Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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To cite this Article Taubert, Kathleen , Kraus, Susanne and Schulze, Bärbel(2002) 'Isothiazol-3(2*H*)-Ones, Part I: Synthesis, Reactions and Biological Activity', Journal of Sulfur Chemistry, 23: 1, 79 — 121
To link to this Article: DOI: 10.1080/01961770208047968
URL: http://dx.doi.org/10.1080/01961770208047968

Sulfur Reports, 2002, Vol. 23, No. 1, pp. 79–121

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ISOTHIAZOL-3(2*H*)-ONES, PART I: SYNTHESIS, REACTIONS AND BIOLOGICAL ACTIVITY

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(Accepted 7 November 2001)

This review deals with methods for the synthesis, reactions and biological activity of isothiazol-3(2*H*)-ones. Monocyclic isothiazol-3(2*H*)-ones have been reported by oxidative cyclization of thiomalonamide derivatives, amides of 3-thionocarboxylic acids and 4,5-dithiaoctanediamides; by cyclocondensation of β-thiosubstituted propenamides and ring contraction of 1,4-thiazepines. Isothiazol-3(2*H*)-ones and their tautomer OH-forms have been investigated. Isothiazol-3(2*H*)-ones and their metal salt complexes are potent industrial microbiocides because of antifungal and antibacterial properties.

Keywords: Isothiazol-3(2*H*)-ones; *S*-oxides; *S*-dioxides; 4,5-dithiaoctanediamides; *O*/*N*-functionalization; Microbiocides; Toxicity; GABA receptor

CONTENTS

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ISSN 0196-1772 print © 2002 Taylor & Francis Ltd
DOI: 10.1080/01961770290015994

1. INTRODUCTION

Isothiazol-3(2*H*)-ones **1–8** are remarkably biological active compounds with antifungal and antibacterial properties for industrial applications and reactive intermediates for the synthesis of various organic substances, including pharmaceutical and agricultural chemicals [1–3]. The 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide **9**, better known as saccharin is one of the most well-known isothiazolone derivatives, which was first prepared by Remsen and Fahlberg 1879 by an oxidative cyclization of *ortho*-toluene-sulfonamide [4]. The 1,2-benzisothiazolones **10** and **11** and their 1,1-dioxides have also been known for a long time and have been extensively reviewed [5–9], most recently by Schulze *et al.* [10].

More than three decades ago the first synthetic monocyclic isothiazol-3(2*H*)-ones **1** ($R = R^1 = H$) with 5-methyl or 5-phenyl substituents were prepared by Goerdeler *et al.* [11a]. This was done by bromination of the appropriately substituted thioacylacetamides. Monocyclic isothiazol-3(2*H*)-ones **1–6** and their oxidized derivatives attract special interest as masked forms of organic functionalities. Furthermore, they are reactive dienophiles in cycloaddition reactions under mild conditions [1,2,10].

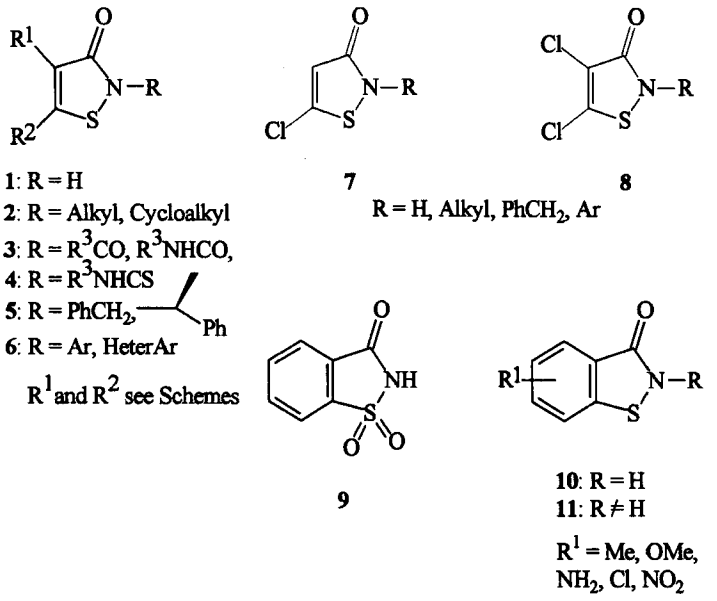
In contrast to the 1,2-benzisothiazol-3(2*H*)-ones **10** and **11** (see Part II) as well as the saccharin derivatives **9**, the syntheses, reactions and properties of monocyclic isothiazolones **1–8** were not reviewed until now (Scheme 1) and are the subject of this article.

2. PREPARATIONS

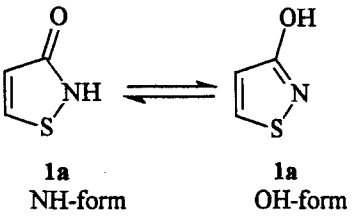
2.1. Isothiazol-3(2*H*)-ones and their Tautomers

Isothiazolones **1** show the possibility of tautomerism between their NH- and OH-forms according to Scheme 2.

UV and IR studies suggest the existence of 3-hydroxyisothiazoles **1** in non-polar solvents like cyclohexane and diethyl ether, while the NH-form predominates in more polar solvents [11a,b,12a,c,13]. X-ray studies on **1a**, its 5-methyl derivative **1c**, and $\mathbf{1r_2}$ (4-Ph) (Scheme 3, 9) confirm the OH-form, but its preference in the solid state

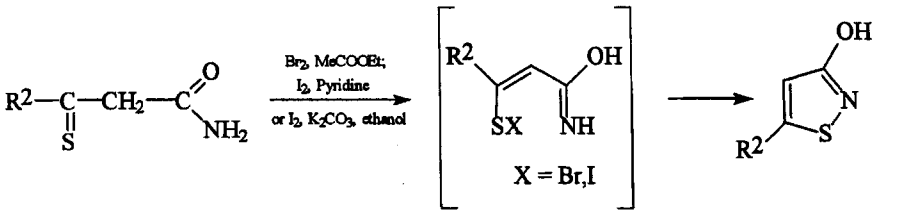


SCHEME 1



SCHEME 2

seems to be caused by dimer formation via intermolecular hydrogen bonds [12b,14a]. The 5-phenyl and 4,5-diphenyl substituted isothiazoles **1b,f** (Scheme 3, 10) were also described as hydroxy derivatives in most cases [11a,12c]. They exhibit a purple colour with ferric chloride and do not show significant IR absorption for a carbonyl group above 1600 cm^{-1}. In methanol, the UV spectra of **1b** and OCH_3-**1b** are very similar suggesting the predominance of the OH-form. The tautomerism of isothiazol-3(2*H*)-ones **1** and its sensitivity to electronic and environmental effects is quite well described by *ab initio* MO theory at various approximation levels (see Table I) [15]. Independent of the approximation level, the OH-form is always predicted as most stable without consideration of environmental effects, even though the extent of the preference is quite different. In particular, the inclusion of correlation energy at the MP2 level favours the aromatic isothiazole structure considerably. Accounting for solvent effects on the basis of quantum chemical continuum models (Self Consistent Reaction Field and Polarizable Continuum Models) leads to a change of the tautomeric equilibrium in favour of the NH-form in all cases.



12 b-d **13**

1a: R^2= H, Scheme 16
1b: R^2= Ph (89%) [11a]
1c: R^2= Me (85%) [11a]
1d: R^2= *t*-Bu (77%) [14b]
1e,f: Scheme 9,10

SCHEME 3

TABLE I Energy differences between the NH- and OH-tautomers of isothiazol-3(2*H*)-ones **1** estimated by *ab initio* MO theory at various approximation levels

Level	ΔE^a
HF/6-31G(d)	0.8
HF/6-311++G(d,p)	5.1
B3LYP/6-31G(d)	4.8
MP2/6-31G(d)	23.1
MP2/6-311++G(d,p)	27.5
SCRF/HF/6-31G(d)[b]	−32.6
SCI-PCM/HF/6-31G(d)[b,c]	−15.3
SCRF//MP2/6-31G(d)[b,c]	−7.4

[a]In kJ/mol. $\Delta E = E_T(\text{NH}) - E_T(\text{OH})$. [b]For a water continuum with a dielectric constant of $\varepsilon = 78.4$. [c] Single-point calculations.

2.2. Synthesis of Monocyclic Isothiazol-3(2*H*)-ones

The general syntheses for isothiazol-3(2*H*)-ones are: (i) the oxidative cyclization of thiomalonamide derivatives and amides of 3-thionocarboxylic acids; (ii) the cyclization of 4,5-dithiaoctanediamides via sulfenyl halogenides; (iii) the cyclocondensation of *β*-thiosubstituted propenamides; (iv) the trichloroacetic acid-mediated ring closure of *N*-substituted (*Z*)-3-(benzylsulfinyl)propenamides; (v) ring contraction of 1,4-thiazepines and (vi) ring enlargement of azetidines and 1,3-dithietanes.

2.2.1. Oxidative Cyclization of Thiomalonamide Derivatives and Amides of 3-Thionocarboxylic Acids

As mentioned above, the first synthesis of **1** was done by oxidative cyclization of **12** by treatment with Br_2/ethyl acetate; I_2/pyridine [11a] or I_2/ethanol/K_2CO_3 (Scheme 3) [14b].

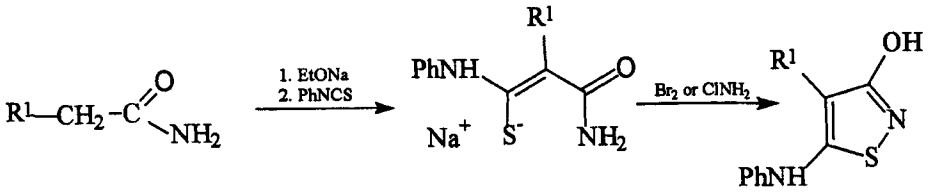
The sulfenyl halogenide **13** generally is assumed to be an intermediate, which cyclizes under HX elimination to the isothiazolones **1b,c**. In the case of the oxidation of **12c** (R^2 = Me) with I_2/pyridine a disulfane was isolated. Its oxidation proceeds

much slower and for this reaction a stronger oxidant (Br_2/ethyl acetate) is needed. The synthesis of the **1g-k** succeeds by oxidation of amides of thiomalonic acids **15**, which are accessible by addition of phenylisothiocyanate on the alkali metal salts of amides of carboxylic acids **14** (R^1 = MeCO, PhCO) [11b], ethyl malonic acid amide **14** (R^1 = COOEt), malonic acid diamide **14** ($R^1 = NH_2CO$) and cyanoacetamide **14** (R^1 = CN), (Scheme 4) [16].

Cyclization of **16** with Br_2 in pyridine results in the formation of 5-amino-4-acetyl-isothiazol-3(2*H*)-ones **1l-n** and **6a** (Scheme 5) [17].

Thiomalonic acid amide derivatives **17**, accessible from cyanoacetamide and dithiocarboxylic acid-*O*,*S*-diester, are well suited adducts for the oxidative cyclization by Cl_2 in acetic acid to 5-alkoxy-4-cyanoisothiazolones **1o** [18]. The obtained **1o** can be phosphorylated to insecticides and acaricides **18** ($R = P(X)(MeO)_2$, X = O or S) (Scheme 6) [19].

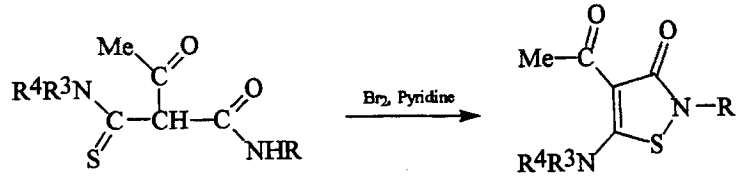
The corresponding derivatives **1p-p$_4$** are formed by the reaction of disodium 2,2-dicyanoethen-1,1-dithiolate **19** with H_2O_2 via **20** and R^3–X [20a,b,21]. The phosphorylated compounds **22** ($R = P(X)(EtO)_2$) have insecticide and fungicide properties



14 **15**

1g: R^1 = MeCO (93%) [11b]
1h: R^1 = PhCO (85%) [11b]
1i: R^1 = COOEt (90%) [11b]
1j: $R^1 = NH_2CO$ (96%) [11b]
1k: R^1 = CN (28%) [16]

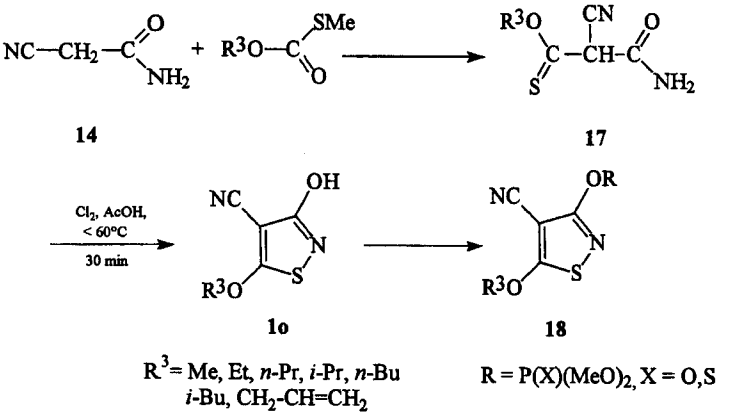
SCHEME 4



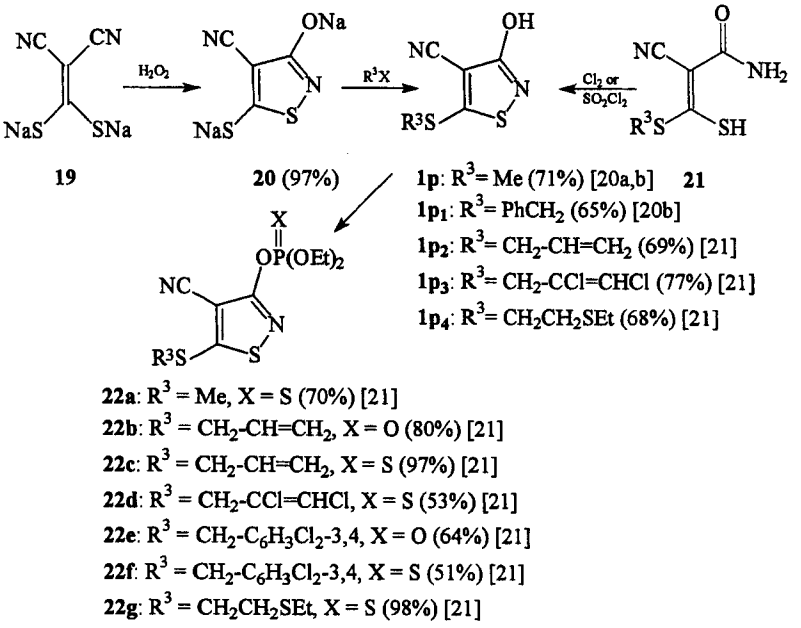
16

1l: R = H, $R^3 = R^4$ = Me (99%)
1m: R = H, $R^3 = R^4 = (CH_2)_4$ (99%)
1n: R = H, $R^3 = R^4 = (CH_2)_2$-O-$(CH_2)_2$ (35%)
6a: R = Ph, $R^3 = R^4$ = Me (26%)

SCHEME 5



SCHEME 6

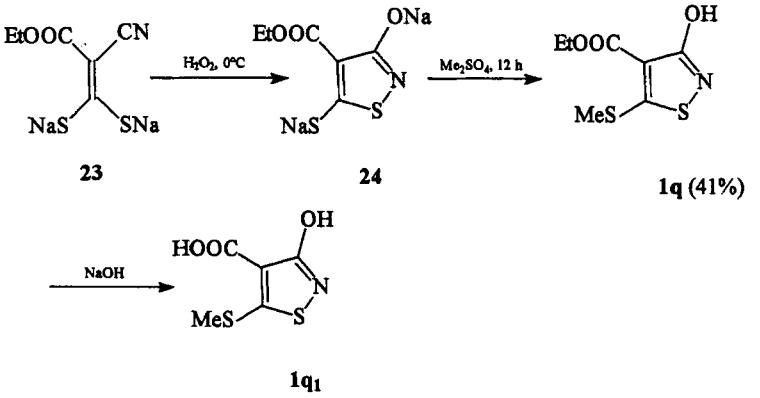


SCHEME 7

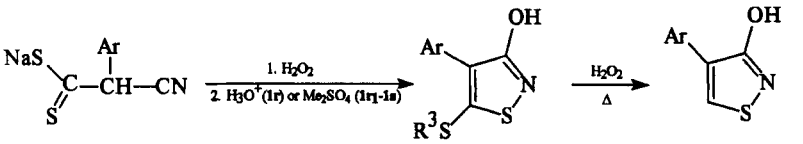
(Scheme 7) [21]. 3-Alkylthio-3-mercapto-2-cyanopropenamides **21** are cyclized by Cl_2 or SO_2Cl_2 to give 4-cyano-5-alkylmercaptoisothiazolones **1p-p$_2$** [22].

The dithiolate salt **23** derived from ethyl cyano acetate gave with H_2O_2 and dimethyl sulfate the isothiazole derivative **1q**. When this ester was boiled under reflux with sodium hydroxide solution **1q$_1$** was formed (Scheme 8) [12a].

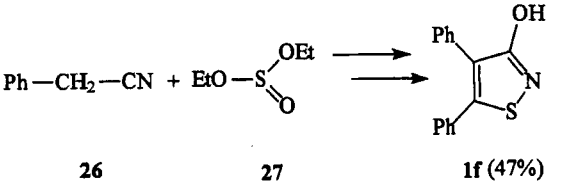
The salts of **25** react with H_2O_2 to give the mercapto derivatives **1r**. One of their most common reactions is *S*-alkylation to **1r$_1$** and **1s**. By using an excess of H_2O_2 the mercapto function of **1r** will be oxidized to its sulfonate, if heat is applied desulfonation will occur (Scheme 9) [12a].



SCHEME 8



SCHEME 9

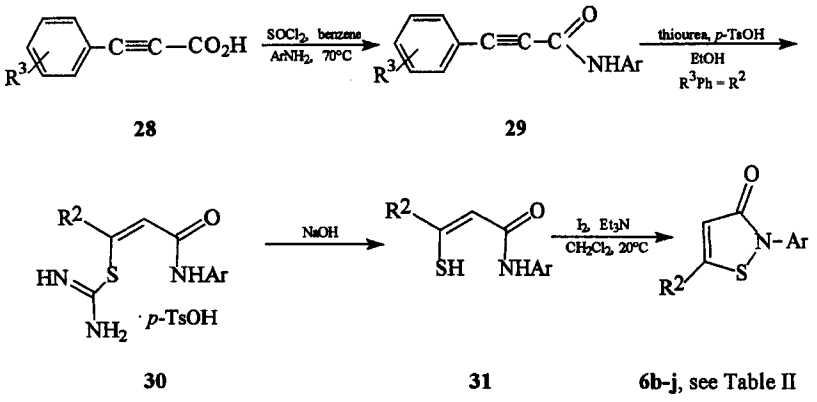


SCHEME 10

4,5-Diphenyl-3-hydroxyisothiazole **1f** is obtained from the reaction of phenylacetonitrile **26** and sulfite **27**, a reaction mechanism has been proposed [12c] (Scheme 10).

The 2,5-diarylisothiazolones **6b-j** ($R^1 = H$, in 4-position) were conveniently prepared by an oxidative cyclization of **31** with iodine and triethylamine (Scheme 11 and Table II) [23,24].

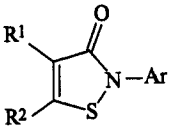
For those 2,5-diphenylisothiazolones **6k-o** with $R^1 \neq H$ in the 4-position a Claisen-like condensation between an *O*-alkyl thionoester **32** and an anilide **33** produces the vinylmercaptanes **34** (Scheme 12 and Table II) [23].



28 **29** **30** **31** **6b-j**, see Table II

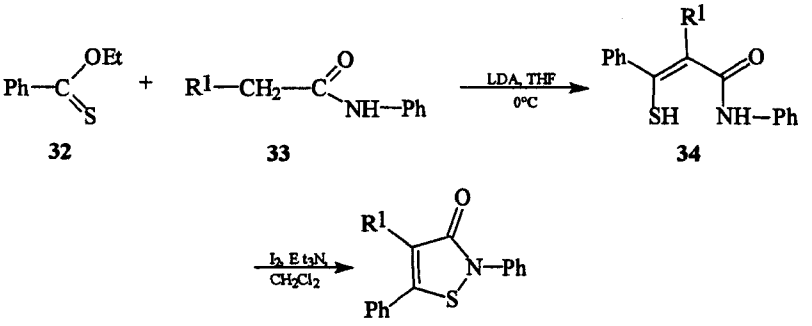
SCHEME 11

TABLE II 2-Aryl- and 2,5-diarylisothiazol-3(2*H*)-ones **6a-v**



Cpd. No.	*Ar*	R^1	R^2	*Yield, %*	*Ref.*
6a	Ph	MeCO	NMe_2	26	17
6b	Ph	H	Ph	67	23,24
6b$_1$	R^3Ph[a]	H	Ph	–	23
6c	Ph	H	R^3Ph[b]	–	23
6d	Ph	H	Cyclohexyl	84	23
6e	4-CNC_6H_4	H	2-ClC_6H_4	73	23
6e$_1$	4-$CO_2EtC_6H_4$	H	2-ClC_6H_4	34	23
6e$_2$	4-$CF_3C_6H_4$	H	2-ClC_6H_4	73	23
6f	Cyclohexyl	H	Ph	8	23
6g	2-bzth[c]	H	Ph	36	23
6h	2-thz[d]	H	Ph	74	23
6i	2-pyr[e]	H	Ph	80	23
6j	3-pyr[e]	H	Ph	55	23
6k	Ph	Ph	Ph	73	23
6l	Ph	MeO	Ph	5	23
6m	Ph	Br	Ph	19	23
6n	Ph	CO_2Et	Ph	38	23
6o	Ph	CN	Ph	24	23
6p	Ph	Ph	H	10	23
6q	Ph	H	PhCO	38	26a, 29
6q$_1$	R^3Ph[f]	H	PhCO	[g]	26a, 29
6r	Ph	H	H	37,64,74	31, 28, 59,171a
6r$_1$	R^3Ph[h,i]	H	H	65	31, 28, 59
6s	3,4-$Cl_2C_6H_3$	Me	H	67	31
6t	2-pyr[e]	H	H	–	171a
6u	3-thie[j]	H	H	–	171b
6v	3-thie[k]	H	H	–	171b

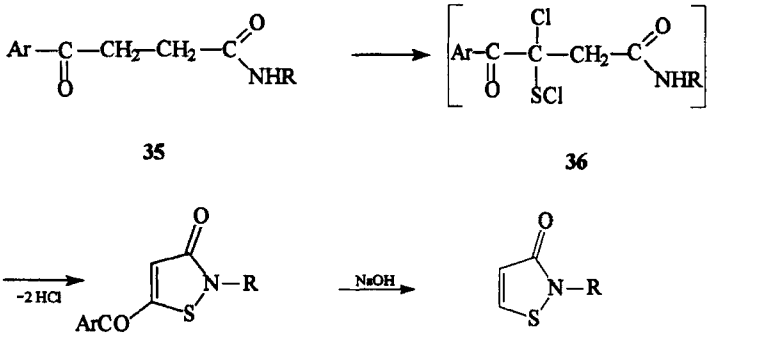
[a]Substituents (R^3) in 2-,3- or 4-position: Me, NH_2, Cl, OMe, CF_3, NO_2, CO_2Et, CO_2H and 4-CO_2-*n*-hexyl, 4-$CONH_2$, 4-$CONMe_2$, 4-CN. [b]Substituents (R^3) in 2-, 3-or 4-position: Cl, OMe, CF_3 and 4-Ph. [c]2-Benzothiazolyl-. [d]2-Thiazolyl-. [e]2-Pyridyl-; 3-pyridyl-. [f]R^3 = 4-MeO, 4-Me, 4-OH, 4-Cl, 4-NO_2. [g]Better than 50% yield. [h]R^3 = 4-MeO, 2-Cl, 3-Cl, 4-Cl, 4-NO_2, 2,4-Cl_2, 2,3-Cl_2, 2,5-Cl_2. [i]**6r$_2$**–**6r$_7$**; R^3 see Scheme 63. [j]3-(2-Methoxycarbonylthienyl)-. [k]3-(2-Methoxycarbonyl-4-methylthienyl)-.



32 **33** **34**

6k-o, see Table II

SCHEME 12



35 **36**

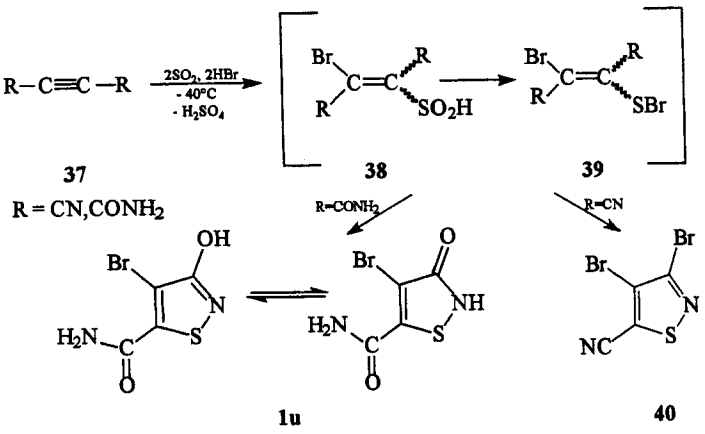
1t: R = H; Ar = Ph (22%) [29]
2d$_4$: R = Me; Ar = 4-MeO-C_6H_4 [26a]
5c-f: R = $PhCH_2$; see Table IV
6q,q$_1$: R = Ar; see Table II

2a: R = Me (90%) [28]
5a: R = $PhCH_2$ (82%) [28]
6r: R = Ph (64%) [28]

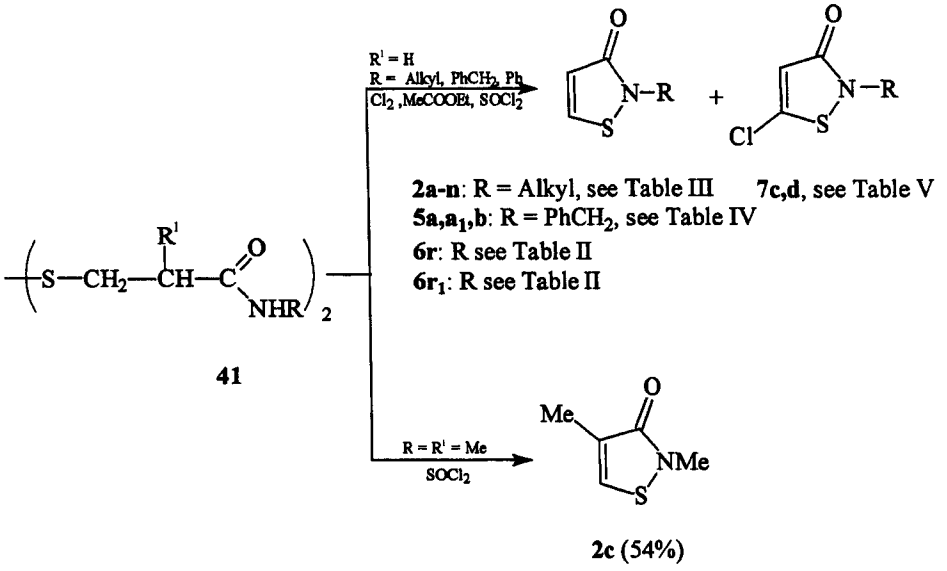
SCHEME 13

5-Aroylisothiazol-3-ones **6q**, **q$_1$** are obtained when β-aroylpropanamides **35** are heated with an excess of thionylchloride. This proceeds by an attack at the "active" α-methylene group with subsequent Pummerer-type rearrangement to α-chlorosulfenyl chlorides **36** (Scheme 13) [26a,29]. The nucleophilic displacement on the 5-aroyl group was found to proceed easily and quantitatively when a benzene solution of **2d$_4$**, **5c,d** or **6q** was stirred with solid sodium hydroxide. The 4,5-unsubstituted derivatives **2a**, **5a** and **6r** were obtained [28].

Isothiazoles are formed by nucleophilic attack of HBr on activated acetylenes **37** (R = CN, $CONH_2$) followed by electrophilic addition of SO_2 in aprotic solvents. Olefinic sulfinic acid **38** and sulfenyl bromide **39** are the intermediates of this reaction. Starting with **37** (R = CN) resulted in the isolation of 5-cyano-3,4-dibromoisothiazole **40** [30a]. On the other hand, a tautomeric equilibrium (44%) of the OH-form **1u** and isothiazol-3(2*H*)-one **1u** (NH-form) in a 1 : 1 ratio was formed from **37** (R = $CONH_2$) (Scheme 14) [30a,b].



SCHEME 14

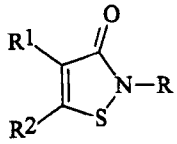


SCHEME 15

2.2.2. *Cyclization of 4,5-Dithiaoctanediamides via Sulfenyl Halogenides*

A convenient and general synthesis of a comprehensive series of 2-substituted isothiazol-3(2*H*)-ones **2**, **5**, **6** ($R \neq H$) was reported by Lewis *et al.* [31,32]. The key step involves the chlorine induced oxidative cyclization of 4,5-dithiaoctanediamides. Several 5-chloroisothiazol-3-ones **7** were also identified as minor reaction products. Some modifications in these known procedures enabled to increase the yield of the isothiazolones [33a]. The cyclization to the specific isothiazol-3-ones **2j** ($R = t$-Bu) [34–36], **5a$_1$** ($R = 4\text{-MeOC}_6H_4CH_2$) [35] and **2o$_1$** ($R = CH_2COOEt$) was effected with 3 equivalents of SO_2Cl_2 (Scheme 15) [35].

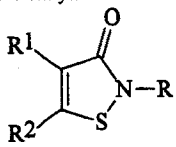
TABLE III *N*-Alkyl- and cycloalkylisothiazol-3(2*H*)-ones **2a-q**



Cpd. No.	*R*	R^1	R^2	*Yield, %*	*Ref.*
2a	Me[a,b]	H	H	33,80,66	31,56,59,28,171a
2b	Me	H	Me	–	11a
2c	Me	Me	H	54,66	31,44
2d	Me[b]	H	$CONH_2$	36	49a
2d$_1$	Me[b]	H	Ph	89	11a
2d$_2$	Me[b]	Ph	MeS	66	12a
2d$_3$	Me[b]	Ph	Ph	40	12c
2d$_4$	Me	H	[c]	60	26a
2e	Et	H	H	53,88,68	31,52,59
2e$_1$	Et	Br	H	56	48
2e$_2$	Et	$CH=CH_2$	H	76	48
2f	Et[a]	H	Ph	–	24,25,11a
2g	*n*-Pr[a]	H	H	85,62	31,59
2h	*i*-Pr	H	H	67	59
2i	*n*-Bu[d]	H	H	92	31
2j	*t*-Bu	H	H	80,80,41	31,34–36,59
2k	Cyclopentyl	H	H	52	31
2l	Cyclohexyl[e]	H	H	65	31
2m	*n*-C_8H_{17}	H	H	94	31
2n	$CH_2CH(Et)C_4H_9$-*n*	H	H	48	31
2o	CH_2OH	H	H	76	72b
2o$_1$	CH_2CO_2Et[a]	H	H	80	35
2o$_2$	CH_2CO_2Me	H	H	50	31
2o$_3$	$CH_2NHC_6H_4$-Cl-4	H	H	69	72b
2o$_4$	$CH(OH)CCl_3$	H	H	90	72b
2p	$CH_2CH_2R^3$[f]	H	H	60	31,72b
2p$_1$	CH_2CH_2Br	H	H	30	72b
2p$_2$	CH_2CH_2Ph	H	Ph	10	23,31
2q	$(CH_2)_5CN$	H	H	48	59

[a]HCl. [b]Synthesis by alkylation of **1** and CH_2N_2 or Me_2SO_4. [c]4-$MeOC_6H_4CO$. [d]see also *n*-C_5H_{11}, *n*-C_6H_{13}, *t*-C_8H_{17}, *n*-C_9H_{19} - *n*-$C_{14}H_{29}$. [e]see Table II, **6f**. [f]R^3 = OH, EtO, PhO, Ph, CO_2Me, CN.

TABLE IV *N*-Benzylisothiazol-3(2*H*)-ones **5a-n**



Cpd. No.	*R*	R^1	R^2	*Yield, %*	*Ref.*
5a	$PhCH_2$	H	H	82, 47	28, 31
5a$_1$	R^3PhCH_2[a]	H	H	40–73	31, 35
5b	CH(Me)Ph	H	H	49	31
5c	$PhCH_2$	H	PhCO	70	29
5d	$PhCH_2$	H	4-ClC_6H_4CO	45	26b
5e	$PhCH_2$	H	2,4,6-$Me_3C_6H_2CO$	60	27
5f	$PhCH_2$	H	3-$NO_2C_6H_4CO$	60	28
5g	(S)-CH(Me)Ph	Br[b]	H	72	48
5n	$PhCH_2$	Me	H	–	32

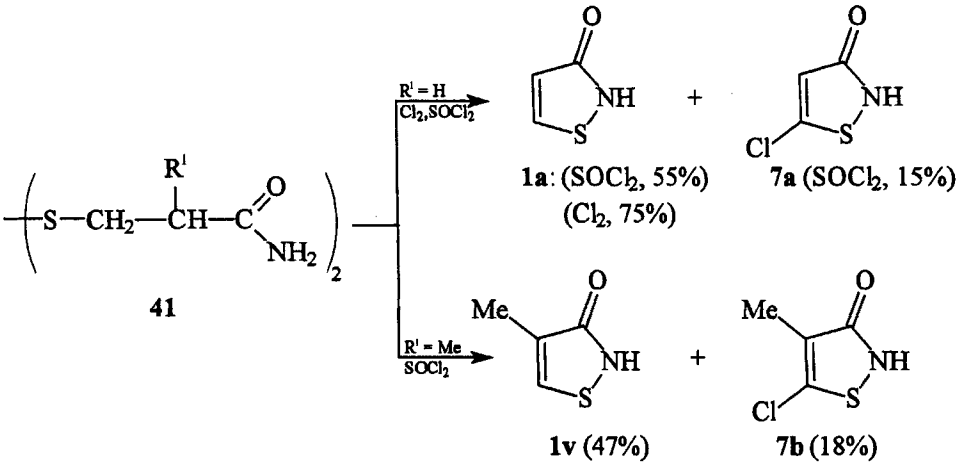
[a]R^3 = 2-Cl, 4-Cl, 4-Me, 4-MeO, 2,4-Cl_2, 3,4-Cl_2. [b]**5h-m**; R^1 see Scheme 25.

N-unsubstituted isothiazol-3(2*H*)-ones were prepared in the same way by oxidative cyclization of 4,5-dithiaoctanediamides (Scheme 16) [31].

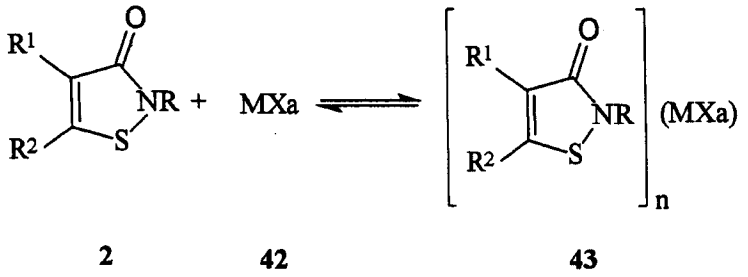
Unfortunately, solutions of the isothiazolones **2**, especially in aqueous or alcoholic media are unstable, leading to reduced biological activity. The instability is caused by the opening of the isothiazolone ring **2** with formation of linear compounds.

Nitrate and nitrite salts **42** of metals such as Ca, Cu, Mg, Mn, Ni, Zn and other metal salts e.g. chlorides, bromides, sulfates, perchlorates, acetates inhibit the ring cleavage and produce stable complexes **43** [37–39a,b]. Nitrate salts exhibit the best stabilizing results [39a,b] (Scheme 17).

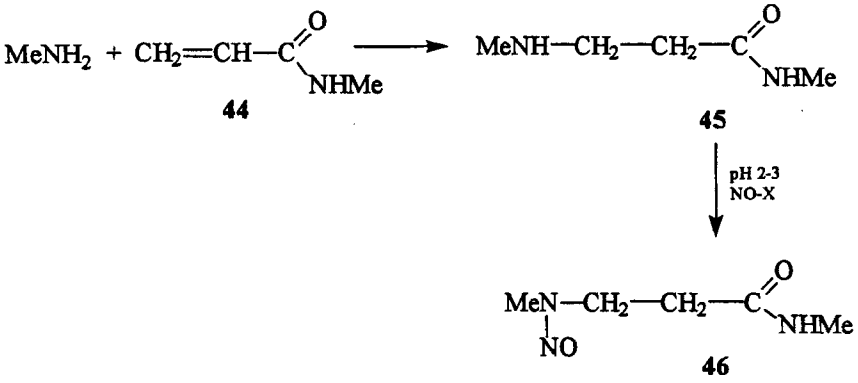
A method of stabilizing isothiazolone microbicides against chemical degradation, using aromatic disufides has been reported [39c]. By-products of the isothiazolone biocides may be converted into nitrosamines by nitrozation if they contain a secondary or tertiary amine group **45** [37–39]. Upon cleavage e.g. of the disulfane **41** ($R^1 = H$) (during amidation), *N*-methylpropenamide **44** is formed as by-product. Addition of monomethylamine to **44** may lead to the formation of the nitrosamine precursor **45** and then to **46** (Scheme 18).



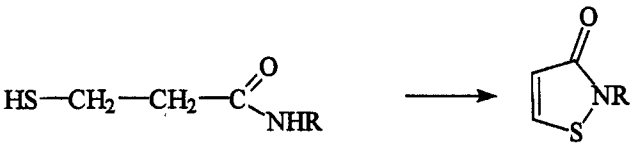
SCHEME 16



SCHEME 17



SCHEME 18



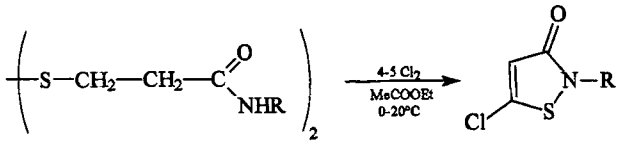
1a: R = H (19%) [40,41]
2a: R = Me (39%) [40,39]

SCHEME 19

The formation of the nitrosamine precursor **45** can be inhibited by use of a nucleophilic scavenger during the amidation reaction, e.g. mercaptan or by selection of other intermediates for the amidation reaction [40a,41]. The isothiazolones **1** and **2** were also obtained by treatment of 3-mercapto-propanamide with chlorine or sulfuryl chloride [40–42]. In this case the yields of nitrosamine are much lower, because the adduct **47** is also the concurrent nucleophile in this procedure (Scheme 19).

Detailed experiments, carried out with **41**, have established the exact conditions (temperature, concentration, proportion of chlorine) for the preferential formation of isothiazolones **1**, **5**, **6** or their 5-chloro **7** and 4,5-dichloro derivatives **8** [42]. It is significant that no 4-mono chlorinated by-products were observed in the reaction mixtures, although the presence of 4,5-dichloro derivatives **8** was noted. So it seems certain that the 5-chloro substituent of the by-products **7a–d** is also introduced in the α-position to the sulfur prior to the formation of the isothiazol-3-one moiety by the chlorination with $SOCl_2$ [31]. A variation of the general method, an incremental concurrent addition procedure, was developed to favour the formation of 5-chloro derivatives **7** in low yields of isolated pure products (Scheme 20) [42].

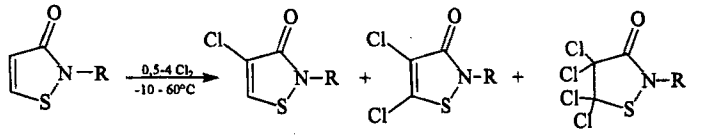
The direct chlorination of 2-*n*-octylisothiazol-3-(2*H*)-one **2m** with 0.5–1 equivalent of chlorine between −40 and −10°C in various solvents gave the starting material in its hydrochloride form and an approximate 1:2 mixture of the 4-chloro **48b** (R = n-C_8H_{17}) and 4,5-dichloro **8f** derivatives [43]. Action of 2–4 equivalents of chlorine at 60°C form 4,5-dichloro derivatives **8** as the major product with some 4,4,5,5-tetrachloro



41
R = Et, *n*-Pr, *n*-Bu, *n*-C_6H_{13}, *n*-C_8H_{17}, Ph

7 (15-25%)
7e-j, see Table V

SCHEME 20



R = Alkyl, Ar, $PhCH_2$

48

8a-f, see Table V

50

SCHEME 21

50 and 4-chloro **48** derivatives as contaminants. Synthesis of further tetrachloro derivatives **50** with R = Alkyl, $PhCH_2$ and Aryl is described in (Scheme 21) [44].

N-Arylsubstituted 4,5-dichloroisothiazolones **8d** (see Table V) were prepared from chloroacetanilides with sodium tosylate, CS_2 and dimethylsulfate [45a,b]. **8e** are prepared from acrylnitrile, cyclohexanol, thiourea and 4 equivalents of chlorine [45b].

Direct chlorination of 4-methylisothiazol-3(2*H*)-ones result in the 2,4-dimethyl-4,5,5-trichloroisothiazol-3(2*H*)-ones **51** (Scheme 22) [32].

On the other hand, the bromination of **1** and **2** with one equivalent of bromine at 80°C gave 4-bromo derivatives **52** in excellent yields (Scheme 23) [31,43].

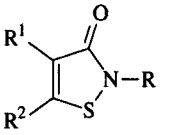
However, it was not possible to obtain the 4,5-dibromo derivatives **53** exclusively in one step from **2**, **5**, **6**. The reaction stops after formation of the 4-bromo **52** and a small amount of 4,5-dibromo derivative **53**, even when an excess of 100–200% bromine was used and the temperature of the reaction mixture was maintained at 80°C for 24 h.

The bromination of various 4-methyl substituted derivatives of **2** with 100% excess bromine at 80°C was also very sluggish and 5-bromo derivatives **54**, were obtained only in a poor yield (Scheme 24) [43].

There is another mild and highly efficient route to a range of usefully functionalized, homochiral 4-substituted isothiazol-3-ones (*S*)-**5h-m** utilizing palladium catalyzed coupling procedures. The bromide (*S*)-**5g**, prepared in a new one-pot procedure from the disulfane **41**, is found to be an excellent substrate for a Stille based functionalization and underwent efficient palladium catalyzed coupling to a variety of stannanes [46–48]. 4-Bromo-2-ethylisothiazolone $\mathbf{2e_1}$ gives 2-ethyl-4-vinylisothiazol-3(2*H*)-one $\mathbf{2e_2}$ in the same way (Scheme 25 and Table III) [48].

Aminofumaramide is treated with hydrogen sulfide in glacial acetic acid to give dithiodisuccinamide **55**, which is converted into the 3-hydroxyisothiazole-5-carboxamide **1w** by oxidation with bromine. Treatment of **1w** with diazomethane gives *O*-methyl derivative, followed by reduction with diborane gives 3-methoxy-5-aminomethylisothiazole hydrochloride **56** in a reasonable yield. Compound **56** is converted into 5-aminomethyl-3-isothiazolol dihydrobromide **57**. Finally **57** gives by treatment

TABLE V Halogen substituted isothiazol-3(2*H*)-ones **7**, **8**, **48**, **49**, **52**, **53**, **54**

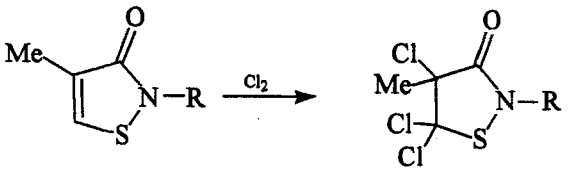


Cpd. No.	*R*	R^1	R^2	*Yield, %*	*Ref.*
7a	H	H	Cl	15	31, 55
7b	H	Me	Cl	18	31
7c	Me	H	Cl	13[a]	31,33b[b],171a
7d	$PhCH_2$	H	Cl	12[a]	31
7e	Et	H	Cl	25	42
7f	*n*-Pr	H	Cl	22	42
7g	*n*-Bu	H	Cl	15	42
7h	*n*-C_6H_{13}	H	Cl	17	42
7i	*n*-C_8H_{17}	H	Cl	18	42
7j	Ph	H	Cl	16	42
8a	H	Cl	Cl	77	31
8b	Me	Cl	Cl	96	31,171a
8c	$PhCH_2$	Cl	Cl	27	31
8d	R^3-Ph[c]	Cl	Cl	–	45
8e	Cyclohexyl	Cl	Cl	59	45b
8f	*n*-C_8H_{17}	Cl	Cl	–	43
48a	CH_3	Cl	H	–	171a
48b	*n*-C_8H_{17}	Cl	H	40	43
48c	CH_3	Cl	CN	–	171a
49	4-ClC_6H_4	Cl	H	37	29
52a	H	Br	H	60	31
52b	Me	Br	H	16	31,171b
52c	*n*-Bu[d]	Br	H	35	43
52d	*t*-Bu	Br	H	56	31
52e	Cyclohexyl	Br	H	75	43
52f	4-ClC_6H_4	Br	H	95	43
52g	4-$ClC_6H_5CH_2$	Br	H	73	43
52h	C_6H_5	Br	C_6H_5	19	23
53a	Me	Br	Br	22	43
53b	*n*-Bu[d]	Br	Br	26	43
53c	Cyclohexyl	Br	Br	20	43
53d	C_2H_4Ph	Br	Br	32	43
54a	Me	Me	Br	9	43
54b	*n*-C_4H_9	Me	Br	15	43
54c	sec-C_4H_9	Me	Br	24	43
54d	*n*-C_8H_{17}	Me	Br	20	43
54e	4-ClC_6H_4	Me	Br	9	43

[a]$SOCl_2$. [b]X-ray of complex with 1,1,2,2-tetrakis(4-hydroxyphenyl)ethane (TEP)[40b]. [c]R^3 = 4-Cl, 4-Br; 2,4-Cl,Br; 2-Cl, 4-Br; 2,4,5-Cl_3; 3-Me, 4-Br; 4-NO_2. [d]see also *n*-C_6H_{13} – *n*-$C_{12}H_{25}$.

with two equivalents of triethylamine a 5-aminomethyl-3-isothiazolol zwitterion, the thiomuscimol **58** (Scheme 26) [49a], in which an isothiazol-3-ol unit is substituted for the carboxy group of the neurotransmitter 4-aminobutanoic acid (GABA).

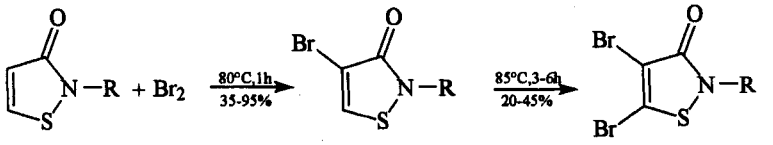
Some thiomuscimol derivatives **60**, in which the amino function is delocalized in a amidinic system exhibit potent binding properties for $GABA_A$ receptors. Alkylation of 5-(methoxycarbonyl)-3-hydroxyisothiazole **1x** with iodomethane and subsequent treatment with $NaBH_4$ and $SOCl_2$ forms compound **59**. The final products **60a, b** were obtained after deprotection of the methylated hydroxyl group in the 3-position



2c,c$_1$, 5n

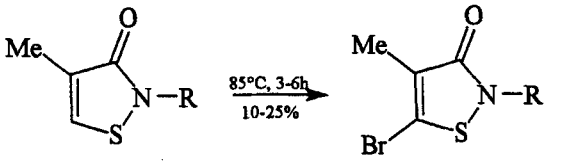
51a: R = Me (68%)
51b: R = *n*-Bu (84%)
51c: R = $PhCH_2$ (81%)

SCHEME 22



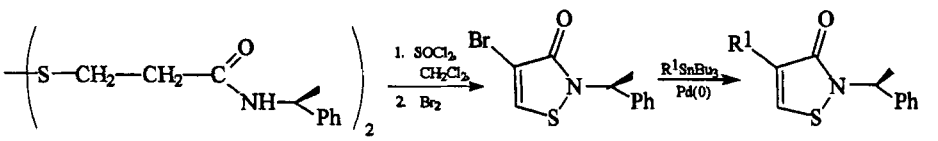
1, 2 **52a-g**, see Table V **53a-d**, see Table V

SCHEME 23



54a-e, see Table V

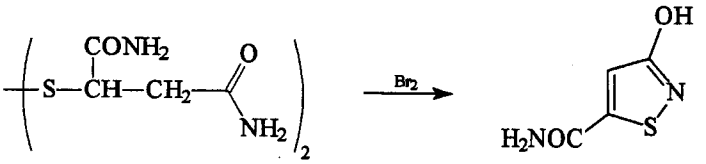
SCHEME 24



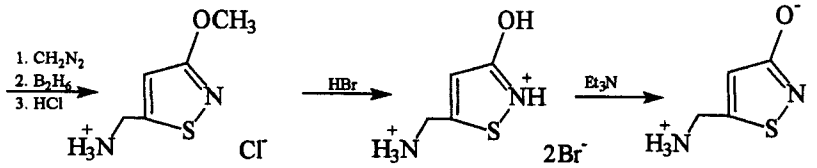
41 **(*S*)-5g**: R = (*S*)CHMePh

5h: R^1 = CH=CH_2
5i: R^1 = C(OEt)=CH
5j: R^1 = COMe
5k: R^1 = C≡CPh
5l: R^1 = 2-pyridyl
5m: R^1 = Ph

SCHEME 25

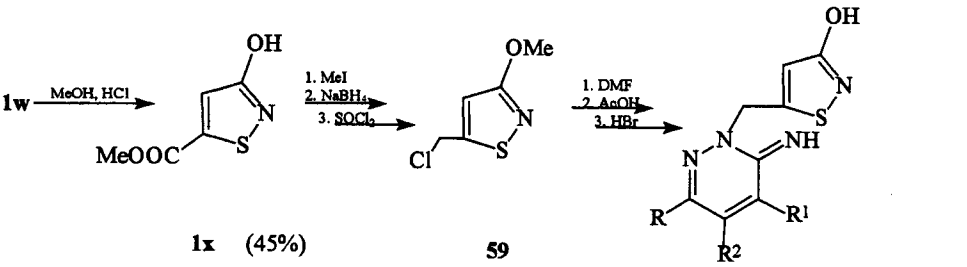


55 **1w**



56 **57** **58**

SCHEME 26



1x (45%) **59**

60a: $R^1 = R^2 = H$, R = 3,4-CH_2O_2Ph

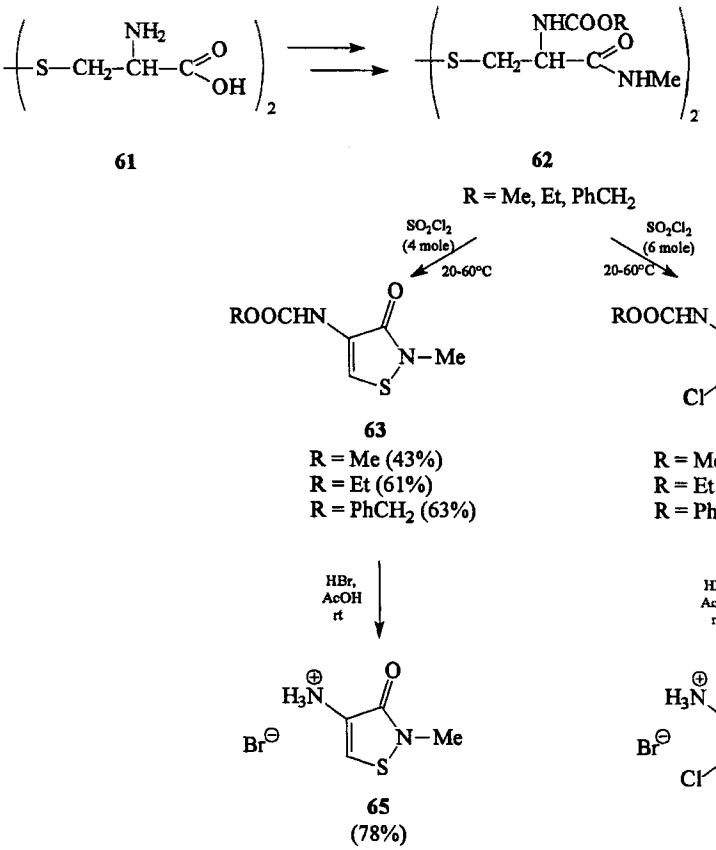
60b: $R^1 = H$, R^2 = Ph, R = Me

SCHEME 27

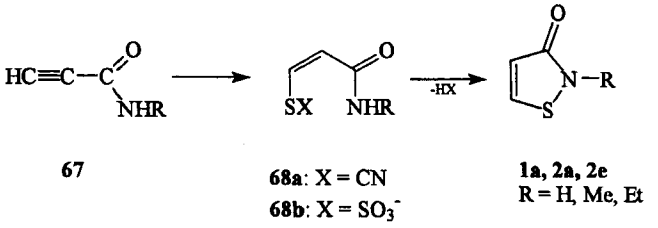
of the isothiazole ring. This was achieved by treatment with hydrobromic acid in acetic acid (Scheme 27) [49b]. A number of 3-isothiazolol bioisosteres of glutamic acid were synthesized [30] and their protolytic and pharmacological properties described [14b,c], see Section 4.

A further heterocyclic agonist/antagonist at GABA is 4,5,6,7-tetrahydroisothiazolo[5,4-c]pyridin-3-ol (thio-THIP) [50,51]; (see Part II). New *N*,*N*′-bis(alkoxycarbonyl)-*L*-cystine bis(methylamides) **62** have been synthesized by the mixed anhydride method from the essential amino acid *L*-cysteine via **61**. These cystine bis(methylamides) **62** have been cyclized with sulfuryl chloride to **63** and **64**. New 4-aminoisothiazolones **65** and **66** have been obtained by deacylation of **63** and **64**, respectively with HBr in acetic acid [52].

In conclusion, the route of oxidative cyclization of 4,5-dithiaoctanediamides has general applicability, but the main problem is the difficult access to the acyclic precursors.



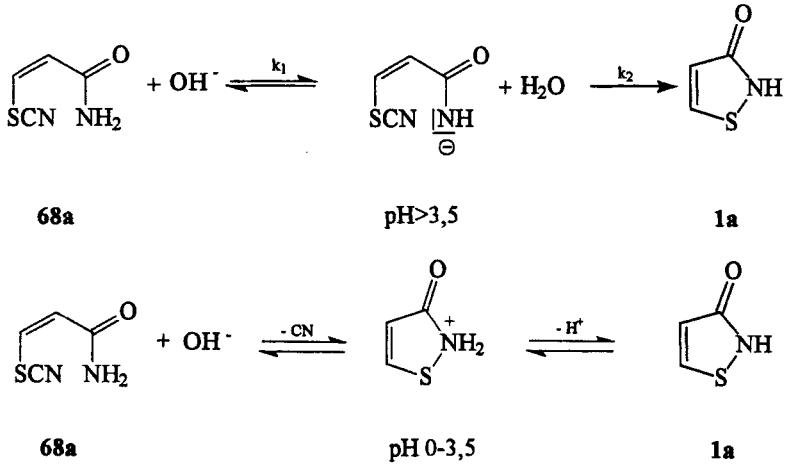
SCHEME 28



SCHEME 29

2.2.3. Cyclocondensation of 3-Thiocyano- and 3-Thiosulfatopropenamides

Another general method for the synthesis of isothiazol-3-(2*H*)-ones **1**, **2** was described by Leonard *et al.* by cyclocondensation [53–57]. A model for this cyclization by the nucleophilic displacement by an amide nitrogen on a sulfanyl intermediate **68** was suggested, in which the ring system was developed from an acetylenic carbonyl compound (Scheme 29) [56]. In the case of propinamide **67** (R = H) itself, an acid-catalysed addition led to a mixture of *cis* and *trans* isomers **68** in a 4 : 1 ratio.



SCHEME 30

The kinetics and mechanism of the cyclization of *cis*-3-thiocyanopropenamide **68a** has been described [57]. The cyclization of *cis*-3-thiocyanopropenamide **68a** to isothiazol-3-one **1a** has been studied over the pH range of 0–5.5 and it is shown that there are two cyclization pathways. Within the pH range 3.5–5.5 the major mechanism is one involving a rapid, unimolecular cyclization of the thiocyanopropenamide anion. In the lower pH range of 0–3.5 the cyclization is only slightly affected by a pH change and the mechanism is characterized by the slower cyclization of the neutral molecule, followed by a rapid proton loss (Scheme 30).

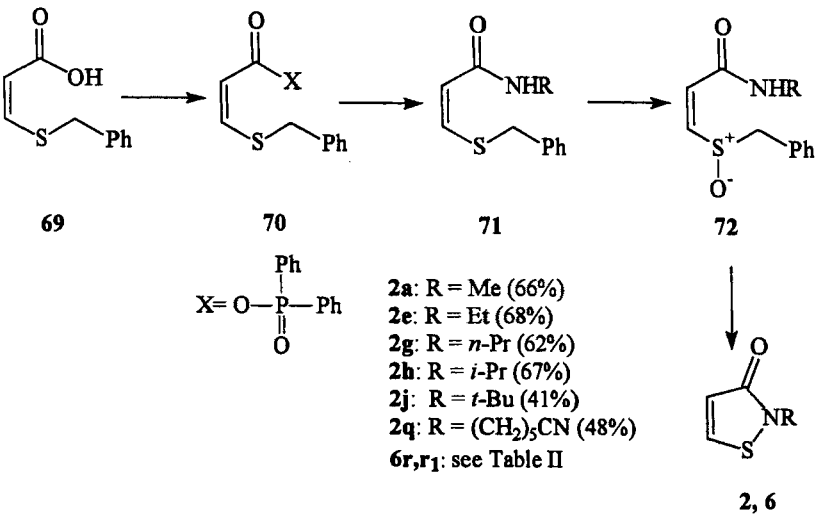
2.2.4. Trichloroacetic Acid-mediated Cyclization of N-substituted (Z)-3-(Benzylsulfinyl)propenamides

The current routes to the synthesis of *N*-substituted isothiazol-3(2*H*)-ones **2a,e,g,h,j** and **6r,r$_1$** are described to proceed via a trichloroacetic acid mediated ring closure of *N*-substituted (*Z*)-3-(benzylsulfinyl)propenamides **72** [59]. Activation of the (*Z*)-3-benzylsulfanylpropenoic acid **69** with diphenylphosphinic chloride furnished the phosphinic ester **70**, which was not isolated but allowed to react directly with various amines. The amides **71** were converted smoothly to the corresponding sulfoxides **72** in all instances by using 3-chloroperbenzoic acid in dichloromethane at −20°C. Cyclization of the sulfoxides in dichloromethane at 0°C using trichloroacetic anhydride gave the corresponding *N*-alkylisothiazol-3(2*H*)-ones **2** and **6** in good yields (Scheme 31).

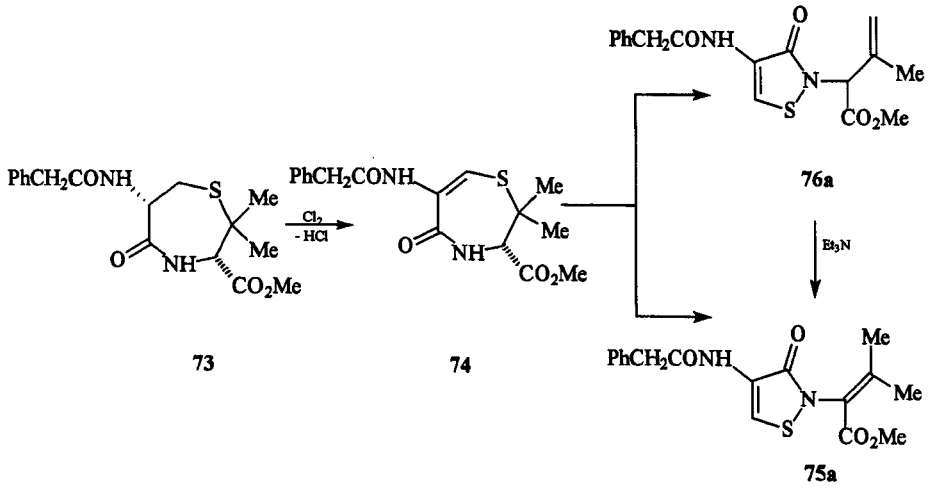
2.2.5. Ring Contraction of 1,4-Thiazepines

Chlorination of the 1,4-diazepine **73** in methylene chloride resulted in the isomeric isothiazolones **75a**, **76a** via rearrangement of **74**. The isothiazolone **76a** was isomerized to **75a** by the action of triethylamine (60%) (Scheme 32) [53,54].

The Pummerer reaction (AcONa in Ac_2O) of the sulfoxide **77** resulted in the quantitative formation of the isothiazolone (*Z*)-**78**. On heating, (*Z*)-**78** was quantitatively isomerized to (*E*)-**78** [60]. A similar ring contraction reaction was also observed by

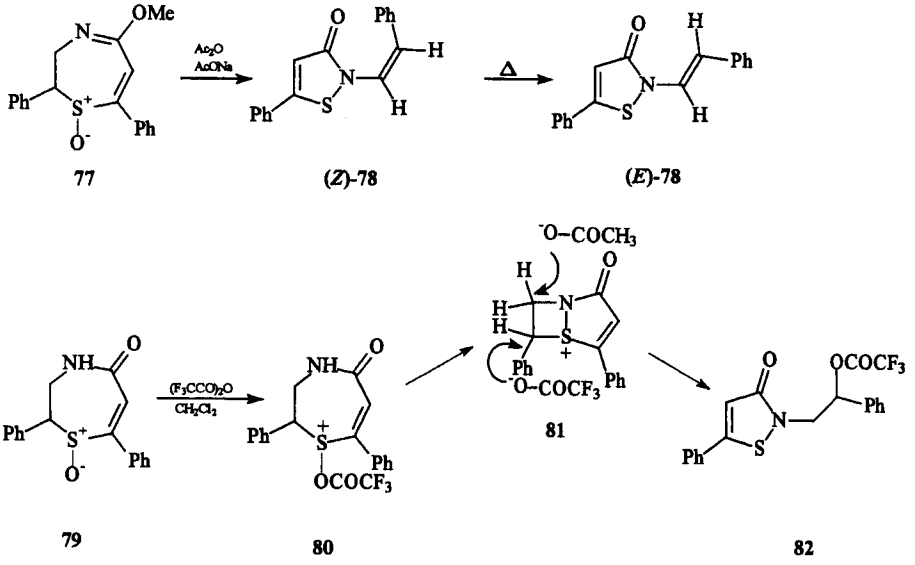


SCHEME 31



SCHEME 32

the Pummerer reaction of the sulfoxide **79** gave (*E*)-**78** as minor product (6%) and a 2-acyloxy-3,4-diphenylpyridine as the major product (68%). On the other hand, treatment of the sulfoxide **79** with trifluoracetic anhydride in dichloromethane gave the isothiazolone **82** in 92% yield as the sole product, instead of **78**. The first step in these reactions is the formation of a sulfonium salt such as **80**. A common bicyclic intermediate **81** was postulated as a result of the intramolecular transannular bond formation between *N* and *S* (Scheme 33). An acetate ion abstracts a proton from the methylene carbon atom adjacent to the nitrogen atom in **81** to produce the (*Z*)-*N*-styrol derivative (*Z*)-**78**, whereas the softer but more nucleophilic trifluoroacetate ion attacks at the benzylic carbon atom by substitution to give **82** [60].



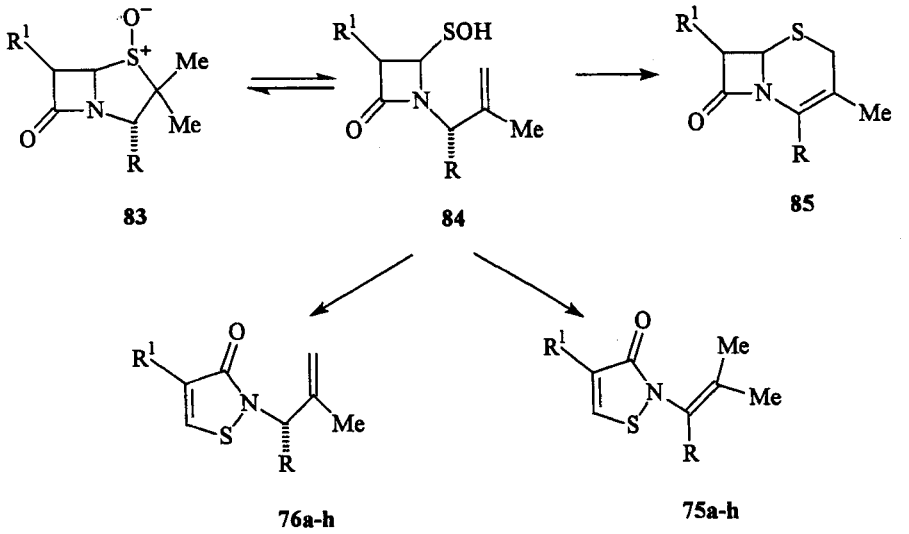
SCHEME 33

2.2.6. Ring Enlargement of Azetidines and 1,3-Dithietanes

Isothiazolones **76** are by-products (15–25%) of the transformation of penicillin sulfoxidemethyl esters into cephalosporine derivatives [62–64]. The thermal or acid-catalyzed rearrangement of penicillin *S*-oxides **83** to cephalosporines **85** has been shown to proceed via a reactive sulfenic acid **84**. The anion of the azetidinsulfenic acid **84** undergoes spontaneous fragmentation and recyclization, giving isothiazolone derivatives **75** and **76** in high yields (Scheme 34) [65,67,69].

The azetidine sulfenic acid **84** recyclisizes under acid catalysis to the cephem **85** or to the isothiazolones **75** and **76** in low yields. Surprisingly, the azetidine sulfenic acid **84h** are quite stable in the crystalline form [65]. On the other hand, in solution it reverts to the sulfoxide **83h**. When the sulfenic acid **84g** was treated with a trace of triethylamine in benzene, there was obtained a crystalline isothiazolone **75g** in high yield. Recently, it has been demonstrated that (2*S*,5*S*,6*S*)-penam sulfoxides **83** can form stable sulfenic acids **84** (R^1 = Phthalimido). The stability of sulfenic acid might be enhanced by the presence of internal hydrogen bond [66]. The selective formation of isothiazolone **75f** by a base catalyzed rearrangement of penicillin *S*-oxide **83f**, is described for the reactions with 2-morpholinethanol, 1-piperidinethanol and triethanolamine [67a]. It appears that the abstraction of the sulfenic acid proton is essential in the azetidinon-isothiazolone transformation because it does not occur when the sulfenic acid is protected by the trimethylsilyl function [65–67]. Therefore, a weak base should effect deprotonation of **84** to the sulfenic acid anion [67b]. Thus, treatment of **84** with 4-methylmorpholine in dichloromethane gave the isothiazolone **75h** in an excellent yield [67b]. The synthesis of **75g** is also possible by an oxidative rearrangement of 4-mercapto-β-lactam **86** with dimethyl sulfoxide via **87** (Scheme 35) [68]. The scission of the four-membered ring may involve the participation of DMSO in an oxidative rearrangement.

The 1,3-dithietanecarboxamides rearrange reversibly in basic media to the corresponding 5-alkylthioisothiazol-3(2*H*)-ones **1y**,**y**$_1$ [97], see Scheme 61.

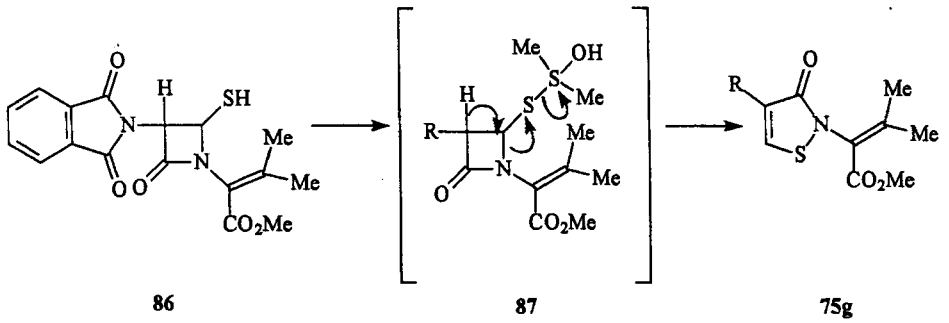


83 **84** **85**

76a-h **75a-h**

75a, 76a: R^1 = $PhCH_2$-CONH; R = CO_2Me [62, 63]
75b, 76b: R^1 = $PhCH_2$-CONH; R = $CO_2CH_2CCl_3$ [63]
75c, 76c: R^1 = $PhCH_2$-CONH; R = $CO_2CH_2C_6H_4$-4-NO_2 [63]
75d, 76d: R^1 = $PhCH_2$-CONH; R = O-CO-C_6H_4-2-NO_2 [64]
75e, 76e: R^1 = $PhOCH_2$-CONH; R = CO_2Me [62]
75f, 76f: R^1 = $PhOCH_2$-CONH; R = $CO_2CH_2CCl_3$ [66]
75g, 76g: R^1 = Phthalimido; R = CO_2Me [65]
75h, 76h: R^1 = Phthalimido; R = $CO_2CH_2C_6H_4$-4-NO_2 [65]

SCHEME 34



86 **87** **75g**

SCHEME 35

3. REACTIONS

3.1. *O/N*-Functionalization

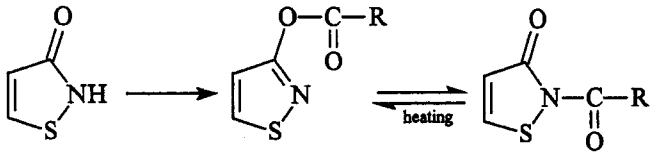
Alkylation [13,49a] and acylation [13,58,70] reactions have been investigated. In aprotic solvents, acylation with acylhalides in the presence of tertiary bases is kinetically controlled leading almost exclusively to 3-acyloxyisothiazoles **3** (Scheme 36) [58].

On heating or standing, a reversible $O \rightarrow N$ migration of the acyl groups occurs [13,58]. The tendency of aliphatic acyl groups (R = Me, Et, Pr, CH_2Cl, MeO) towards migration to nitrogen is inversely related to the size of the groups. For R = Ph or substituted Ph little or no *N*-acyl derivative results [58]. However, acylation with isatoic anhydride **88** provided the *O*-anthraniloyl derivative **89** together with isothiazolo[2,3b]-quinazolin-9-one **90** formed by cyclization of the *N*-anthraniloyl derivative (Scheme 37) [70].

Under these conditions, the favoured $N \rightarrow O$ migration competes with dehydration to the quinazolinone and it was shown that $O \rightarrow N$ migration does not occur [70].

The alkylation of isothiazoles **1** with diazomethane [13,49a] and alkylhalide/metal salt [13] yields a mixture of the *O*- and *N*-methyl derivatives **2a,d** in almost equal amounts. This has been shown by comparison of the UV spectra of the OH-compounds **1a** and **1c** with those of 2-ethylisothiazol-3(2*H*)-one **2e** (R = Et) in appropriate solvents [13]. The use of triethyloxonium fluoroborate, a much bulkier reagent, resulted in 70% *O*-alkylation (Scheme 38) [13]. However, 3-hydroxyisothiazole with a phenyl substituent in the 5- or 4-position [11a,12a] or the 4,5-diphenyl [12c] substituted derivative provided more *N*-methyl derivatives.

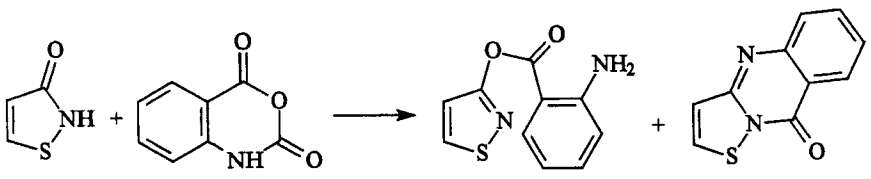
It can generally be stated that acylation and alkylation reactions in non-polar solvents are controlled by the relative rates of the attack on the two tautomers and not so much by the lactam/lactim ratio. Obviously tautomers interchange more rapidly than they react with the electrophiles, but this might not always be the case. Dealkylation of 3-alkoxyisothiazoles **2** leads to the corresponding isothiazolones **1** (R^1 = H, COOH, NH_2; R^2 = H) [71]. On the one hand, the reaction of several isothiazol-3(2*H*)-ones **1** with alkyl and aryl isocyanates provides very high yields (59–100%) of the 2-carbamoylisothiazol-3(2*H*)-ones **3** (Scheme 39) [72a].



1a **3**

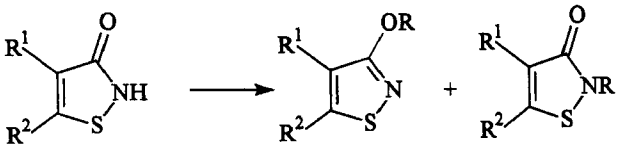
R = H, Me, Et, *n*-Pr, *i*-Pr, $ClCH_2$, MeO, EtO, Ph, $PhCH_2$

SCHEME 36



1a **88** **89** **90**

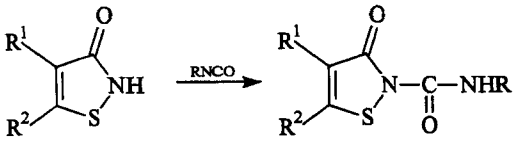
SCHEME 37



1a,b,c,r,u

2a: $R^1 = R^2 = H$, R = Me (91%) (1:1) [13]
2d: $R^1 = H$, $R^2 = NH_2CO$, R = Me (76%) (1:1) [49a]
2d$_1$: $R^1 = H$, $R^2 = Ph$ (89%, N-Me) [11a]
2d$_2$: $R^1 = Ph$, $R^2 = MeS$ (66%, N-Me) [12a]
2d$_3$: $R^1 = R^2 = Ph$ (40%, N-Me) [12a]

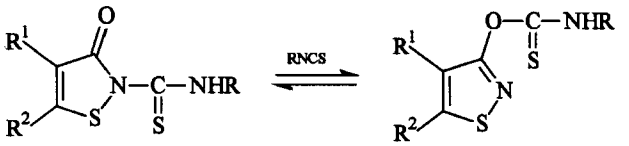
SCHEME 38



1 **3**

R^1 = H, Me, CN, Br
R^2 = H, Me, MeS, Cl
R = Me, Et, CH_2CO_2Et, Ph, 3-ClC_6H_4, 2-ClC_6H_4, 4-Me-C_6H_4-SO_2

SCHEME 39

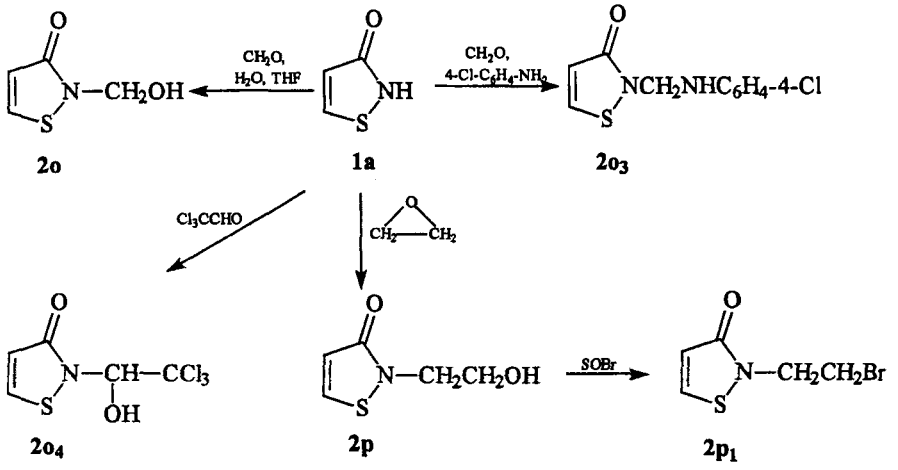


4a: $R^1 = R^2 = H$, N-CSNHMe (24%)
4b: $R^1 = H$, $R^2 = H$, N-CSNHBu (17%)
4c: $R^1 = H$, $R^2 = Me$, R = Et (85%) (2:1)

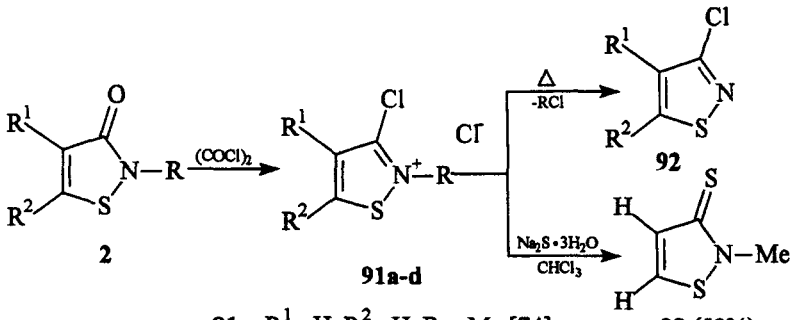
SCHEME 40

The reaction of **1a**, **1c** and **52a** with isothiocyanates, produces the *N*/*O* isomers of the thiocarbamoyl derivatives **4** in a 2:1 mixture [72a]. These observations may be rationalized when assuming an initial exocyclic attack of the reagent at the hydroxy group, followed by migration of the carbamoyl group to the nitrogen of the heterocyclic ring. In the case of the thiocarbamoyl compounds, the latter step is not complete and an equilibrium is reached (Scheme 40). The reaction of **1a** with benzoylisothiocyanate gave only the 2-(benzoylamino-thiocarbonyl)-isothiazol-3(2*H*)-one **4** (57%) [73].

N-hydroxyalkylation and the synthesis of Mannich bases of isothiazolones **1** have been described [72b]. Hydroxymethylation of **1a** with formaldehyde provided **2o** in good yield (76%). While **2o** is stable in the solid state it reverts immediately to **1a** in protic solvents. Compound **1a** reacts with chloral to yield the hydroxy derivative **2o$_4$**.



SCHEME 41



91a: R^1= H, R^2= H, R = Me [74]
91b: R^1= Ph, R^2= H, R = Me [24]
91c: R^1= Ph, R^2= Br, R = Et [24]
91d: R^1= R^2= $(CH{=}CH)_2$, R = Me [24]

SCHEME 42

Treatment of a methanolic solution of **1a** with aqueous formaldehyde and various primary and secondary amines provided the Mannich bases, e.g. **2o$_3$**, which are stable in non-protic solvents. Reaction of **1a** with ethylene oxide gives **2p** and the treatment of **2p** with thionyl bromide provides the 2-bromo ethyl derivative **2p$_1$** (Scheme 41) [72b].

Isothiazolones **2** have been chlorinated with oxalyl chloride or phosgene to yield the 3-chloroisothiazolium salts **91** [24,74], which may be thermally degraded to 3-chloroisothiazole **92**, in low yield [24]. The salt **91a** reacts with sodium sulfide hydrate in chloroform to give **93** in 58% yield (Scheme 42) [75].

3.2. Ring Opening Reactions

The *S–N* bond of isothiazolones is an ambiphilic reaction centre. Thus, an electrophilic attack at the nitrogen atom or a nucleophilic attack at the sulfur atom are possible.

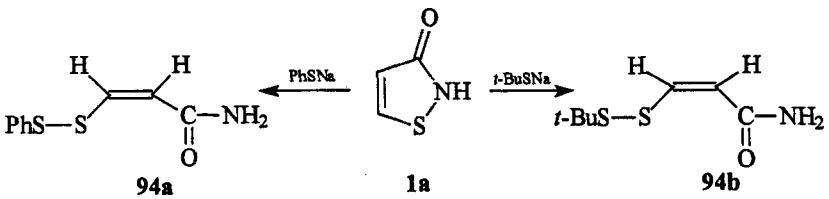
Nucleophilic attack of the *S–N* bond of isothiazolones is reversible [56]. The mechanism for cyanide ion attack has been established by kinetic studies [57a,b]. Cyanide ions rapidly regenerate the *cis*-3-thiocyanopropenamides **68** from the isothiazolones **1a** and **2a** (Scheme 29, 30). The *S–N* bond in **1a** is also cleaved by treatment with sodium thiophenolate and sodium *tert*-butyl mercaptide leading to a mixture of disulfanides **94a,b** (Scheme 43) [56].

The *S–N* bond in **1** was also attacked by SO_3^{2-} leading to the Bunte salts *cis*-**68b-b$_3$** in high yields [76], but nitrite, thiocyanate and halide ions had no effect in aqueous solution. In addition, *trans*-**68a** (R = H) is formed in low yield from **1a**. *Cis*-**68b** and *cis*-**68b$_3$** were isolated in their pure forms and characterized (Scheme 44).

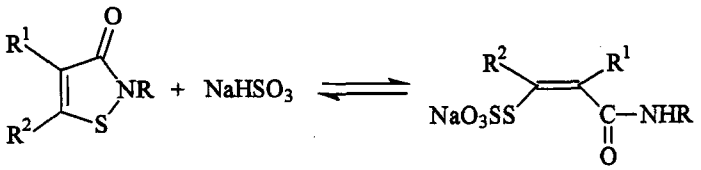
N-Alkylisothiazolones **2** having a free 5-position are readily dimerized by bases to high melting, insoluble 2,4-bismethylene-1,3-dithietanes **96** (85–88%). The dimerization process has been proposed to involve attack of the 5-anion on the *S–N* bond of a second molecule of **2** and a sequence of ring opening to **95** and ring closure reaction to **96** proceeds (Scheme 45) [77]. Dithietanes **96** were also obtained from the *N*-substituted 5-aroylisothiazol-3(2*H*)-ones **5c,d** (R = $PhCH_2$) and **6q** (R = Ph) by treatment with bases such as 5N sodium hydroxide or sodium ethoxide in ethanol [26a,28].

N-Ethylisothiazolone undergoes cleavage of the *S–N* bond when subjected to nucleophilic attack by carbanions, yielding a series of *cis*-alkylmercaptopropenamides **98** [79]. Under basic conditions the reaction is shown to be reversible, the stability of the product being apparently dependent upon the degree of substitution at the carbanion site (Scheme 46).

The attack by tertiary carbanions of **2** is not observed. The products from tertiary attack have been independently synthesized and shown to undergo intermolecular

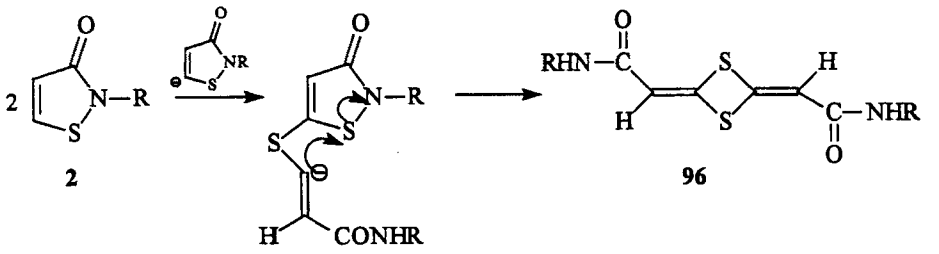


SCHEME 43



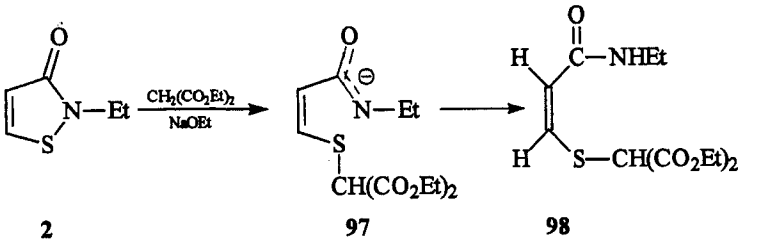
68b: $R^1 = R^2 = H$, R = Me
68b$_1$: $R^1 = H$, $R^2 = Cl$, R = Me
68b$_2$: $R^1 = R^2 = Cl$, R = Me
68b$_3$: $R^1 = R^2 = H$, R = *n*-C_8H_{17}

SCHEME 44

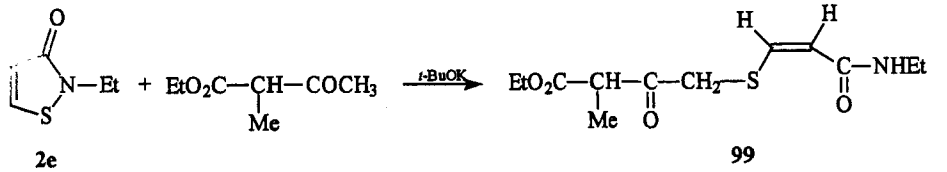


95 R = Me, Et, Ph, $PhCH_2$, Me-CHBr

SCHEME 45



SCHEME 46



SCHEME 47

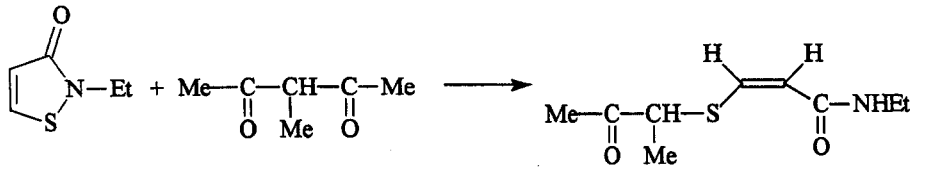
migration, yielding the products of attack at the less substituted carbanion centre (Scheme 47) [78].

3-Methylpentane-2,4-dione **100** gives rise to **101** as major product with simultaneous deacylation (Scheme 48) [78].

HCl adds across the *S–N* bond of isothiazolones **2c** to provide the corresponding ring opened sulfenyl chloride, which can be selectively trapped by norbonene to give **103** (20%) [80]. Compound **2c** exists in equilibrium with the ring opened sulfenyl chloride **102** (Scheme 49). However, when a solution of **2c** in 2-propanol was heated with aqueous HCl at 80°C for several hours, no degradation was observed. Trapping with 1-octyne is also possible.

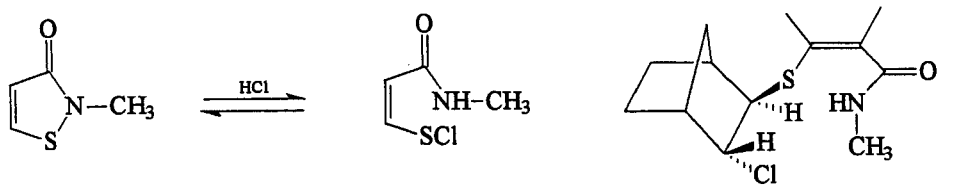
3.3. Oxidation

Oxidation of isothiazol-3(2*H*)-ones **1** and **2** using *meta*-chloroperoxybenzoic acid gave isothiazolone 1-oxides **104** and **105** in good yields (Scheme 50) [12a,29,69,81,82].



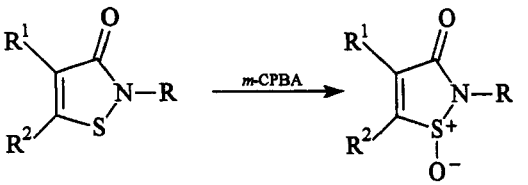
100 **101**

SCHEME 48



2c **102** **103**

SCHEME 49



1, 2

104a-c: R = H, see Table VI
105a-n: R ≠ H, see Table VI

SCHEME 50

Other oxidants, including nitric acid, dinitrogen tetroxide, and chromic acid were specific in converting isothiazolones to their 1-oxides, see Table VI [81]. By the oxidation of (*S*)-**5g** a highly functionalized (*S*)-1-oxide **105p** as major isomer could be isolated (Scheme 51) [48]; see also **105o** (see Table VI) [83].

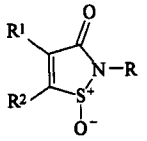
Enantiomerically pure 3-oxo-2-(1-phenylethyl)-5-isothiazolidinyl-1-oxide radicals, prepared from the corresponding 5-phenylseleno compound **106** [83–85] undergo addition reactions with 2-alkenyl-tributyltin derivatives to give isothiazolidone 1-oxides **107** and **108** with good-to-excellent diastereoselectivity (Scheme 52).

The oxidation of **1** and **2** using *meta*-CPBA yields also 1,1-dioxides **109a-o** (Scheme 53) [12a,34,35,81,86]; see also the synthesis of the 1,1-dioxides **109p** (R = H) and **109q-s** (R = Ar or $R^3C_6H_4SO_2NH$) by oxidation of isothiazoles [88a] or the salts **110** (see Table VII) [10,88,89].

3.4. Cycloadditions

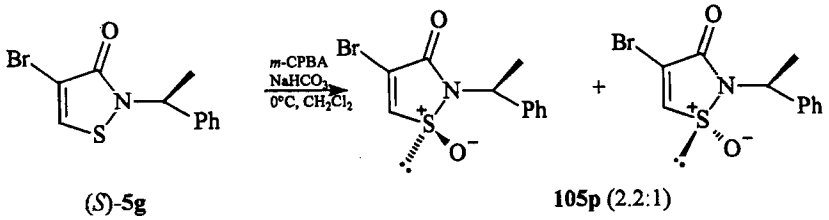
Isothiazol-3(2*H*)-one 1-oxides [47,48,83,90] and 1,1-dioxides [34,35b,86,90,91] are reactive dienophiles and will undergo Diels–Alder cycloaddition reactions under mild

TABLE VI Isothiazol-3(2*H*)-one 1-oxides **104**, **105**



Cpd. No.	*R*	*R*^{1}	*R*^{2}	*Yield. %*	*Ref.*
104a	H	H	H	60[a,b], 35[c]	81
104b	H	Br	Me	46[a], 100[b], 54[d]	81
104c	H	Cl	Cl	50[b]	81
105a	Me	Ph	$MeSO_2$	–	12a
105b	t-C_8H_{17}	H	H	100[a]	81
105c	$C{=}CMe_2$ | $CO_2CH_2CCl_3$	$NHCOCH_2Ph$	H	26[a]	69
105d	$CH-i$-Pr | CO_2Me	$NHCOCH_2Ph$	H	–	87
105e	Ph	H	COPh	61[a]	29
105f	3,4-$Cl_2C_6H_3$	CH_3	H	89[a]	81
105g	CONHMe	H	H	80[a]	81
105h	CONHEt	H	H	70[a]	81
105i	$CONHCH_2CO_2Et$	H	H	61[a]	81
105j	CONHPh	H	CH_3	67[a]	81
105k	CONH-3-ClC_6H_4	H	H	87[a]	81
105l	CONH-2,5-$Cl_2C_6H_3$	H	H	72[a]	81
105m	CONH-3,4-$Cl_2C_6H_3$	H	H	81[a]	81
105n	CONH-3,4-$Cl_2C_6H_3$	H	CH_3	72[a]	81
105o		H	H	82[a,e]	83
105p		Br	H	88[a,e]	48
105q	Et	Br	H	53[a]	48

[a] *m*-CPBA was used as oxidant. [b] Dinitrogen tetroxide. [c] Nitric acid. [d] Chromic acid. [e] *S*/*R* (2,2:1).

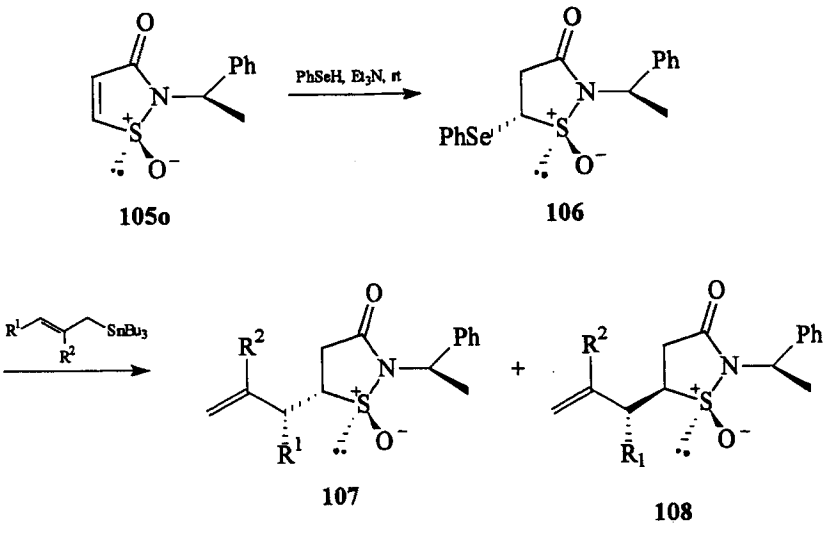


(*S*)-**5g** **105p** (2.2:1)

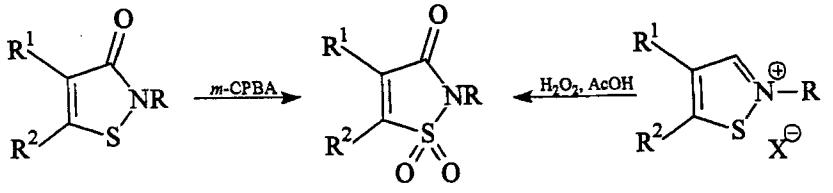
SCHEME 51

conditions. 1,3-Dipolar cycloaddition reactions of isothiazol-3(2*H*)-one 1,1-dioxides have proven to be good processes for the synthesis of the several heteroannelated derivatives [35a].

In contrast, the non-oxidized isothiazol-3(2*H*)-ones are referred to as poor dienophiles, which were unreactive with several of the more reactive dienes. Only the



SCHEME 52



SCHEME 53

2,6-dichlorobenzonitrile oxide **111** reacts with the isothiazolones **6r** and **6q** and is reported as an exception and gives **113** via transformation of the primary cycloadducts **112** (Scheme 54) [92]. Mesitonitrile oxide (Ar = 2,4,6-$Me_3C_6H_2$) adds with unexpected site selectivity to the carbonyl double bond of **6** yielding the monoadduct and bis-adduct.

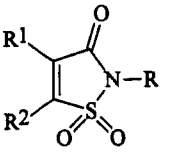
3.5. Ring Transformations

Whilst photoisomerization of isothiazoles to thiazoles is well documented, examples of this reaction occurring with isothiazol-3(2*H*)-ones are less common. The irradiation of isothiazolones **2j,l**, **5a** and **6r** in benzene for 24 h gave the corresponding thiazolones **114** in high yields (70–88%) (Scheme 55) [93]. The isomerization probably involves the homolysis to a biradical, which cyclizes to an α-lactam and subsequently undergoes ring expansion (Scheme 55).

The irradiation of **75a** leads to the thiazole **115** and desulfurization products (Scheme 56) [94].

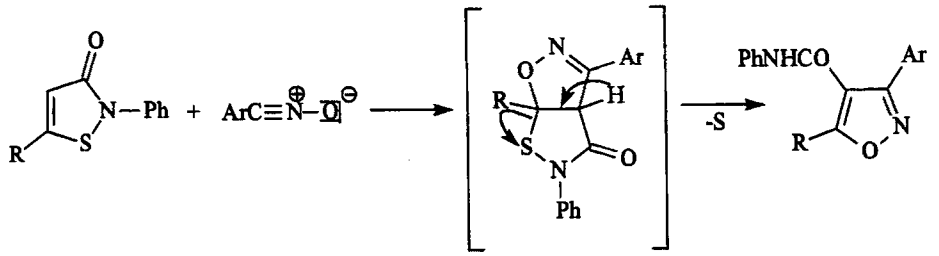
The reaction of 5-aroylisothiazolones **5c,d** and **6q** with hydroxylamine, phenylhydrazine and semicarbazide was found to give 1,2,5-oxathiazole **116** and 1,2,3-thiadiazole

TABLE VII Isothiazol-3(2*H*)-one 1,1-dioxides **109**



Cpd. No.	*R*	R^1	R^2	*Yield, %*	*Ref.*
109a	H	H	H	50	81
109b	H	H	Me	20	81
109c	*t*-Bu	H	H	74,97	34,35a,86
109d	*t*-Bu	H	Br	96	35
109e	t-C_8H_{17}	H	H	82	81
109f	CH_2COOEt	H	Br	78	35a
109g	CH_2COOEt	H	H	88	35a
109h	4-ClC_6H_4	H	H	83	86
109i	3,4-$Cl_2C_6H_3$	Me	H	51	81
109j	$PhCH_2$	H	H	84	86
109k	4-$MeOC_6H_4CH_2$	H	H	69,88	86,35a
109l	$Me_3CCH_2Cme_2$	H	H	73	86
109m	CONHEt	H	H	44	81
109n	CH – *i*–Pr | CO_2Me	$NHCO_2CH_2Ph$	H	–	87
109o	H	Ph	H	–	12a
109p	H[a]	Me	Me	80	88a
109q	$R^3C_6H_4$[b]	Me	Me	38–84	88d
109r	$R^3C_6H_4$[c]	H	$R^4C_6H_4$	10–26	88b
109s	$R^3C_6H_4SO_2NH$[d]	Me	Me	30–61	89b
109t	3-thie[e]	H	H	–	171b

[a] R^1, R^2 = Me, Et, *n*-Pr, Ph[88a,b]. [b] R^3 = H, 4-MeO, 2-Cl, 2,6-Cl_2, 4-CO_2H, 4-CO_2Me, 4-CH_3SO_2, 4-NO_2. [c] R^3 = H, 2-Me, 4-Me, 4-MeO, 2-Cl, 2-F, 4-Cl, 4-F, 4-NO_2 R^4 = 3-CF_3, 4-CF_3, 4-MeO. [d] R^3 = H, 4-Me, 3-NO_2, 4-NO_2, 4-Br. [e] 3-(2-Methoxycarbonylthienyl).



6r: R = H
6q: R = PhCO

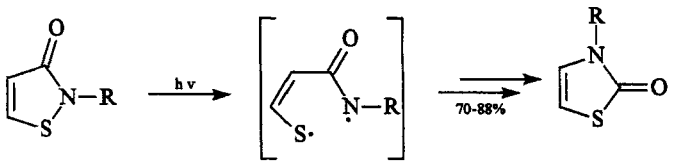
111 Ar = 2,6-$Cl_2C_6H_3$

112

113

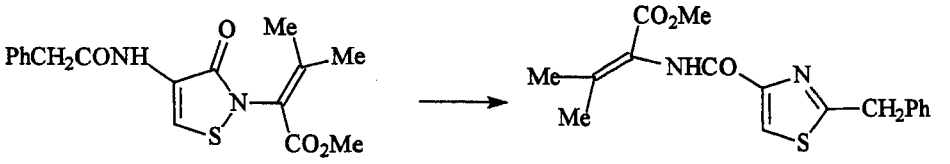
SCHEME 54

117 and **118**, respectively. In a similar manner, reaction of **5c** with hydrazine was reported to give **118** (Ar = C_6H_5, 86%) (Scheme 57) [12b]. The reaction of **5c,d** and **6q** with phenylhydrazine in refluxing ethanol was found to give sulfur-free products, which were characterized as 3-phenylhydrazono-3-aroylpropanamides [26c].



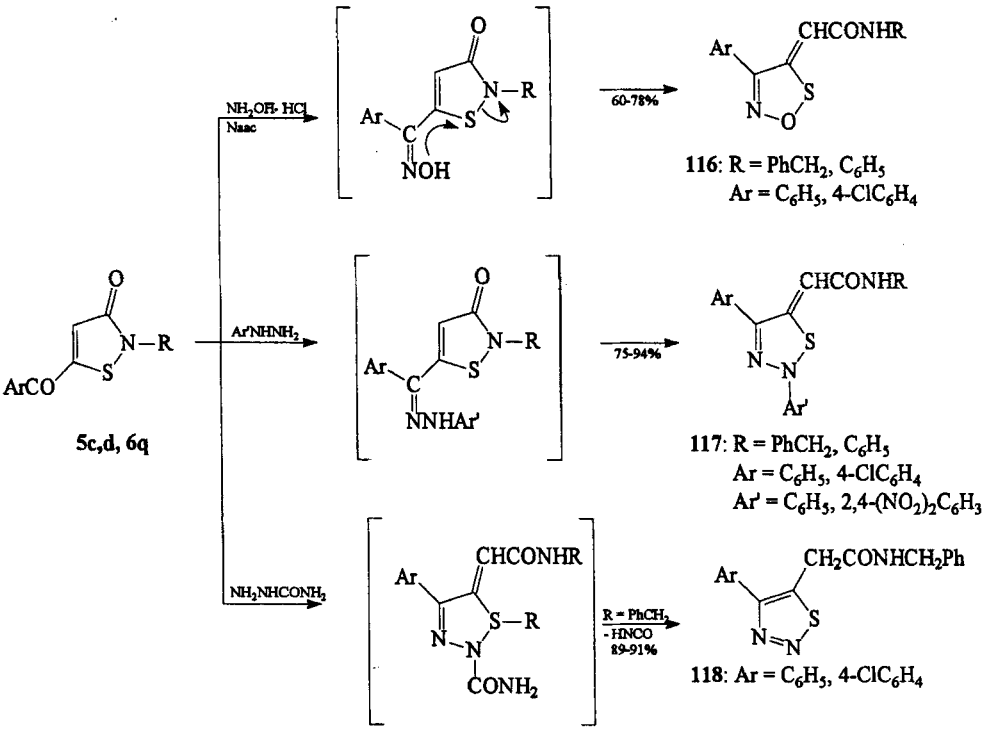
2j,l, 5a, 6r **114**
R = *t*-Bu, Cyclohexyl, $PhCH_2$, Ph

SCHEME 55



75a **115**

SCHEME 56



5c,d, 6q

116: R = $PhCH_2$, C_6H_5
Ar = C_6H_5, 4-ClC_6H_4

117: R = $PhCH_2$, C_6H_5
Ar = C_6H_5, 4-ClC_6H_4
Ar' = C_6H_5, 2,4-$(NO_2)_2C_6H_3$

118: Ar = C_6H_5, 4-ClC_6H_4

SCHEME 57

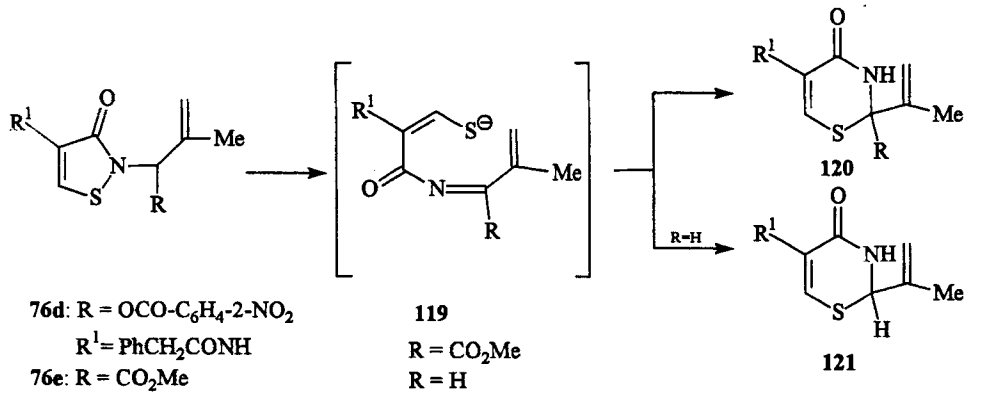
3.6. Ring Enlargement Reactions

Isothiazolone **76e** is transformed into 1,3-thiazine **120** by heating in dimethylacetamide solution to 140°C for 18 h (R = CO_2Me) (Scheme 58) [87]. An explanation for this rearrangement is a base catalyzed formation of the acylimine **119** (R = CO_2Me) which is then trapped by the neighbouring thiolate.

1,3-Thiazin-4-one **121** (R^1 = $PhCH_2CONH$) is formed by reduction of **76d** (R = $OCO\text{-}C_6H_4\text{-}2\text{-}NO_2$) in tetrahydrofuran with powdered zinc dust at 0°C for 30 min (85%) [64]. The same compound **121** (R^1 = $PhOCH_2CONH$) can also be obtained by heating to reflux in DMF [87].

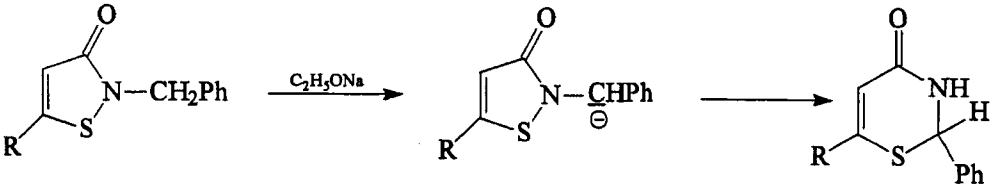
The reaction of the sterically hindered mesitoyl group in **5e** with sodium ethoxide in ethanol has been found to yield a ring transformation to dihydrothiazinone **122** (Scheme 59) [27].

A novel synthesis of 3,4-dihydro-1,3-thiazin-4(2*H*)-ones **124** made use of a carbene addition-ring expansion sequence [95,96]. The rhodium-catalyzed reaction of diazo compounds with 2-substituted isothiazol-3(2*H*)-ones **2e**, resulted in an intermediate sulfonium ylide **123**, which rearranged to the six-membered ring compound **124** by a 1,2-shift (58–91%). This reaction sequence is notable in that it involves a new type of *S–N* cleavage of the isothiazole ring system including carbenes (Scheme 60).



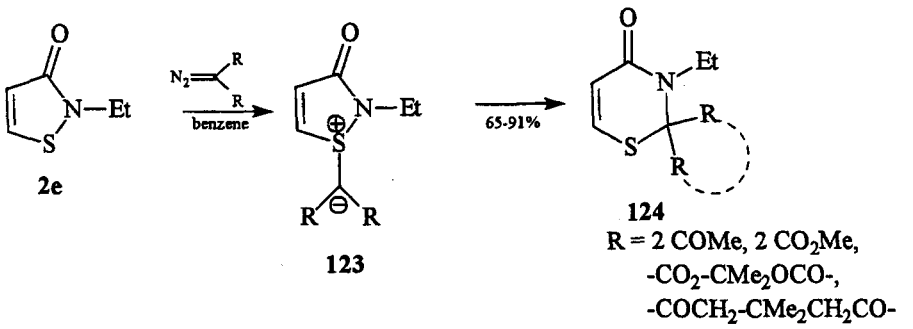
76d: R = $OCO\text{-}C_6H_4\text{-}2\text{-}NO_2$
R^1 = $PhCH_2CONH$
76e: R = CO_2Me
R^1 = $PhOCH_2CONH$

SCHEME 58

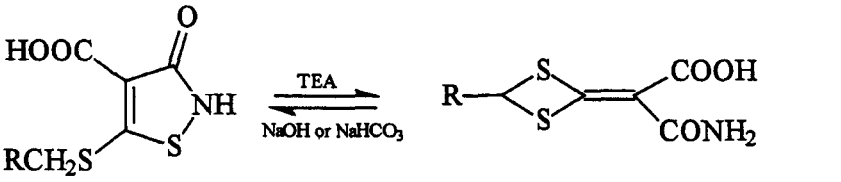


5e: R = $2,4,6\text{-}Me_3C_6H_2CO$

SCHEME 59



SCHEME 60



SCHEME 61

3.7. Ring Contraction Reactions

The isothiazolylthio acetic acid derivatives **1y,y_1** rearrange reversibly in basic media to the corresponding 1,3-dithietanecarboxamides (Scheme 61) [97].

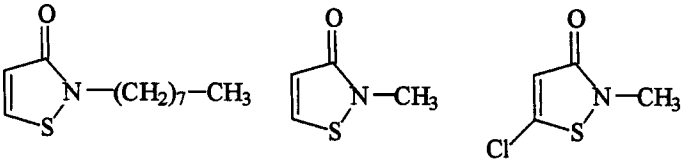
N-Benzyl-3-isothiazolones bearing a free 5-position are readily dimerized by base to 2,4-bis-methylene-1,3-dithietanes (Scheme 45) [77]; see Section 3.2.

4. BIOLOGICAL ACTIVITY

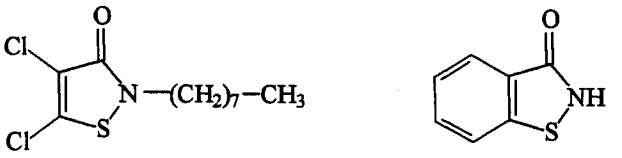
Various isothiazol-3-ones and their metal salt complexes are potent industrial microbiocides, because of their antifungal and antibacterial properties, particulary the 2-octyl compound **2o**, mixtures of 2-methylisothiazol-3(2*H*)-one **2a** with its 5-chloro analogue **7c** and 1,2-benzisothiazol-3(2*H*)-one **10** [2,98,99]. The very high biocidal activity of 5-chloroisothiazolone **7c** arises in part because of the preferential formation of a highly reactive thioacyl chloride [99–101].

Below are the trade names of some common isothiazolones that are used as microbiocides [98].

Kathon® CG: 0.35% 2-methylisothiazol-3(2*H*)-one **2a** (MI),
1.15% 5-chloro-2-methylisothiazol-3(2*H*)-one **7c** (CMI),
23.0% magnesium salts (chloride and nitrate),
75.5% water



2o (OIT) **2a** (MI) **7c** (CMI)



8f (DCOIT) **10** (BIT)

SCHEME 62

Kathon® 886: 14% active compounds,
Proxel: 60–90% 1,2-benzisothiazol-3(2*H*)-one **10** (BIT), see Part II
OIT: 2-*n*-octylisothiazol-3(2*H*)-one **2o**,
DCOIT: 4,5-dichloro-2-*n*-octylisothiazol-3(2*H*)-one **8f**.

Since the monocyclic isothiazolone derivatives control the growth of algae, they are used as industrial biocides [102] in the paper-making industry [103–107] and in cooling systems [108–112]. They have been recommended as preservatives to prevent fungal growth in a wide range of manufactured goods, such as emulsion paints [113–117a,b], wood varnishes [118–120], adhesives [121], and natural and artificial leather [122]. They protect objects immersed in seawater from attack by algae and marine creatures [123–130]. Isothiazolones have found many uses for preventing microbiological degradation of hydrophilic solutions for silver halide photographic materials [131–133].

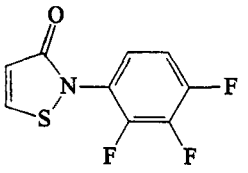
Antifouling polymer membranes contain biocidal isothiazolones [134]. Polyurethane compositions with improved long-term resistance against microbial attack have been developed [135,136]. Isothiazolones are incorporated into PVC [137a,b], hydroxystyrene polymers [138] and polyphenolic compounds for controlled-release formulations [139]. Immobilized biocides for aqueous medium were investigated, e.g. Kathon 287 T was immobilized on Amberlite XAD-7HP with potentiating agents [140]. Isothiazolones in chlathrate compounds are microbiological coatings which reduce skin irritation [141–143] (see Section 5). Industrial antiseptic and antifungal agents containing hydrogen peroxide donors and isothiazolones are especially useful for materials containing reducing substances [144]. There are synergistic bactericidal, fungicidal and algicidal compositions containing isothiazolones [145,146].

CMI/MI has been widely used during the last 20 years for the preservation of aqueous systems in cosmetics, e.g. in rinse-off products [99,147–153]. They have a broad spectrum of activity against fungi and bacteria at very low concentrations [153]. The allergic contact potential has been known for many years [106,154–157]. For the synergism in the preservation of cosmetics see [158]. The development of resistance to MI **2a** and CMI **7c** under laboratory conditions is described [159–161].

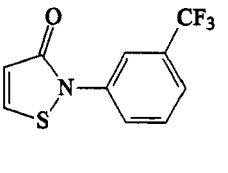
The isothiazolone derivatives are also used as agrochemicals [7,9,18]. Isothiazolones with herbicidal and fungicidal activity were found [162–165].

A series of 2,5-diarylisothiazolones **6b-q** [23] have been to reported to inhibit the IL-1β-induced breakdown of bovine nasal septum cartilage in an organ culture assay. These compounds represent a novel, non-peptide lead series approach to the mediation of the chronic cartilage breakdown associated with arthritic disease. *N*-arylisothiazolones **6r$_2$–r$_6$** are also telomerase inhibitors [166–168] and inhibitors of bacterial two-component signal transduction systems (**6r$_{2-4}$**) [169–170]. Covalent modification of the interleukin-5 receptor by isothiazolones (**2a, 6r,t, 7c, 8b, 48a,c, 52b**) leads to inhibition of the binding of interleukin-5 [171a] (Scheme 63). The inhibition of p56^{lck} tyrosine kinase activity by methyl 3-(*N*-isothiazolonyl)-2-thiophencarboxylate **6u,v,r$_7$, 109t** was found [171b], where by cystein-SH groups within the p56^{lck} catalytic domain react with the isothiazolone ring, leading to ring opening and disulfide bond formation with the p56^{lck} enzyme. Various 3-isothiazolylvinylcephalosporins show antibacterial activities [172a,b].

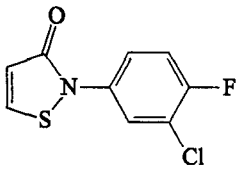
The bioisosteric substitution of the carboxy group is an important approach in the development of selective neurotransmitter receptor ligands. The central inhibitory



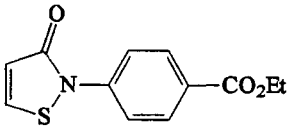
6r$_2$
TFPI



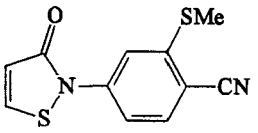
6r$_3$
TMPI



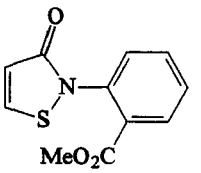
6r$_4$
CFPI



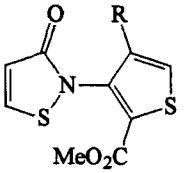
6r$_5$
4-EOIB



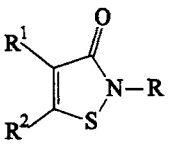
6r$_6$
MOIB



6r$_7$
2-EOIB

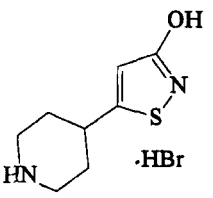


6u: R = H
6v: R = Me

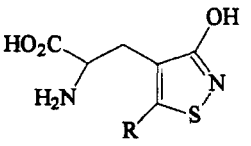


6r,t: R = C_6H_5, 2-pyr, $R^1 = R^2 = H$
2a: R = Me, $R^1 = R^2 = H$
7c, 8b, 48a,c, 52b: R = Me, see Table V

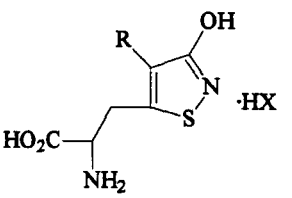
SCHEME 63



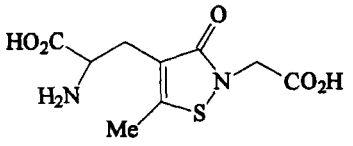
126



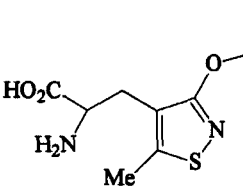
127a: R = Me, thio-AMPA
127b: R = *t*-Bu, thio-ATPA



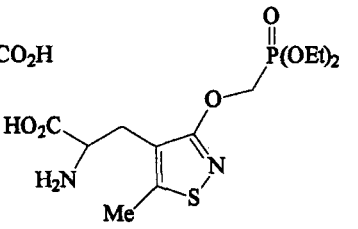
128a: R = H, X = Cl
128b: R = Br, X = Br



129



130



131

SCHEME 64

and excitatory neurotransmitters are 4-amino-butanoic acid (GABA) and glutamic acid (Glu), which are capable of adopting receptor subtype-specific conformations. The isothiazole unit is an effective bioisostere of the carboxy group in GABA [49a–d] and in Glu [14b,c]. The two isothiazol-3-ol GABA-analogues thiomuscimol **58** [49a–d,173] and thio-THIP [50,51] (see Part II) also interact selectively at the $GABA_A$ receptor site. The nonannulated analoga 5-(4-piperidyl)isothiazol-3-ol (thio-4-PIOL) **126** [174], which behaves as a low efficacy partial agonist at $GABA_A$ receptors in cultured cortical neurons, showed no efficacy in oocytes but produced pure antagonist effects with a binding/functional affinity ratio between those observed for the agonists and antagonists [175].

The entropy was found as the predominant driving force of binding to human recombinant $\alpha_x\beta_3\gamma_2$ GABA receptors [176].

The 3-isothiazol amino acids thio-AMPA **127a**, thio-ATPA **127b** and the analogues **128a, b** were shown to be selective AMPA receptor agonists of widely different potency [14b]. The stereochemistry of (*S*)-thio-ATPA **127b** was studied by X-ray crystallographic analysis and its molecular pharmacology has been described as a new very potent and selective agonist at homomerically expressed ionotropic GluR5, and may be a valuable tool for the investigation of desensitization properties of AMPA receptors [177]. The AMPA receptor agonist, thio-AMPA was converted into the selective NMDA antagonist **129** in which a 3-isothiazolone unit is a bioisosteric analogue of the peptide bond of the NMPA antagonist, γ-(R)-Glu-Gly [14c]. The isomeric 3-oxygenated isothiazole amino acid **130**, and the corresponding isothiazole phosphono amino acid **131** were also synthesized, and were shown to be selective AMPA receptor antagonists [14c]. A review and theoretical study by a high level *ab initio* calculations up to G2(MP2) theory are made for many of these structures [178].

5. TOXICITY

Isothiazolones belong to the class of allergy-releasing compounds [106,154–157]. The derivatives 5-chloro-2-methylisothiazol-3(2*H*)-one **7c** (CMI), 2-methylisothiazol-3(2*H*)-one **2a** (MI) and benzisothiazol-3(2*H*)-one **10a** (BIT) have attracted particular attention. It is generally accepted that MI/CMI may cause skin sensitization in humans. It appears in clinical studies that a concentration of 100 mg/l causes skin sensitization in 1–7 % of the exposed population. Studies with the two individual isothiazolones have revealed that both compounds are sensitizers, with CMI being more potent than MI [106,154,157]. Isothiazolones in paints have been reported to cause airborne contact dermatitis [179–182].

The active biocide ingredients in Kathon® formulations are also potent contact sensitizers [154,183–190]. Effects of the stimulation with the biocides are the induction of tyrosine phosphorylation in human cells [184–186] and cloned DETC are specifically activated.

The acute, subacute and subchronic toxicity of MI/CMI have been evaluated in several studies in rats, mice, guinea pigs and dogs [106]. Toxicity results indicate that Kathon® CG was moderately to highly toxic to rats and highly toxic to rabbits as a result of oral administration, and moderately toxic to rabbits when applied dermally [106]. Kathon® CG and Kathon® 886 have been evaluated in a number of mutagenicity assays by several authors [106,189]. Thin layer chromatography separation of the compounds and subsequent identification by GC/MS indicated that MI was non-mutagenic while CMI was mutagenic in strain TA 100 of *Salmonella typhimurium* [189].

6. CONCLUSIONS

Monocyclic isothiazol-3(2*H*)-ones and their oxidized derivatives continue to find many synthetic applications, e.g. as reactive dienophiles, in ring transformation and ring enlargement reactions.

Isothiazol-3(2*H*)-ones and their metal salt complexes are potent industrial microbiocides because of their antibacterial and antifungal properties, e.g. 2-methyl- (MI), 2-octyl-(OIT), 5-chloro-2-methyl- (CMI) and 4,5-dichloro-2-octylisothiazol-3(2*H*)-one (DCOIT). They are used as agrochemicals due to their herbicidal and fungicidal activity.

The isothiazol unit is also an effective bioisostere of the carboxy group in 4-amino butanoic acid (GABA) and glutamic acid (Glu). The 3-isothiazol amino acids thio-AMPA, thio-ATPA and analogues were shown to be selective AMPA agonists. Isothiazolones CMI and MI belong to the class of allergy-releasing compounds and have attracted particular attention.

Acknowledgement

Financial support by Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie is gratefully acknowledged.

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