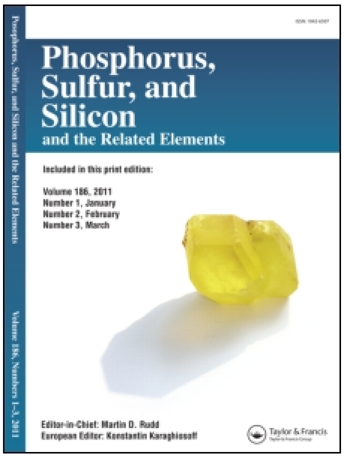

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Addition Reactions With 1,3-Thiazole-5(4*H*)-Thiones; Synthesis of Spirocyclic AND FUSED BICYCLIC SULFUR HETEROCYCLES

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To cite this Article Heimgartner, Heinz(1991) 'Addition Reactions With 1,3-Thiazole-5(4*H*)-Thiones; Synthesis of Spirocyclic AND FUSED BICYCLIC SULFUR HETEROCYCLES', Phosphorus, Sulfur, and Silicon and the Related Elements, 58: 1, 281 — 293

To link to this Article: DOI: 10.1080/10426509108040636

URL: http://dx.doi.org/10.1080/10426509108040636

Phosphorus, Sulfur, and Silicon, 1991, Vol. 58, pp. 281–293
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ADDITION REACTIONS WITH 1,3-THIAZOLE-5(4*H*)-THIONES; SYNTHESIS OF SPIROCYCLIC AND FUSED BICYCLIC SULFUR HETEROCYCLES

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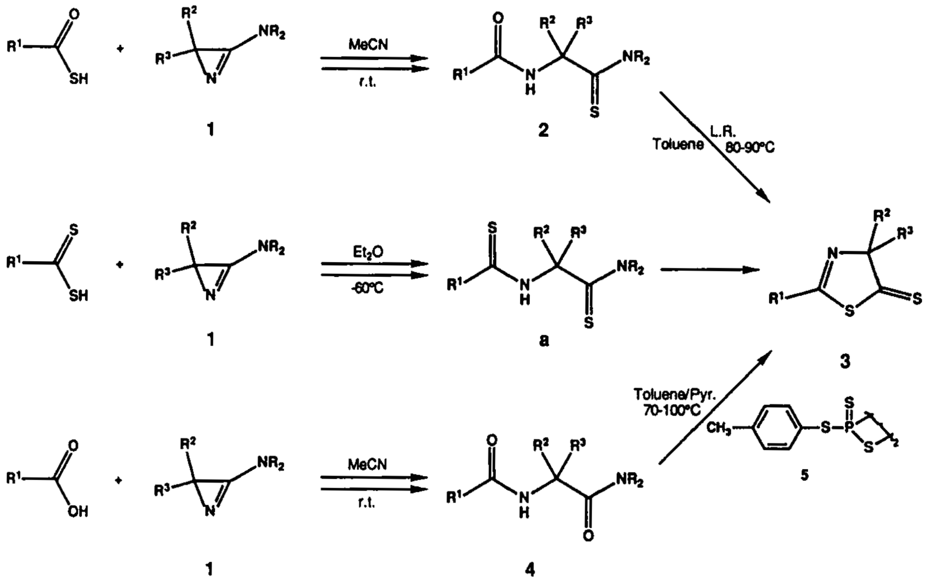
Abstract Various 1,6-dithiaspiro heterocycles can be synthesized from 1,3-thiazole-5(4*H*)-thiones *via* 1,3-dipolar cycloadditions, *Diels-Alder* reactions, ring expansion of oxiranes, and C-alkenylation followed by radical cyclization. 1,3-Thiazole-5(4*H*)-thiones with a vinyl substituent at C(4) are photochemically transformed into fused polycyclic compounds or, after C-alkylation to the corresponding 4,5-dihydro-5-mercapto-1,3-thiazoles, into fused bicyclic compounds *via* radical cyclization. With mCPBA, 1,3-thiazole-5(4*H*)-thiones are oxidized to thionoxides, which fail to undergo cycloaddition reactions.

INTRODUCTION

Some years ago, we discovered a convenient synthesis of 4,4-disubstituted 1,3-thiazole-5(4*H*)-thiones **3**, a scarcely known class of 5-membered sulfur heterocycles.[1] The reaction of 3-amino-2*H*-azirines **1** with either thiocarboxylic acids at r.t., followed by thionation with *Lawesson*-reagent [3a], or with dithiocarboxylic acids at -60°C leads to the formation of **3** in good yield[2] (Scheme 1). Also diamides of type **4**, prepared in excellent yield from **1** and carboxylic acids, can be transformed into **3** using the modified *Davy*-reagent[3b] 2,4-bis(4-methylphenylthio)-1,3,2λ^5,4λ^5-dithiaphosphetane-2,4-dithione (**5**).[4]

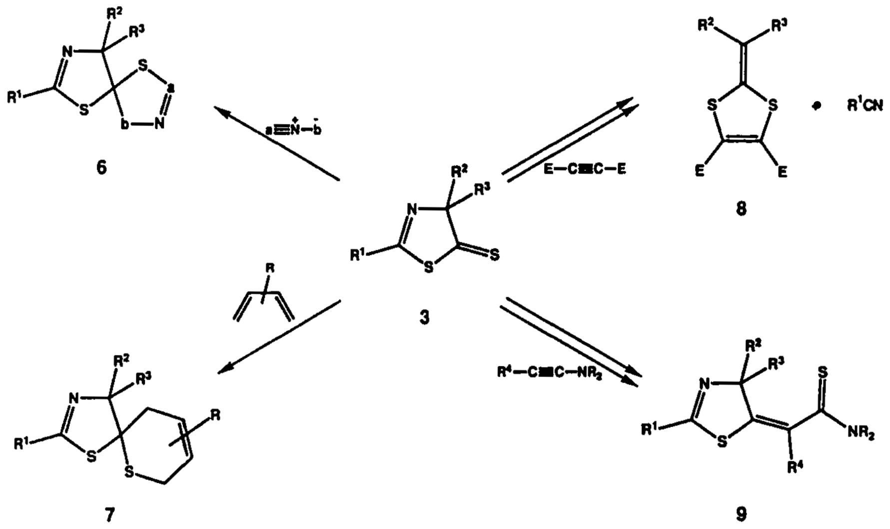
It has been shown that the exocyclic C,S-double bond of the heterocycle **3** behaves as a powerful dipolarophile[5-8] and as a dienophile[9], *e.g.* 1,3-dipolar cycloadditions, as well as *Diels-Alder* reactions, with **3** yield dithiaspiro-

SCHEME 1



heterocycles of type **6** and **7** (Scheme 2), respectively. Other reactions which may proceed *via* a cycloaddition step are the transformation of **3** and electron deficient acetylenes into dithiafulvenes **8**[10] and the formation of thioamides of type **9** with ynamines.[11]

SCHEME 2



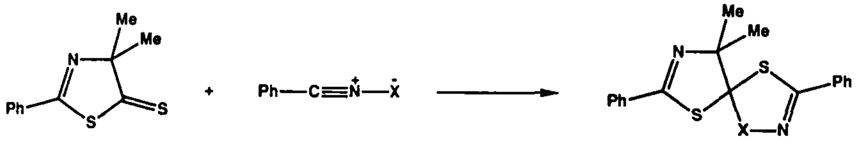
SYNTHESIS OF DITHIASPIRO-HETEROCYCLES

1,3-Dipolar Cycloadditions

The concept of 1,3-dipolar cycloadditions, developed by *Huisgen* about 30 years ago, has proved to be very useful for the synthesis of 5-membered heterocycles.[12] In contrast to the large number of known dipolarophiles with C,C- and C,N-triple bonds and with C,C-, C,N-, and C,O-double bonds, the number of 1,3-dipolar cycloaddition reactions involving C,S-double bonds is modest. One aspect of special interest of the latter additions is the regioselectivity, which in the case of nitrile ylides as 1,3-dipoles is dependent on the type of thiocarbonyl group[13-15] and on the substituents of the nitrile ylide.[16]

The 1,3-dipolar cycloaddition of **3a** and the nitrilium betaines **10-12** (benzonitrile oxide, phenylimine, and diphenylmethylide, respectively) proceed in a regiospecific manner to give the spiro compounds **13-15** in *ca.* 85% yield[6] (Scheme 3).

SCHEME 3



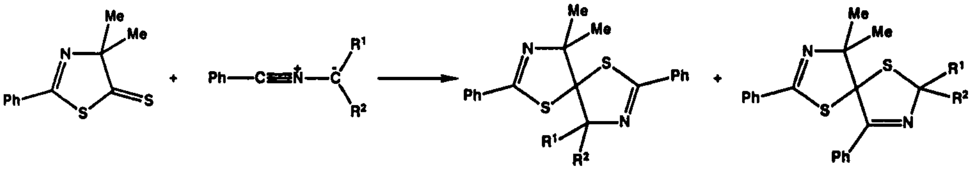
3a

10 X=O
11 X=PhN
12 X=Ph₂C

13 X=O
14 X=PhN
15 X=Ph₂C

Again, a regiospecific addition occurs with benzonitrile 4-nitrobenzylide (**16**, R^1 = $C_6H_4NO_2$, R^2 = H), whereas cycloadditions with benzonitrile 2-propylide, methylide, and benzylide yield mixtures of two cycloadducts **17** and **18** (Scheme 4), formed *via* regioisomeric transition states. The observed regioselectivity is in accord with substituent effects discussed by *Houk* on the basis of FMO-treatment.[16] The effects can be summarized as follows: Benzonitrile ylides with electron-withdrawing substituents R^1 and/or R^2, which tend to be linear dipoles, lead preferentially to adducts of type **17**, whereas the main product of reaction with benzonitrile ylides with electron-donating substituents are of type **18**.

SCHEME 4

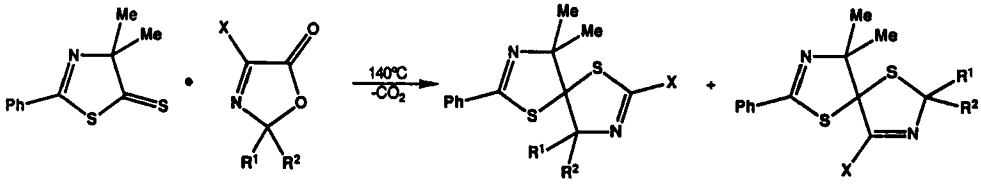


3a 16 17 18

$R^1 = R^2 = Me$	1	:	16
$R^1 = R^2 = H$	1	:	2.4
$R^1 = Ph; R^2 = H$	7	:	1
$R^1 = R^2 = Ph$	>20	:	1
$R^1 = C_6H_4NO_2; R^2 = H$	>20	:	1

Recently we succeeded in generating nitrile ylides with benzylthio-, arylthio-, and alkoxy-substituents, respectively, on the nitrile C-atom (C(1)) by thermolysis of the correspondingly substituted 1,3-oxazole-5(2*H*)-ones **19**.[7,17] The cycloadditions of **3a** and the thio-substituted nitrile ylides again yield exclusively adducts of type **21**, irrespective of the kind of substituents R^1 and R^2 (Scheme 5). On the other hand, the 2-propoxy-substituted dipoles lead to a mixture of **20** and **21**.[18] Obviously, S- and O-substituents at C(1) of the nitrile ylide greatly influence the

SCHEME 5



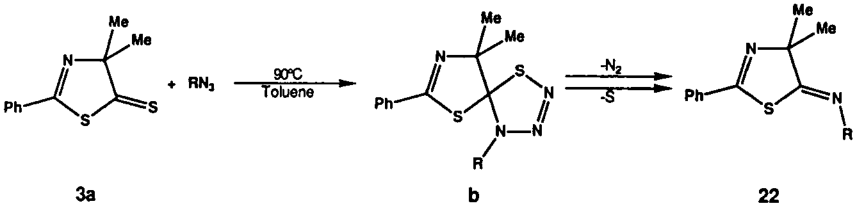
3a 19 20 21

$X = PhCH_2S; R^1\text{-}R^2 = \text{-}(CH_2)_5\text{-}$	-		only
$X = Me_2CHO; R^1\text{-}R^2 = \text{-}(CH_2)_5\text{-}$	1	:	10
$X = NaphthS; R^1 = Ph; R^2 = CF_3$	-		only
$X = Me_2CHO; R^1 = Ph; R^2 = CF_3$	4	:	9

regioselectivity of the cycloaddition and hence the geometry of the dipole. This influence also follows from optimization of dipole geometry with the AMPAC program[19] (AM1 Hamiltonian): S- and O-substituents stabilize the bent nitrile ylide geometry more than the linear one.[20]

As a last example of 1,3-dipolar cycloadditions with the C,S-double bond of **3a**, the reaction of azides is shown in Scheme 6. In toluene at 90°C 1,3-thiazole-5(4*H*)-imines **22** are formed as well as elemental sulfur and nitrogen.[9] We interprete the formation of **22** *via* a cycloaddition to give intermediate **b** and successive loss of N_2 and S.

SCHEME 6

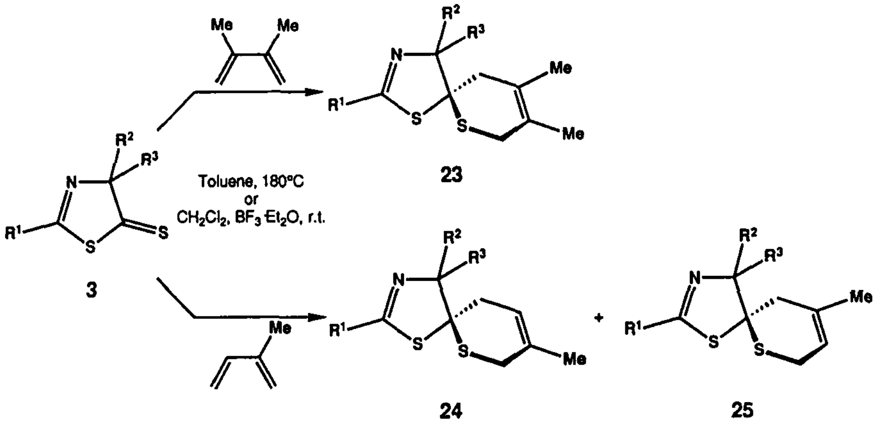


Diels-Alder Reactions

Dithiaspiro[4.5]decanes are available from 1,3-thiazole-5(4*H*)-thiones **3** and buta-1,3-dienes *via* hetero-*Diels-Alder* reactions. For example, heating of **3a** and 2,3-dimethylbuta-1,3-diene in toluene in a sealed tube to 180°C gives adduct **23** in about 73% yield.[9] The same product is formed under much milder conditions (CH_2Cl_2, r.t.) when $BF_3.Et_2O$ is used as a catalyst (Scheme 7).

The reaction of **3** and isoprene (2-methylbuta-1,3-diene) yields a mixture of two isomeric adducts **24** and **25**, formed *via* two regioisomeric transition states. The ratio **24/25** is dependent on the reaction conditions: whereas **3a** at 180°C yields a 1:1 mixture, the ratio is 3:1 in the *Lewis*-acid catalyzed reaction.[9] According to the FMO-energies, calculated with the AMPAC program[19], the *Diels-Alder* reaction proceeds as a $HOMO_{Diene}$-$LUMO_{C=S}$ controlled reaction. Decrease of the LUMO-energy of **3** is responsible for the

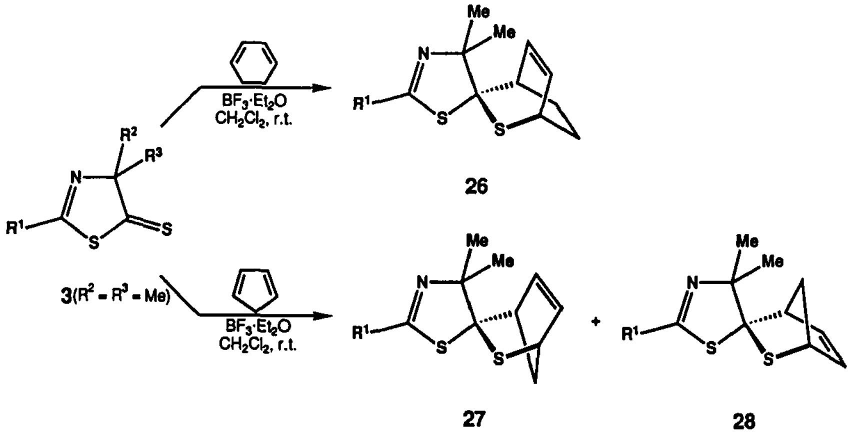
SCHEME 7



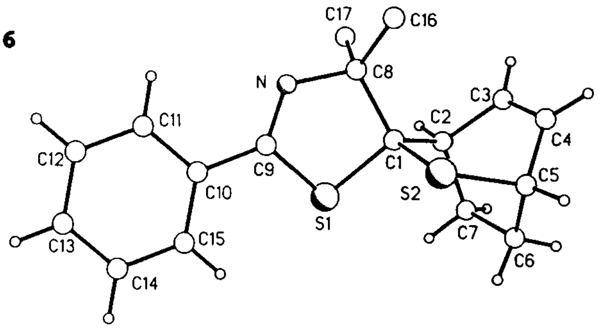
accelerated reaction in the presence of *Lewis*-acid. The orbital control should lead to **25** as the main product; failure of this prediction can be ascribed to steric interactions with the C(2)-methyl group of the diene.

Cyclic 1,3-dienes and **3** also undergo *Lewis*-acid catalyzed *Diels-Alder* reactions. With cyclohexa-1,3-diene only one adduct **26** is formed, which was shown by X-ray crystallography to be the isomer with the S-atom of the 5-membered ring in the *exo*-position (Scheme 8). In contrast, cyclopenta-1,3-diene and **3** yield a mixture of two cycloadducts **27** and **28** in a ratio of *approx.* 5:1. This difference again can be explained by steric effects.

SCHEME 8



X-Ray structure of *Diels-Alder* adduct **26**

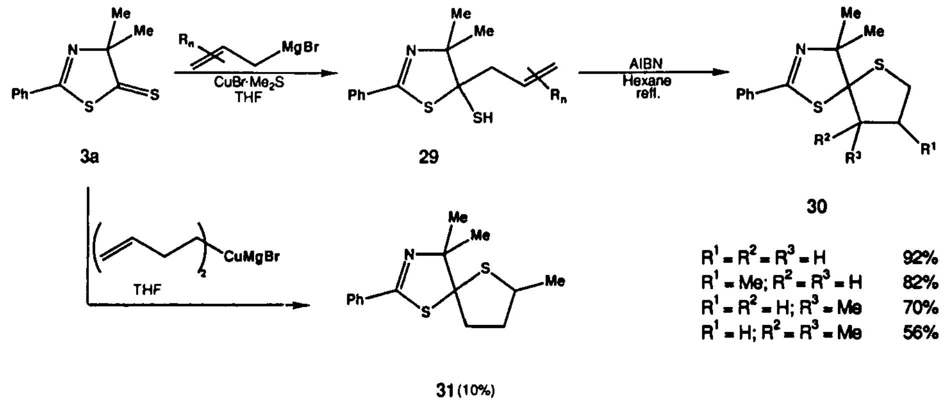


Radical Cyclizations

A different approach to dithiaspiro heterocycles is outlined in Scheme 9. It has been shown that 1,3-thiazole-5(4*H*)-thiones **3** react with organometallic reagents either *via* thiophilic or carbophilic addition.[21,22] *E.g.* Organolithium compounds react exclusively on the exocyclic S-atom of **3**, whereas the corresponding cuprates (generated *in situ* from organolithium or magnesium compounds and CuBr.Me_2S in THF at 0°C) lead to addition at C(5). Again a carbophilic attack is observed with allylmagnesium bromide in ether, but with other *Grignard*-reagents we obtained S- as well as C-alkylation.

Treatment of **3a** with differently substituted allylmagnesium halides in the presence of CuBr.Me_2S under the above mentioned conditions yields 5-allyl-4,5-dihydro-1,3-thiazole-5-thioles **29** (Scheme 9). On heating in the presence of

SCHEME 9



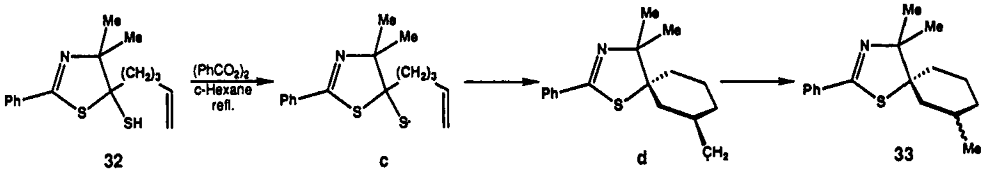
$R^1 = R^2 = R^3 = H$	92%
$R^1 = Me; R^2 = R^3 = H$	82%
$R^1 = R^2 = H; R^3 = Me$	70%
$R^1 = H; R^2 = R^3 = Me$	56%

the radical initiator α,α-azoisobutyronitrile (AIBN) in hexane under reflux, cyclization to spiro heterocycles **30** occurs in fair-to-good yield.[23,24] In an analogous way the 5-propinyl-1,3-thiazole-5-thiole derivative cyclizes to give the 7,8-unsaturated spiro compound only in low yield.

The formation of a 5-membered ring in this radical cyclization seems to be strongly preferred: Treatment of **3a** with a 3-butenylcuprate in THF yields, besides the reduction product of **3a**, small amounts of spiro[4.4] heterocycle **31** but none of the corresponding spiro[4.5] compound. The primarily formed 5-(3-butenyl)-adduct of **3a** could not be detected. Obviously, radical cyclization occured spontaneously under the reaction conditions of alkenylation.

The scope of this radical cyclization seems to be rather limited. Only one reaction leading to another than the spiro[4.4] system could be realized: from the two alternative ring closures of **32** to a 6- or 7-membered ring, only the former one, leading to **33** in 55% yield, is observed (Scheme 10). Radicals **c** and **d** are certainly intermediates of this cyclization. All attempts to construct larger rings by this procedure failed.

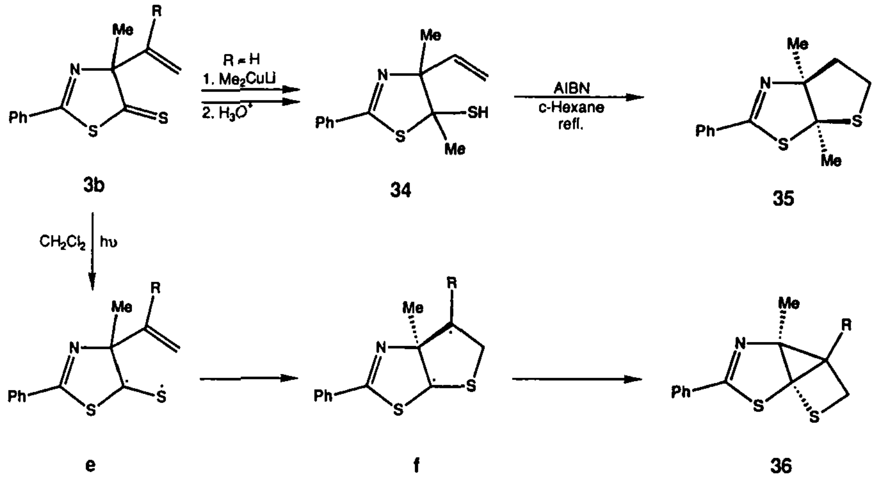
SCHEME 10



The fused 5,5-ring system **35** has also been formed by radical cyclization of 4,5-dihydro-4-vinyl-1,3-thiazole-5-thiole **34**, prepared *via* carbophilic addition of Me_2CuLi to **3b** (Scheme 11). According to NMR-analysis, **34** is a 1:1 mixture of the *cis*- and *trans*-diastereomer. The thiopheno[3,2-*d*][1,3]thiazole **35** could be isolated in 47% yield, *i.e.* the *cis*-isomer of **34** cyclizes quantitatively.

The 4-vinyl-1,3-thiazole-5(4*H*)-thiones of type **3b** are photochemically unstable. Irradiation of the red oils with UV-light (λ > 300 nm) leads to tricyclic compounds **36** as colourless oils.[25] Biradicals **e** and **f** are likely intermediates of the intramolecular 2+2-cycloaddition of C=S and C=C bond.

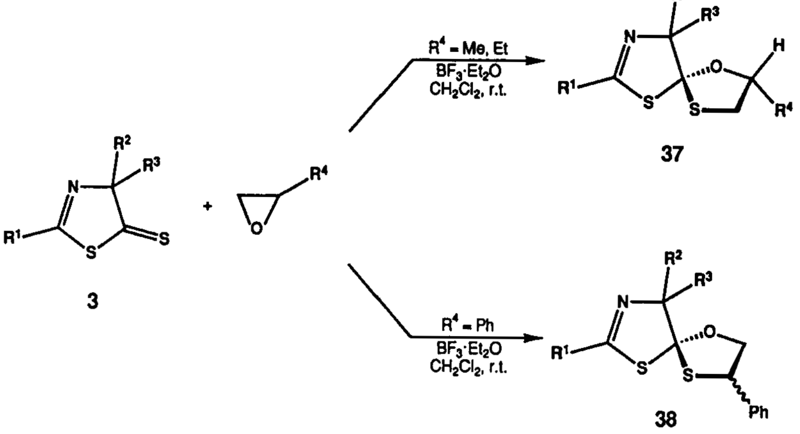
SCHEME 11



Ring Enlargement of Oxiranes

Addition of $BF_3.Et_2O$ to a CH_2Cl_2-solution of 1,3-thiazole-5(4*H*)-thiones **3** and oxiranes at room temperature leads to the formation of spirocyclic compounds of type **37** and **38** in 70-90% yield[26] (Scheme 12). This reaction parallels the ring expansion of oxiranes with ketones to give cyclic 5-membered acetals (cf. [27]). A remarkable influence of the oxirane-substituent has been observed in the reaction with **3a**: whereas 2-methyl and 2-ethyloxirane in a regio- and stereoselective way yield a single adduct, which has been shown to be the *cis*-isomer **37**, the reaction of 2-phenyloxirane leads to a mixture of *cis*- and *trans*-**38**. It should be mentioned that the regioselectivity of the reaction with alkylsubstituted oxiranes is contrary to that of the reaction with phenylsubstituted ones.

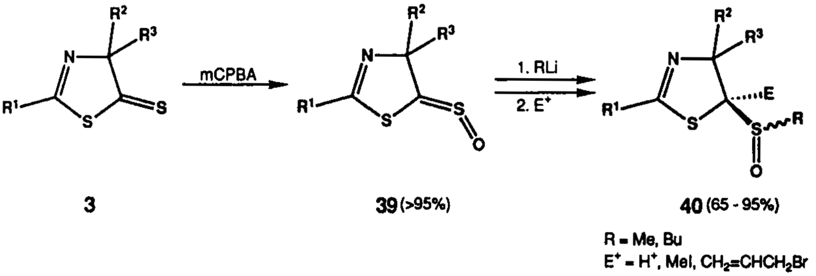
SCHEME 12



SYNTHESIS AND REACTIONS OF 1,3-THIAZOLE-5(4*H*)-THIONOXIDES

Oxidation of the red 1,3-thiazole-5(4*H*)-thiones **3** with one equivalent of 3-chloroperbenzoic acid (mCPBA) in ether at 0°C leads within a few seconds to the corresponding thionoxides (sulfines) **39** (Scheme 13), which after recrystallization are isolated as stable, colourless crystals in excellent yield.[26] Under these conditions, the exocyclic S-atom is oxidized selectively, no other product could be detected. Surprisingly, all attempts to perform a 1,3-dipolar cycloaddition or a *Diels-Alder* reaction with **39** thus far have failed. This result, which is not in accordance with expectations based on calculated FMO's and electron densities (AMPAC program[19]), is not completely understood.

SCHEME 13



Reaction of **39** in THF with alkyllithium compounds occurs already at -70°C at the exocyclic S-atom. The resulting carbanion can be trapped at *ca.* -40°C by protonation or alkylation with methyliodide or allylbromide. After column chromatography, the oily sulfoxides **40** are isolated in pure form. It has been shown that under the described conditions a single isomer of **40** is formed. But when water is added after warming the reaction mixture of **39** and MeLi (-70° → 0°C), two isomeric sulfoxides of type **40** are isolated by crystallization and chromatography, respectively, in a ratio of *ca.* 10:1.

CONCLUSIONS

All described reactions with 1,3-thiazole-5(4*H*)-thiones occur at the exocyclic C,S-double bond, which is the most reactive part of this heterocyclic system. Several approaches for the synthesis of bicyclic ring systems containing different heteroatoms have been presented. Whereas the scope of cycloaddition reactions is shown to be rather general, radical cyclizations of 4- and 5-alkenyl-4,5-dihydro-1,3-thiazole-5-ols are limited to the formation of 5- and 6-membered rings. The reaction of 1,3-thiazole-5(4*H*)-thiones with oxiranes is an example of the synthesis of spiro-heterocycles *via* ring expansion of small ring compounds.

ACKNOWLEDGEMENTS

The support of our work by the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG, Basel*, is gratefully acknowledged. I also thank my able and diligent coworkers, whose names are cited in the references, for their skill and enthusiasm during the work in the laboratory.

Crystallographic Data of **26**

Crystallized from	hexane/ether
Colour	colourless
Molecular formula	$C_{17}H_{19}NS_2$
Formula weight	301.46
Space group	$P2_1/c$
	monoclinic, centrosym.
Z	4
a [Å][a)]	10.182(2)
b [Å]	12.166(2)
c [Å]	13.230(2)
β [°]	108.25(1)
V [Å^3]	1556.3(4)
Calc. density [g/cm^3]	1.286
Temp. of data collection [°C]	21
Radiation (Graphite monochrom.)	MoK_α
Diffractometer	*Nicolet-R3*
2θ(max)	46°
Reflections collected	3101
Unique total	2731
Observed reflections ($I>2,5\sigma(I)$)	2088
Variables	204
R, R_w	0.039, 0.044
Weighting scheme w	$(\sigma^2(F)+0.00041F^2)^{-1}$
μ(MoK_α) [cm^{-1}]	3.18

a) Cell dimensions were obtained from 25 reflections with 20°< 2θ <26°.

Structure solution and refinement performed by *Dr. Beverly R. Vincent* with SHELXTL, version 5.1. All crystallographic data are deposited with the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

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