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BENZOTHIETES—VERSATILE SYNTHONS FOR THE PREPARATION OF HETEROCYCLES

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BENZOTHIETES—VERSATILE SYNTHONS FOR THE PREPARATION OF HETEROCYCLES

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Thermal or photochemical ring opening transforms benzo[*b*]thiete to *o*-thiobenzoquinonemethide, a highly reactive 8π electron system. Cycloaddition reactions or linear additions with subsequent cyclizations lead to larger heterocyclic rings. A variety of compounds containing sulfur and possibly further heteroatoms like nitrogen, oxygen or phosphorus in normal, medium and large ring systems can be synthesized on this route.

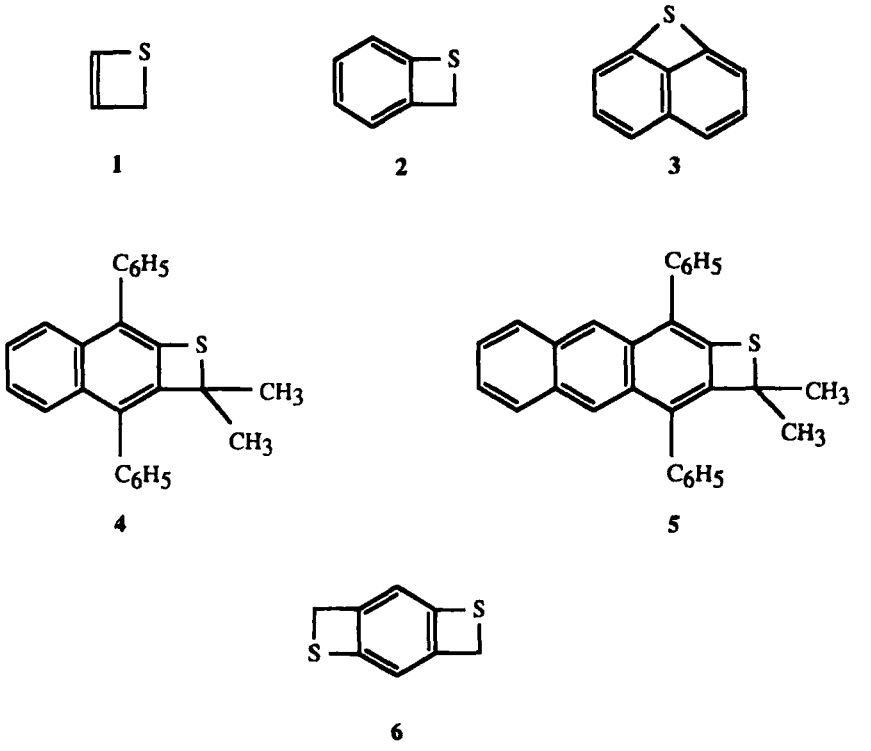
Key words: Ring opening, cycloaddition, cyclization, periselectivity, regioselectivity, stereoselectivity.

CONTENTS

1. INTRODUCTION 24
2. SYNTHESIS OF BENZO[*b*]THIETES 25
3. PROPERTIES OF BENZO[*b*]THIETES 27
3.1. *Spectroscopic Characterization* 27
3.2. *Reactivity* 28
4. SYNTHETIC APPLICATIONS OF BENZO[*b*]THIETES 34
4.1. *Reaction with Alkenes* 34
4.2. *Reaction with Alkynes* 39
4.3. *Reaction with C=N Double Bond Systems (Imines, Oximes)* 39
4.4. *Reaction with Nitriles* 43
4.5. *Reaction with Azo Compounds* 44
4.6. *Reaction with Carbonyl Compounds* 45
4.7. *Reaction with Nitroso Compounds* 48
4.8. *Reaction with Allenes and Heterocumulenes* 48
4.9. *Reaction with Amines* 50
4.10. *Reaction with P-Nucleophiles* 52
4.11. *Miscellaneous* 53
5. OUTLOOK 54
REFERENCES 55
SUBJECT INDEX 57
AUTHOR INDEX 59

1. INTRODUCTION

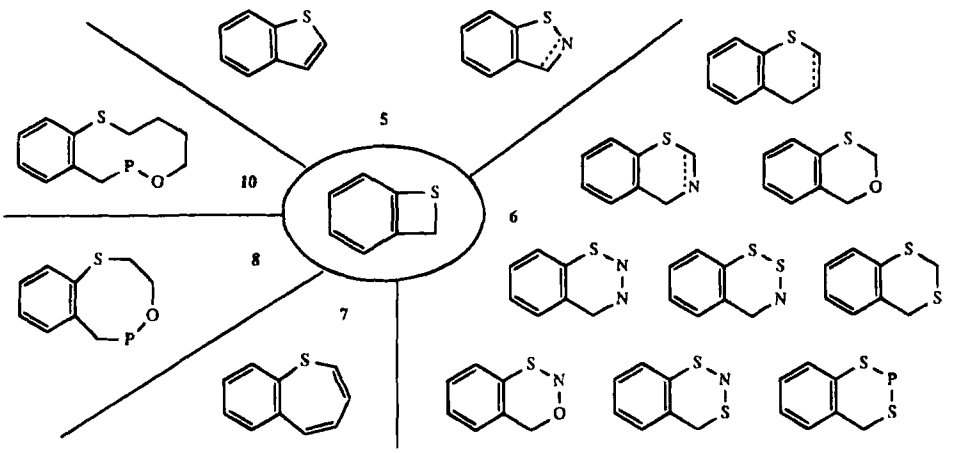
Contrary to the parent system 2*H*-thiete **1**[1] benzo[*b*]thiete (2*H*-1-benzothiete) **2** is at room temperature a fairly stable compound. Besides some simple derivatives of **2** the corresponding naphtho- and anthra-condensed systems **3–5** are known.[2-5] Very recently we synthesized benzo[1,2-*b*:4,5-*b'*]bisthiete **6**[6], a highly reactive bisdiene.



SCHEME 1

Finally, the corresponding β-thiolactones 2-oxo-2*H*-1-benzothiete,[7-9] 2-oxo-2*H*-naphtho[2,3-*b*]thiete[8,10] and 2-oxo-2*H*-naphtho[2,1-*b*]thiete[10] should be mentioned in this context.[11]

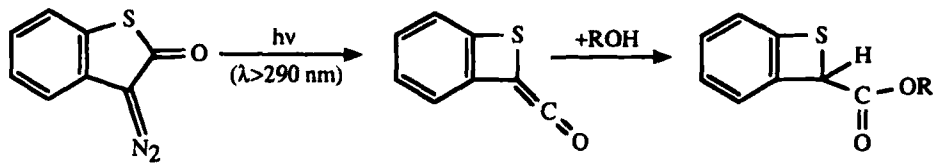
Due to its convenient access and the high reactivity, benzo[*b*]thiete **2** can be used for the synthesis of a variety of sulfur heterocycles. Scheme 2 provides a survey over some ring enlargement reactions generating 5-, 6-, 7-, 8- and 10-membered ring systems in which *one* benzo[*b*]thiete has been incorporated. Furthermore, addition reactions, in which *two* or more benzo[*b*]thiete moieties are involved, lead to 8-membered and higher ring compounds—up to thiocrown ethers with 32 ring atoms.



SCHEME 2

2. SYNTHESIS OF BENZO[*b*]THIETES

Despite of some earlier attempts[7,12–15] and the successful preparation of the corresponding sulfone,[15–19] the first synthesis of a benzo[*b*]thiete could be performed in 1976.[20] The photochemical extrusion of nitrogen from 3-diazobenzo[*b*]thiophen-2(3*H*)-one **7**, followed by a Wolff rearrangement, yields the ketene **8** which spontaneously adds nucleophiles. Thus, the esters **9–11** could be obtained.[11,20,21]



7 **8**

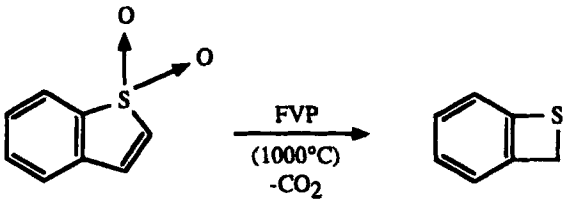
9 (R = CH_3)

10 (R = $C(CH_3)_3$)

11 (R = $CH_2C_6H_5$)

SCHEME 3

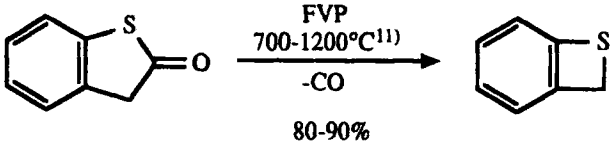
A multi-step degradation of **10** furnished the parent compound H **2**;[22] however, **2** is much more easily accessible by some flash pyrolytic methods (flash vacuum pyrolysis: FVP). Benzo[*b*]thiophene 1,1-dioxide **12** undergoes an unusual thermal cleavage in which carbon dioxide is eliminated instead of sulfur dioxide. Besides 45 % **2**, 8 % benzene and very small amounts of benzo[*b*]thiophene and benzo[*b*]furan were isolated.[23,24]



12 2 (45 %)

SCHEME 4

Another elegant preparation of **2** is based on the thermal decarbonylation of benzo[*b*]thiophen-2(3*H*)-one **13**.[25]

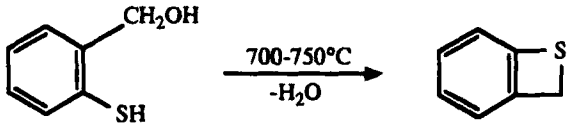


13 2

SCHEME 5

The FVP technique can also be used for the transformation **7** → **8**.[25] However, alkyl or acetyl groups on C-3 of **13** obstruct the generation of 4-membered rings.

The most convenient method for the preparation of **2** consists in the thermolysis of 2-mercaptobenzyl alcohol **14**.[26,27] Side products were not detected, and the amount of unreacted starting material can be reduced by increasing the contact time.[28] Fifty grams of pure **2** per hour can be generated in a suitable flow system. Instead of the hydroxy compound the chloro compound can be used, too.[28]

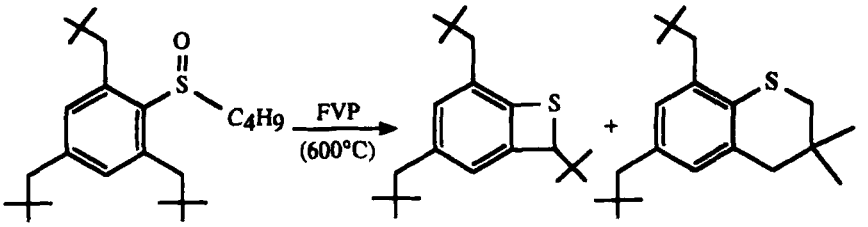


14 2

SCHEME 6

Principally, the same process can be applied for the transformation of 2,5-bis(hydroxymethyl)-1,4-benzenedithiol to benzo[1,2-*b*:4,5-*b*']bisthiete **6**.[6]

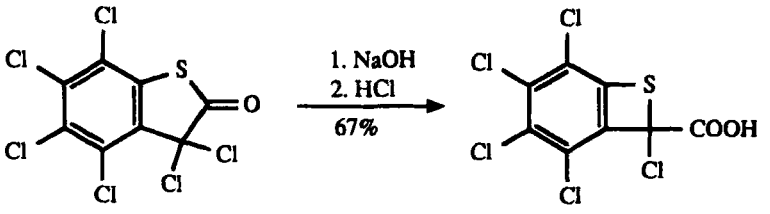
2-*tert*-Butyl-4,6-dineopentylbenzo[*b*]thiete **16** was obtained by flash vacuum pyrolysis of butyl 2,4,6-trineopentylphenyl sulfoxide **15**.[29]



15 16 (54%) 17 (25%)

SCHEME 7

A ring contraction related to **7** → **8** was performed by applying a Favorsky rearrangement.[30]



18 19

SCHEME 8

3. PROPERTIES OF BENZO[*b*]THIETES

Benzo[*b*]thiete **2** is a colorless liquid with a boiling point of 32 °C at 0.02 torr. It solidifies at −12 °C in the refrigerator and can be stored at this temperature neat or dissolved in toluene for many months.

3.1. *Spectroscopic Characterization*

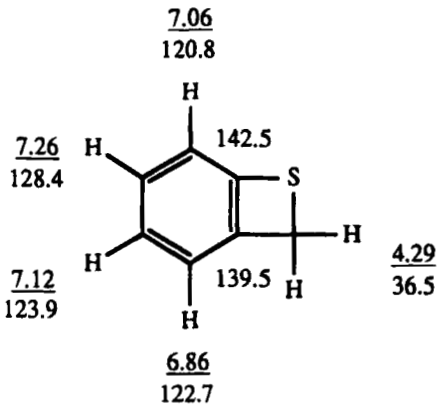
Benzo[*b*]thiete **2** shows a UV absorption which resembles that of an electron rich benzene derivative like thiophenol.[31]

	λ_{max} [nm] (ϵ) in hexane or heptane		
2	288 (1820)	242 (11850)	203 (18500)
Thiophenol	280 (610)	236 (8300)	205 (21000)

Characteristical IR bands are found in the neat phase at 3055, 2935, 1575, 1445 and 735 cm^{-1}. The ^1H and ^{13}C NMR data are summarized in Table 1:

TABLE 1 ^{1}H and ^{13}C NMR data of benzo[*b*]thiete **2**

a) Chemical shifts in $CDCl_3$ (δ values)



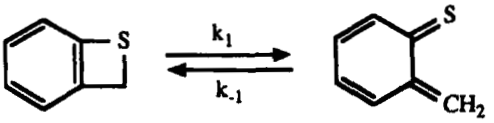
b) Matrix of coupling constants ($|^{n}J|$ in Hz)

	2-H	3-H	4-H	5-H	6-H	C-2	C-2a	C-3	C-4	C-5	C-6	C-6a
2-H	—	1.7	0.1	1.6	0.4	149.9						9.5
3-H		—	7.5	1.2	0.9	2.8		161.1		6.7		5.0
4-H			—	7.8	1.0				160.3		6.5	
5-H				—	7.7			8.4		161.4		5.0
6-H					—				6.7		167.4	
C-2						—	40.1					
C-2a							—	61.5				61.0
C-3								—	57.0			
C-4									—	58.5		
C-5										—	58.5	
C-6											—	61.5
C-6a												—

The PE spectrum of benzo[*b*]thiete **2** is discussed in lit.[25]

3.2. *Reactivity*

The high reactivity of benzo[*b*]thiete **2** is due to the facile thermal or photochemical opening of the 4-membered ring.



2 **2'**

SCHEME 9

The rate constant k_1 amounts to $1.8 \cdot 10^{-4}$ s^{-1} in toluene at 100 °C, which corresponds to an activation energy $\Delta G_{373}^{\neq}$ of 120 kJ·mol^{-1}.[32] Since k_{-1} is many orders of magnitude greater, the equilibrium lies almost totally on the side of the closed form **2.** There is no chance for spectroscopic detection of **2'** in the thermal equilibration.

The photostationary state depends—as one would expect—strongly on the wavelength. Irradiation at 280 nm leads to a ratio **2:2'** = 57:43 at 12 K in an argon matrix.[31] The thermal equilibration does not take place under these conditions. Therefore it was possible to obtain a UV/VIS spectrum of the *o*-thiobenzoquinonemethide **2'**. It contains bathochromically shifted maxima in comparison to **2:**[31]

λ_{max} [nm]	466	370	297	248	214
ϵ [l·M^{-1} cm^{-1}]	3000	1100	1600	5250	23100

Additionally to these $\pi\pi^*$ transitions CNDO calculations predict an $n\pi^*$ transition at longer wavelengths; however, until now such an absorption could not be experimentally verified.

Irradiation with $\lambda > 370$ nm turns the dark red matrix colorless; **2'** is completely reconverted to **2.**[31]

The other known benzo[*b*]thiete systems behave similarly; solely an extreme steric hindrance might stabilize the *o*-thiobenzoquinonemethide valence isomers.[33] Fig. 1 illustrates the valence isomerization **2** ⇄ **2'**.

The calculation of the energy difference $\Delta\Delta H$ between **2** and **2'** turned out to be more complicated as expected. The EHMO method favors the isomer **2'** much too much[34], the STO-3G ab initio calculation on the other hand favors strongly the bicyclic system **2.**[35] We decided to introduce in Fig. 1 the ΔH_f values obtained by semiempirical quantum mechanics (MNDO); they give the best fit with the experimentally determined $\Delta G^{\neq}$ value.[32]

Another interesting aspect of the molecular theory concerns the frontier orbitals. Fig. 2 shows the HOMO and the LUMO of **2'** and their correlations with the frontier orbitals of electron rich and electron deficient olefins. The *o*-thiobenzoquinonemethide possesses a relatively high lying HOMO and an extremely low lying LUMO. Therefore electrophilic as well as nucleophilic reagents can easily attack.

The orbital coefficients reveal a *periselective reaction* at the exocyclic positions. Furthermore electron rich alkenes should yield with high *regioselectivity* 2*H*-1-benzothiopyran derivatives with substituents X on C-2 (correlation A). Both predictions could be verified without any exception.

In the case of electron deficient alkenes two different modes of addition appear to be possible. A slight preference for 3-substituted 2*H*-1-benzothiopyrans can be assumed (correlation B). However, an exact prediction is more difficult in the latter case, because besides the energies and the coefficients of the frontier orbitals some information is needed about the resonance integrals for the CC and the CS bonds emerging from the transition state.

Let us consider the reaction of benzo[*b*]thiete **2** with 4-substituted styrenes.[37] The bent Hammett plot in Fig. 3 reveals that—in agreement with the FMO prediction—electron

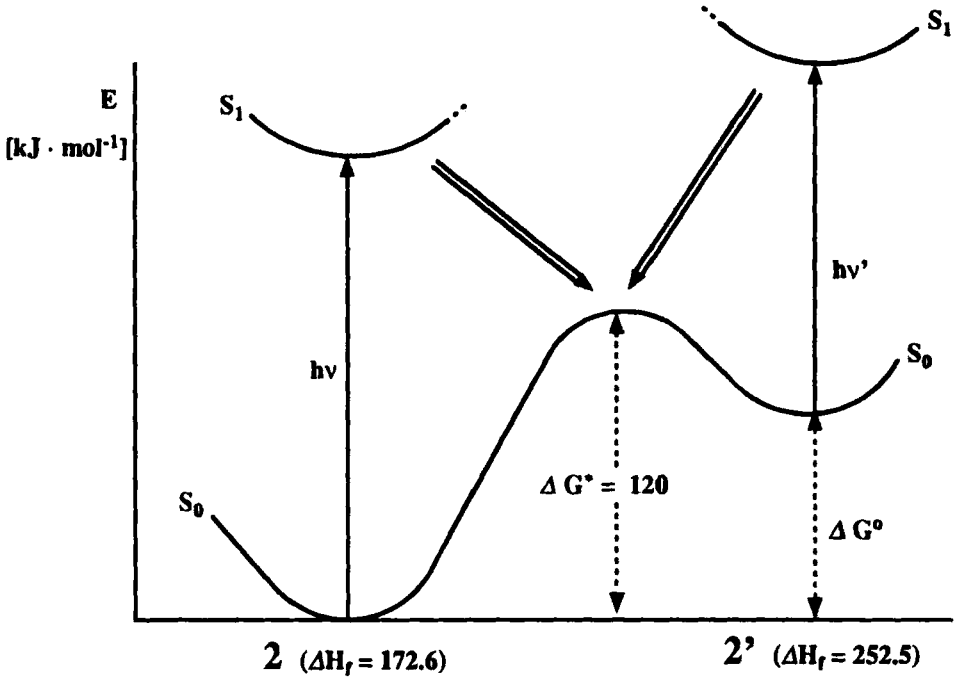
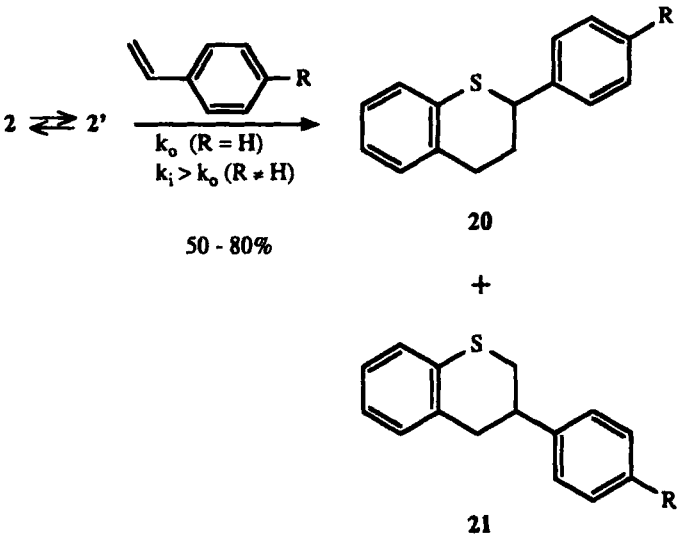


FIGURE 1. Valence isomerization benzo[*b*]thiete (**2**) ⇄ *o*-thiobenzoquinonemethide (**2'**). The experimental activation energy Δ G* corresponds to the reaction in toluene at 100 °C. The enthalpies of formation ΔH_f were calculated by applying the MNDO method.[32]

releasing as well as electron withdrawing substituents enhance the rate of the [8π + 2π] cycloaddition.



R = H, CH_3, C_6H_5, $COCH_3$, F, Cl, Br, OCH_3, $N(CH_3)_2$, NO_2

SCHEME 10

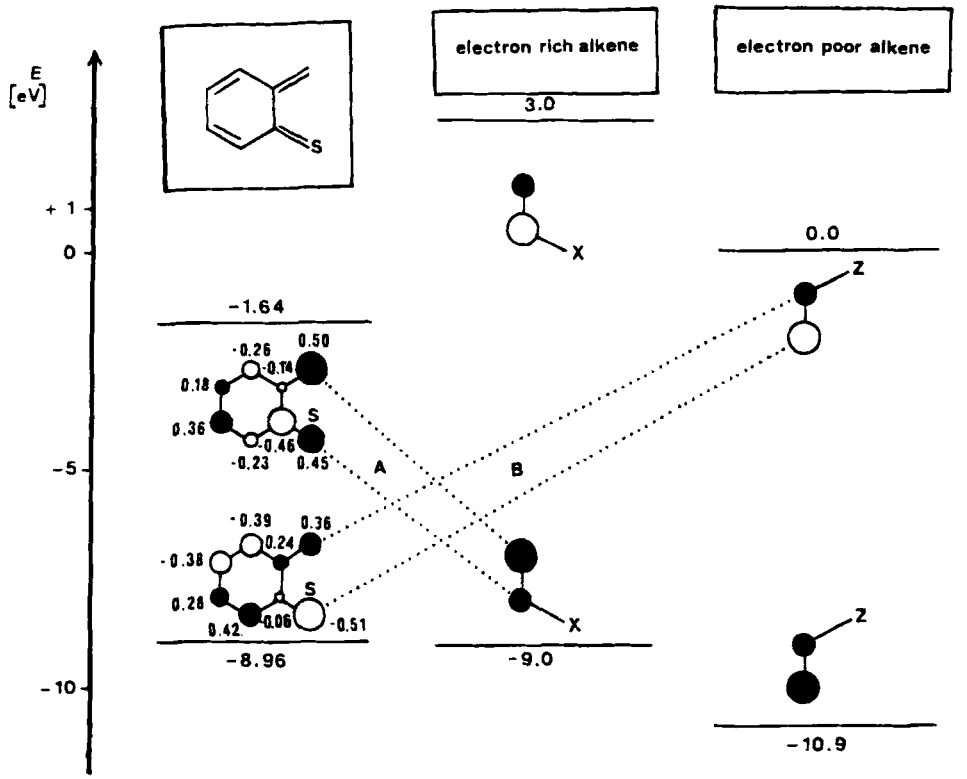


FIGURE 2. Frontier orbitals of *o*-thiobenzoquinonemethide **2**, calculated according to the MNDO method, and estimation of the peri- and regioselectivity of cycloadditions with olefins.[36]

The ratio of the *regioisomers* **20:21** varies between 92:8 and 37:67. Styrenes with electron releasing substituents favor the formation of 2-aryl-3,4-dihydro-2*H*-1-benzothiopyrans **20**, whereas electron withdrawing substituents lead to the 3-aryl isomers **21** as main products. In the first case the reaction seems to be strictly controlled by the interaction LUMO (**2'**)—HOMO (styrene); in the latter case both frontier orbital interactions are relevant. Even an FMO correlation based on a Hückel MO calculation gives for all examples a correct prediction of the main regioisomer.[37]

Nevertheless, the cycloaddition of benzo[*b*]thiete **2** with alkenes is more complex than the above results indicate. It turned out that the process is only stereoselective, if (*E*)-configurated olefins are used. (*Z*)-Configurated alkenes may lead to a partial or total loss of the *stereochemistry*. Some typical examples are summarized in Scheme 11 and Table 2.[36]

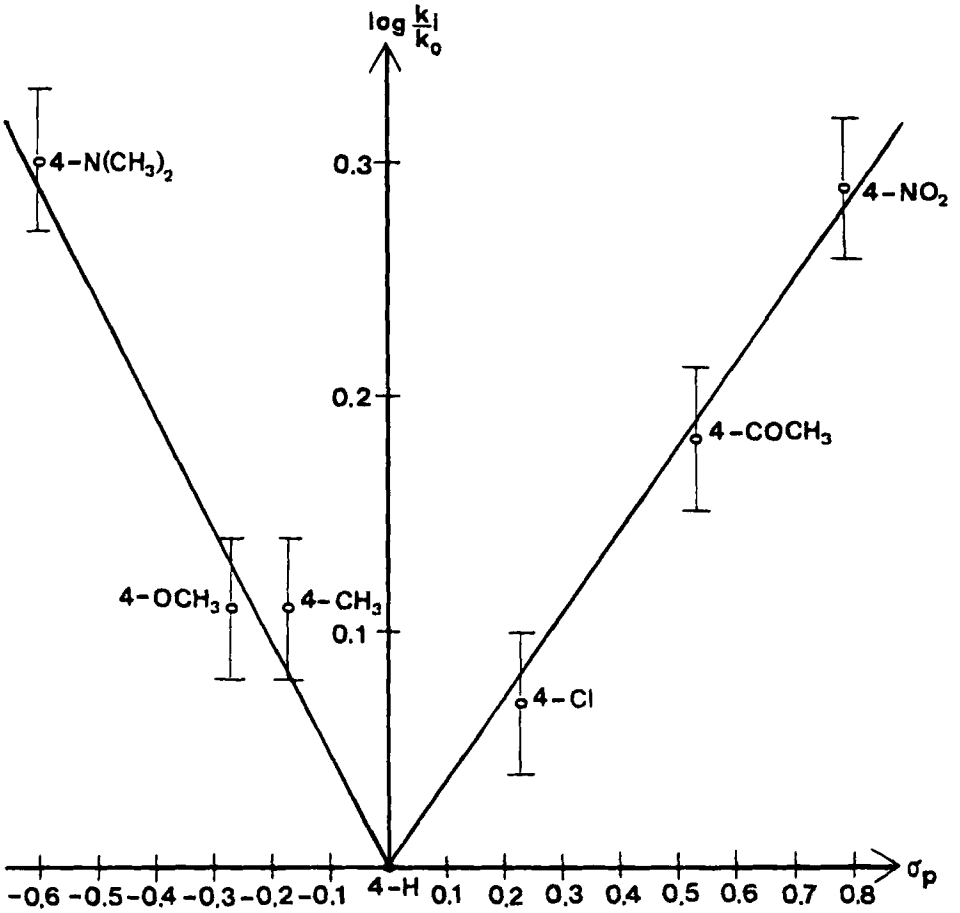
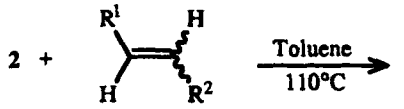
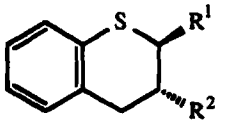


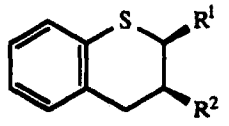
FIGURE 3. Hammett plot of the relative rates k_i/k_o of the cycloaddition reaction of benzo[*b*]thiete **2** and 4-substituted styrenes (Scheme 10).[37]



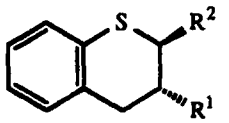
22



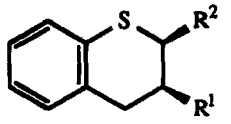
trans-23



cis-23



trans-24



cis-24

SCHEME 11

TABLE 2 Cycloaddition reactions of benzo[*b*]thiete **2** and β-methoxystyrene or crotonic acid methyl ester (Scheme 11).[36]

			Relative yields of **23** and **24**					
22	R^1	R^2	*trans*-**23**	*cis*-**23**	*trans*-**24**	*cis*-**24**	Regioselectivity [%]	Retention of configuration [%]
(*E*)-**22a**	C_6H_5	OCH_3	—	—	80	—	≥99	≥99
(*Z*)-**22a**	C_6H_5	OCH_3	—	—	76	—	≥99	≤1
(*E*)-**22b**	CH_3	CO_2CH_3	57	—	11	—	84	≥99
(*Z*)-**22b**	CH_3	CO_2CH_3	2	23	—	7	79	93

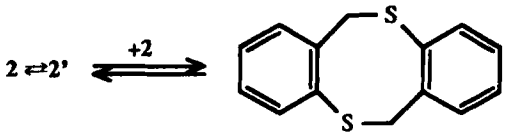
(*E*)-H Configurated olefins give generally better yields than the corresponding (*Z*)-isomers. The regioselectivity is high for electron rich alkenes and somewhat lower for electron deficient alkenes.

(Z)-Enol ethers such as (*Z*)-**22a** form *trans*-configurated cycloadducts; i.e. the original stereochemistry gets totally lost. (Z)-Configurated α,β-unsaturated esters yield a mixture of stereoisomers in which the original stereochemistry of the alkene predominates.

The mechanistic explanation for these results involves an unsymmetrical transition state which may be a consequence of the formation of a C−C single bond and a much longer C−S single bond. The *o*-thiobenzoquinonemethide **2′** resembles a biradicaloid with a weakly polar character.[38] Obviously, a 1,6-diradical is formed in the first reaction step and the subsequent closure of the 6-membered ring competes with a rotation about the original C=C double bond. (An isomerization of the olefin could be excluded under the reaction conditions).

Besides alkenes and alkynes many compounds with hetero double and triple bonds like C=N, C=O, C=S, N=N, N=O, N=S, P=S, C≡N, C≡P etc. are capable of cycloaddition reactions with benzo[*b*]thiete **2**. The regio- and stereochemistry of these processes will be discussed in Chapter 3. Moreover, a final item shall be mentioned here. What happens if the valence isomerization **2** ⇆ **2′** is thermally or photochemically induced in the absence of a reaction partner?

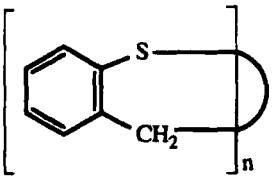
The photolysis at room temperature does not give any secondary product. The thermal ring opening **2** → **2′** initiates the generation of 6*H*, 12*H*-dibenzo[*b*,*f*][1,5]dithiocin **25**.[22,24,27,35]



25

SCHEME 12

In special cases higher cyclooligomers are found.[28,39]



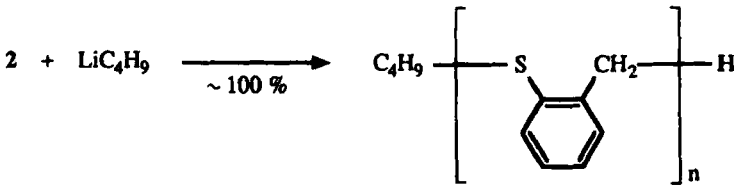
26 (n = 3, 4, 5, 6, 7, 8)

SCHEME 13

Principally this seems to be a convenient synthesis of thiocrown ethers, and additional research work should be done in order to optimize the yields for $n \leq 6$. The cyclic octamer (n = 8), a 32-membered ring is too large for reasonable interior complexation of metal ions.

The dimerization to **25** has to be regarded as a process competitive to any other addition or cycloaddition reaction of **2'**. The product formation is controlled by the kinetics; the less reactive the added reagent is, the more **25** is obtained. However, the percentage of **2** consumed for the dimerization is not definitely lost because the reverse reaction **25** → **2** can be achieved by FVP (700 °C, $4 \cdot 10^{-3}$ mbar, yield: 67%).

It is not well understood why the cyclodimerization and particularly the cyclooligomerizations are so much favored in comparison to linear polymerization reactions. Exclusively in the presence of butyllithium we were able to generate linear oligomers **27**.[28]



27 (n = 1, 2, 3, ...)

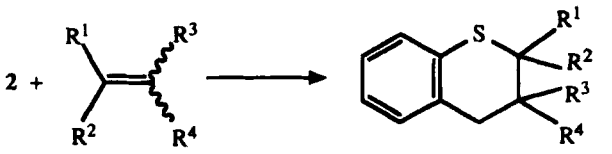
SCHEME 14

4. SYNTHETIC APPLICATIONS OF BENZO[*b*]THIETES

The reaction schemes 15–50 in Chapter 4 show numerous synthetic applications of benzo[*b*]thiete **2.** All these reactions are performed in toluene at 90–110 °C, unless other conditions are specified.

4.1. *Reaction with Alkenes*

As already pointed out in Chapter 3.2., benzo[*b*]thietes react with electron rich olefins as well as with electron deficient olefins. Nevertheless, quite normal alkenes like 1-octene or cyclohexene are also capable of an [8π + 2π] cycloaddition yielding 3,4-dihydro-2*H*-1-benzothiopyrans **29**. Table 3 gives a survey over some reactions with mono- and 1,2-disubstituted olefins. The regio- and stereochemistry was already discussed in Chapter 3.2.



28 29

SCHEME 15

Table 4 summarizes cycloaddition reactions with 1,1-disubstituted alkenes. Apparently capto-dative olefins react scarcely; the reason for this exception is not known.

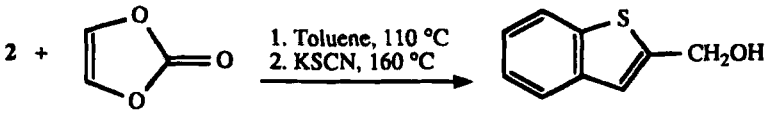
TABLE 3 Reaction of benzo[*b*]thiete **2** with mono- or 1,2-disubstituted olefins **28.**

	3,4-Dihydro-2*H*-1-benzothiopyran **29**				
Alkene **28** (R^2,R^4 = H)	R^1		R^3	Yield [%]	Literature
1-Octene	C_6H_{13}		H	22	40
	H		C_6H_{13}	12	40
Methyl acrylate	H		CO_2CH_3	52	22
	CO_2CH_3		H	13	22
(*Z*)-Methyl cinnamate	C_6H_5		CO_2CH_3	16	40
	CO_2CH_3		C_6H_5	10	40
(*E*)-Methyl cinnamate	C_6H_5		CO_2CH_3	25	40
	CO_2CH_3		C_6H_5	18	40
Diethyl fumarate	$CO_2C_2H_5$		$CO_2C_2H_5$	97	36
Diethyl maleate	$CO_2C_2H_5$		$CO_2C_2H_5$	40	36
(*E*)-1,2-Bis(phenylsulfonyl)ethene	$SO_2C_6H_5$		$SO_2C_6H_5$	63	41
Cyclohexene		$-(CH_2)_4-$		81	27
2-Cyclohexenone		$-(CH_2)_3-CO-$		25	22
		$-CO-(CH_2)_3-$		6	28
2,5-Dihydrofuran-2-one		$-CH_2-O-CO-$		21	41
Maleic anhydride		-CO-O-CO-		75	41
N-Phenylmaleimide		$-CO-N(C_6H_5)-CO-$		77	22,27
Coumarin		$-o-C_6H_4-O-CO-$		22	41

TABLE 4 Reaction of benzo[*b*]thiete **2** with 1,1-disubstituted and 1,1,2-trisubstituted olefins **28.**

	3,4-Dihydro-2*H*-1-benzothiopyran **29**					
Alkene **28**	R^1	R^2	R^3	R^4	Yield [%]	Literature
2-Methoxypropene	CH_3	OCH_3	H	H	43	27
1-Morpholinocyclohexene	NC_4H_8O	$(CH_2)_4$		H	59	28
α-Methylstyrene	CH_3	C_6H_5	H	H	17	40
	H	H	CH_3	C_6H_5	9	40
Methyl methacrylate	CH_3	CO_2CH_3	H	H	11	40
	H	H	CH_3	CO_2CH_3	20	40
1-Methoxy-1-(4-nitrophenyl)ethene	OCH_3	4-$NO_2C_6H_4$	H	H	4	40

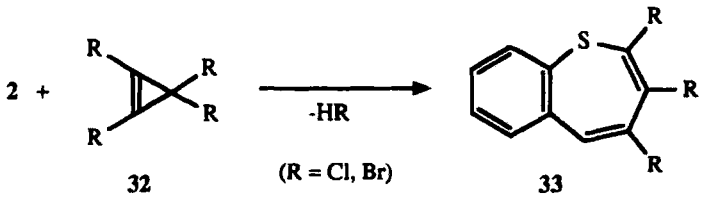
The Schemes 16 and 17 show two special applications of this cycloaddition leading to 5- and 7-membered rings, respectively.[41]



30 31

SCHEME 16

Contrary to the primary product formed by benzo[*b*]thiete **2** and vinylene carbonate **30** the intermediate cycloadducts of **2** and tetrachlorocyclopropene or tetrabromocyclopropene **32** cannot be isolated; a spontaneous dehydrohalogenation furnishes the benzo[*b*]thiepin **33.** Due to the dimerization of **2** the yields of **31** and **33** are poor (3–20 %).

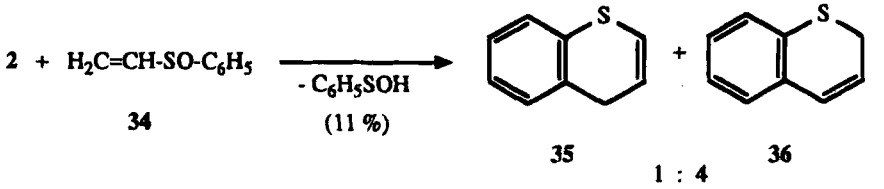


32 33

SCHEME 17

Better yeilds of derivatives of benzo [*b*] thiophene and benzo [*b*] thiepin can be obtained in the reaction of **2** and diazo compounds and vinyldiazo compounds, respectively.[42]

Spontaneous elimination reactions are also involved in the cycloaddition processes of acetylene equivalents like **34:**[41]

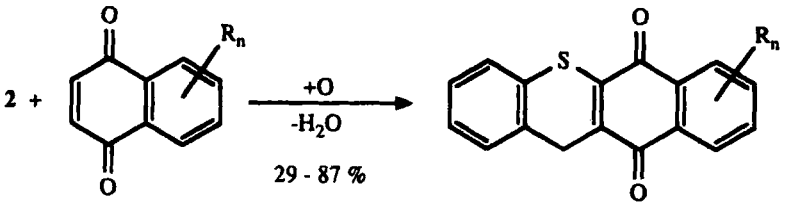


34 35 36

1 : 4

SCHEME 18

Cycloaddition and autoxidation is a typical reaction sequence of **2** and 1,4-benzoquinones or 1,4-naphthoquinones.[41,42] (The absence of oxygen permits often the isolation of the primary adducts).

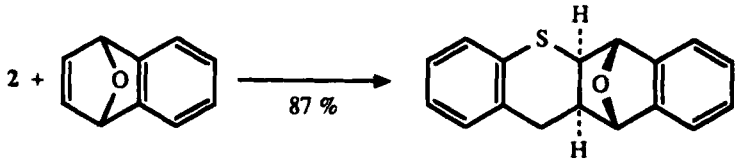


37 38

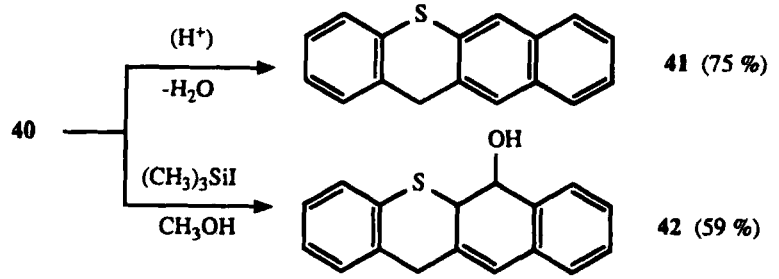
R = H, OH, OCH_3, $OCOCH_3$ n = 1,2

SCHEME 19

An efficient access into the series of sulfur-analogous tetracyclins is also possible by applying the cycloaddition of **2** and 1,4-epoxynaphthalene **39**.[41,42]

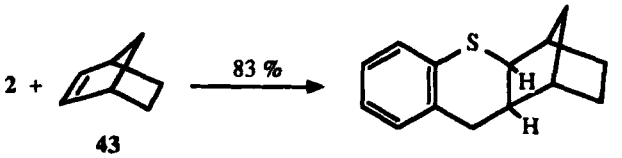


39 40



SCHEME 20

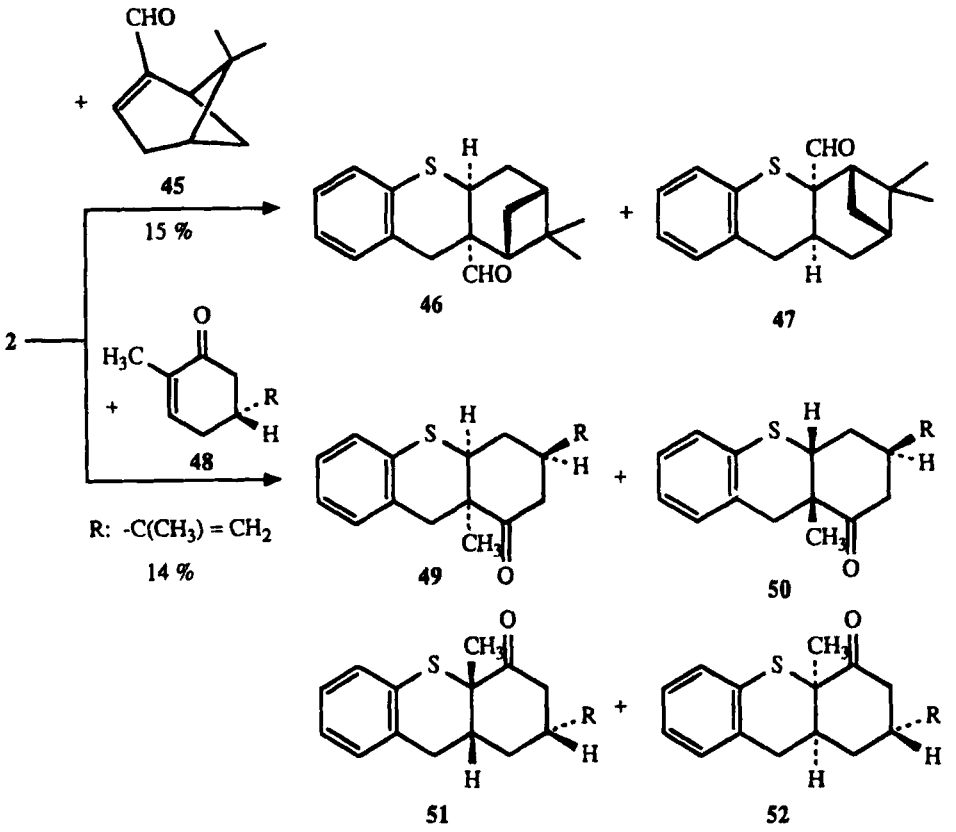
Obviously, pronounced π-side selectivity determines the stereochemistry of the cycloadduct **40**. Similar observations can be made for the reactions of **2** and norbornene **43**.[41]



43 44

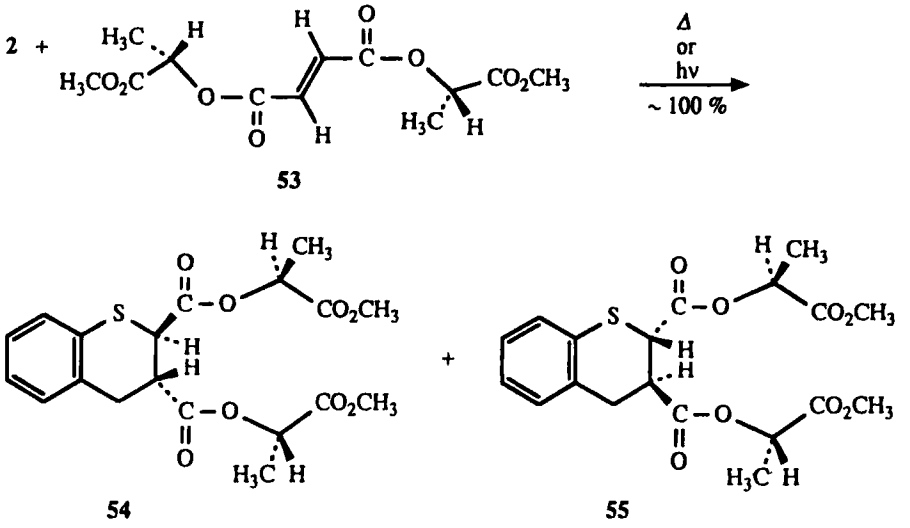
SCHEME 21

Of course, pairs of enantiomers are formed in such cycloaddition reactions, but optically pure chiral reaction partners may lead to an asymmetric induction. Benzo[*b*]thiete **2** attacks the prochiral sp^2 carbon atoms of (1R)-(−)-myrtenal **45** exclusively from the Si side. Both regioisomers **46** and **47** are generated in a 1:1-ratio with a diastereomeric excess de > 96 %. Less steric hindrance in the reaction with R-(−)-carvone **48** permits on the other hand an attack from both π sides.[41]



SCHEME 22

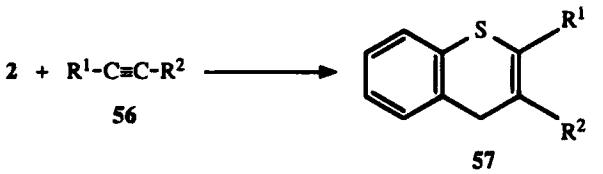
Open-chain olefins like fumaric acid esters with chiral alcohol components cause only a small diastereoselectivity—in the thermal as well as in the photochemical reaction. Besides the temperature the concentration plays an important role.[43] The thermal process in boiling toluene yields the stereoisomers in a ratio of 39:61; the photochemical variant gives in diluted solution in cyclohexane ($c \sim 10^{-4}$mol/l) a similar ratio of 32:68. Enhancing the concentration to $c \approx 0.7$ mol/l leads to a ratio of 54:46, i.e. the selectivity is again poor, but it is reversed.



SCHEME 23

4.2. *Reactions with Alkynes*

A convenient synthesis of 4*H*-1-benzothiopyrans **57** via cycloaddition of benzo[*b*]thiete **2** and alkynes **56** is shown in Scheme 24.[22]



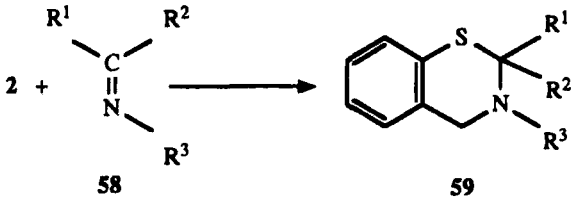
R^1	R^2	Yield
CO_2CH_3	CO_2CH_3	65 %
$-(CH_2)_6-$		90 %

SCHEME 24

The newly generated double bond in **57** is not reactive enough to add a second molecule **2.**

4.3. *Reactions with C=N Double Bond Systems (Imines, Oximes)*

A variety of classes of compounds **58** containing C=N double bonds enter cycloaddition reactions with benzo[*b*]thiete **2.** A high regioselectivity is typical for these processes. Scheme 25 and Table 5 show the formation of 3,4-dihydro-2*H*-1,3-benzothiazines **59.**



58 59

R^1, R^2 = H, Alkyl, Aryl R^3 = Alkyl, Aryl, OH, OR, NR_2

SCHEME 25

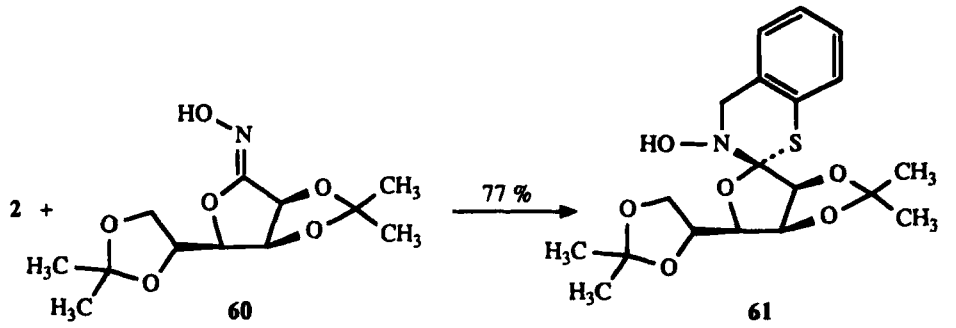
TABLE 5 Reaction of benzo[b]thiete **2** with azomethines, oximes, oxime ethers and azines **58** (Scheme 24).

R^1	R^2	R^3	3,4-Dihydro-2*H*-1,3-benzothiazines **59**: Yield [%]	Literature
C_6H_5	H	C_6H_5	69–91	44,45
C_6H_5	H	4-$OCH_3C_6H_4$	71	44
C_6H_5	H	4-ClC_6H_4	72	44
4-$CH_3C_6H_4$	H	4-ClC_6H_4	71	44
4-ClC_6H_4	H	C_6H_5	74	45
4-$OC_{12}H_{25}C_6H_4$	H	C_6H_5	76	45
CH_3	CH_3	C_6H_5	18	45
CH_3	CH_3	$CH(CH_3)_2$	4[a]	45
C_2H_5	C_2H_5	$CH(CH_3)_2$	2	45
CH_3	H	OH	41	46
CH_3	CH_3	OH	66	46
-$(CH_2)_5$-		OH	72	46
C_6H_5	H	OH	8	46
4-$NO_2C_6H_4$	H	OH	1	46
C_6H_5	H	OCH_3	4	46
C_6H_5	H	N=CH-C_6H_5	23	45

a) Small yield caused by side reactions.[45]

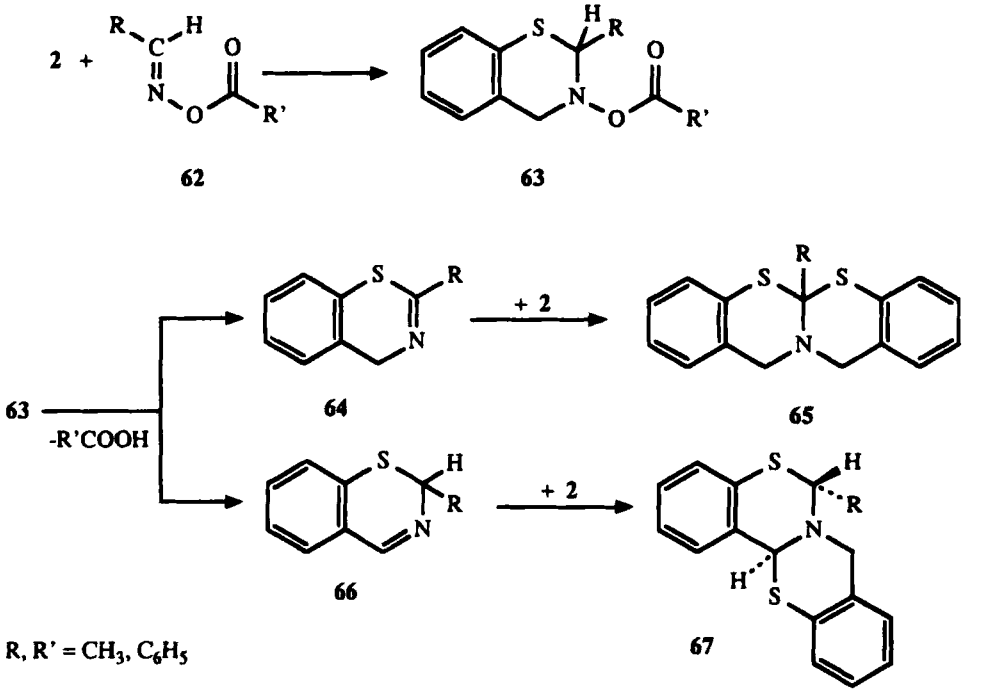
Contrary to oximes, hydrazones containing an N-H bond do not enter a cycloaddition with **2**; they behave similarly to amines (Chapter 4.9.).

In addition to the principally observed regioselectivity, which can be explained by the FMO theory,[46] a strict stereoselectivity was established for the oxime **60** in Scheme 26.[46]



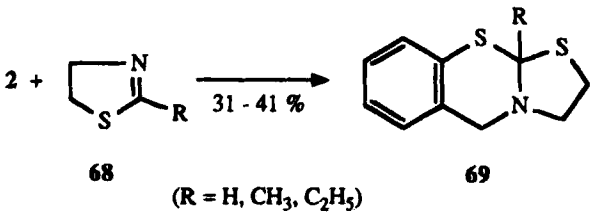
SCHEME 26

Oxime esters **62** can also be used for this cycloaddition; however, one has to take into account an elimination which generates again a C=N double bond suitable for a second cycloaddition (yield ≤ 21 %).[46]



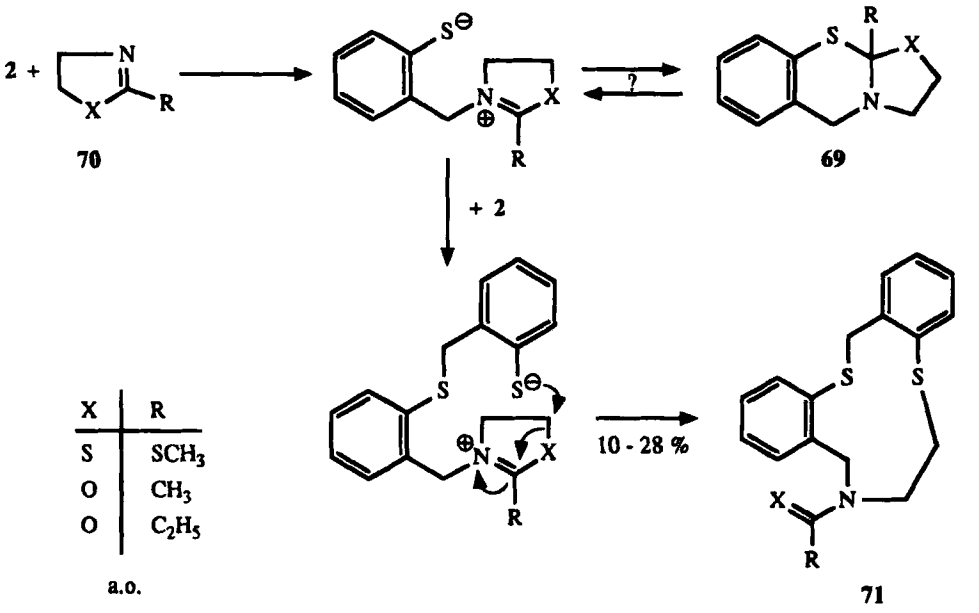
SCHEME 27

Principally, the reactive C=N double bond can be incorporated in a ring system. The 4,5-dihydrothiazoles **68** for example yield the 2,3-dihydro-5*H*,10a*H*-thiazolo[2,3-*b*][1,3]benzothiazines **69**.[45]



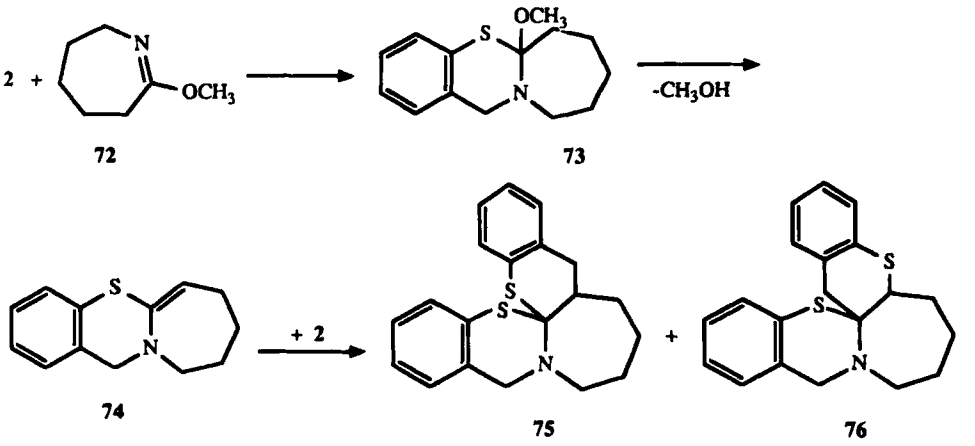
SCHEME 28

A further hetero substituent R in **68** or a 4,5-dihydrooxazole system induces the formation of 2:1-adducts **71**.[45]



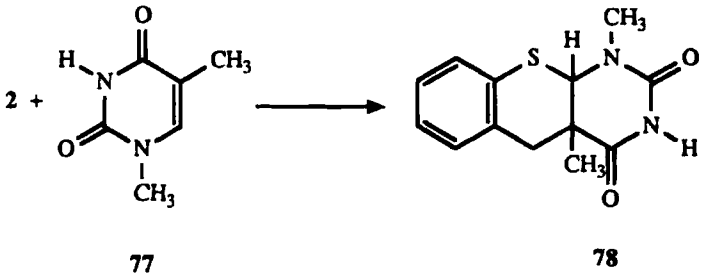
SCHEME 29

Although the C=N double bonds of lactim ethers and oxazolines are absolutely comparable, a different reaction behavior is observed. The primary cycloadducts **73** eliminate methanol and add a second molecule of benzo[*b*]thiete **2** generating the regioisomeric polycyclic compounds **75** and **76** (yield 22 %).[45]



SCHEME 30

CN bonds of heteroaromatic compounds do not react with **2**—not even in compounds like thymine where tautomeric forms with "genuine" C=C or C=N double bonds exist. 3-Methylthymine **77**, however, reacts because the tautomerization to an aromatic ring is blocked by the methyl group. A regioselective cycloaddition takes place at the CC double bond.[45]

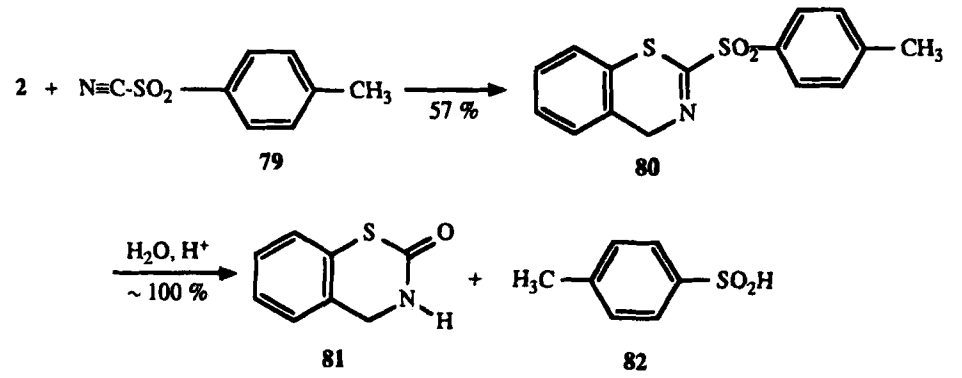


SCHEME 31

A related process was established for (2S)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine. The latter compound contains two C=N double bonds but the cycloaddition occurs at an intermediately formed C=C double bond. This reaction and some further examples with C=N double bond systems have been discussed in the literature.[45]

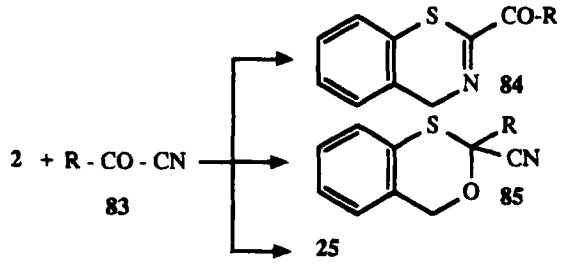
4.4. *Reaction with Nitriles*

Nitriles are relatively inert with respect to cycloaddition reactions to benzo[*b*]thiete **2.** Exceptions are observed for electron deficient systems like tosyl isocyanide **79.**[39] The cycloadduct **80** can be hydrolyzed to 1,3-benzothiazin-2-one **81** which can be regarded as a cycloadduct of **2** and isocyanic acid. Isocyanates normally do not add.



SCHEME 32

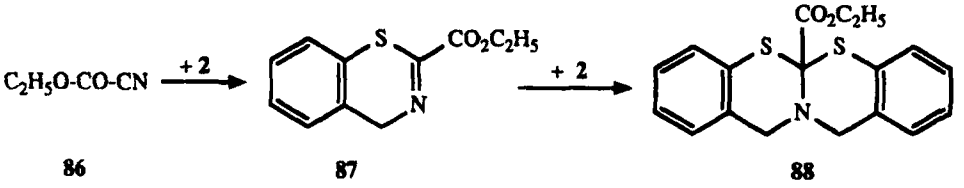
Whereas phenylglyoxylic acid nitrile (benzoyl cyanide) reacts with **2** like **79**, pyruvic acid nitrile is attacked at the C≡N triple bond as well as at the C=O double bond. However, the dimer **25** is in both cases the main product.[39]



R	84 : 86 : 25
CH_3	14 : 3 : 83
C_6H_5	7 : -- : 93

SCHEME 33

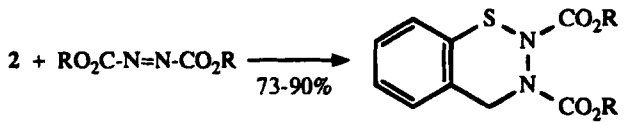
The CN double and triple bonds in **84** and **85** are not suitable for further cycloadditions under normal conditions; however, the cyanoformic acid ester **86** shows such a twofold cycloaddition.[39]



SCHEME 34

4.5. *Reaction with Azo Compounds*

Azodicarboxylic acid diesters **89** are well-known dienophiles. Benzo[*b*]thiete **2** adds **89** generating 3,4-dihydro-2*H*-1,2,3-benzothiadiazines **90** in good yields.[47,48]



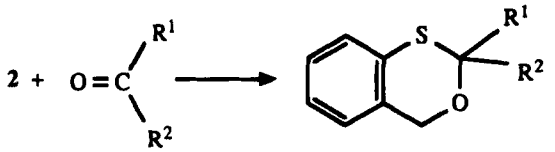
89 **90**

(R = C_2H_5, $C(CH_3)_3$, C_6H_5, $CH_2C_6H_5$)

SCHEME 35

4.6. *Reaction with Carbonyl Compounds*

The FMO theory predicts that especially electron deficient C=O double bonds should be capable of cycloaddition to the 8π system of the ring-opened benzo[*b*]thiete.[49] Orbital control as well as charge control lead to the same prediction, namely to the formation of 4*H*-3,1-benzoxathiins **92**.[49]



91 **92**

SCHEME 36

Simple aldehydes and ketones are inert or react sluggishly under normal conditions in hetero-Diels-Alder reactions. However, **2** is so reactive that even aldehydes like butanal or benzaldehyde generate small amounts of the corresponding 4*H*-3,1-benzoxathiins **92** in addition to the dimer **25.** Butanal, cyclohexanecarboxaldehyde, 2-naphthalenecarboxaldehyde, 9-phenantrenecarboxaldehyde, 2-pyridinecarboxaldehyde, and 2-furancarboxaldehyde (furfural) furnish yields of 10% or less.

Table 6 shows that electron withdrawing substituents strongly increase the yields of **92**.[41,50]

TABLE 6 Reaction of aldehydes **91** (R^2 = H) with benzo[*b*]thiete **2**.[41,50]

Aldehyde **91**	R^1	4*H*-3,1-Benzoxathiin **92** (Yield in %)
Trichloroacetaldehyde	CCl_3	69
Methyl glyoxylate	CO_2CH_3	72
Benzaldehyde	C_6H_5	6
4-Methylbenzaldehyde	4-$CH_3C_6H_4$	8
4-(Dimethylamino)benzaldehyde	4-$N(CH_3)_2C_6H_4$	13
4-Chlorobenzaldehyde	4-ClC_6H_4	7
2,3,5-Trichlorobenzaldehyde	2,3,5-$Cl_3C_6H_2$	22
Terephthaldialdehyde	4-$CHOC_6H_4$	12
4-Cyanobenzaldehyde	4-CNC_6H_4	20
4-Nitrobenzaldehyde	4-$NO_2C_6H_4$	11
2,4-Dinitrobenzaldehyde	2,4-$(NO_2)_2C_6H_3$	45

Ketones with electron withdrawing substituents in the α-position like α-oxo carboxylic acids and their derivatives are also suitable reaction partners (Table 7).[49]

TABLE 7 Reaction of 2-oxo carboxylic esters and amides **91** with benzo[*b*]thiete **2**.[49]

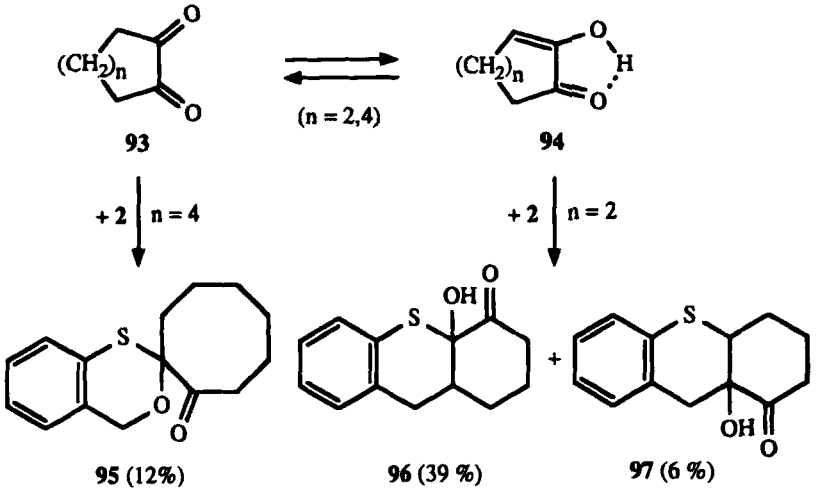
Carbonyl Component **91**	R^1	R^2	4*H*-3,1-Benzoxathiin **92** (Yield in %)
Methyl pyruvate	CH_3	CO_2CH_3	21
Ethyl pyruvate	CH_3	$CO_2C_2H_5$	25
Diethyl mesoxalate	$CO_2C_2H_5$	$CO_2C_2H_5$	79
N-Methylisatin	-CO-N(CH_3)-o-C_6H_4-		60
Alloxan	-CO-NH-CO-NH-CO-		77

Aliphatic 1,2-diketones can also be applied for the cycloaddition with **2**; however, only *one* carbonyl group reacts. Aryl alkyl substituted 1,2-diones react selectively on the aliphatic side. Diarl diketones like benzil or 2,2'-dipyridyl do not react at all.

TABLE 8 Reaction of 1,2-diketones **91** with benzo[*b*]thiete **2**.[49]

Carbonyl component **91**	R^1	R^2	4*H*-3,1-Benzoxathiin **92** (Yield in %)
2,3-Butanedione	CH_3	$COCH_3$	20
2,3-Pentanedione	CH_3	COC_2H_5	8
	C_2H_5	$COCH_3$	13
1-Phenyl-1,2-propanedione	CH_3	COC_6H_5	15
Ninhydrin	-CO-*o*-C_6H_4-CO-		89

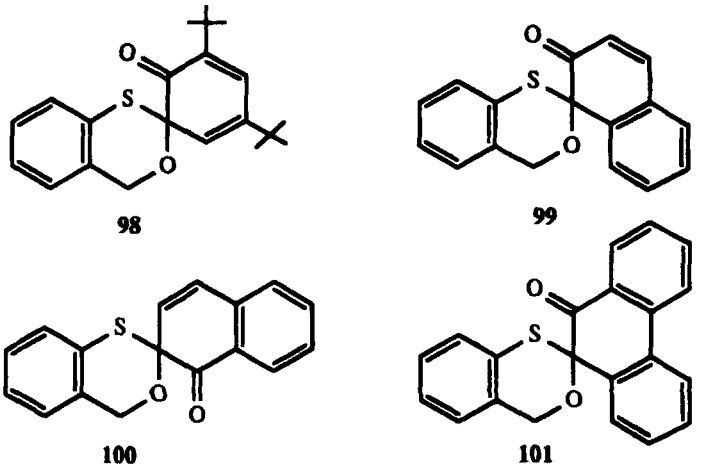
1,2-Diketones with a considerable enolization tendency show a more complicated behavior. The comparison between 1,2-cyclohexanedione and 1,2-cyclooctanedione is very instructive.[49]



SCHEME 37

The ratio of the two thioxanthene derivatives **96** and **97** corresponds neither to the regioselectivity of electron rich alkenes nor to the preferred orientation in the addition of electron poor alkenes.

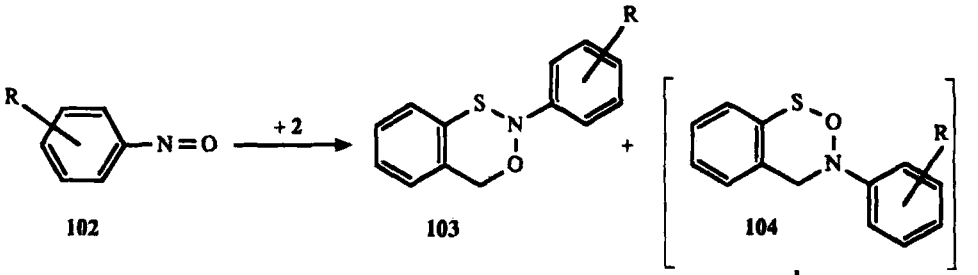
Conjugated enones normally react chemoselectively at the C=C double bond; cyclopropenones are an exception.[49] Finally *o*-quinones shall be discussed in this Chapter. Contrary to *p*-quinones they react chemoselectively at the C=O double bond. 3,5-Di-*tert*-butyl-1,2-benzoquinone, 1,2-naphthoquinone and 9,10-phenanthrenequinone form in good yields (56–91 %) the spiro compounds **98–101** shown in Scheme 38.[49]



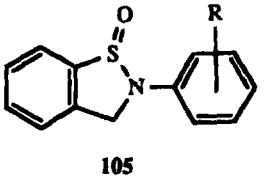
SCHEME 38

4.7. *Reaction with Nitroso Compounds*

The cycloaddition of benzo[*b*]thiete **2** and nitrosobenzenes **102** is not regioselective as one would expect on the basis of a comparison with the cycloaddition of carbonyl compounds. However, only *one* primary adduct can be isolated, namely a 4*H*-3,1,2-benzoxathiazine **103**. The isomeric 4*H*-2,1,3-benzoxathiazines **104** rearrange spontaneously under the reaction conditions to 2,3-dihydro-1,2-benzothiazole 1-oxides **105**.[51]

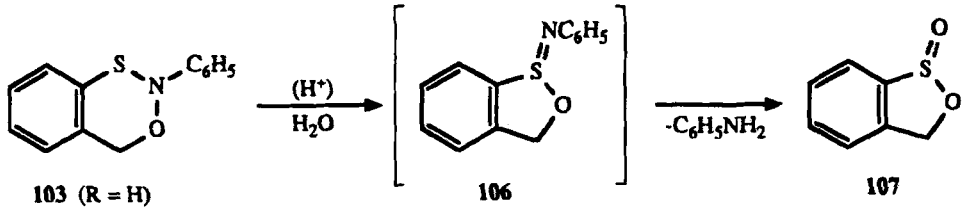


R	103 : 105	Total Yield [%]
H	32 : 68	99
2-CH_3	15 : 85	100
2-Cl	4 : 96	99
4-CH_3	-- : 100	10
4-$N(CH_3)_2$	-- : 100	8



SCHEME 39

The primary products **103** are thermally stable; a cleavage is only observed in the presence of acids (Scheme 39).[51] Hydrolysis yields 3*H*-2,1-benzoxathiole 1-oxide **107** and aniline.

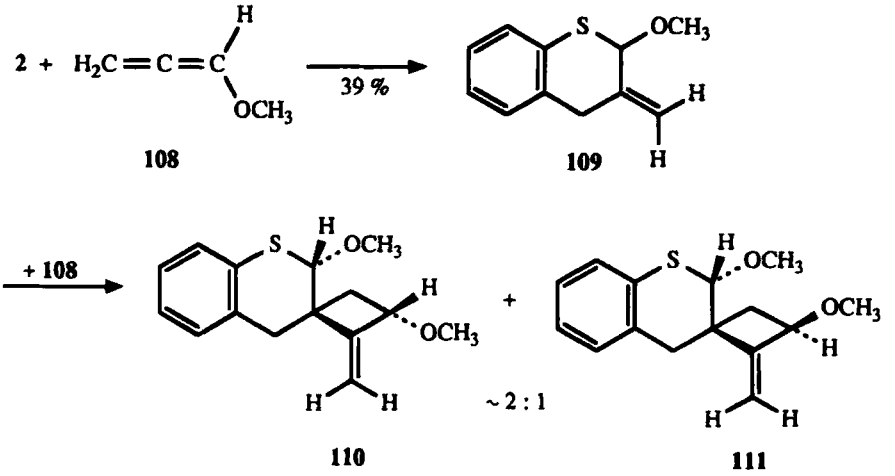


SCHEME 40

4.8. *Reaction with Allenes and Heterocumulenes*

Electron rich allenes like 1-methoxypropadiene **108** react with benzo[*b*]thiete **2** to 3-methylene-3,4-dihydro-2*H*-1-benzothiopyrans **109**. Surprisingly, **109** enters a second

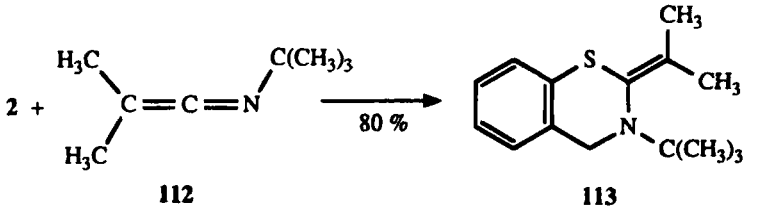
cycloaddition with an allene **108** and not with **2.** Additionally to the chemo- and regioselectivity a high diastereoselectivity is observed. The formation of three chiral centers could principally lead to eight stereoisomers but only **110** and **111** and the corresponding enantiomers were obtained.[52] Obviously **109** is solely attacked by **108** from the side opposite to the methoxy group on C-2.



108 **109** **110** **111**

SCHEME 41

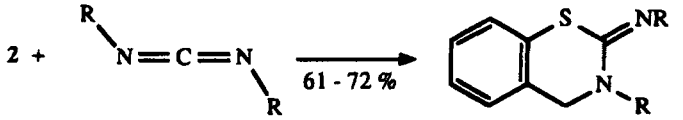
Ketenes like diphenylketene do not react with benzo[*b*]thiete; ketenimines react at the C=N double bond. Thus 3,4-dihydro-2*H*-1,3-benzothiazines with an exocyclic double bond in the 2-position are formed.[52]



112 **113**

SCHEME 42

A similar reaction was found for carbodiimides **114.**



114 **115**

(R = C_6H_{11}, $CH(CH_3)_2$)

SCHEME 43

Finally the reaction of **2** with *N*-sulfinylamines **116** shall be discussed in this chapter. This cycloaddition yields selectively 4*H*-1,2,3-benzodithiazine 2-oxides **117**.[52]

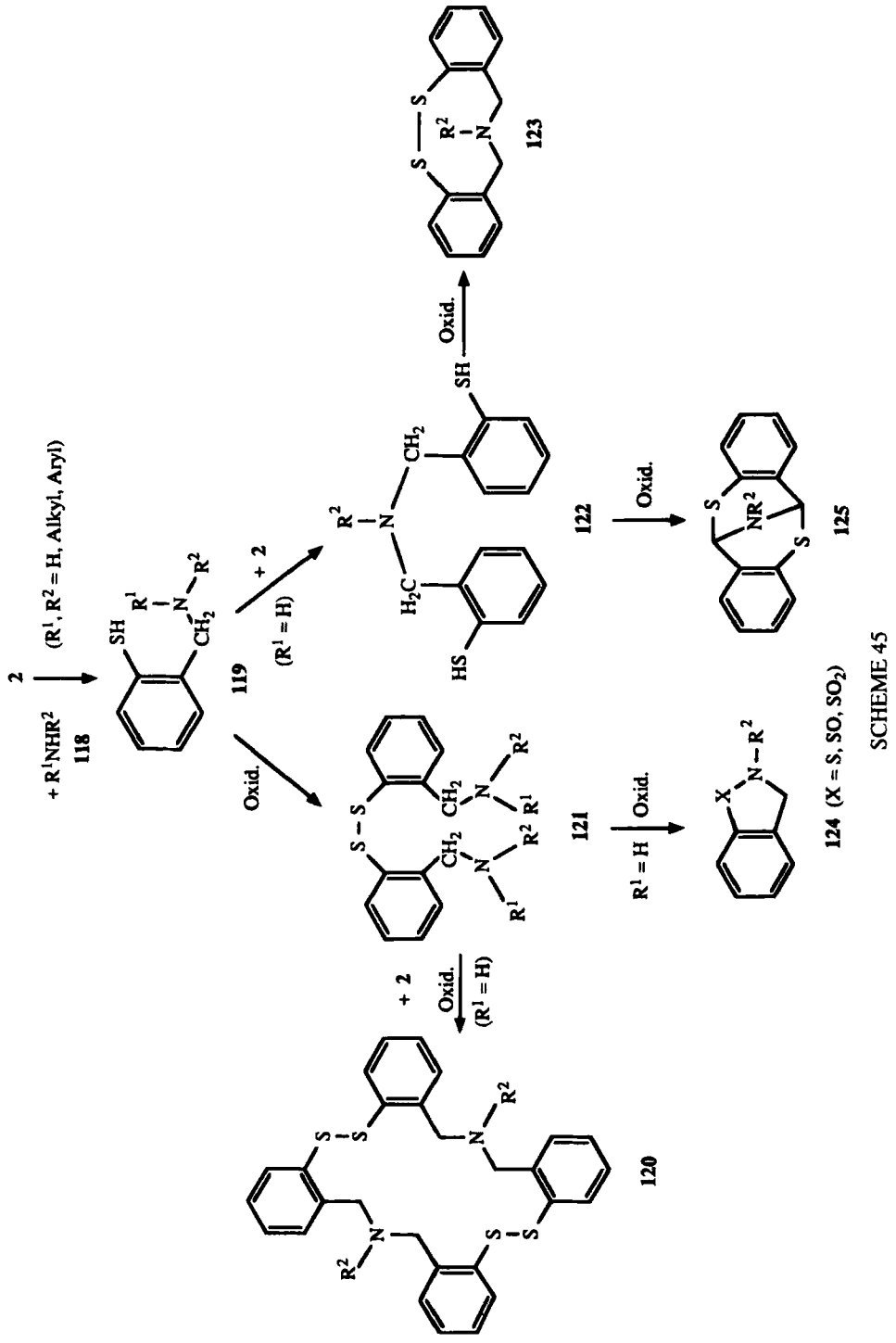
116 **117**

R	Yield [%]
C_6H_{11}	32
C_6H_5	71
4-O $CH_3C_6H_4$	81

SCHEME 44

4.9. *Reaction with Amines*

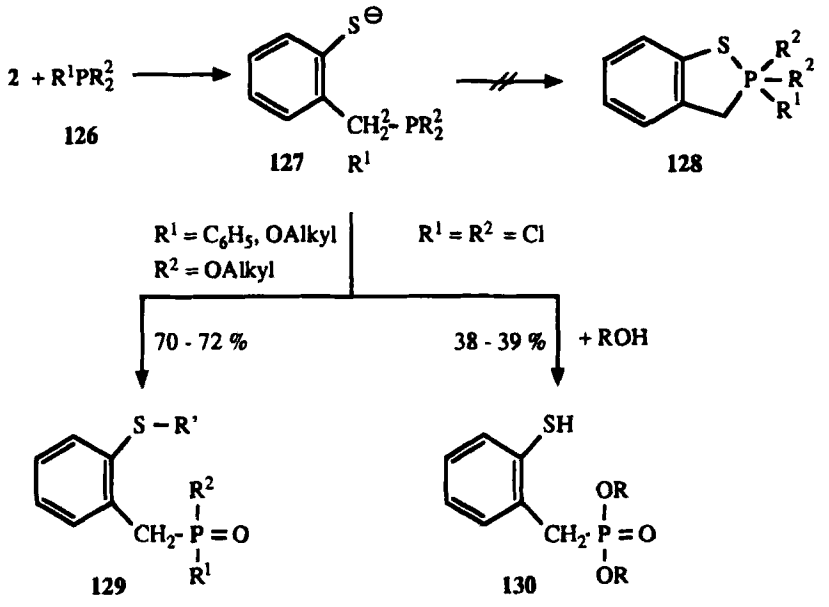
Ammonia as well as primary and secondary amines **118** add to benzo[*b*]thiete **2** yielding 2-(aminomethyl)thiophenols **119** as primary products.[27,53] Provided that **119** still contains a reactive NH group, a second molecule **2** can be involved. The linear adducts often form heterocyclic ring systems on (aut)oxidation. Thus, the disulfide **121** leads into the series of benz[*d*]isothiazoles **124.** Whereas oxidation with *m*-chloroperbenzoic acid provides (in good yields) the sulfoxide and the sulfone **124** (X = SO, SO_2), respectively, the autoxidation to **124** (X = S) seems to be a rather complicated process—mainly due to the fact that amines themselves are sensitive towards oxidation. The linear 2:1 adducts **122** are oxidized to 6,12-dihydro-6,12-iminodibenzo[*b,f*][1,5]dithiocins **125**; small amounts of 12,13-dihydro-11*H*-dibenzo[*c,h*][1,2,6]dithiazonins **123** were also obtained. Finally a sequence of altogether four addition and two oxidation reactions yields the 1,2,10,11,6,15-tetrathiadiazacyclooctadecene system **120** (R^2 = C_6H_5).[32] Dimer **25** or higher oligomers of **2** do not provide an entrance into the reaction scheme 45; however, the *S*-oxides **124** can be prepared by the addition of nitroso compounds to **2** (Chapter 4.7.).



SCHEME 45

4.10. *Reaction with P-Nucleophiles*

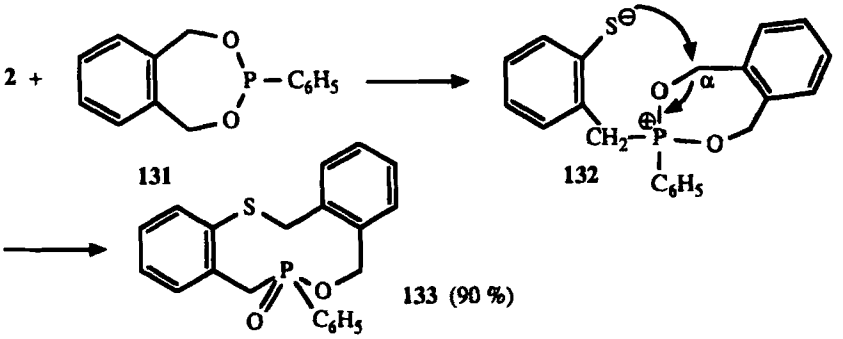
Trialkyl phosphites or dialkyl arylphosphinates **126** add to the *o*-quinoid form of benzo[*b*]thiete to yield the phosphonates or phosphinates **129**. This transformation takes place by intermolecular migration of an alkyl group from the oxygen to the sulfur atom, a variant of the Arbuzov reaction. The rearrangement can be avoided by the consecutive action of PCl_3 and an alcohol.[54,55]



(R,R' = Alkyl)

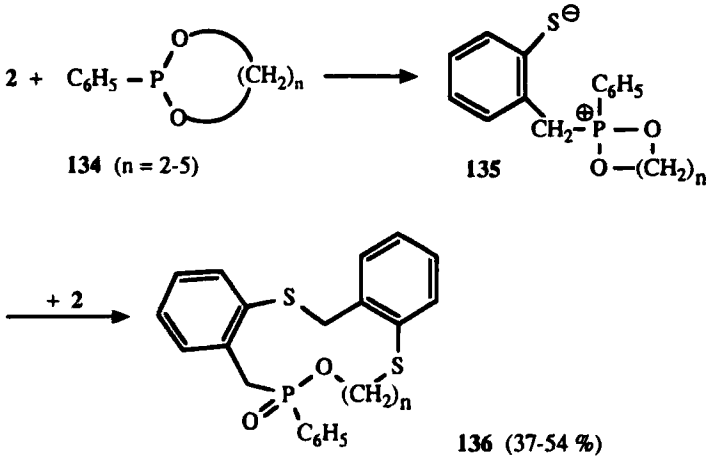
SCHEME 46

A direct ring closure **127** → **128** does not occur. Nevertheless, phosphorus heterocycles can be prepared by the application of cyclic esters[54,55] which permit an S_N1 attack of the thiophenolate on the α-carbon atom, for example:



SCHEME 47

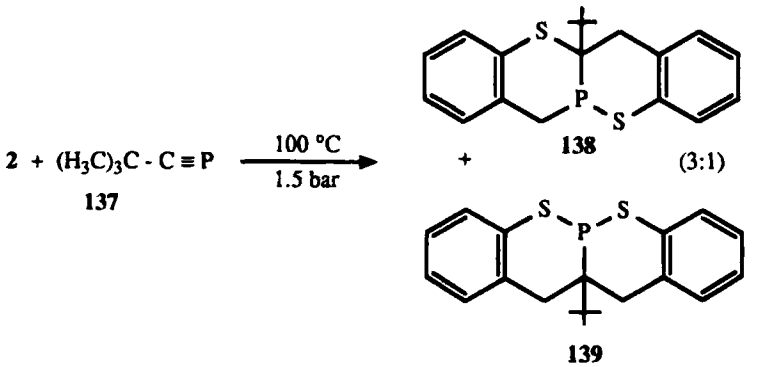
Besides phenyl substituted C atoms, tertiary carbon atoms are capable of this ring enlargement.[55] An *intramolecular* S_N2 mechanism fails because of the strain which would be implicated in the transition state. An *intermolecular* process takes place in this case; consequently macrocyclic 1:2-adducts **136** are generated.[54,55]



SCHEME 48

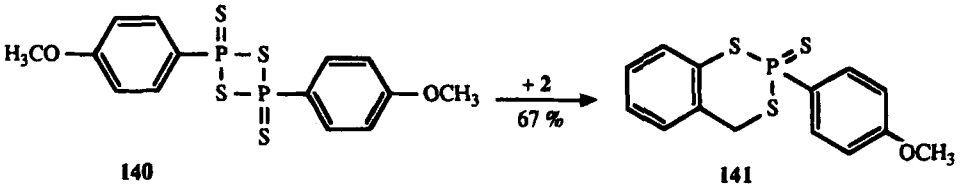
4.11. *Miscellaneous*

Notwithstanding the various syntheses of heterocycles in the previous schemes, there are many further examples of cycloaddition reactions of benzo[*b*]thiete **2** and 2π components which have not been investigated in detail. C=S double bonds as well as CP or PS multiple bonds should be mentioned in this context. Low boiling points of the reagents, e.g. CS_2 (b.p. 46 °C) or $(CH_3)_3C\text{-}C{\equiv}P$ (b.p. 65 °C) require thermal reactions under pressure. The photochemical variant presupposes the photostability of the reagent and the products and is therefore sometimes no real alternative. Whereas for CS_2 and thioketones more investigations on the structures of the products still have to be done, (2,2-dimethylpropylidyne)-phosphine **137** gives in poor yields two 1:2-adducts which we regard as the tetracyclic compounds **138** and **139**.[56]



SCHEME 49

Much better results were obtained for the reaction of **2** and Lawesson's reagent **140**.[28] A P=S double bond acts formally as 2π component in a strictly regioselective cycloaddition.



140 **141**

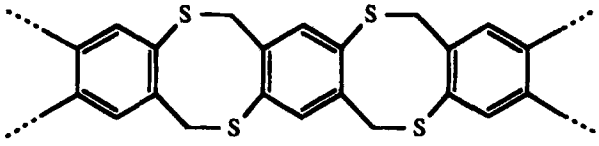
SCHEME 50

Reactions of benzo[*b*]thiete **2**, in which the bicyclic skeleton is preserved, have hardly been investigated. Smooth electrophilic displacement reactions on the benzene ring and oxidation processes on the sulfur[30] probably have the best chances.

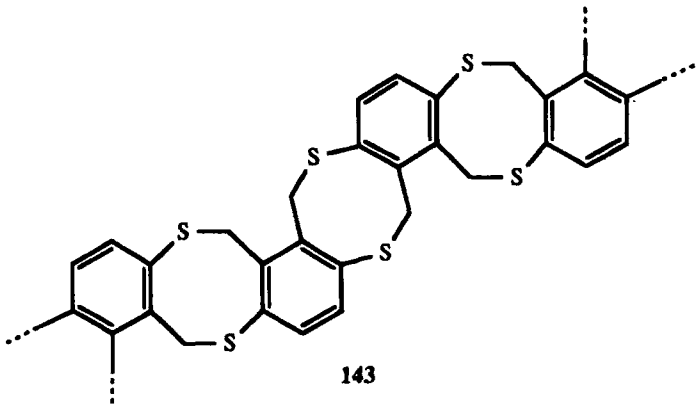
5. OUTLOOK

This review presents a variety of reactions of benzo[*b*]thiete **2** which proved to be an extremely versatile reagent—especially for the preparation of heterocycles. On the whole, [4+2] cycloaddition reactions predominate and further investigations should mainly focus on [4+1] and [4+3] processes. Since the reactive species *o*-thiobenzoquinonemethide **2'** is principally only present in very low concentrations, [1] and [3] components which are stabilized by complexation seem to be most promising. Of course, the metal complexation of benzo[*b*]thiete itself could also lead to novel reaction types.

We are concentrating our efforts now on arenes and hetarenes with two or more anellated thiete rings. Such compounds should be very useful for the generation of band and starburst structures. Even in the absence of reaction partners polymerisation processes should be feasible:



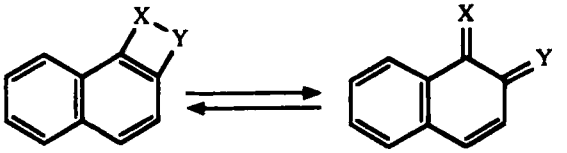
142[6]



143

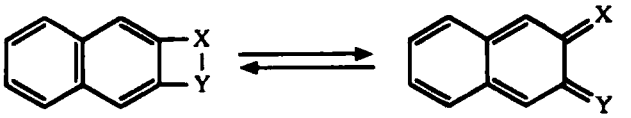
SCHEME 51

Different anellation sites of the 4-membered rings may cause a different reactivity. The ring opening in the compounds **144** for example should have a much lower activation barrier as in the isomer **146**.



144 **145**

X = S, Y = CH_2
or
X = CH_2, Y = S



146 **147**

SCHEME 52

First results support this assumption.[57]

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