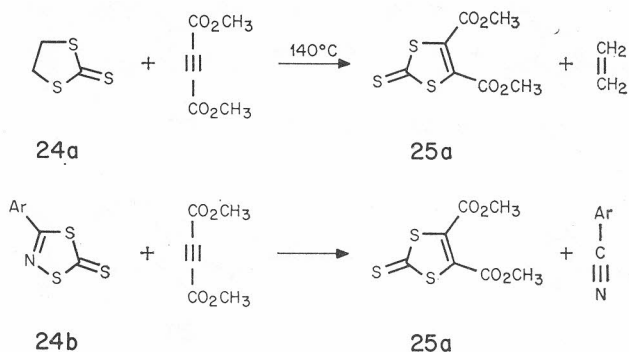


These two reaction types are formulated in Scheme 12 (cf. also ref.³³). Both reactions are described³² as concerted, pericyclic reactions, namely as the so called isodesmic, sigmatropic 8-centered cycloaddition (22 \rightarrow 23) and as isodesmic 8-centered cyclodismutation (24 \rightarrow 25), respectively (cf. ref.³² and literature quoted therein).

For the reaction type 22 \rightarrow 23 many examples are known which have been comprehensively covered.³² Further papers have appeared lately.^{34,55} Less frequent are however, the reactions of type 24 \rightarrow 25. To the best of our knowledge, the first of such reactions were described by Easton and Leaver^{36,37} and by Noël and Vialle.³⁸ Thereby, 1,3-dithiolan-2-thione 24a reacted with dimethyl acetylenedicarboxylate (butyndioic dimethylester) to give 1,3-dithiol-2-thione 25a (Scheme 13) in quantitative yield.³⁶

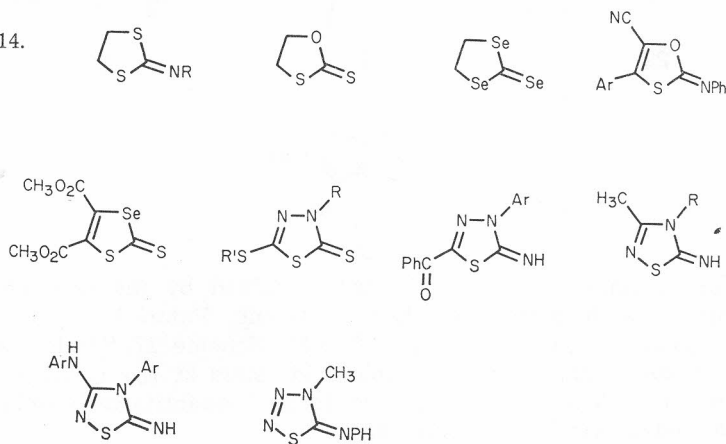
Analogous thermal reactions of 24a have also been observed with propynoic esters and with dehydrobenzene (benzyne), while tolan, for instance,

Scheme 13.



only reacts after photochemical excitation (see literature quoted in ref.³²). No experimental information is found for the formation of 25a from 24a described in ref.³⁸; these results could not be later reproduced by Behringer³⁹ (but also cf. Scheme 17).

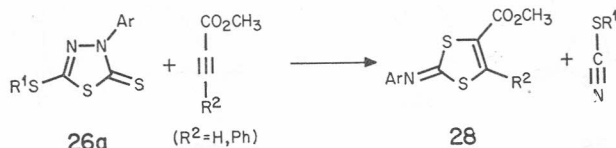
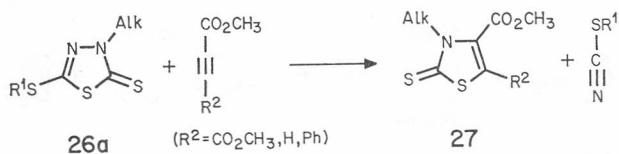
Scheme 14.



Scheme 14 contains a few further types of five-membered heterocycles which react with electron-deficient acetylenes according to $24 \rightarrow 25$ (cf. ref.³²). For most of the listed compounds it was found that cyclosubstitution takes place exclusively with participation of the sulfur atom in the ring. 2-Alkylthio- Δ^2 -1,3,4-thiazolin-5-thiones 26 are the only exception⁴⁰ (Scheme 15). Acetylene-dicarboxylic esters, propynoic esters and phenylpropynoic esters react with *N*-alkyl derivatives 26a to 4-thiazolin-2-thiones of type 27, *i. e.* cycloaddition occurs at the ring *N*- and not ring *S*-atom. In contrast, the corresponding *N*-aryl derivatives 26b react with propynoic acid and phenylpropynoic acid in cyclosubstitution reactions via the ring *S*-atom to form dithiol derivatives 28.

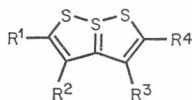
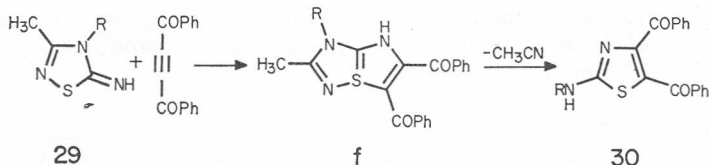
For the conversion of $24 \rightarrow 25$, many of the quoted papers formulate a reaction mechanism *via* a bicyclic adduct of type f (Scheme 16).^{32,41} Even though these intermediates, which contain one hypervalent *S*-atom, have not been directly detected to date, their intermediate occurrence cannot be

Scheme 15.



excluded. Compounds containing hypervalent S-atoms, e. g. bicyclic 6a-thia-thiophenes 31, are known (cf. ref.³⁹ and literature quoted therein).

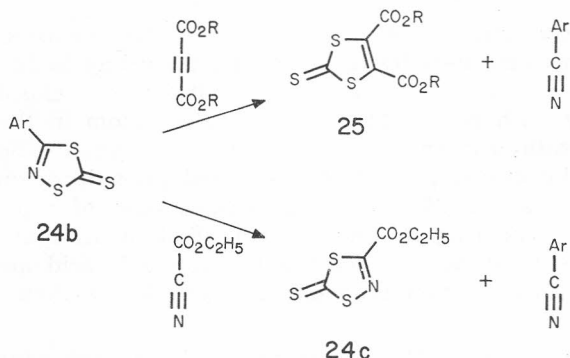
Scheme 16.



31

Thus, for instance, heterocycle 31 was obtained by the reaction of 1,2-dithiol-3-thiones with *p*-methoxy-phenylacetylene. Paton has also recently reported on cyclosubstitutions of type 24 → 25 (Scheme 17).^{42,43} It was found that the reactions of 24b with butyrdioic acid esters at 135 °C are completed within 10 minutes. The aryl cyanide is formed quantitatively whereas 25 could be isolated in yields of around 85%.

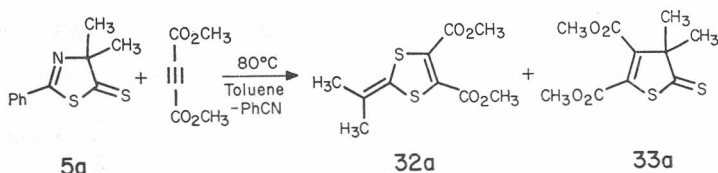
Scheme 17.



Contradicting information on this reaction, first mentioned by Noël and Vialle³⁸, can be found in the literature³⁹. Cyanoacetic acid esters react with 24b at 115 °C; after a reaction time of 40 hours, 24c was isolated in 83% yield.

After finding, as mentioned in Chapter 2, a simple method for the synthesis of 2-thiazolin-5-thiones 5, we investigated the reactions of these heterocycles with electron-deficient acetylenes. The thermolysis of 4,4-dimethyl-2-phenyl-2-thiazolin-5-thione 5a in toluene, at 80 °C in the presence of butyndioic acid dimethylester, leads in 78% yield to 1,4-dithiafulvene 32a (Scheme 18).³³ As a by-product 2,3-dihydrothiophene-2-thione 33a was isolated after chromatography in about 2% yield. At a higher reaction temperature,

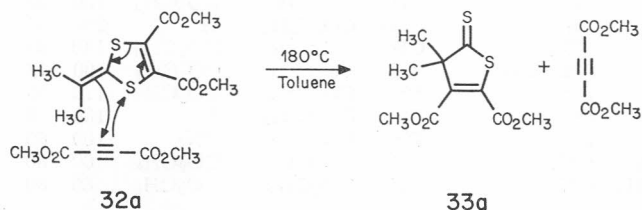
Scheme 18.



the ratio of products 32a/33a shifts in favour of 33a: at 150 °C it equals approx. 1:1, and at 180 °C 1:2. Benzonitrile was an additional product formed in this reaction.

The formation of 33a is caused by a secondary reaction of 32a. Control experiments at 180 °C have shown that the rearrangement 32a → 33a is not intramolecular as 32a is stable at these temperatures when no acetylenic-acid esters are present. However, isomerization to 33a at the same temperature, in the presence of acetylenic-acid esters proceeds easily. This result can most

Scheme 19.



easily be explained by the mechanism formulated in Scheme 19, which corresponds to the one for the formation of 32a from 5a.

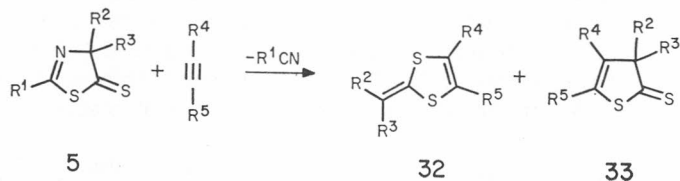
A number of other electron-deficient acetylenes reacted, analogously to butyndioic acid esters, with 5a in a cyclosubstitution (see Table II). A mixture of products 32 and 33 was also observed for the reaction with propynoic acid methyl ester, in which, however, 33 was found to be the main product. The product ratios were 1:3 at 145 °C and 1:7 at 160 °C. More drastic conditions were necessary for the conversion with phenylpropynoic acid ethyl ester: At 200 °C the dithiafulvene of type 32 was isolated in only 50% yield. A smooth reaction, however, occurred with dicyano acetylene⁴⁴ at 100 °C.

Treatment of a solution of 5a and anthranilic acid in tetrahydrofuran with isoamyl nitrite at 60 °C gave in 47% yield benzodithiafulvene 34 (Scheme 20), as well as traces of an isomer, probably benzodihydrothiophene-2-thione. The formation of 34 shows that benzyne⁴⁵, formed intermediately, also reacts in cyclosubstitution with 5a.

The results obtained in experiments, designed to determine substituent effects in the nitrile which is eliminated, are also worth mentioning. For this purpose, 5a, *p*-nitrophenyl- and *p*-methoxyphenyl-derivatives (5f and 5g, resp.) were converted with butyndioic acid dimethylester at 60 °C, as

TABLE II

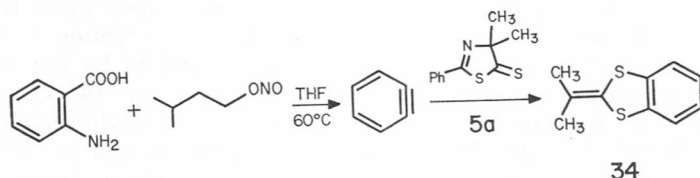
Reaction of 2-Thiazolin-5-thiones 5 with Electron Deficient Acetylenes



5	R ¹	R ²	R ³	R ⁴	R ⁵	Temp./°C	Yields/0/0		32/33
							32	33	
a	Ph	CH ₃	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	80	78	2	40/1
a	Ph	CH ₃	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	150	quantitative	—	1/1 ^a
a	Ph	CH ₃	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	180	quantitative	—	1/1 ^a
a	Ph	CH ₃	CH ₃	CO ₂ C ₂ H ₅	H	145	26	69	1/3
a	Ph	CH ₃	CH ₃	CO ₂ C ₂ H ₅	H	160	11	72	1/7
a	Ph	CH ₃	CH ₃	CO ₂ C ₂ H ₅	Ph	200	57	—	—
a	Ph	CH ₃	CH ₃	CN	CN	100	70	—	—
a	Ph	CH ₃	CH ₃	Benzyne	—	60	45	—	—
b	Ph	Ph	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	100	95	—	—
b	Ph	Ph	CH ₃	CO ₂ C ₂ H ₅	H	200	53 ^b	—	—
c	Ph	CH(CH ₃) ₂	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	140	35	—	—
d	Ph	CH=CH ₂	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	100	73	—	—
e	Ph	Ph	Ph	CO ₂ CH ₃	CO ₂ CH ₃	110	90	—	—
e	Ph	Ph	Ph	CO ₂ C ₂ H ₅	H	180	79	—	—
e	Ph	Ph	Ph	CN	CN	100	65	—	—
f	C ₆ H ₄ NO ₂	CH ₃	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	60	80	—	—
g	C ₆ H ₄ OCH ₃	CH ₃	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	60	80	—	—

^a Determined by ¹H-NMR-spectroscopy.^b (1 : 1)-mixture of (E)- and (Z)-isomer.

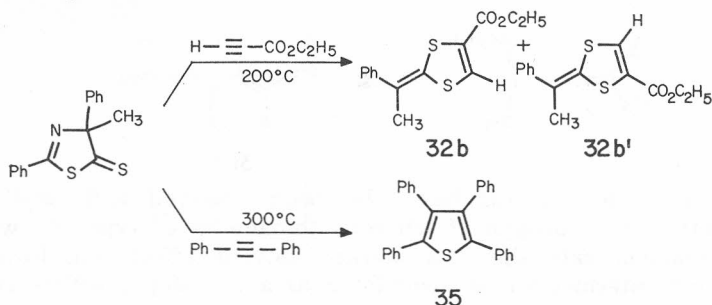
Scheme 20.



well as with phenylpropynoic acid ethyl ester at 200 °C, and the product yields were determined by gas-chromatography. The reaction rate for 5a, 5f and 5g in the first case is the same within experimental error. With phenylpropynoic acid ester, however, a marked difference was observed: whereas with 5a 20% of the dithiafulvene of type 32 was detected after 120 minutes, the nitro- as well as the methoxyderivatives (5f and 5g, resp.) reacted more slowly; in both cases only 7% of the product of type 32 was found after the same time.

The corresponding transformation of 4-methyl-2,4-diphenyl-2-thiazolin-5-thione **5b** with acetylene derivatives required slightly higher temperatures. However, these reactions proceed more uniformly and in the chosen reaction conditions the only products found were dithiafulvenes. Propynoic acid ethylester formed a 1:1-ratio of the (E/Z)-isomers **32b** and **32b'** (Scheme 21) in 53% overall yield.

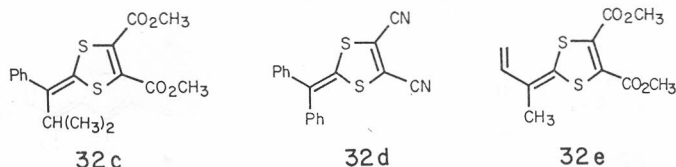
Scheme 21.



Heating of **5a** and **5b** in the presence of diphenylacetylene (tolan) resulted in a reaction only around 300 °C. In both cases the same main product tetraphenylthiophene (**35**) was formed in addition to a large number of by-products which, however, occurred in negligible yields. The reaction pathway leading to this product is still unclear. Nevertheless, it has been widely reported that **35** is formed when tolan is heated in the presence of a variety of sulfur-containing compounds.⁴⁶

Of the examples listed in Table II, three structurally interesting compounds have been reproduced in Scheme 22. The preparation of these compounds

Scheme 22.

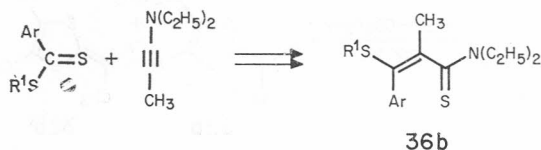
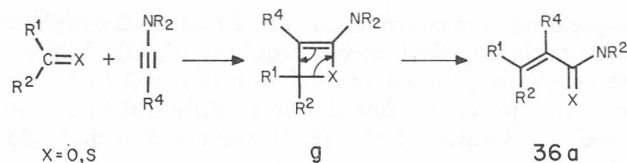


was also achieved by the reaction of the corresponding 2-thiazolin-5-thiones **5c**, **5e** and **5d** with butyndioic acid dimethylester and dicyano acetylene, respectively. **32c** and **32d** are stable compounds; **32e**, however, polymerizes easily in solution, but is stable in crystalline form.

4. REACTIONS OF 2-THIAZOLIN-5-THIONES WITH YNAMINES

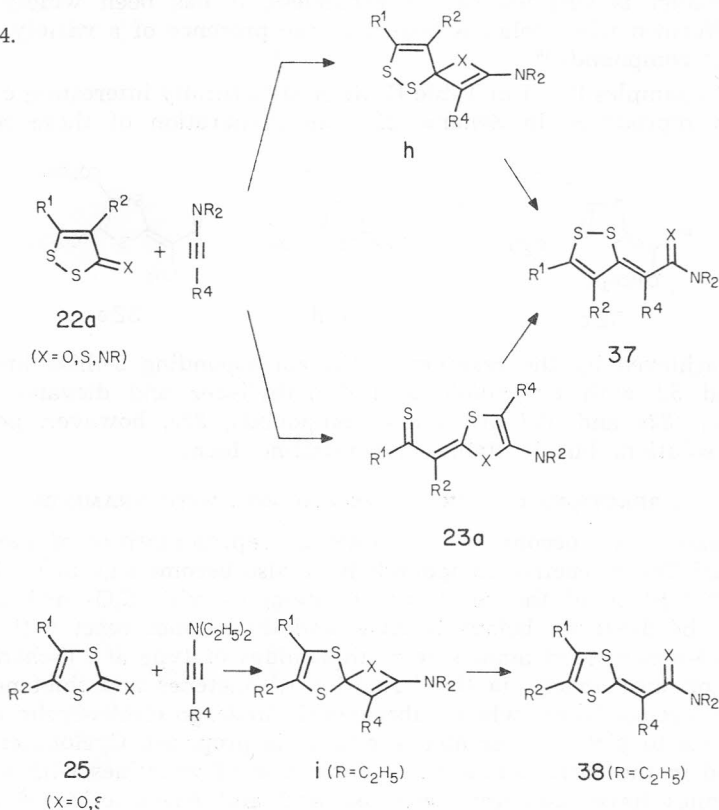
Ynamines have become well known as representatives of electron-rich acetylenes.⁴⁷ These reactive compounds have also become significant in organic synthesis.^{48,49} Some of the reactions of ynamines with C,O- and C,S-double bonds will be discussed below. Ketones and thioketones react with ynamines to form α,β -unsaturated amides resp. thioamides of type **36a** (Scheme 23).⁴⁹⁻⁵¹ The reaction mechanism via the formation of oxetenes and thietenes of type **g** in [2+2] cycloaddition, which subsequently undergo electrocyclic ring opening reactions to yield the isolated products, is proposed. Cyclobutenes, which are formed in the corresponding transformation of ynamines with α,β -unsaturated ketones have, however, been isolated and characterized.⁵² Analogous

Scheme 23.



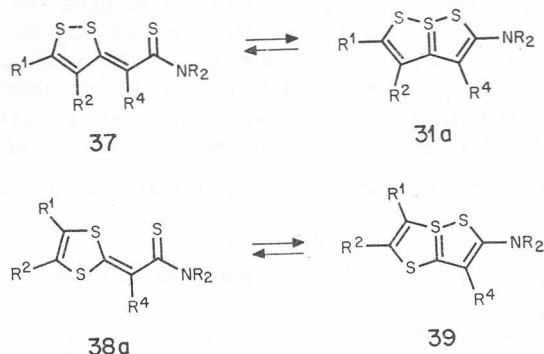
reactions in polar solvents have also been observed with aryl dithioesters and 1-diethylamino-propyne,⁵³ whereby thioamides of type 36b were formed. As the reaction rate shows a marked solvent effect, the formation of a 4-membered intermediate is formulated as a two-step reaction via a dipolar species.⁵³ Dithiolones and dithiolthiones react with ynamines via [3+2]- as well as [2+2]-cycloadditions. In Scheme 24 two such transformations are outlined. The reaction of ynamines with 1,2-dithiol-derivatives 22a yields in most cases products of type 23a, the formation of which can be explained via [3+2] cycloaddition reaction (cf. Chapter 3).⁵⁴ In the case of heterocycles

Scheme 24.



with $R^2 = H$, $X = S$, thioamides and 1,6,6a λ^4 -trithiapentalenes **31a**, respectively, were found as by-products (Scheme 25). It has been shown that the latter could be obtained by the isomerization of **23a**. However, compounds **23a** are stable under the reaction conditions, which suggests that for the direct formation of **31a** a mechanism via the spiroheterocycle **h** and **37** (Scheme 24) must be taken into account. Furthermore, an analogous reaction sequence has been put forward for the transformation of 1,2-dithiol-3-thiones (**22a**, $X = S$) with tolan and other acetylenes which, among others, lead to 1,6,6a λ^4 -trithiapentalenes of type **31a**.^{39,55,56}

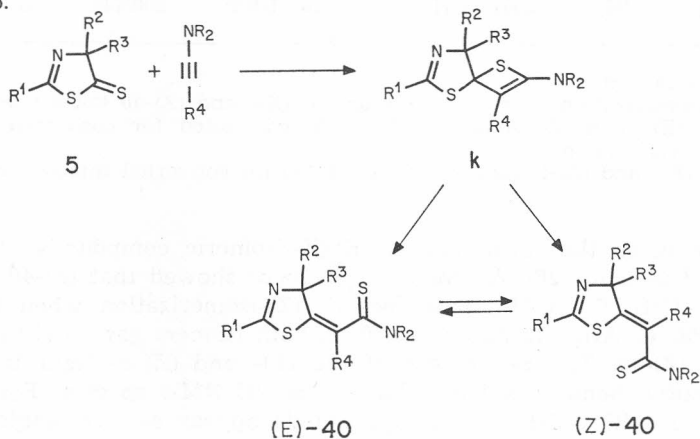
Scheme 25.



1,2-Dithiol-2-ones and -thiones **25** react with ynamines to give thioamides of type **38** (Scheme 24) in moderate yields,⁵⁷ whereby *i* is a plausible intermediate. NMR experiments show that these compounds are mixtures of (*E/Z*)-isomers. The isomerization of **38a** to 1,3a λ^4 -trithiapentalenes (Scheme 25) is also proposed for the interpretation of NMR-data.^{39,58}

The reactions of 2-thiazolin-5-thiones **5** with ynamines are described below.⁵⁹ These compounds, synthesized by our group (see Chapter 2) react with ynamines almost exclusively *via* [2+2] cycloaddition to the exocyclic C,S-double bond. Only in the reaction with 1-(*N*-methylanilino)-propyne was a small amount of by-product, probably 5-(*N*-methylanilino)-2,3-dihydrothiophen-2-thione of type **33** (cf. Table II), observed.

Scheme 26.



As a typical example the reaction of thiazolinthione 5a with 1-diethylaminopropyne is outlined below. A solution of 5a in approx. 1.2 equivalents of ynamine is sealed in a glass-tube and heated to 50 °C for two hours. After evaporation of the solvent, the residue was chromatographed on silica gel with pentane/ether. Thereupon, the main product (E)-40 ($R^1 = \text{Ph}$, $R^2, R^3, R^4 = \text{CH}_3$, $R = \text{C}_2\text{H}_5$) with a m. p. = 125–128 °C was obtained in 87% yield. The thioketone of type (E)-41 was isolated as a red oil in 7% yield. Spectroscopic data was used for structure elucidation. In the ^{13}C -NMR-spectrum the $\text{C}=\text{S}$ resonance of thioamides appears in the range of 190–205 ppm whereas $\text{C}=\text{S}$ of 41 absorbs at about 220 ppm. Major differences are also apparent in the UV- and mass-spectra. (E)-40 in ethanol shows an intensive absorption maximum at 282 nm, with long-wavelength shoulders at 328 and 392 nm. On the other hand, the spectrum of 41 has its strongest absorption maximum at 556 nm ($\epsilon = 13800$). In the mass spectrum of 41, an intensive peak for the elimination of SH appears, which is missing in the spectrum of (E)-40.

The results of further reactions are summarized in Table III.

TABLE III
Reaction of 2-Thiazolin-5-thiones 5 with Ynamines^a

5	2-Thiazolin-5-thione			Ynamine		React. time Temp./°C	Yields (%)	
	R ¹	R ²	R ³	R ⁴	NR ₂		(E)-40	41
a	Ph	CH ₃	CH ₃	CH ₃	N(C ₂ H ₅) ₂	50/2h	87 ^b	7
b	Ph	Ph	CH ₃	CH ₃	N(C ₂ H ₅) ₂	90/3h	86	traces
e	Ph	Ph	Ph	CH ₃	N(C ₂ H ₅) ₂	90/3h	64	traces
a	Ph	CH ₃	CH ₃	CH(CH ₃) ₂	N(C ₂ H ₅) ₂	20/40h	74	25
e	Ph	Ph	Ph	CH(CH ₃) ₂	N(C ₂ H ₅) ₂	110/5h	60	—
a	Ph	CH ₃	CH ₃	C(CH ₃) ₃	N(C ₂ H ₅) ₂	200/70h	no reaction	
a	Ph	CH ₃	CH ₃	Ph	N(C ₂ H ₅) ₂	110/14h	76 ^c	—
a	Ph	CH ₃	CH ₃	Si(CH ₃) ₃	N(C ₂ H ₅) ₂	160/3h	45 ^d	—
a	Ph	CH ₃	CH ₃	SPh	N(C ₂ H ₅) ₂	200/14h	50	—
a	Ph	CH ₃	CH ₃	CH ₃	N(CH ₃)Ph	200/14h	60	—
l	CH ₃	CH ₃	CH ₃	SPh	N(C ₂ H ₅) ₂	200/14h	50	—
l	CH ₃	CH ₃	CH ₃	CH ₃	N(CH ₃)Ph	200/14h	55	—

^a Cf. Schemes 26 and 27.

^b At 200 °C isomerization to a (1:1)-mixture of (E)- and (Z)-40 takes place.

^c Mixture of (E)- and (Z)-isomer (1:6); yield calculated for converted thiazolinthione, 78% conversion.

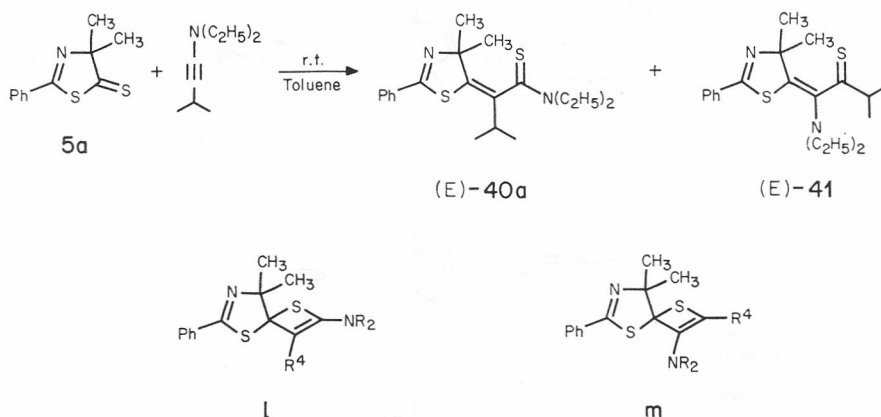
^d Mixture of (E)- and (Z)-isomer; yield calculated for converted thiazolinthione, 54% conversion.

In some cases the formation of (E)/(Z)-isomeric compounds of type 40 was observed (Scheme 26). A control experiment showed that (E)-40 ($R^1 = \text{Ph}$, $R^2, R^3, R^4 = \text{CH}_3$, $R = \text{C}_2\text{H}_5$) undergoes (E)/(Z)-isomerization when heated in toluene to 200 °C. After 15 hours at 200 °C, both isomers gave a (1:1)-mixture of (E)- and (Z)-40. The assignment of the (E)- and (Z)-configuration of the exocyclic double bond was based largely on ^1H -NMR spectra. For the (E)-isomer with $R^2, R^3 = \text{CH}_3$, the methyl signals appear as two singlets in the

range of 1.9—1.6 ppm whereas the spectra of the corresponding (Z)-isomer contain only one singlet. Additional evidence for this assignment was found in the spectrum of the compound with $R^4 = \text{Ph}$, where the methyl groups on C(4) of isomer (E)-40 absorbed at 1.85 and 1.7 ppm; the (Z)-40 isomer spectrum, however, showed only one singlet at approx. 1.4 ppm. This high-field shift can be explained by the anisotropy effect of the phenyl-group on the exocyclic C,C-double bond.

The highest yield of thioketone of type 41 was realised in the reactions with 1-dimethylamino-2-methyl-butyne in toluene (Scheme 27). Whereas the transformation of 5a to (E)-40a and 41 already occurred at room temperature,

Scheme 27.



temperature, only a 50% conversion took place after three weeks at 100 °C for the corresponding reaction with the isopropyl derivative 5c. In the case of 5a the product ratio 40 : 41 was approx. 3 : 1.

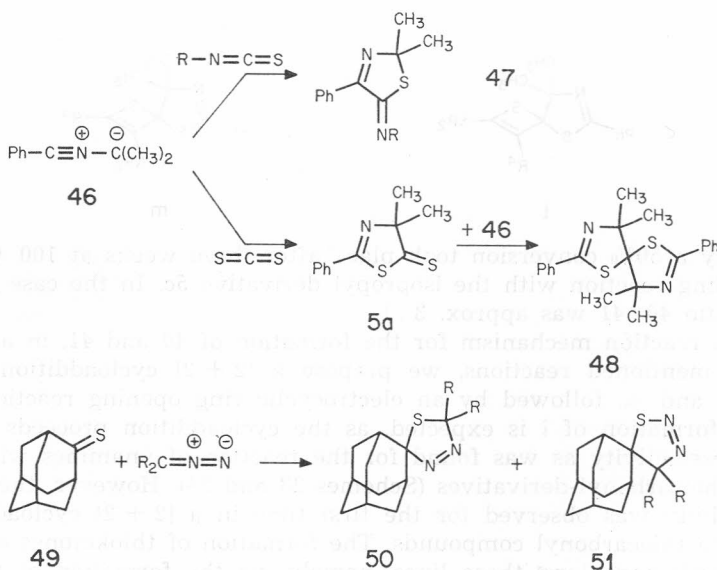
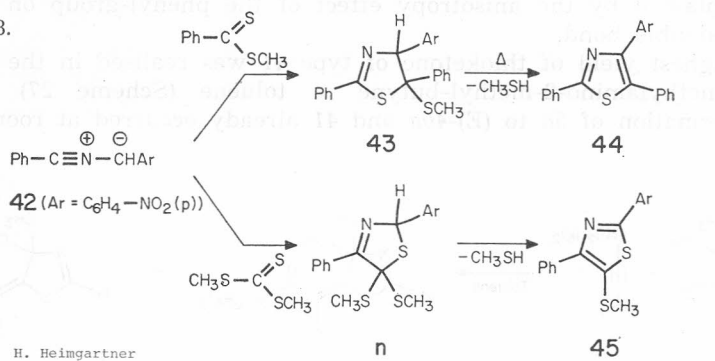
As the reaction mechanism for the formation of 40 and 41, in analogy to the above-mentioned reactions, we propose a [2 + 2] cycloaddition to yield thietenes l and m, followed by an electrocyclic ring opening reaction.⁵⁹ Thereby, the formation of l is expected, as the cycloaddition proceeds with the same regioselectivity as was found for the reaction of ynamines with carbonyl- and thiocarbonyl-derivatives (Schemes 23 and 24). However, the »wrong« regioselectivity was observed for the first time in a [2 + 2] cycloaddition of ynamines to thiocarbonyl compounds. The formation of thioketones of type 41 must be explained along these lines, namely *via* the formation of the intermediate m.

5. REACTIONS OF 2-THIAZOLIN-5-THIONES WITH 1,3-DIPOLAR SPECIES

The concept of 1,3-dipolar cycloadditions⁶⁰ developed by Huisgen more than 20 years ago has proved to be a very useful method for the synthesis of five-membered heterocycles.⁶¹ In addition to C,C-double- and C,C-triple-bonds, a number of hetero(C,X)-double bonds have been used as dipolarophiles. The number of examples of 1,3-dipolar cycloadditions to C=S-double bonds is, in comparison with the large number of converted compounds with C,C- and C,N-double bonds, relatively modest.

The examples of 1,3-dipolar cycloadditions to C,S-double bonds, chosen for Scheme 28, illustrate in particular one aspect of the reaction: the regioselectivity of cycloaddition is — contrary to the reaction with carbonyl groups — obviously strongly dependent on the type of substituent on the thiocarbonyl group.³¹ While the reaction of benzonitrile ylide 42, generated *in situ*,

Scheme 28.

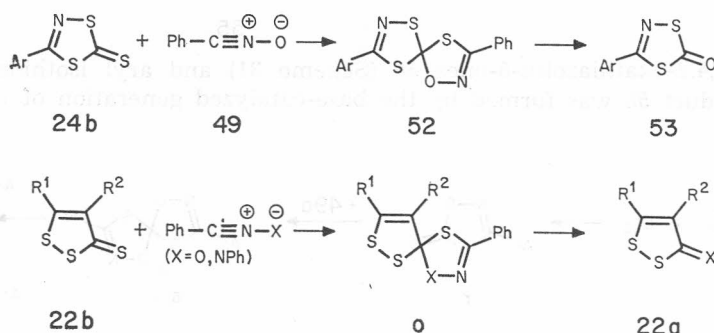


with dithiobenzoic acid methylester gave initially a *cis*, *trans* mixture of 2-thiazolines 43 and then on warming the reaction mixture thiazole 44 in good yields, the transformation with trithiocarbonic acid dimethylester gave directly thiazole 45 at 0 °C.⁶³ Obviously, the latter was produced by the elimination of methanethiol from the primary adduct *n*. Both formulae 44 and 45 clearly show that cycloaddition to both C,S-double bonds proceeds with opposite regioselectivity: in 44 the S-atom is connected to the phenyl-substituted »nitrile-C-atom« of 42, whereas in 45 it is joined to the *p*-nitrophenyl substituted »ylid-C-atom«.

Likewise, the 1,3-dipolar cycloadditions of nitrile ylides to C,S-double bonds of hetero-allenes also show differing regioselectivities. In this way, the photochemically generated nitrile ylide 46 reacts with isothiocyanates to give 3-thiazolines of type 47,^{64,65} whilst it has been reported that the bis-adduct 48 is formed with carbon disulfide.⁶⁶ The precursor of 48 should, therefore, be the 2-thiazolin-5-thione 5a (but see Scheme 32). A (1:1)-adduct and its dehydromer had already been isolated formerly for the reaction of 42 with carbon disulfide and arbitrarily the opposite addition regioselectivity was assumed for their formation.⁶³

Adamantanthione (49) has repeatedly been used as a dipolarophile. The 1,3-dipolar cycloaddition with diazomethane leads to mixtures of both isomers 50 and 51.⁶⁷ An apolar solvent favours the formation of 50, whilst in polar solvents the regioisomeric cycloaddition which gives 51 dominates. Heterocycles with exocyclic C,S-double bonds have also been used as dipolarophiles in 1,3-dipolar cycloadditions. For instance, the reaction of 24b with benzonitrile oxide 49 yields a (1:1)-adduct, namely the spiro compound 52 (Scheme 29).^{38,42,43} On warming 52 decomposes to give the oxo-compound 53 and

Scheme 29.



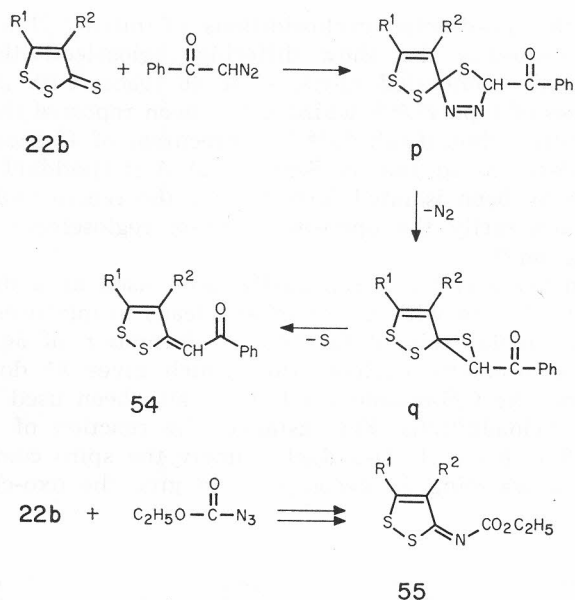
phenylisothiocyanate.³⁸ The reaction can, therefore, be preparatively used for the conversion of a thiocarbonyl group to a carbonyl group. Analogous reactions of 22b with benzonitrile oxide and diphenylnitrile imine have been described.^{70,71} It was, however, not possible in such cases to isolate the spiro-cyclic(1:1)-adduct which spontaneously eliminated phenylisothiocyanate to form type 22a compounds.

Diazocompounds and azides also undergo smooth 1,3-dipolar cycloadditions to the C,S-double bond of 1,2-dithiol-3-thiones 22b (Scheme 30). In this way the reaction with diazoketones, *e.g.* benzoyldiazomethane, was observed to form 1,2-dithiol-3-ylidene-ketones of type 54.³⁵

The primary formation of spirane *p* followed by a ring contraction reaction to give *q* via elimination of nitrogen and sulfur extrusion is a probable reaction mechanism. The formation of imine 55 in the reaction of 22b with azidoformic acid ethylester can be explained analogously.⁷³

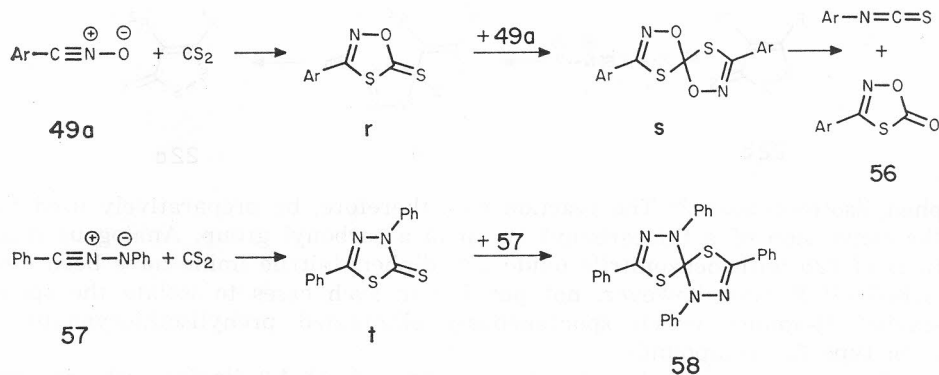
C,S-Double bonds of heterocumulenes have also proven to be very reactive dipolarophiles. Carbon disulfide is in a special position in this respect as the reaction with 1,3-dipoles usually leads to (1:2)-adducts which, however, have not been always isolated. Thus, the reactions of nitrile oxides 49a with CS₂

Scheme 30.



leads to 1,4,2-oxathiazolin-5-ones **56** (Scheme 31) and aryl isothiocyanates.⁷⁴ The bis-adduct **58** was formed by the base-catalyzed generation of the diphe-

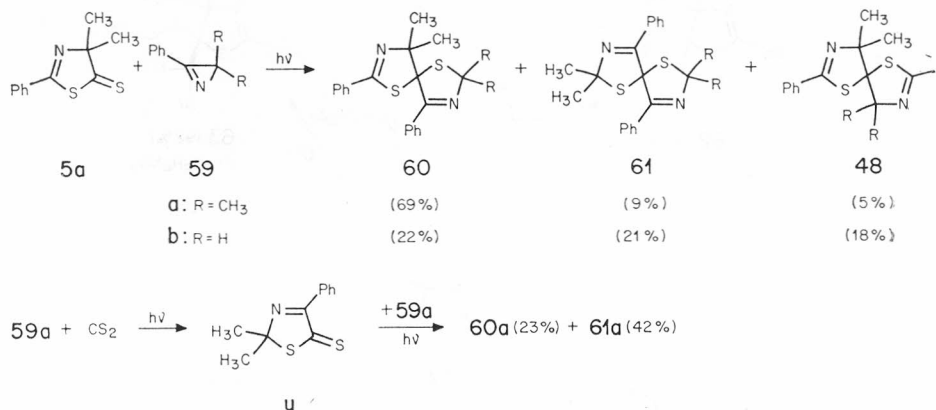
Scheme 31.



nylnitrile imine **57** from benzoic acid phenylhydrazide chloride in CS_2 in 63% yield.⁷⁵ In both reactions the formation of a (1 : 1)-adduct *r* resp. *t*, is assumed. Their exocyclic C,S-double bond reacts very quickly with a second 1,3-dipole to give *s* and **58**, respectively. In an independent experiment it was shown that *t*, synthesized *via* a different route, and **57** really react swiftly and almost quantitatively to yield **58**.⁷⁵

Having succeeded in synthesizing the intermediate **5a** postulated in Scheme 28 according to the pathway described in Chapter 2,³¹ we reacted it with a further equivalent of **46**. Photolysis of the 2H-azirine **59a** in pentane generated **46**.⁷⁶ Surprisingly, three isomeric spirocycles, namely the two symmetric compounds **61a** and **48a** and the main product **60a**,³¹ were formed (Scheme 32).

Scheme 32.



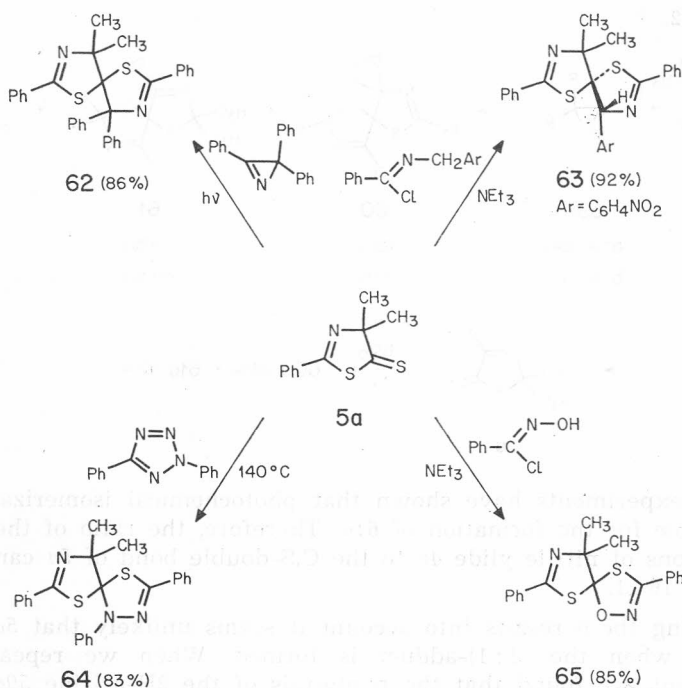
Control experiments have shown that photochemical isomerization of **60a** is responsible for the formation of **61a**. Therefore, the ratio of the two addition orientations of nitrile ylide **46** to the C,S-double bond of **5a** can be estimated at about 16 : 1.

Taking these results into account it seems unlikely that **5a** is the intermediate when the (2 : 1)-adduct is formed. When we repeated Padwa's⁶⁰ experiment, we found that the photolysis of the 2H-azirine **59a** in CS₂ leads to two isomeric (2 : 1)-adducts, **60a** and **61a** (Scheme 32). The structure of the main product is consistent with the one described.⁶⁶ This finding suggests that **u** and not **5a** is the primary adduct formed.

An analogous result to the above one was obtained when 2H-azirine **59b** was irradiated in the presence of **5a** (Scheme 32).⁷⁷ Uniform cycloadducts were formed in the transformations collected in Scheme 33. It is evident that the formation of spiro-heterocycles must proceed via regioselective 1,3-cycloaddition, whereby benzonitrilio-diphenylmethanid, -(*p*)-nitrophenyl-methanid, -phenylimine and -oxide, respectively, act as dipolar species. In contrast to the above, the photolysis of 2,3-diphenyl-2H-azirine (**59c**) in the presence of **5a** affords three isomers, *cis*- and *trans*-**66** and **67** (Scheme 34).⁷⁷ The ratio of regioisomeric products in the addition of benzonitrilio-phenylmethanid is, therefore, about 1 : 7, in which regioselectivity of the formation of the main product corresponds to that shown in Scheme 33.

The regioselectivity described^{76,77} in these experiments for the cycloadditions of benzonitrile ylides to **5a** (Table IV) is in accord with substituent effects discussed by Houk⁷⁸. Even more surprising was, therefore, the fact that the conversion of oxazaphosphol **68** with **5a** in boiling toluene leads to two isomeric (1 : 1)-adducts **69** and **70** (Scheme 35). The formation of **69** as the main product is in flagrant contradiction to the regioselectivity observed so far for the benzonitrilio-hexafluoro-2-propanid.^{28,79,76} As the preferred formation of **69** is also not in accord with Houk's usually so reliable theoretical considerations, it is assumed that **69** is not formed via 1,3-dipolar cycloaddition of the free nitrile ylide.⁷⁷ An alternative mechanism *via* ionic intermediates is formulated.⁷⁷

Scheme 33.



Scheme 34.

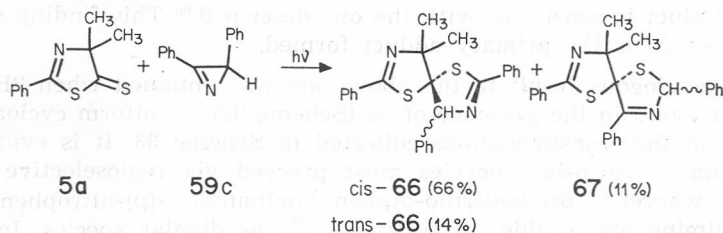
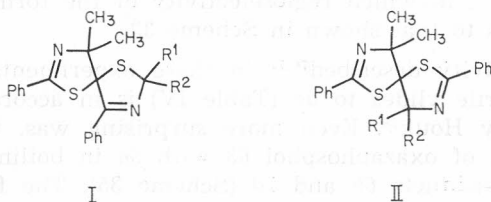


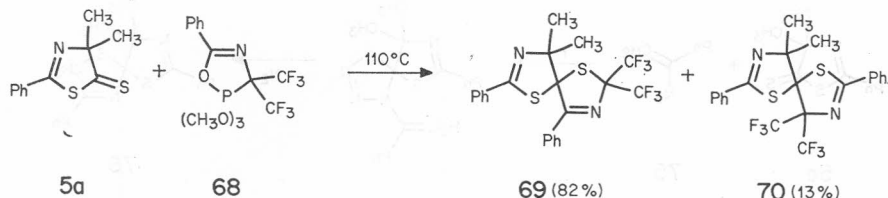
TABLE IV

Regioselectivity of the 1,3-Dipolar Cycloaddition of 2-Thiazolin-5-thione 5a with Benzonitriliummethanides



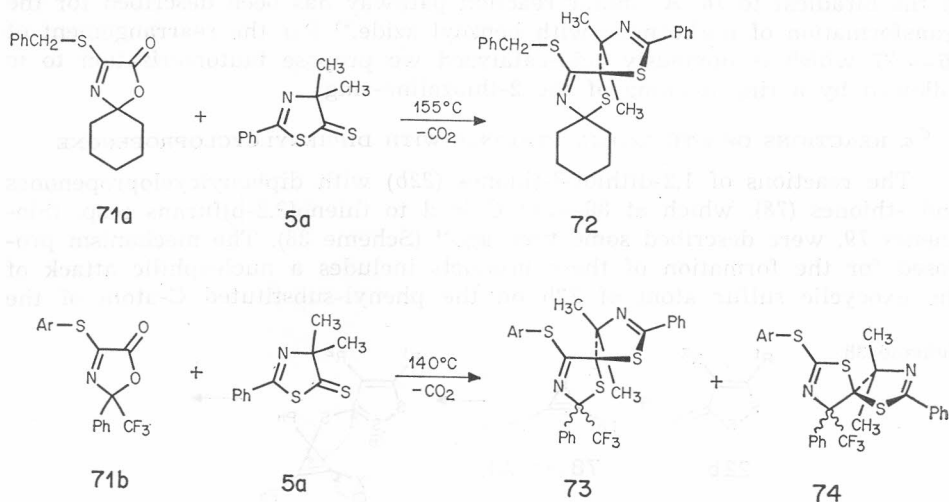
R ¹ = R ² = CH ₃	16 : 1
R ¹ = R ² = H	2,4 : 1
R ¹ = Ph, R ² = H	1 : 7
R ¹ = R ² = Ph	< 1 : 20
R ¹ = C ₆ H ₄ NO ₂ (p), R ² = H	< 1 : 20

Scheme 35.



Recently, we succeeded for the first time in generating nitrile ylides with benzylthio- and arylthio-substituents on the »nitrile-C-atom« by thermal reaction of the correspondingly substituted 3-oxazolin-5-ones.⁸⁰ Thus, 3-oxazolin-5-one 71a reacts with 5a at 155°C *via* CO₂-elimination to give the spiro compound 72 in 74% yield (Scheme 36). Therefore, the regioselectivity corresponds to that of benzonitrilio-dialkylmethanids. The thermal reaction of 71b, however, in the presence of 5a gives a mixture of the two regioisomeric cycloadducts 73 and 74 which can be attributed to the influence of the CF₃-group on the dipolar species.⁷⁸

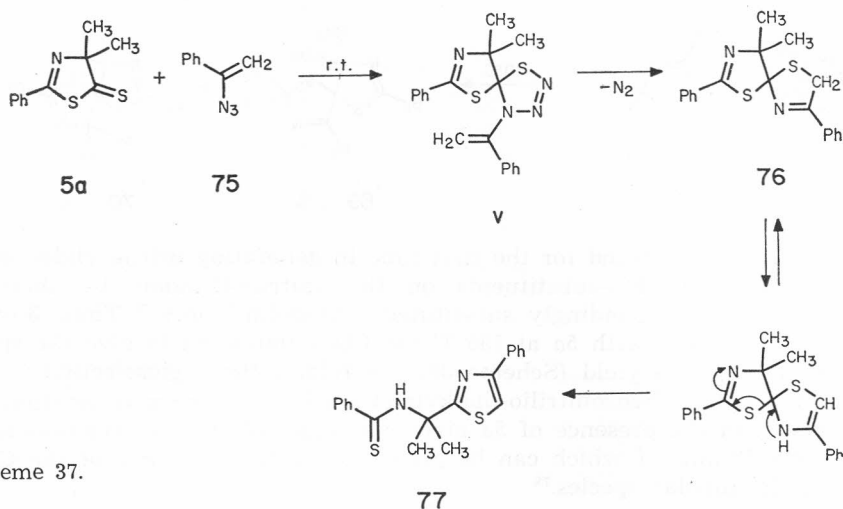
Scheme 36.



Ar = β -Naphthyl

The reaction of 5a with α -azidostyrene (75) gave a mixture of both products 76 and 77 after a thermal reaction, as well as by UV-irradiation⁷⁷ (Scheme 37). Rearrangement of 76 to 77 proceeds during the work-up procedure and, therefore, the former could not be isolated pure. 76 is again a spiro compound which, however, is not identical to the isomers 60b, 61b and 48b shown in Scheme 32.

The 1,3-dipolar cycloaddition of the benzonitrilio-methanid can, therefore, be excluded as a pathway for the formation of 76. Probably, a primary cycloaddition to *v*, where the azido-group acts as 1,3-dipolar species takes place. Analogous cycloadditions to C,S-double bonds are known.^{81,82} Spontaneous elimination of nitrogen could either proceed *via* a thiaziridine followed by a »vinylcyclopropane-cyclopentene«-type rearrangement or by direct cyclization



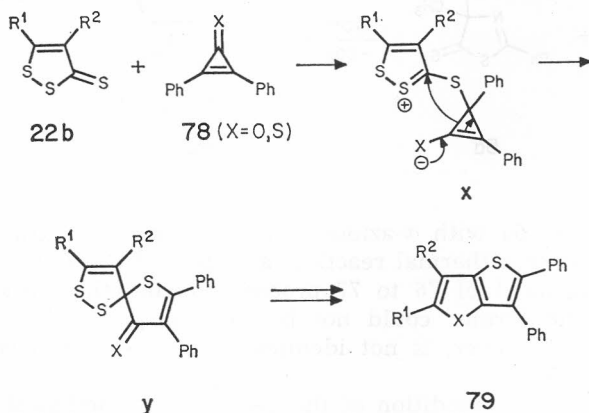
Scheme 37.

of the biradical to 76. A similar reaction pathway has been described for the transformation of norbornene with benzoyl azide.⁸³ For the rearrangement of 76 \rightarrow 77 which is obviously acid-catalyzed we propose tautomerization to *w* followed by a ring opening of the 2-thiazoline-ring.

6. REACTIONS OF 2-THIAZOLIN-5-THIONES WITH DIPHENYLCYCLOPROPENONE

The reactions of 1,2-dithiol-3-thiones (22b) with diphenylcyclopropenones and -thiones (78), which at 80–130 °C lead to thieno[3,2-b]furans resp. thio-phenes 79, were described some time ago⁸⁴ (Scheme 38). The mechanism proposed for the formation of these products includes a nucleophilic attack of the exocyclic sulfur atom of 22b on the phenyl-substituted C-atom of the

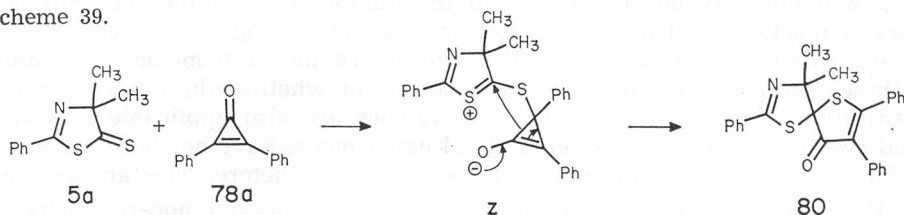
Scheme 38.



cyclopropenone. The intermediate *x* could then react *via* the proposed spiro compound *y* to 79.

In a comparable reaction of the 2-thiazolin-5-thione 5a with 78a we have been successful in isolating the spiro compound 80, analogue of *y* (Scheme 39).⁸⁵

The conversion in toluene at 130 °C afforded yellow crystals of 80 in 30% yield. We assume that the formation of 80 proceeds via the zwitterion intermediate *z* analogously to the reaction depicted in Scheme 38.

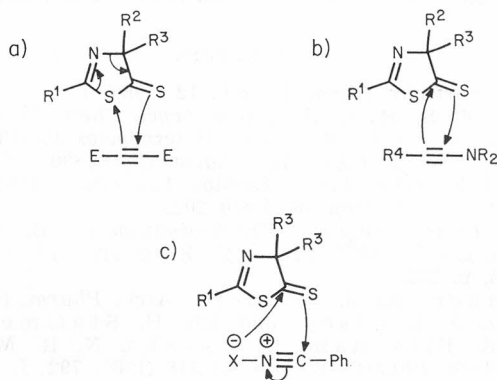


yield. We assume that the formation of 80 proceeds via the zwitterion intermediate *z* analogously to the reaction depicted in Scheme 38.

7. CONCLUSIONS

This review has shown that 4,4-disubstituted 2-thiazolin-5-ones have become available by simple syntheses. These heterocycles, hardly known to date, have proven to be very versatile and reactive molecules in a number of transformations. Essentially, three types of reactions are discussed and compared to analogous examples (Scheme 40):

Scheme 40.



a) Reactions with electron-deficient acetylenes proceed *via* elimination of nitriles to 1,3-dithiafulvenes, a not well-researched but interesting heterocycle. These transformations can be classified as [3 + 2] cycloadditions which are often found for heterocycles with exocyclic C,S-double bonds. Thiazolinthione takes part in the reaction as a three-centered system, *i. e.* as a 1,3-dipolar species.

b) Ynamines, contrary to the electron-deficient acetylenes, react in [2 + 2] cycloaddition to the exocyclic C,S-double bond. The postulated intermediate thietene undergoes a ring opening reaction to the isolated products. Of particular interest are the two examples in which for the first time the ynamines react with the »wrong« regioselectivity.

c) Nitrilium-betaines react cleanly in 1,3-dipolar cycloaddition to the exocyclic C,S-double bond to form isolable dithio-spiro compounds. In these [2 + 3] cycloadditions thiazolinthione acts as a two-centered species, *i. e.* as dipolarophile.

The reactions described here have an exemplary character. We believe there will not only be an increase in the number of examples but different types of reactions will be soon found for these interesting heterocycles. Future experiments will have to be carried out to determine the scope and limitations of these reactions. The question, for instance, of whether the observed cyclo-substitutions with electron-deficient acetylenes are also applicable to double bond systems remains unanswered. Trial experiments have not been successful so far, even though analogous reactions with other heterocycles are known.⁸⁶

Furthermore, the observation that ynamines undergo non-regioselective addition to the C,S-double bond of **5a** must be looked into. In accord with the above is the result that the regioselectivity of the 1,3-dipolar cycloaddition of benzonitrilium-betaines to C,S-double bonds is extremely sensitive to the variation of the substituents on the dipolar species.

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POVZETEK

Sinteze in reakcije 2-tiazolin-5-tionov, nove vrste žveplovih heterociklov

Heinz Heimgartner

Opisane so sinteze 4,4-disubstituiranih 2-tiazolin-5-tionov, ki so bili dosedaj le stežka dostopni. Tovrstne spojine so obstojne in z njimi potekajo številne pretvorbe. V prvi skupini opisanih reakcij so ciklosubstitucije, ki potekajo pri segrevanju in ob prisotnosti acetenov s pomanjkanjem elektronov. Pri tem nastanejo 1,3-ditiazulveni prek eliminacije nitrila. Tiazolintioni se obnašajo drugače pri reakcijah z inamini. Pri segrevanju nastanejo tiazoliniliden-tioamidi in -tioketoni. Reakcija poteka prek |2+2| cikloadicije, nakar sledi elektro-ciklično odpiranje obroča. V tretjo skupino reakcij se uvrščajo pretvorbe z 1,3-dipolarnimi reagenti. Z *in situ* tvorjenimi benzonitrilijevimi betaini potekajo 1,3-dipolarne cikloadicije na eksociklično dvojno vez C—S in nastanejo ditia-spiro[4.4]nanadieni.