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Isothiazoles (1,2-thiazoles): synthesis, properties and applications

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Abstract. The most recent achievements in the chemistry of isothiazoles are generalised and systematised. The main applications of isothiazole derivatives are surveyed. The bibliography includes 293 references.

I. Introduction

Isothiazoles constitute a relatively novel class of heterocyclic compounds. Their ancestor, 1,2-thiazole, was first obtained in 1956.[1]

Other 1,2-azoles had been rather well studied by that time, both theoretically and with respect to their practical applications. Further rapid progress in the chemistry of isothiazole and intense studies into the synthesis and chemical conversions of its derivatives carried out in the 1960 – 1990's were caused primarily by the extraordinarily broad range of useful properties manifested by various representatives of this class of compounds. Isothiazole-containing penicillins and cephalosporins competed successfully with ampicillin in their activities against gram-positive and gram-negative bacteria.[2,3] In the last decade of the 20th century, some isothiazole derivatives were found to be efficient in the treatment of Alzheimer's disease,[4] as antiinflammatory, antithrombotic and anticonvulsive drugs [5,6] and serine protease inhibitors;[7,8] physiologically active compounds interacting with glutamate receptors were synthesised.[9] Auxin transport inhibitors based on isothiazoles [10–14] are added to herbicides to enhance their activity. Isothiazole derivatives manifest synergistic effects when added to other biocidal preparations.[15–19] Compositions containing isothiazole derivatives are used as protectors for polymers, dyes, detergents [20] and leather goods,[21] for decontamination of pigments, latexes, foodstuffs [22] and waste,[23] as antifouling agents,[24,25] *etc*. Recently, isothiazoles have been patented for use in colour photography for stabilisation of photomaterials [26,27] and as an inkbase for printers.[28,29] Industrial production of some isothiazolones, which represent broad-spectrum biocides and are safe for human beings, animals and environment, has begun.[30]

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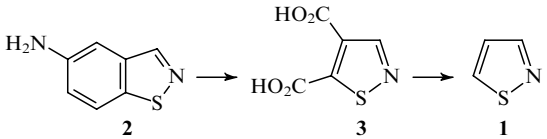
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The first data on the chemistry of isothiazoles were reviewed by Wooldridge *et al*.[31,32] Further progress in the synthesis and conversions of isothiazoles is documented in the reviews [33–39] some of which are inaccessible for Russian readers as well as in the monographs [40–45] where isothiazoles are considered only in conjunction with other heterocyclic compounds. The fundamental monograph by Houben-Weyl,[46] which contains more than 500 references including some published in 1992, represents the most systematic and full generalisation of the experimental data on the chemistry of 1,2-thiazoles. The first review devoted to the physical and chemical properties of 1,2-azoles was published in Russian in 1979.[47] In addition, isothiazoles and their benzoannelated analogues are discussed in 'Comprehensive Organic Chemistry'.[48]

The necessity for systematisation and generalisation of the newest data on isothiazoles stems from the appearance, in the past decade, of a great number of publications devoted to the synthesis, conversions and applications of this class of compounds. The material described here covers original papers and patent data published over the period 1993 – 2001 inclusive. In some cases, earlier sources concerned with the methods for isothiazole synthesis are cited for the sake of completeness.

II. Synthesis of isothiazoles

Isothiazole (**1**) was first prepared by the oxidation of 5-amino-1,2-benzoisothiazole (**2**) with an alkaline solution of potassium permanganate with subsequent decarboxylation of isothiazole-4,5-dicarboxylic acid (**3**).[1,49]



2 **3** **1**

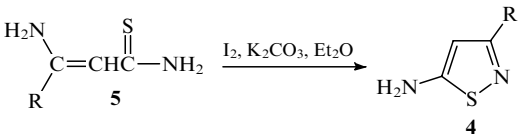
This synthetic procedure has a purely historical significance. Later, isothiazoles were synthesised from simpler and more accessible compounds.

1. Synthesis of isothiazoles based on cyclisation reactions

The main methods for the construction of the isothiazole ring are based on cyclisation of compounds containing N–C–C–C–S fragments and heterocyclisation of compounds containing nitrogen, sulfur and carbon atoms.

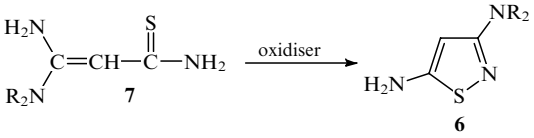
a. Synthesis of isothiazoles from compounds containing the N–C–C–C–S group

The construction of the isothiazole ring from compounds containing a preformed N–C–C–C–S fragment is the most attractive approach. Thus various 5-aminoisothiazole derivatives **4** can be prepared by the oxidation of 2-aminoalk-1-enethiocarboxyamides **5**.[50]



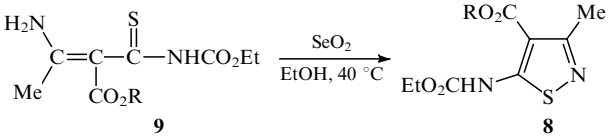
R = Et, Pr^i, Bu^n, Bu^i, Bu^t, cyclo-C_6H_{11}.

Oxidation of 3-amino-3-(dialkylamino)thioacrylic acid amides **7** gives the 3,5-diaminoisothiazole derivatives **6**.[51]



R = Alk.

A procedure for the synthesis of alkyl 3-methyl-5-ethoxycarbonylaminoisothiazole-4-carboxylates (**8**) by the oxidation of substituted thioamides **9** with selenium dioxide has been developed recently.[52]

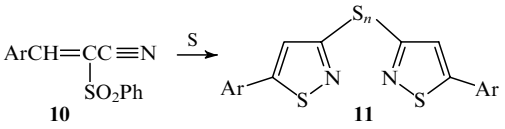


R = Me, Et.

b. Synthesis of isothiazoles from sulfur and compounds containing the C–C–C–N fragment

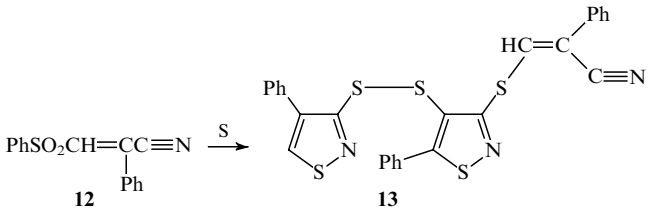
The construction of the isothiazole ring from sulfur and compounds containing the C–C–C–N fragment is relatively little studied. This approach makes use mainly of nitriles.[46]

Thus the electrolysis of 3-aryl-2-phenylsulfonylacrylonitriles (**10**) in acetonitrile or DMF using a chemically active sulfur–graphite electrode affords bis(5-arylisothiazol-3-yl) di- or trisulfides (**11**).[53]



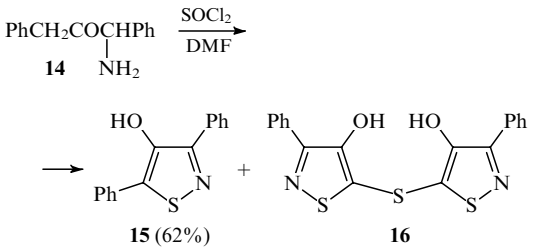
Ar = Ph, 4-MeC_6H_4, 4-PhC_6H_4; n = 2, 3.

In the case of 2-phenyl-3-phenylsulfonylacrylonitrile (**12**), di(isothiazolyl) disulfide **13** containing the (*Z*)-2-cyano-2-phenylvinylthio group in position 3 of one of the isothiazole rings was obtained.[53]

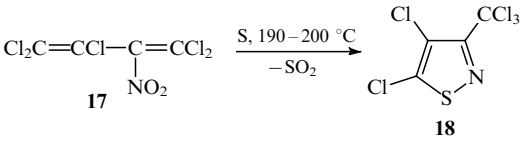


It is believed that electrochemical synthesis of sulfur-containing compounds consists in the elimination of the phenylsulfonyl group with concomitant addition of a polysulfide anion produced upon electroreduction of elemental sulfur.

According to the patent data,[54] substituted α-amino ketones react with thionyl chloride to give the corresponding 4-hydroxyisothiazoles. Thus the reaction of amino ketone **14** with $SOCl_2$ in DMF yields isothiazole **15**. When thionyl chloride was used in excess, the reaction products contained both isothiazole **15** and di(isothiazolyl) sulfide **16**.



The authors of the present review together with Yu A Oldekop have demonstrated[55–57] that heating of 2-nitropentachlorobuta-1,3-diene (**17**) with sulfur resulted in its heterocyclisation and the formation of 4,5-dichloro-3-trichloromethylisothiazole (**18**).

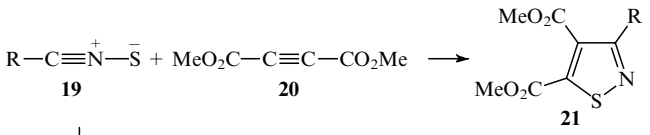


This reaction offers a new approach to the construction of the isothiazole ring. It is known that the reaction of halobutenes and -butadienes with sulfur is used for the synthesis of the corresponding halogenothiophenes.[58] In the case of nitrodiene **17,** the reaction follows a different route: the heterocyclisation involves the nitro group and is accompanied by the evolution of sulfur dioxide. The yield of isothiazole **18** reaches 52%. Tetrachlorothiophene (yield 4%) is the side product in this reaction. Apparently, the reaction has a radical character, since sulfur molecules exist in the form of reactive biradicals S_n at high temperature.[59]

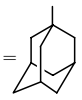
c. Synthesis of isothiazoles using cycloaddition and condensation reactions

The methods for the synthesis of isothiazoles using cycloaddition and condensation reactions of compounds containing a set of essential fragments are the most well-studied and attract, as before, the attention of investigators.

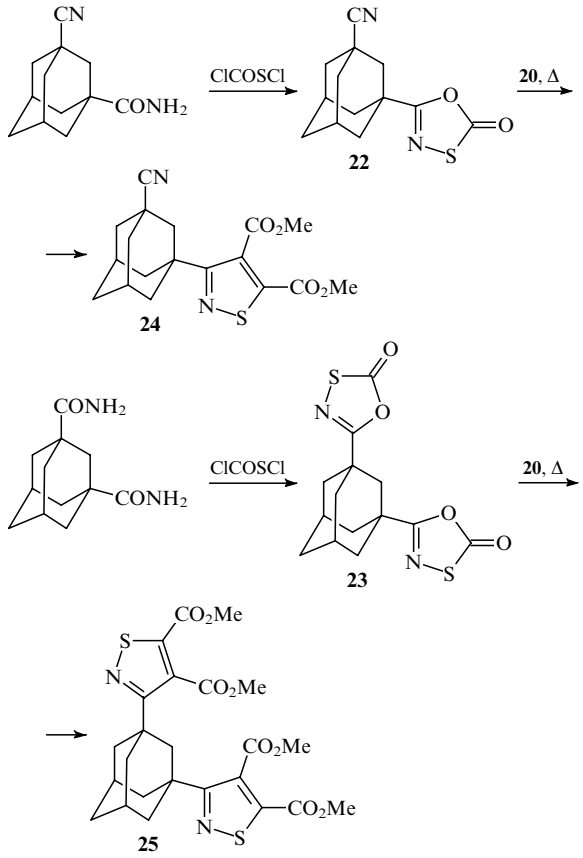
Thus the 1,3-dipolar cycloaddition of nitrile sulfide **19** to dimethyl acetylenedicarboxylate (**20**) yields the isothiazole derivative **21** the structure of which has been confirmed by X-ray diffraction analysis.[60]



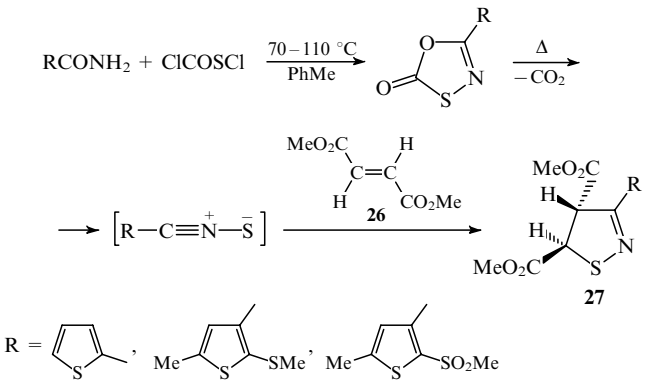
R =



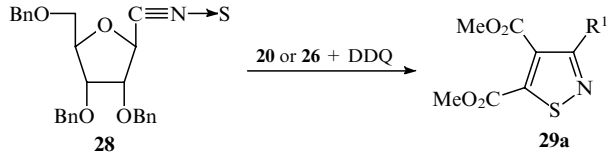
The reactions of 1-cyano-3-(2-oxo-1,3,4-oxathiazol-5-yl)adamantane (**22**) and 1,4-bis(2-oxo-1,3,4-oxathiazol-5-yl)adamantane (**23**) prepared from the corresponding adamantanecarboxamides and chlorosulfenylcarbonyl chloride with the alkyne **20** result in the decarboxylation of the oxathiazolone fragment. The reactions of the nitrile sulfides formed with the alkyne **20** proceed as 1,3-dipolar cycloadditions and yield 1-cyano-3-(4,5-dimethoxycarbonylisothiazol-3-yl)adamantane (**24**) and 1,3-bis(4,5-dimethoxycarbonylisothiazol-3-yl)adamantane (**25**), respectively.[61]

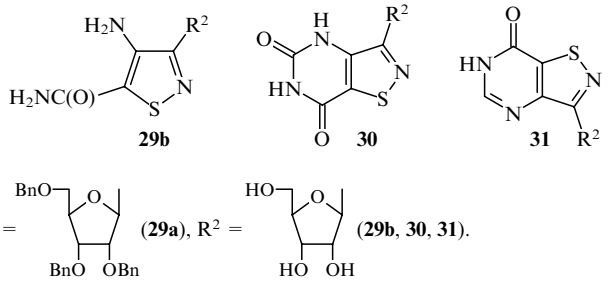


The reaction of nitrile sulfides of the thiophene series with dimethyl fumarate (**26**) gives substituted 4,5-dihydroisothiazoles **27**.[62]



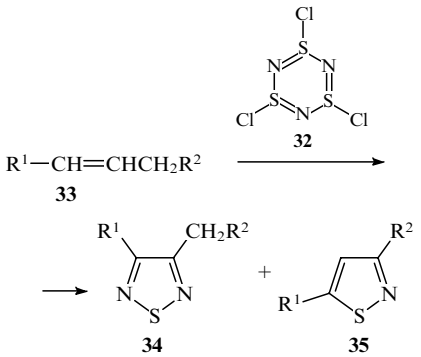
The cycloaddition of 3,4,6-tri-*O*-benzyl-2,5-anhydro-D-allononitrile *N*-sulfide (**28**) to dimethyl acetylenedicarboxylate (**20**) or dimethyl fumarate (**26**) followed by the oxidation of the reaction products with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) results in *O*-benzyl-3-(β-D-ribofuranosyl)isothiazolecarboxylate **29a**, which was used for the preparation of the C-nucleoside **29b** and isothiazolo[4,5-*d*]pyrimidine analogues of the natural C-nucleosides pyrazofurin (**30**) and formycin (**31**).[63]



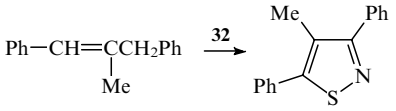


The use of 1,3,5-trichloro-1,3,5,2,4,6-trithiatriazine (**32**) seems to be very promising for the synthesis of isothiazoles.

It was found that ordinary allylic compounds of the type **33** react with the reagent **32** as two-carbon units to give 1,2,5-thiadiazoles **34** and as three-carbon units to give isothiazoles **35**. The ratio of compounds **34** and **35** depends on the reaction conditions and the nature of the substituents.[64]

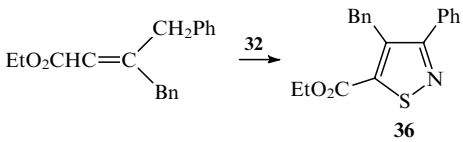


Thus 1,3-diphenylpropene (**33**, $R^1 = R^2 = Ph$) reacts with two equivalents of compound **32** in boiling CCl_4 to give 3,5-diphenylisothiazole **35** in 53% yield. The introduction of a substituent at the central carbon atom of the allylic system suppresses the formation of thiadiazoles. 4-Methyl-3,5-diphenylisothiazole was obtained from 2-methyl-1,3-diphenylpropene without any admixtures of the corresponding thiadiazole.



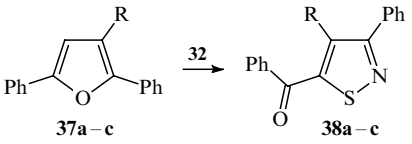
The presence of terminal electron-withdrawing groups in the allylic derivatives **33** increases their reactivities with respect to the reagent **32**.[64]

In the case of non-symmetrical allylic compounds, the reaction proceeds regiospecifically and affords an isomer with the electron-withdrawing group adjacent to the sulfur atom of the ring. Thus the reaction of the trimer **32** with ethyl 3,3-dibenzylacrylate affords isothiazole **36** in 66% yield.[64]



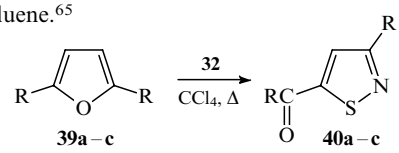
Trithiatriazine trichloride **32** can be used for the preparation of isothiazole derivatives from other heterocyclic compounds.

It was shown[65–67] that treatment of di- and trisubstituted furans **37a–c** with trithiatriazine trichloride **32** in boiling CCl_4 results in their one-step conversion into 5-benzoylisothiazoles **38a–c** in high yields.



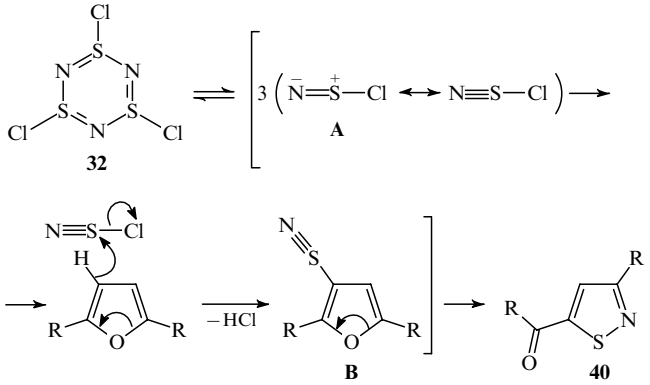
R = H (**a**), Ph (**b**), Br (**c**).

2,5-Disubstituted furans **39a–c** give similar products **40a–c** (yields 50%–60%) with compound **32** upon boiling in CCl_4 or toluene.[65]



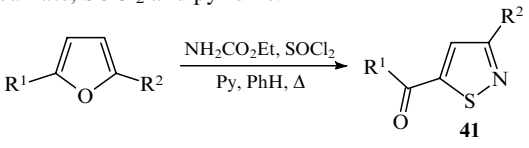
R = 4-MeC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**), Bu^t (**c**).

It is assumed that heating of 1,3,5-trichloro-1,3,5,2,4,6-trithiatriazine (**32**) results in its fragmentation and the formation of the reactive monomer **A** which attacks the furan molecule to give the intermediate **B**. Recyclisation of the latter affords isothiazoles.[65]



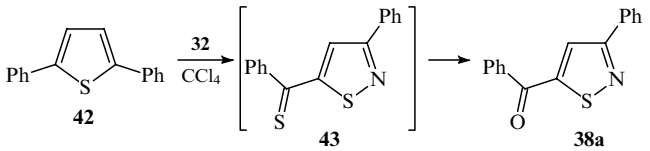
It has been shown [68] that fully substituted furans do not react with the reagent **32**, since the elimination of HCl requires the presence of a hydrogen atom in the β-position of the starting furan.

Yet another route to the synthesis of 5-acylisothiazoles **41** is based on the reaction of 2,5-disubstituted furans with ethyl carbamate, $SOCl_2$ and pyridine.[68]

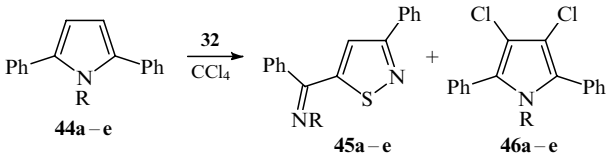


R^1 = R^2 = Ph, 4-MeC_6H_4, Bu^t; R^1 = 4-$MeOC_6H_4$, R^2 = 4-$NO_2C_6H_4$.

In contrast with 2,5-diphenylfuran (**37a**), the reaction of 2,5-diphenylthiophene (**42**) with the reagent **32** gives 5-benzoyl-3-phenylisothiazole (**38a**) in low yield. Presumably, the latter is formed upon oxidation of the intermediate 5-thiobenzoyl derivative **43**.[69]



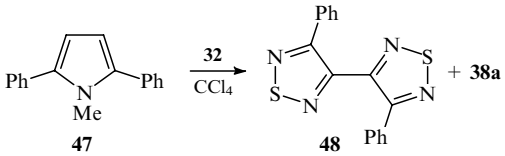
Reactions of *N*-substituted 2,5-diphenylpyrroles **44a–e** with compound **32** afford mixtures of thiazolyl-substituted imines **45a–e** and 3,4-dichloropyrrole derivatives **46a–e**. The ratio of the reaction products depends on the nature of the substituent R.[69]



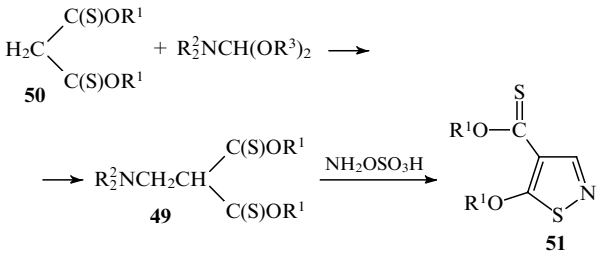
R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-$O_2NC_6H_4$ (**c**), MeOC(O) (**d**), $Bu^tOC(O)H$ (**e**).

Compounds **45b**,**e** are formed as two geometrical isomers. Imine **45b** is easily hydrolysed to give ketone **38a**. The imine **45d** formed from *N*-methoxycarbonylpyrrole (**44d**) is completely hydrolysed even at room temperature to give ketone **38a**.

It is of note that the reaction of 1-methyl-2,5-diphenylpyrrole (**47**) with the reagent **32** follows a different route and results in the formation of bi(1,2,5-thiadiazol-3-yl) **48**; 5-benzoyl-3-phenylisothiazole (**38a**) is formed in only trace amounts.[69]



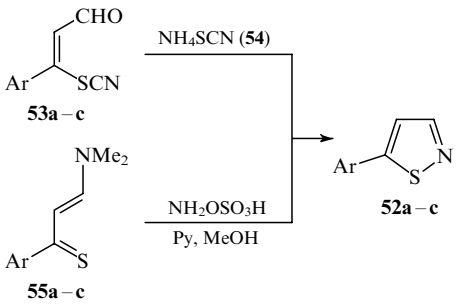
Condensation of 2-dialkylaminomethyldithiomalonates **49**, the reaction products of dithiomalonates **50** with formamide acetals, with hydroxylamine-*O*-sulfonic acid results in isothiazoles **51**.[70]



R^1, R^3 = Me, Et; R^2 = Me, Ph.

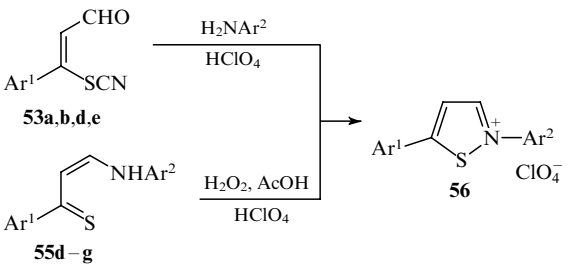
Schulze *et al.*[71] have developed two procedures for the synthesis of isothiazoles **52a–c** containing fluoro-substituted aryl groups. The first of them is based on the reaction of β-thiocyanatocinnamaldehydes **53a**,**b** with ammonium thiocyanate (**54**). Isothiazoles **52a**,**b** were obtained in good yields (~60%). In this case, ammonium thiocyanate (**54**) acts as a source of ammonium required for ring closure. It is noteworthy that ammonium thiocyanate (**54**) was employed previously for the preparation of 4- and 5-alkylisothiazoles.[72]

The second route is based on the use of enamino thiones **55a–c** as starting compounds; their reaction with hydroxylamine-*O*-sulfonic acid gives isothiazoles **52a–c**. In this case, the yields reach 98%.



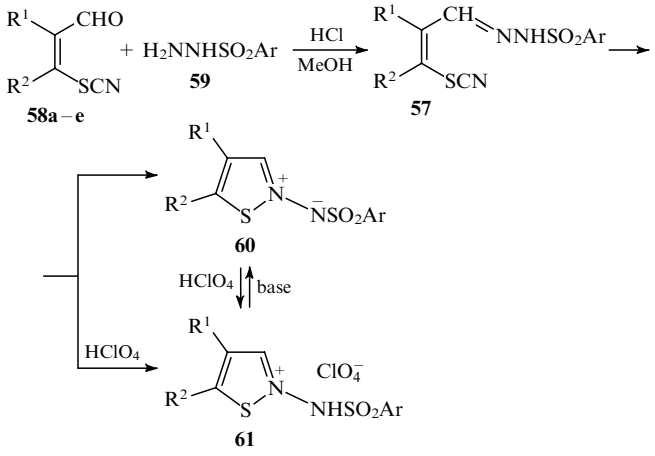
Ar = 4-$CF_3C_6H_4$ (**a**), 3-$CF_3C_6H_4$ (**b**), 3-FC_6H_4 (**c**).

Approaches to the synthesis of isothiazolium salts **56** were developed based on cinnamaldehydes **53a**,**b**,**d**,**e** and enamino thiones **55d–g**.[71]



Ar^1 = 4-$CF_3C_6H_4$ (**53a**, **55f**), 3-$CF_3C_6H_4$ (**53b**, **55g**), 4-FC_6H_4 (**53d**, **55d**), 4-$MeOC_6H_4$ (**53e**, **55e**); Ar^2 = Ph, 4-$MeOC_6H_4$.

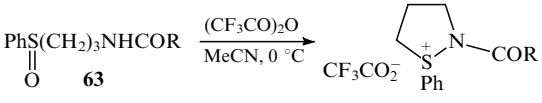
4-Thiocyanato-1-aza-1,3-dienes **57** prepared from β-thiocyanato α,β-unsaturated aldehydes **58** and arenesulfonohydrazides **59** undergo cyclocondensation to yield *N*-arylsulfonylisothiazol-2-ylimines **60** and the corresponding *N*-arylsulfonyl-2-aminoisothiazolium salts **61**.[73]



R^1 = R^2 = Me (**a**); R^1 = Ph, R^2 = Me (**b**);
R^1-R^2 = $(CH_2)_n$, *n* = 3 (**c**), 4 (**d**), 5 (**e**);
Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 2,4,6-$Me_3C_6H_2$, 2,4,6-$Pr^i_3C_6H_2$.

Thus, depending on the nature of the substituents R^1, R^2 and Ar, the reactions of unsaturated thiocyanato aldehydes with arenesulfono hydrazides afford different products. Isothiazoles are formed directly from compounds **58a**,**b**, whereas alicyclic thiocyanato aldehydes **58c**–**e** yield stable hydrazones **57**. Treatment of the latter with perchloric acid yields isothiazolium salts **61c**–**e**.

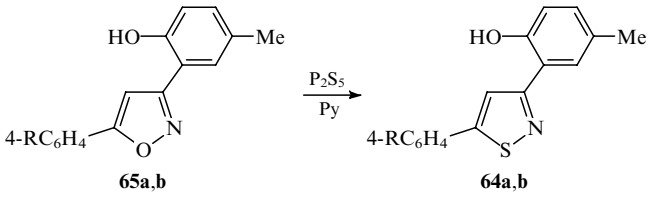
A convenient procedure for the synthesis of *N*-acylisothiazolidinium trifluoroacetates **62**, which includes treatment of *N*-acylamino sulfoxides **63** with trifluroacetic anhydride, has been developed.[74]



R = Bu^t, Ph.

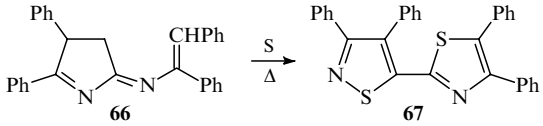
2. Synthesis of isothiazoles from other heterocyclic compounds

Methods of synthesis of substituted isothiazoles from other heterocyclic compounds find wide application despite the fact that they belong to the most ancient ones. Thus 3,5-disubstituted isothiazoles **64a**,**b** were prepared from isoxazoles **65a**,**b** by the reaction with phosphorus pentasulfide in pyridine.[75]

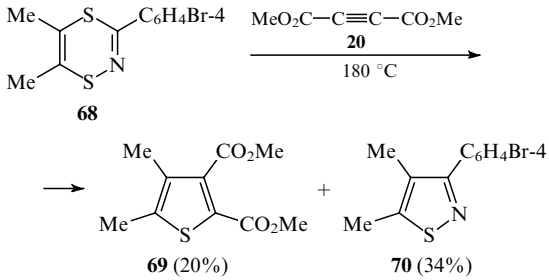


R = H (**a**), MeO (**b**).

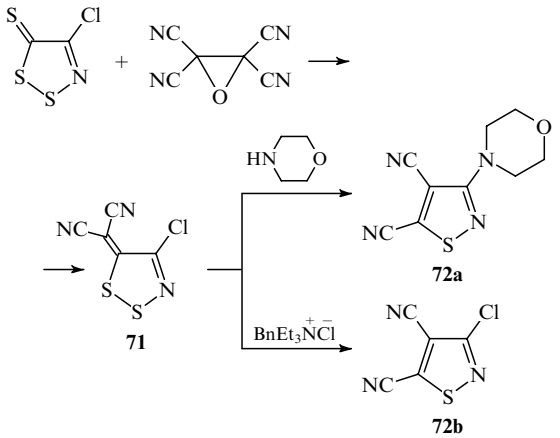
The reaction of 2-imino-3,4-dihydro-2*H*-pyrrole **66** with sulfur on heating is accompanied by dehydrogenation and incorporation of the sulfur atom into the pyrrole ring resulting in the previously unknown thiazolylisothiazoles **67**.[76]



The thermal fragmentation of 1,4,2-dithiazines in the presence of dienophiles aimed at the synthesis of 1,4-dithyines has been studied.[74] It was found that 1,4,2-dithiazine derivatives **68** react with dimethyl acetylenedicarboxylate (**20**) on heating in *o*-dichlorobenzene to give a mixture of dimethyl 4,5-dimethylthiophene-2,3-dicarboxylate (**69**) and 3-(4-bromophenyl)-4,5-dimethylisothiazole (**70**). The latter is formed upon thermolysis of dithiazine **68** and is accompanied by a loss of the sulfur atom from position 4.[77]

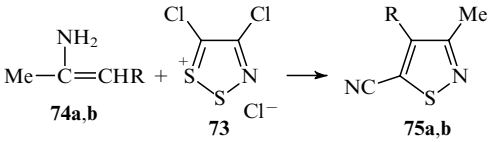


A new method for the synthesis of the isothiazole ring from 4-chloro-5-dicyanomethylidene-5*H*-1,2,3-dithiazole (**71**) prepared by the condensation of 4-chloro-1,2,3-dithiazole-5-thione with tetracyanoethylene oxide has been proposed recently. Treatment of the nitrile **71** with morpholine or benzyltriethylammonium chloride gives 3-morpholino- (**72a**) and 3-chloroisothiazole-4,5-dicarbonitriles (**72b**), respectively.[78]



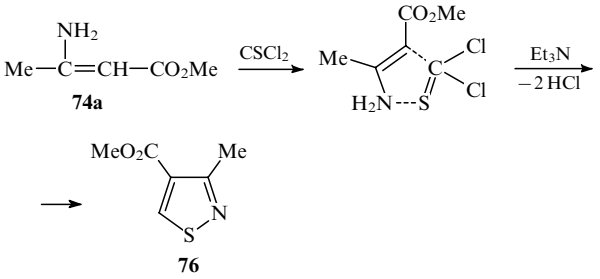
A new simple procedure for the synthesis of isothiazoles from primary enamines and 4,5-dichloro-1,2,3-dithiazolium chloride (**73**) has been developed. Thus the reaction of methyl 3-aminocrotonate (**74a**) and 3-aminocrotononitrile (**74b**) with the salt **73** under mild conditions (20 °C, dichloroethane) afforded

4-methoxycarbonyl-5-cyano-3-methylisothiazole (**75a**) and 4,5-dicyano-3-methylisothiazole (**75b**).[79]



R = CO_2Me (**a**), CN (**b**).

Presumably, the conversion of enamine **74a** into isothiazole **75a** upon treatment with the salt **73** proceeds similarly to its conversion into isothiazole **76** under the action of thiophosgene used by Woodword *et al.* in the synthesis of colchicine back in 1965.[80]

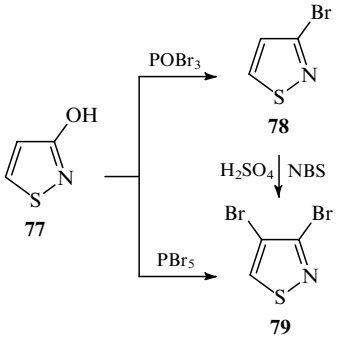


3. Synthesis of isothiazole derivatives by modification of compounds containing the isothiazole ring

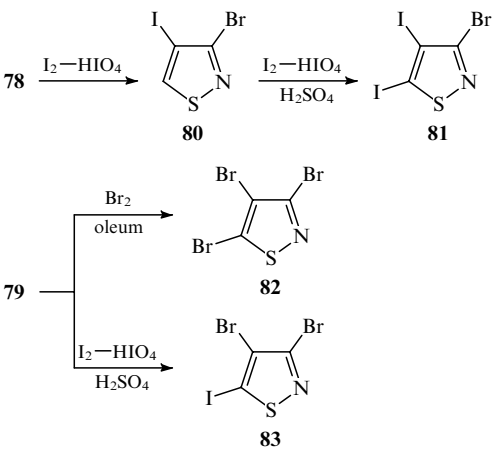
The syntheses of functionalised isothiazoles by exchange of substituents in the isothiazole ring or by transformation of the side chain of accessible derivatives are well documented.[46]

a. Substitution reactions

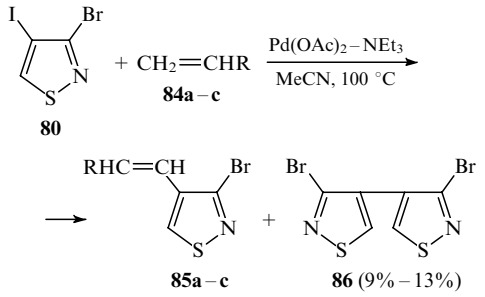
Recently, Russian chemists have developed novel procedures for the synthesis of halogenated isothiazoles.[81–83] Thus bromo- and iodoisothiazoles **78**–**83** have been synthesised from the readily available 3-hydroxyisothiazole (**77**).[81]



NBS, *N*-bromosuccinimide.

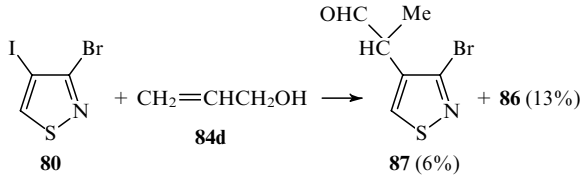


The possibility of synthesis of alkenylhaloisothiazoles by palladium-catalysed cross-coupling of the halogen derivatives **80** and **83** with the terminal alkenes **84a**–**d** (the Heck reaction) has been studied.[82] It was found that 3,4-dibromo-5-iodoisothiazole (**83**) does not react with alkenes under the reaction conditions. 3-Bromo-4-iodoisothiazole **80** enters into the Heck reaction with the alkenes **84a**–**c** in the presence of the catalytic system $Pd(OAc)_2$–NEt_3 to give 4-alkenyl-3-bromoisothiazoles **85a**–**c**. 4,4′-Bi(3-bromoisothiazole) (**86**) is the side product in this reaction; it is also formed in the absence of the alkene.

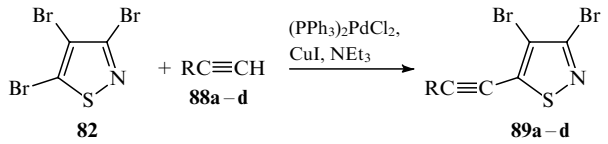


R = Ph (**a**, 60%), CO_2Me (**b**, 29%), CN (**c**, 33%).

3-Bromo-4-(1-oxopropan-2-yl)isothiazole (**87**) and biisothiazolyl **86** were isolated from a complex mixture of reaction products of isothiazole **80** with allyl alcohol (**84d**).



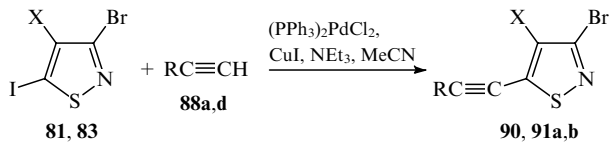
Under conditions of metal-complex catalysis, bromo- and iodoisothiazoles react with terminal alkynes.[83] Thus tribromoisothiazole (**82**) reacts with phenylacetylene (**88a**), oct-1-yne (**88b**), propargyl alcohol (**88c**) and methoxymethylacetylene (**88d**) in the presence of $(PPh_3)_2PdCl_2$ even at 20 °C to give the cross-coupling products (**89a**–**d**).



R = Ph (**a**), n-C_6H_{13} (**b**), CH_2OH (**c**), CH_2OMe (**d**).

The highest yields (20%–56%) were obtained with 4 mol.% of $(PPh_3)_2PdCl_2$. 1,4-Diphenylbuta-1,3-diyne was isolated as a side product in the reaction of isothiazole **82** with phenylacetylene **88a**.

It should be noted that unsubstituted acetylene does not enter into the cross-coupling reaction with isothiazole **82** even at 80 °C; the reaction mixture contained only 3,4-dibromoisothiazole (**79**), the partial reduction product of the tribromide **82**. Compound **79** did not react with phenylacetylene, *i.e.*, only the bromine atoms in position 5 were active in the cross-coupling reaction. 5-Iodoisothiazoles were found to be the most reactive compounds. The reactions of 3,4-dibromo-5-iodoisothiazole (**83**) and 3-bromo-4,5-diiodoisothiazole (**81**) with terminal alkynes **88a**,**d** occur in the presence of 2 mol.% of $(PPh_3)_2PdCl_2$ and result in the corresponding 3,4-dibromo-5-alkynyl- (**90**) and 3-bromo-4-iodo-5-alkynylisothiazoles (**91a**,**b**).

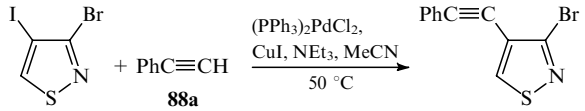


81, 83 90, 91a,b

Compounds	X	R
90	Br	Ph
91a	I	Ph
91b	I	CH_2OMe

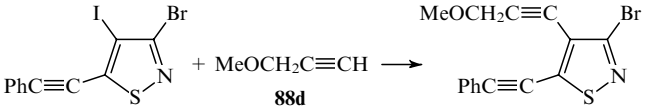
The side reaction products of terminal alkynes with 3,4-dibromo-5-iodoisothiazole (**83**) and 3-bromo-4,5-diiodoisothiazole (**81**), *viz*., the dibromide **79** and 3-bromo-4-iodoisothiazole (**80**), represent the reduction products of iodine in position 5.

3-Bromo-4-iodoisothiazole (**80**) enter into cross-coupling reactions with phenylacetylene (**88a**) under conditions of metal-complex catalysis to give 3-bromo-4-(phenylethynyl)isothiazole (**92**).[83]



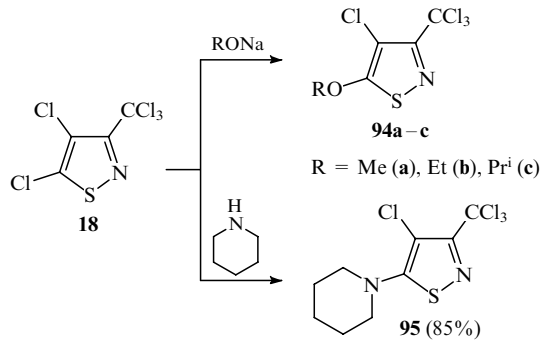
80 92 (49%)

3-Bromo-4-(3-methoxyprop-1-ynyl)-5-(phenylethynyl)isothiazole (**93**), the first representative of isothiazoles with two alkynyl substituents, was synthesised by the reaction of 3-bromo-4-iodo-5-(phenylethynyl)isothiazole (**91a**) with methoxymethylacetylene (**88d**) under similar conditions.[83]

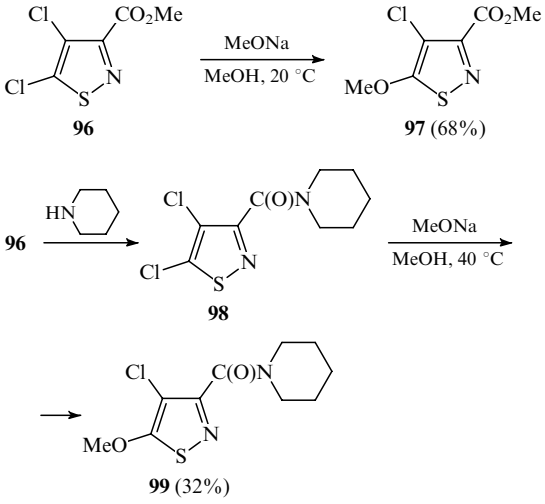


91a 93 (42%)

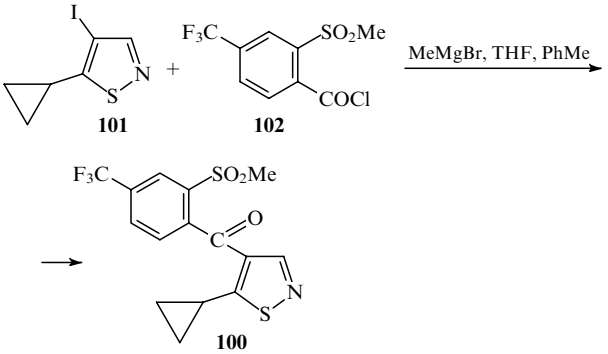
4,5-Dichloro-3-trichloromethylisothiazole (**18**) reacts smoothly with various nucleophilic reagents resulting in the substitution of the chlorine atom in position 5 of the isothiazole ring. Thus its reactions with sodium methoxide, ethoxide and isopropoxide afford the corresponding 5-alkoxy-4-chloro-3-trichloromethylisothiazoles (**94a–c**) in 73%–78% yields. The reaction of isothiazole **18** with piperidine results in 4-chloro-5-piperidino-3-trichloromethylisothiazole (**95**).[56]



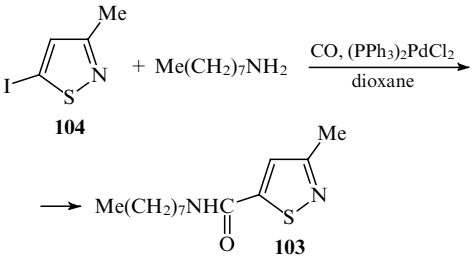
The reaction of methyl 4,5-dichloroisothiazole-3-carboxylate (**96**) with sodium methoxide in methanol at 20 °C proceeds in a similar way and yields methyl 5-methoxy-4-chlorothiazole-3-carboxylate (**97**).[84] At a higher temperature, the saponification of the ester **96** occurs. The reaction of sodium methoxide with 4,5-dichloroisothiazole-3-carboxylic acid piperidide (**98**) prepared by treatment of the ester **96** with piperidine yields compound **99**, the substitution product of the methoxy group for the chlorine atom in position 5.[84]



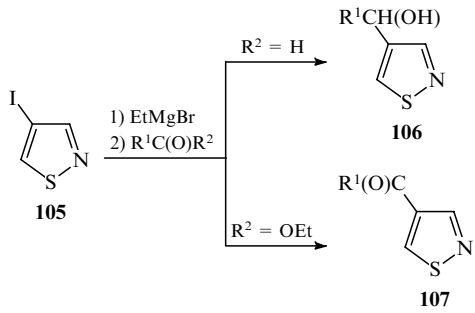
A vast variety of 4-aroyl- and 4-hetaroylisothiazoles were prepared from substituted 4-iodoisothiazoles.[85–88] This is exemplified in the synthesis of 5-cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl)isothiazole (**100**) from 5-cyclopropyl-4-iodoisothiazole (**101**) by treatment with methylmagnesium bromide and 2-methylsulfonyl-4-trifluoromethylbenzoyl chloride (**102**).



N-Alkylisothiazolecarboxamides are synthesised from iodoisothiazoles by treatment with CO and amines in the presence of palladium catalysts.[89] Thus *N*-octyl-3-methylisothiazole-5-carboxamide (**103**) was prepared by heating a 5-iodo-3-methylisothiazole (**104**)–octylamine–triphenylphosphine mixture in an atmosphere of CO (10 atm) in the presence of $(PPh_3)_2PdCl_2$ (100 °C, 6 h).



A convenient regiospecific method for the synthesis of isothiazole derivatives of the type **106** and **107** based on the reactions of thiazol-4-ylmagnesium bromide (prepared from 4-iodoisothiazole (**105**) and ethylmagnesium bromide) with carbonyl compounds has been developed.[90]



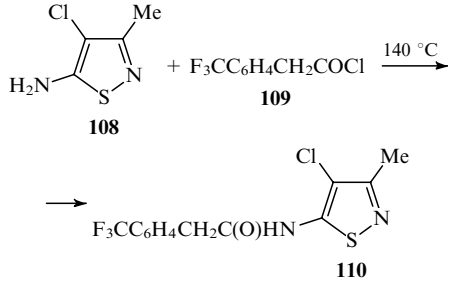
R^1 = Ph, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, Ph; R^2 = H, OEt.

For the first time, isothiazolyl gold(I) complexes were prepared by the reaction of isothiazol-5-yllithium with gold(I) chloride or tetrahydrothiophene(pentafluorophenyl)gold; their protonation or alkylation gave the corresponding isothiazolinylidene complexes.[91]

b. Modification of amino, hydroxy, carboxy and other groups and functionalisation of the side chain in isothiazole derivatives

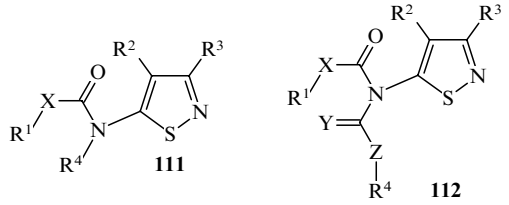
In-depth studies into biological properties of functionalised isothiazoles carried out in the past decade were aimed at the development of methods for the synthesis of such compounds based on the known amino- and hydroxyisothiazoles, isothiazolecarboxylic acids and their chlorides, *etc*., and by functionalisation of the side chain.[46]

Heating of a 5-amino-4-chloro-3-methylisothiazole (**108**)–(4-trifluoromethylphenyl)acetyl chloride (**109**) mixture in xylene gave *N*-isothiazol-5-ylamide **110**.[92]



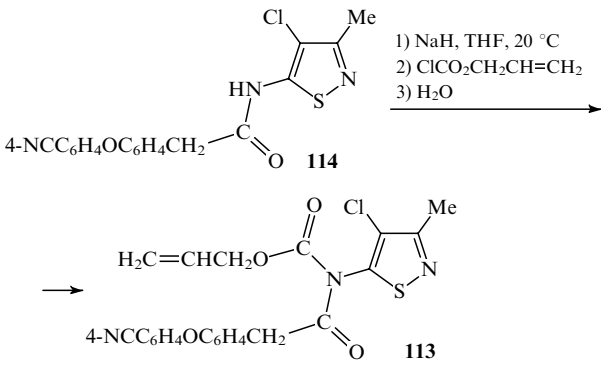
A vast variety of novel useful *N*-isothiazol-5-ylamides have been prepared starting from structurally more complex acid chlorides and aminoisothiazoles containing various substituents in positions 3 and 4.[92,93]

The methods for the synthesis of acylated 5-aminoisothiazoles of the type **111** and **112** have been developed.[94–96]

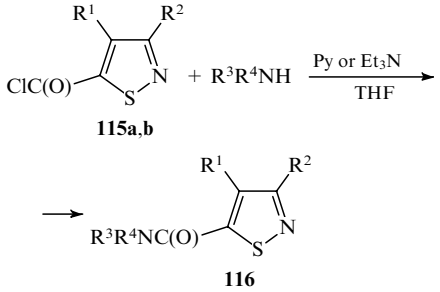


R^1, R^2, R^3, R^4 = H, CN, NO_2, CHO, alkyl, halogenoalkyl, alkoxyalkyl, alkoxy, alkylthio;
X = alkylene, alkyleneoxy; Y, Z = O, S.

For example, acylated 5-aminoisothiazole **113** was prepared from 4-chloro-5-[4-(4-cyanophenoxy)phenyl]acetylamino-3-methylisothiazole (**114**) by treatment with NaH in tetrahydrofuran and then with a twofold excess of allyloxycarbonyl chloride.[95]



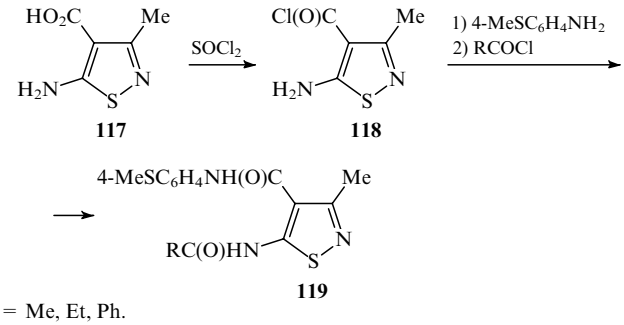
Carboxylic acids and acid chlorides of the isothiazole series are convenient starting compounds in the synthesis of isothiazolecarboxamides. Thus a series of biologically active amides **116** have been synthesised from 3-methylisothiazole-5-carbonyl chloride (**115a**) and 3,4-dichloroisothiazole-5-carbonyl chloride (**115b**) and various amines in the presence of triethylamine or pyridine.[97–101]



R^1 = H, R^2 = Me (**115a**); R^1 = R^2 = Cl (**115b**);
R^3 = Ph, $C_6H_5SO_2$, 4-ClC_6H_4, 1,2,4-triazolyl, pyrazolyl, piperazinyl;
R^4 = H, Et.

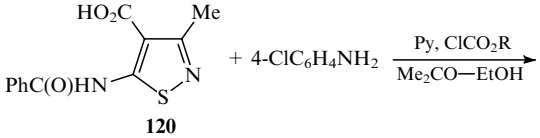
Amides **116** (R^3 = Het, R^4 = H) can be prepared by the reaction of 3,4-dichloroisothiazole-5-carboxamide with derivatives of the corresponding heterocylic compounds.[101]

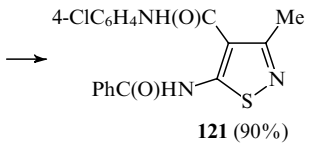
5-Amino-3-methylisothiazole-4-carboxylic acid (**117**) is the starting compound in the synthesis of structurally more complex amides. Thus the reaction of the chloride **118** with 4-methylthioaniline and subsequent acylation with acid chlorides yields 5-acylaminoisothiazole-4-carboxamides **119**.[102]



R = Me, Et, Ph.

The reaction of 5-benzoylamino-3-methylisothiazole-4-carboxylic acid (**120**) with *p*-chloroaniline in the presence of pyridine as the catalyst and alkoxycarbonyl chloride as the activating reagent gave 5-benzoylamino-3-methylisothiazole-4-carboxylic acid (**121**) *p*-chloroanilide.[103]

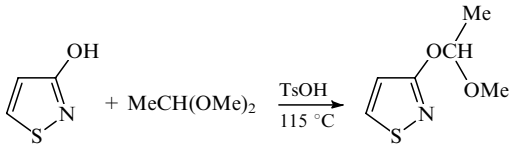




121 (90%)

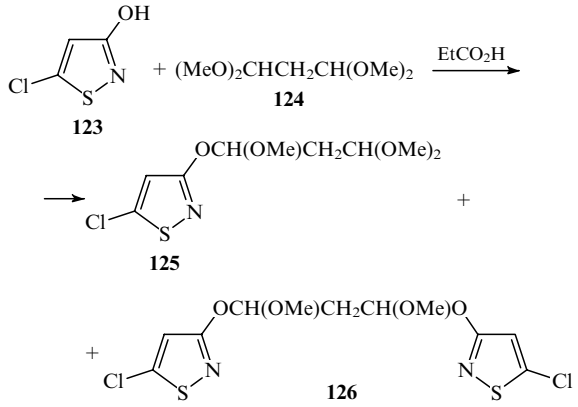
R = Me, Et, Pr^n.

3-Hydroxyisothiazole and its 4-halogeno derivatives react with acetals in the presence of toluene-*p*-sulfonic acid to give mixed acetals. For example, the reaction of isothiazole **77** with acetaldehyde dimethyl acetal results in 3-(1-methoxyethyloxy)isothiazole (**122**).[104]



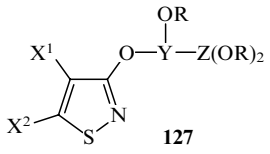
77 **122** (23%)

The reaction of 5-chloro-3-hydroxyisothiazole (**123**) with malonic dialdehyde bis(dimethylacetal) (**124**) in propionic acid yields a mixture of 5-chloro-3-(1,3,3-trimethoxypropyl)oxyisothiazole (**125**) and 1,3-bis(5-chloroisothiazol-3-yloxy)-1,3-dimethoxypropane (**126**).[105]



123 **124** **125** **126**

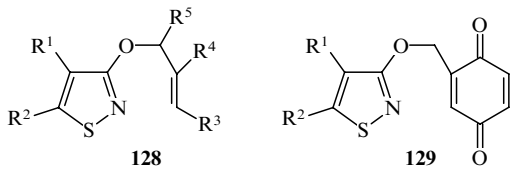
A great number of isothiazole derivatives of the general formula **127** have been prepared using a similar approach.



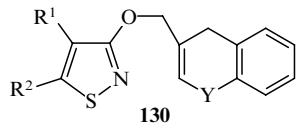
127

R = Alk(C_1-C_{18}); X^1 = H, Br, Cl, Me; X^2 = H, Br, Cl;
Y–Z = $HC(CH_2)_nCH$.

4,5-Disubstituted 3-hydroxyisothiazoles react with various allylic bromides to give alkenyl ethers of 3-hydroxyisothiazoles **128**–**130**.[106]



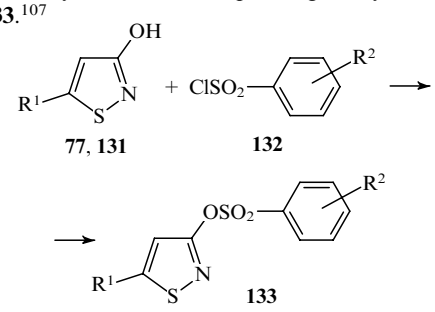
128 **129**



130

R^1, R^2 = H, Cl, alkyl(C_1-C_4); R^3 = H, alkyl, alkenyl, alkynyl, Ph, *etc.*;
R^4, various electron-withdrawing groups;
R^5 = H, alkyl; Y = O, S, SO_2.

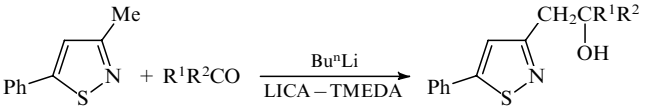
The condensation of isothiazole **77** and its 5-methylthio derivative **131** with arenesulfonyl chlorides **132** in the presence of a base yields the corresponding 3-arylsulfonyloxyisothiazoles **133**.[107]



77, **131** **132** **133**

R^1 = H (**77**), SMe (**131**); R^2 = H, 4-Me, 2-NO_2, 4-NO_2, 4-Br, 2-CO_2Et.

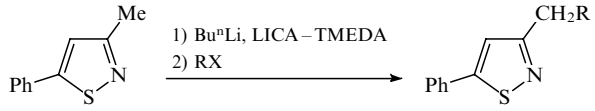
Aldehydes and ketones can be used for the functionalisation of isothiazoles. The reaction of the lithium derivative prepared by the metallation of 3-methyl-5-phenylisothiazole (**134**) with n-butyllithium in the presence of a lithium isopropylcyclohexylamide–*N*,*N*,*N*′,*N*′-tetramethylenediamine system (LICA–TMEDA) with carbonyl compounds leads to hydroxy derivatives **135**.[108]



134 **135**

R^1 = H, R^2 = Et, CH=CH_2, Ph, CH=CHPh;
R^1-R^2 = $(CH_2)_n$, *n* = 4, 5; R^1 = Ph; R^2 = Me, CH=CH_2, Ph, CH=CHPh.

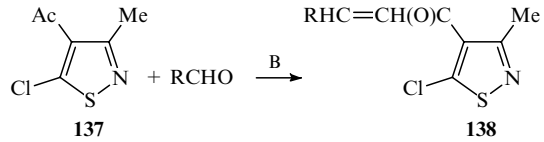
The alkylation of a lithium derivative of isothiazole **134** with alkyl iodides or bromides gives compounds **136a**–**c** in up to 83% yields.[109]



134 **136a**–**c**

R = Me, X = I (**a**); R = Bn, X = Br (**b**); R = Bu, X = Br (**c**).

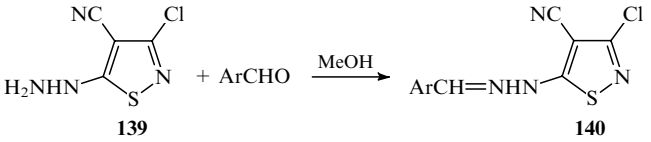
The condensation of 4-acetyl-5-chloro-3-methylisothiazole (**137**) with some aromatic and heterocyclic aldehydes involves the methyl group of the acetyl group rather than the methyl group in position 3 of the isothiazole ring to give α,β-unsaturated carbonyl compounds **138**.[110]



137 **138**

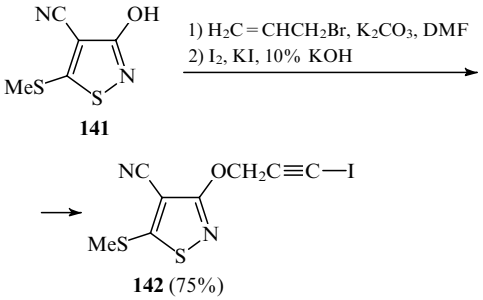
R = 2-ClC_6H_4, 4-ClC_6H_4, 4-$Me_2NC_6H_4$, 2-furyl.

(3-Chloro-4-cyanoisothiazol-5-yl)hydrazine (**139**) reacts with aromatic aldehydes to give the corresponding (3-chloro-4-cyanoisothiazol-5-yl)hydrazones **140**.[111]

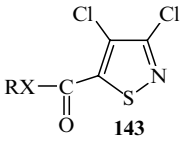


Ar = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3-$O_2NC_6H_4$, 2,4-$(O_2N)_2C_6H_3$, 4-HOC_6H_4, 2-HOC_6H_4, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$.

Treatment of 4-cyano-3-hydroxy-5-methylthioisothiazole (**141**) with allyl bromide in the presence of potassium carbonate in DMF and subsequent treatment with iodine, potassium iodide and KOH yield the iodopropargyloxy derivative **142**.[112] Other cyanoisothiazole derivatives containing various alkyl, alkenyl and alkynyloxy(thio) groups in positions 3 and 5 were synthesised using a similar approach.[112]



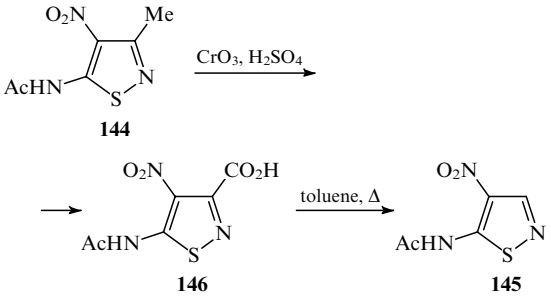
3,4-Dichloroisothiazole-5-carboxylic acid derivatives **143** (X = O, S; R is substituted alkyl, aryl and heterocyclic residues containing halogen, CN, NO_2, carbonyl, halogenalkylthio and other groups) have been synthesised recently from the acid chloride **115b**.[113]



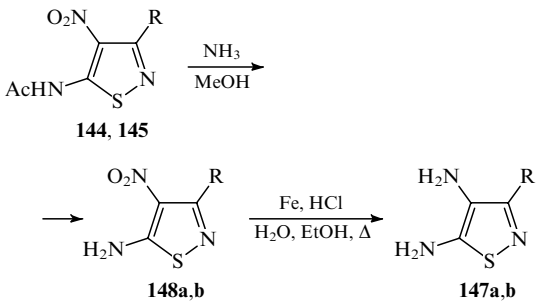
4. Miscellaneous reactions for the synthesis of isothiazole

The preparation of 3-substituted 4,5-diaminoisothiazoles used in the synthesis of novel heterocyclic systems (see Section III) is based on the conversions of 5-acetylamino-3-methyl-4-nitroisothiazole (**144**) which is readily obtainable from the commercially available 5-amino-3-methylisothiazole hydrochloride.[114]

Isothiazole **145** non-substituted in position 3 is formed upon oxidation of isothiazole **144** to carboxylic acid **146** and subsequent decarboxylation.

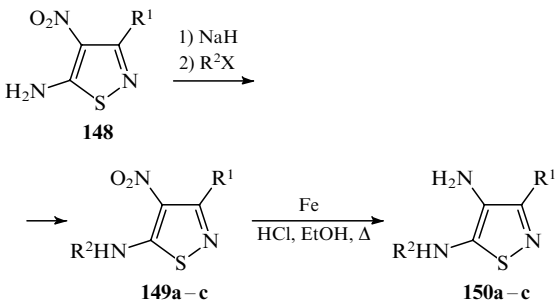


4,5-Diaminoisothiazoles **147a**,**b** are obtained from compounds **144** and **145** by deacetylation and reduction of the nitro group in the derivatives **148a**,**b**.[114]



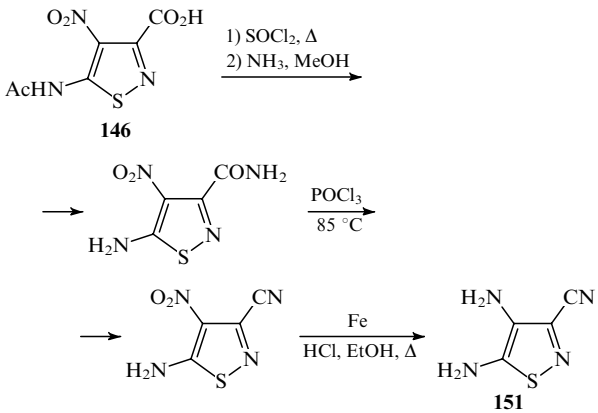
R = Me (**a**), H (**b**).

5-(*N*-Alkylamino)-4-nitroisothiazoles **149a**–**c** were synthesised in high yields by the alkylation of sodium salts of 5-amino-4-nitroisothiazoles **148**. The reduction of the nitro group in compounds **149a**–**c** gives 5-(*N*-alkylamino)-4-aminoisothiazoles **150a**–**c**.[115]

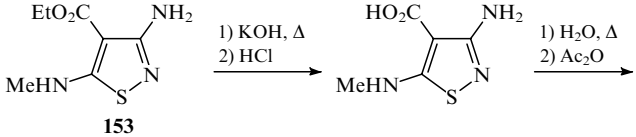


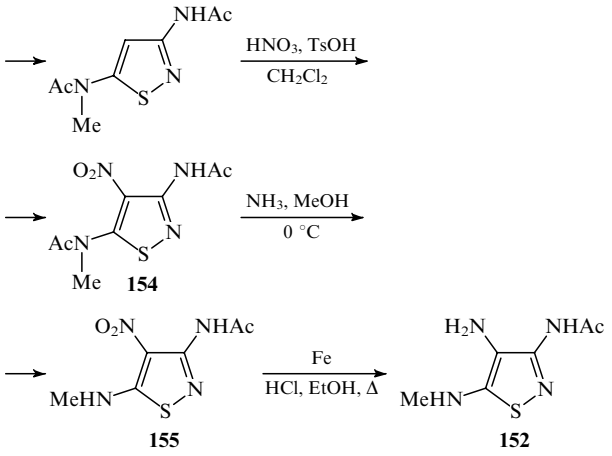
R^1 = R^2 = Me (**a**); R^1 = H, R^2 = Me (**b**); R^1 = Me, R^2 = Bu^n (**c**).

4,5-Diamino-3-cyanoisothiazole (**151**) was obtained from 5-acetylamino-4-nitroisothiazole-3-carboxylic acid (**146**) in four steps which included the conversion of the carboxy group into the nitrile group and the reduction of the nitro derivative to diamine **151**.[115]

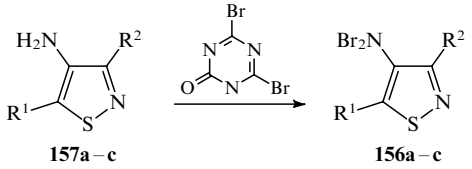


3-Acetamido-4-amino-5-(*N*-methylamino)isothiazole (**152**) is the starting compound in the synthesis of novel annelated heterocycles. This is prepared from ethyl 3-amino-5-(*N*-methylamino)-isothiazole-4-carboxylate (**153**) which is converted into the nitro derivative **154** in several steps. Selective removal of the acetyl protective group from the amino group in position 5 by treatment with methanolic ammonia and subsequent reduction of the 3-acetamido-5-(*N*-methylamino)-4-nitroisothiazole (**155**) formed completes the synthetic scheme.[115,116]





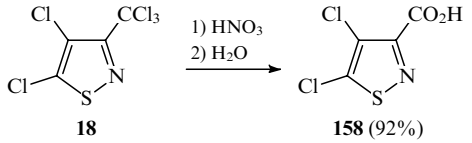
4-Dibromoaminoisothiazoles **156a–c** used in the synthesis of the bisisothiazolopyrazine system are prepared by the reaction of 4-aminoisothiazoles **157a–c** with dibromoisocyanuric acid.[117–119]



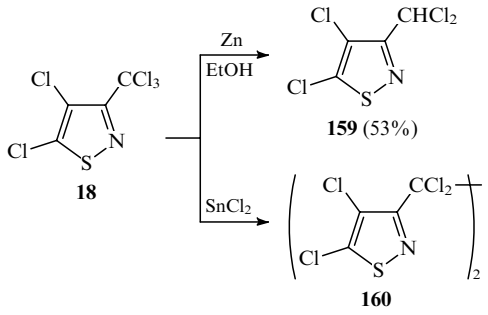
R^1 = Br: R^2 = Me (**a**), Ph (**b**); R^1 = R^2 = Cl (**c**).

A procedure for the synthesis of 3,4-dichloro-5-cyanoisothiazole by the chlorination of the reaction product of carbon disulfide with NaCN in DMF [120] has been improved.[121] 3,4-Dichloro-5-cyanoisothiazole synthesised (yield ~ 88%) was converted into 3,4-dichloroisothiazole-5-carboxylic acid, which is employed in the synthesis of efficient plant growth regulators. Analogously, 3,5-dichloroisothiazole-4-carboxylic acid was prepared from 3,5-dichloro-4-cyanoisothiazole.[122]

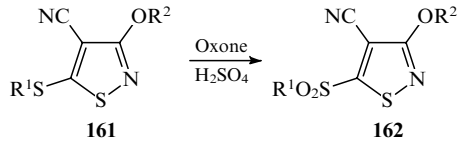
4,5-Dichloroisothiazole-3-carboxylic acid (**158**) was prepared by hydrolysis of the trichloromethyl group of 4,5-dichloro-3-trichloromethylisothiazole (**18**) with fuming nitric acid and subsequent treatment of the reaction mixture with water.[56]



The direction of reduction of the isothiazole **18** depends on the nature of the reducing agent. Boiling with zinc powder in ethanol results in the partial reduction of the trichloromethyl group and the formation of 4,5-dichloro-3-dichloromethylisothiazole (**159**). When tin dichloride is used, isothiazole **18** undergoes dechlorodimerisation resulting in 1,2-bis(4,5-dichloroisothiazol-3-yl)tetrachloroethane (**160**) in high yield.[56]

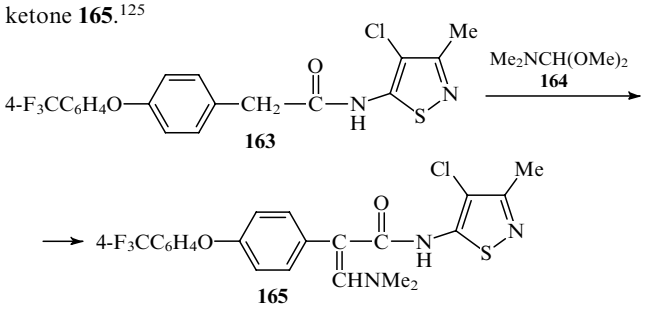


The oxidation of 3-alkoxy-5-alkyl-4-cyanothioisothiazoles **161** under the action of Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) involves selectively the exocylic sulfur atom and affords the corresponding 5-alkylsulfonylisothiazoles **162** in high yields.[123, 124]

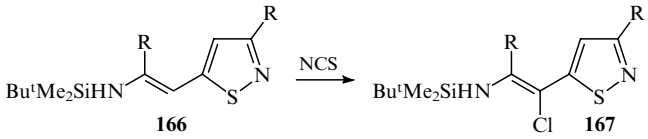


R^1, R^2 = H, C_1-C_{12}-alkyl, C_2-C_7-alkenyl, C_3-C_7-alkynyl, C_3-C_7-cycloalkyl, Ph, PhO.

The oxidation of the methylene group in substituted acetamide **163** by dimethylformamide dimethylacetal (**164**), which can be regarded as a variant of the condensation reaction associated with the elimination of two MeOH molecules, gives enamino ketone **165**.[125]



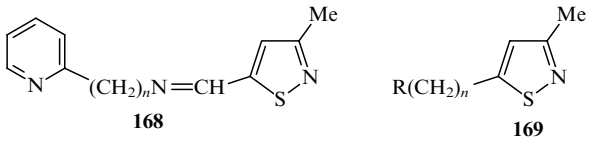
The chlorination of 5-[2-(*N*-*tert*-butyldimethylsilylamino)vinyl]isothiazoles **166** with *N*-chlorosuccinimide (NCS) proceeds selectively at the vinyl group resulting in the *Z*-isomers of isothiazole **167**.[126]



R = 4-ClC_6H_4, Ph.

The monochlorination of related compounds with *N*-chlorosuccinimide also proceeds in a selective manner.

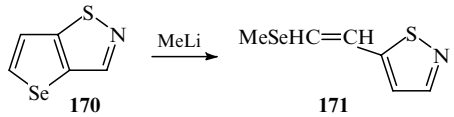
Isothiazoles **168** and **169** react with AgO_3SCF_3 to give dimeric silver(I) complexes the isothiazole fragment in which is linked to the metal centre through the nitrogen atom.[127]



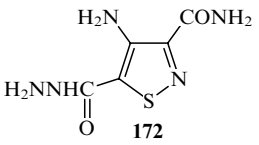
n = 1, 2.

R = $[Et_2N(CH_2)_2]_2N$, *n* = 1;
R = MeS, *n* = 2.

Treatment of selenolo[2,3-*d*]isothiazole (**170**) with methyllithium yields a mixture of compounds including isothiazole **171**.[128]



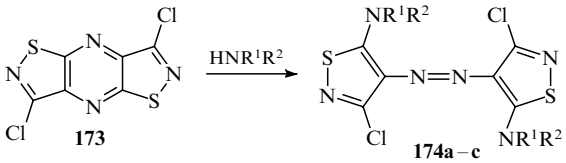
Treatment of 5-substituted 4,5-dihydro-3-ethoxycarbonylisothiazolo[4,3-*d*]pyrimidin-7(6*H*)-ones with hydrazine is accompanied by the opening of the dihydropyrimidinone ring and the formation of 4-amino-3-carbamoyl-5-hydrazinocarbonylisothiazole (**172**).[129]



172

It is of note that the ring opening reactions in bicylic isothiazole derivatives described above present purely theoretical interest.

The reactions of 3,7-dichlorodiisothiazolo[4,5-*b*:4′5′-*e*]pyrazine (**173**) with benzylamine, aniline and morpholine are accompanied by the opening of the pyrazine ring to give *N*,*N*′-bis-(5-amino-3-chloroisothiazol-4-yl)diazenes (**174a–c**). The reaction of compound **173** with benzylamine gives 3,7-bis(benzylamino)bisisothiazolo[4,5-*b*:4′5′-*e*]pyrazine (yield 5%) as a side product.[130]



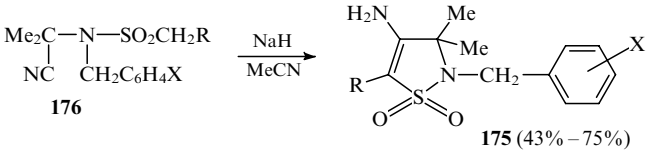
173 **174a–c**

R^1 = H, R^2 = Bn (**a**, 25%); R^1 = H, R^2 = Ph (**b**, 25%);
R^1-R^2 = $(CH_2)_2O(CH_2)_2$ (**c**, 28%).

A mechanistic scheme for the synthesis of compounds **174a–c** has been proposed. Its first step consists in the addition of the amine at the C=N bond of the pyrazine ring. Interestingly, the reaction of compound **173** with MeONa in MeOH results in 5,6-dimethoxy-3-chloroisothiazolo[4,5-*b*]pyrazine, *i.e.*, in the opening of one of the isothiazole rings. The difference in the behaviour of compound **173** in the reaction with the alkoxide anion and amines is explained by the difference in their basicities as well as by the presence of a mobile hydrogen atom in the amines which ensures their addition at the multiple bonds of the pyrazine ring.[130]

5. Synthesis of isothiazole 1,1-dioxides

Methods for the synthesis, reactions and biological properties of isothiazole 1,1-dioxides were reviewed in 1997.[131] Here we consider only the most recent publications. Thus a novel procedure for the synthesis of 4-amino-3,3-dimethyl-2,3-dihydroisothiazole 1,1-dioxide derivatives **175** based on substituted *N*-benzyl-*N*-sulfonylaminonitriles **176** has been developed recently. The cyclisation was performed by treatment with sodium hydride in acetonitrile.[132]



176 **175** (43%–75%)

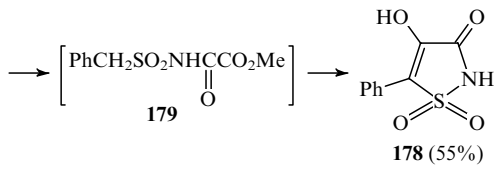
R = H, Me, Ph; X = H, 4-Cl, 3-Cl.

Other 4-amino-2,3-dihydroisothiazole 1,1-dioxide derivatives,[133] particularly compounds containing a cyano group in position 5, were prepared using analogous methods.[134–136]

In the presence of bases, phenylmethanesulfonamide (**177**) reacts with dimethyl oxalate to give 4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (**178**). It is assumed that the linear methyl *N*-(benzylsulfonyl)oxalamidate **179**, which is formed first, undergoes further cyclisation. A complex of dioxide **178** with DMF has been prepared.[137]



177

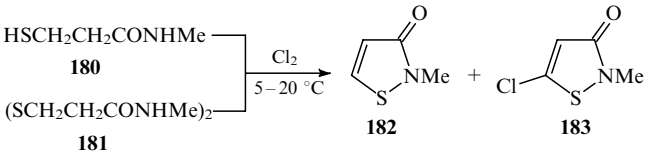


179 **178** (55%)

6. Synthesis of dihydroisothiazolones

Among representatives of this group, dihydroisothiazol-3-ones possessing high biological activities hold the greatest interest. The data on these compounds are summarised in the review.[138]

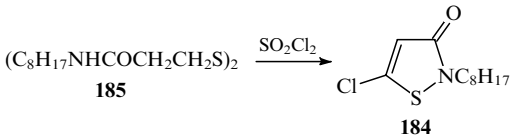
Some novel data on the synthesis of dihydroisothiazolones have been published recently. Thus the chlorination of 2-(*N*-methylcarbamoyl)ethanethiol (**180**) or bis[2-(*N*-methylcarbamoyl)ethyl] disulfide (**181**) gave a mixture of 2,3-dihydro-2-methylisothiazol-3-one (**182**) and 5-chloro-2,3-dihydro-2-methylisothiazol-3-one (**183**).[139]



180 **181** **182** **183**

Isothiazol-3-ones **182** and **183** can also be prepared by treatment of compounds **180** and **181** with thionyl chloride.[140,141]

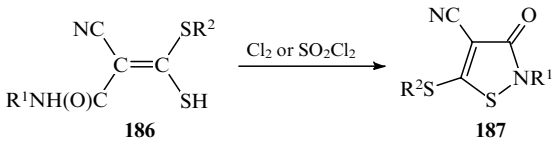
5-Chloro-2,3-dihydro-2-octylisothiazol-3-one (**184**) was synthesised by treatment of disulfide **185** with SO_2Cl_2.[142]



185 **184**

The clathrate of compound **184** containing four molecules of 4,4′-dihydroxydiphenylmethane manifests increased solubility in water.

A procedure for the synthesis of isothiazol-3-one derivatives **187** from 3-alkylthio-2-cyano-3-mercaptoacrylamides **186** has been developed.[143]



186 **187**

R^1, R^2 = H, lower alkyl, alkenyl, alkynyl, aryl, aralkyl, hetarylalkyl.

The synthesis of isothiazol-3-ones devoid of highly toxic and carcinogenic nitrosoamines has been described in a patent.[144]

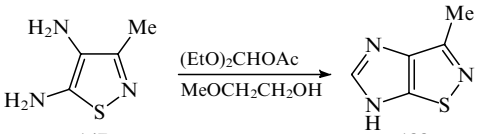
III. Chemical transformations of isothiazoles

Isothiazoles manifest aromatic properties and enter into the same reactions as other heteroaromatic compounds. Ring opening and transformations of the isothiazole ring, which give either functionalised alkenes or other heterocyclic compounds, deserve special attention. Addition reactions of isothiazoles leading to novel bisheterocyclic structures containing an isothiazole fragment are especially attractive. Oxidation reactions of the sulfur atom of the isothiazole ring yield reactive dioxides and present significant interest.[64]

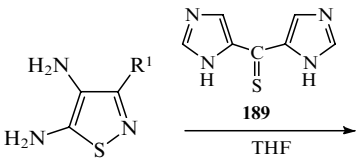
1. Condensation reactions

In recent years, isothiazole derivatives were used as starting compounds for the synthesis of several novel bicyclic compounds. Thus the reaction of 4,5-diamino-3-methylisothiazole (**147a**) with diethoxymethyl acetate affords 3-methylimidazo[4,5-*d*]-isothiazole (**188a**) in low yield. Unsubstituted imidazo[4,5-*d*]iso-

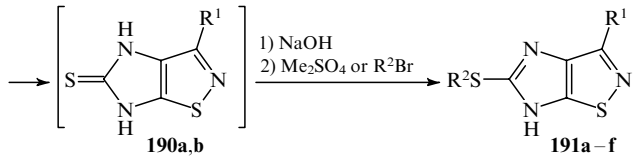
thiazole could not be prepared from compound **147b**.[114] Isothiazoles **147a**,**b** easily undergo cyclisation with thiocarbonyldiimidazole (**189**) to give unstable thiones **190a**,**b** which are methylated *in situ* in alkaline media under the action of Me_2SO_4 to give 5-methylthioimidazo[4,5-*d*]isothiazoles (**191a**,**b**) in good yields. Sodium salts of thiones **190a**,**b** are also alkylated by benzyl and allyl bromides to give the corresponding imidazo[4,5-*d*]isothiazoles **191c**–**f** in preparative yields.[114, 115]



147a **188a**



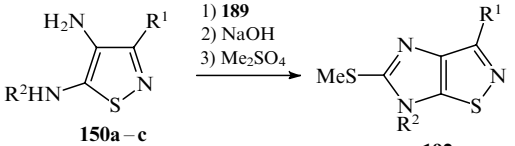
147a,**b**



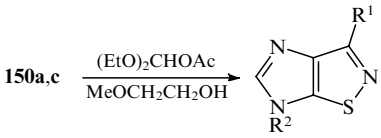
190a,**b** **191a**–**f**

$R^1 = R^2 =$ Me (**191a**); $R^1 =$ H, $R^2 =$ Me (**191b**);
$R^1 =$ Me, $R^2 =$ Bn (**191c**); $R^1 =$ Me, $R^2 =$ All (**191d**);
$R^1 =$ H, $R^2 =$ Bn (**191e**); $R^1 =$ H, $R^2 =$ All (**191f**).

6-Alkyl-5-methylthioimidazo[4,5-*d*]isothiazoles **192a**–**c** were prepared by treatment of 5-(*N*-alkylamino)-4-aminoisothiazoles **150a**–**c** with thiocarbonyldiimidazole (**189**) and subsequent methylation. The reactions of isothiazoles **150a**,**c** with diethoxymethyl acetate result in compounds **193a**,**c**.[115]



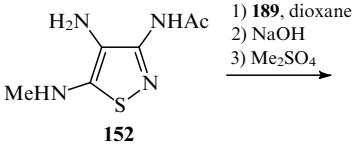
150a–**c** **192a**–**c**



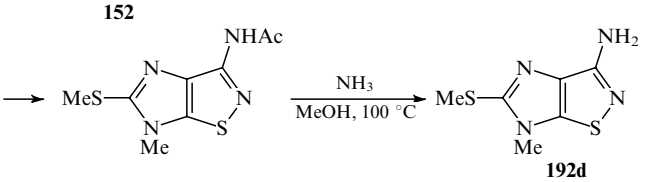
150a,**c** **193a**,**c**

$R^1 = R^2 =$ Me (**a**); $R^1 =$ H, $R^2 =$ Me (**b**); $R^1 =$ Me, $R^2 = Bu^n$ (**c**).

3-Amino-6-methyl-5-methylthioimidazo[4,5-*d*]isothiazole (**192d**) was obtained in good yield by successive treatment of 3-acetamido-4-amino-5-(*N*-methylamino)isothiazole (**152**) with thiocarbonyldiimidazole (**189**) and dimethyl sulfate.[115]



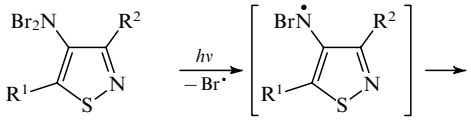
152



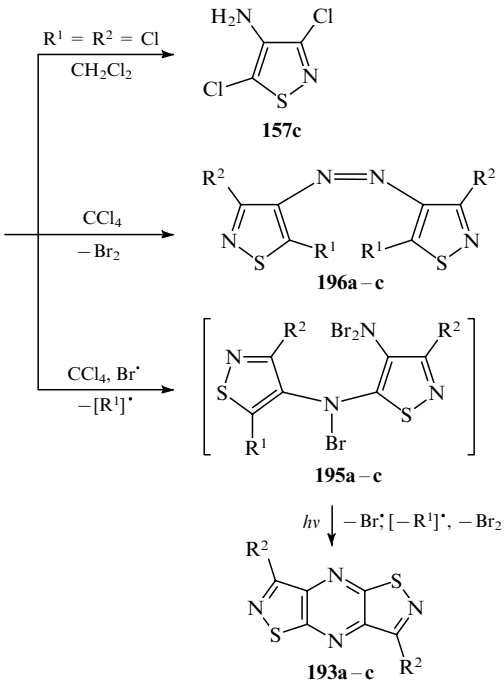
192d

It should be noted, however, that not all 4,5-diamino-3-R-isothiazoles yield annelated products. Thus isothiazole **151** containing a cyano group in position 3 does not react with either diethoxymethyl acetate or thiocarbonyldiimidazole.[115]

Two approaches to the synthesis of 3,7-disubstituted bisisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines **193a**–**c,** the first compounds containing a novel heterocyclic system, have been proposed.[117–119] It was found that the reaction of 3,5-dichloro-4-dibromoaminoisothiazole (**156c**) with a Cu(0)–collidine system affords 3,7-dichlorodiisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**193c**) in 67% yield.[117] Zlotin *et al.*[118] suggested that this reaction has a radical character and studied the effect of UV light on isothiazoles **156a**–**c**. Irradiation of compounds **156a**,**c** with a mercury lamp results in the cleavage of the N–Br bond and the formation of radicals **194a**,**c**; their further transformations depend on the nature of the solvent used. Thus in dichloromethane, isothiazole **156c** is converted into 4-amino-3,5-dichloroisothiazole virtually completely (**157c**). In CCl_4, 3,7-disubstituted diisothiazolo[4,5-*b*:4′,5′-*e*]pyrazines **193a**,**c** (yields 58% and 76%, respectively) are the main reaction products of compounds **156a**,**c**; their formation seems to proceed *via* the intermediate compounds **195a**,**c**. *N*,*N*′-Di(isothiazol-4-yl)diazenes **196a**,**c** (yields 37% and 13%, respectively) were identified as the side products.[118]



156a–**c** **194a**–**c**

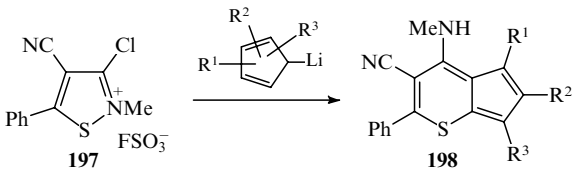


157c **196a**–**c** **195a**–**c** **193a**–**c**

$R^1 =$ Br, $R^2 =$ Me (**a**), Ph (**b**); $R^1 = R^2 =$ Cl (**c**).

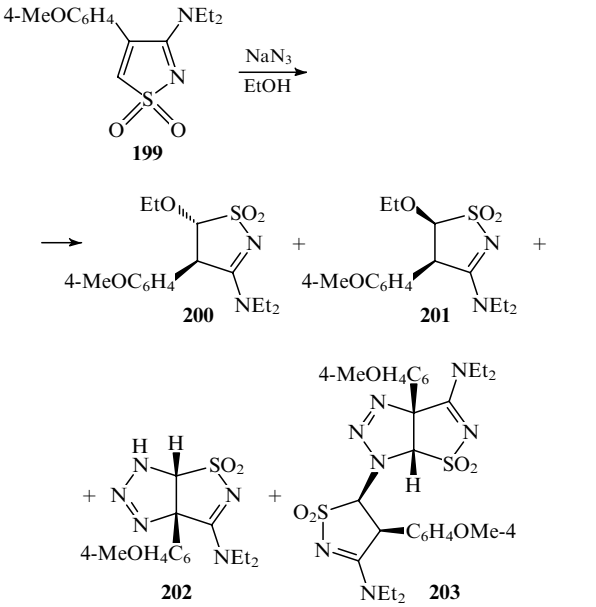
5-Bromo-4-dibromoamino-3-phenylisothiazole (**156b**) manifests a similar behaviour upon irradiation with UV light; 3,7-diphenyldiisothiazolo[4,5-*b*:4′,5′-*e*]pyrazine (**193b**) and *N*,*N*′-bis(5-bromo-3-phenylisothiazol-4-yl)diazene (**196b**) are the main reaction products.[119]

The isothiazolium salt **197** is condensed with cyclopentadienyl-, *tert*-butylcyclopentadienyl- and di-*tert*-butylcyclopentadienyllithium to give thialenes **198**.[145]

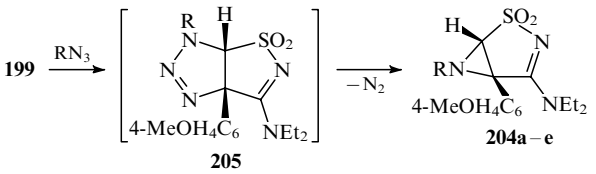


$R^1 = R^2 = R^3 = H$; $R^1 = Bu^t$, $R^2 = R^3 = H$;
$R^1 = R^3 = H$, $R^2 = Bu^t$; $R^1 = R^3 = Bu^t$, $R^2 = H$.

Reactivities of certain isothiazole 1,1-dioxide derivatives have been studied.[146] It was found that 3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide (**199**) reacts with sodium azide in ethanol to give a mixture of dihydroisothiazole oxides **200** and **201** and isothiazolotriazoles **202** and **203** in a ratio 72 : 12 : 9 : 7.[146]



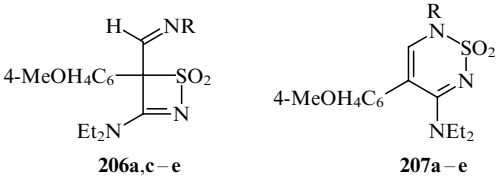
Cycloaddition of the dioxide **199** to arylalkyl and aryl azides results in *N*-arylalkyl- or *N*-arylthiadiazabicyclo[3.1.0]hexene **204**. The unstable cycloadducts **205**, which are formed first (in some cases, they were isolated from the reaction mixture), easily eliminate the nitrogen molecule.

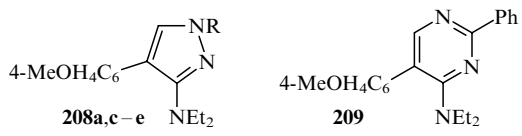


R = Ph (**a**), Bn (**b**), $PhCH_2CH_2$ (**c**), $4\text{-}MeOC_6H_4$ (**d**), $4\text{-}O_2NC_6H_4$ (**e**).

Thermal rearrangement of *N*-aryl- and *N*-phenyl-substituted bicyclic compounds **204a**,**c**–**e** affords 1,2-thiazete 1,1-dioxides **206a**,**c**–**e**, 1,2,6-thiadiazine 1,1-dioxides **207a**,**c**–**e** and pyrazole derivatives **208a**,**c**–**e**. Under optimum conditions, compound **207a** was isolated in 51% yield.

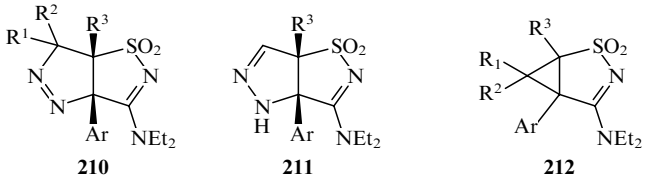
If the aziridine nitrogen atom has a benzyl substituent (compound **204b**), the reaction follows a different route to afford the thiadiazine derivative **207b** and pyrimidine **209**.[147]





R = Ph (**a**), Bn (**b**), $PhCH_2CH_2$ (**c**), $4\text{-}MeOC_6H_4$ (**d**), $4\text{-}O_2NC_6H_4$ (**e**).

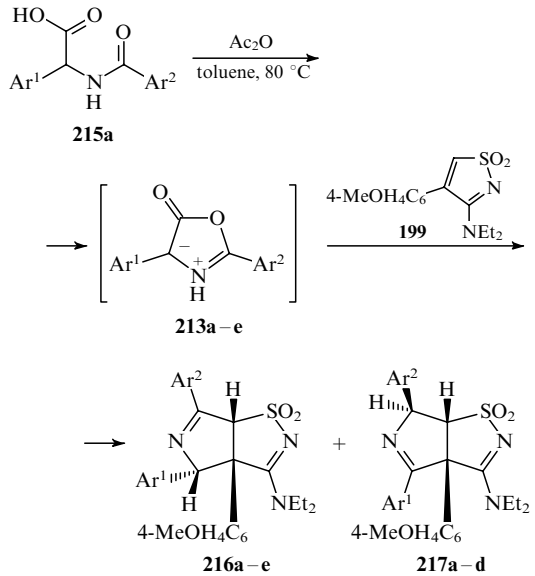
4-Aryl-3-diethylamino-5-R-isothiazole 1,1-dioxides enter into cycloaddition reactions with diazoalkanes to give bicyclic compounds **210** with high regio- and stereoselectivity. The reaction with diazomethane yields a mixture of tautomeric pyrazolines **210** ($R^1 = R^2 = H$) and **211**. Thermolysis of compounds **210** and **211** follows two routes. The loss of the nitrogen molecule leads to 2-thia-3-azabicyclo[3.1.0]hex-3-ene 2,2-dioxides **212**. Elimination of SO_2 and diethylcyanamide from the cycloaddition products results in the corresponding pyrazoles.[148]



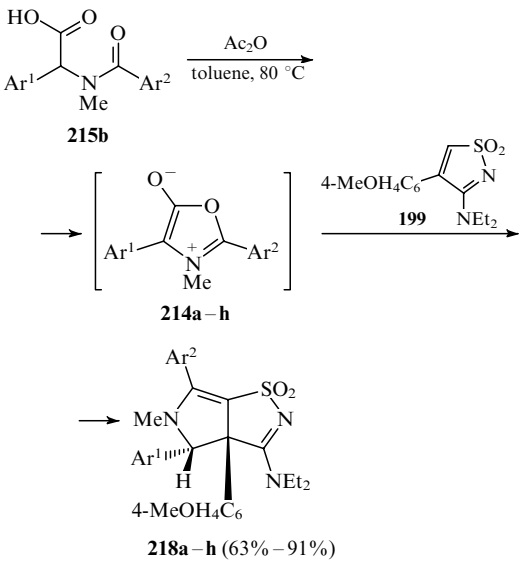
$R^1 = R^2 = H$, Me; $R^1 = H$, $R^2 = CO_2Et$; $R^3 = H$, Me, Ph;
Ar = Ph, $4\text{-}MeC_6H_4$, $4\text{-}MeOC_6H_4$.

The readily available dioxide **199** enters into cyclocondensation reactions with oxazolones **213a**–**e** and munchnones **214a**–**h**, which are prepared by cyclisation of (*N*-aroylamino)arylacetic acids **215a**,**b**.[149]

The reactions with compounds **215a** afford 4,6-diaryl-3-diethylamino-3*a*,4-dihydro-3*a*-(4-methoxyphenyl)-6*aH*-pyrrolo[3,4-*d*]-isothiazole 1,1-dioxides (**216a**–**e**) (yields 60%–74%) and their isomers **217a**–**d** (yields 5%–13%). 4,6-Diaryl-3-diethylamino-3*a*-(4-methoxyphenyl)-5-methyl-3*a*-4-dihydropyrrolo[3,4-*d*]isothiazole 1,1-dioxides **218a**–**h** are the main products in the reaction with munchnones **214a**–**h**.[149]

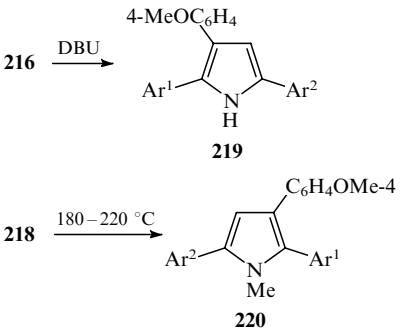


Compounds **216**, **217**	Ar^1	Ar^2
a	Ph	Ph
b	$4\text{-}ClC_6H_4$	Ph
c	Ph	$4\text{-}ClC_6H_4$
d	$4\text{-}MeC_6H_4$	Ph
e	Ph	$4\text{-}MeC_6H_4$



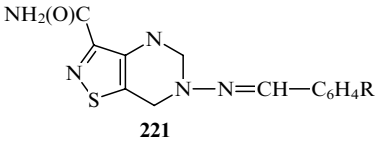
Compound 218	Ar^1	Ar^2	Compound 218	Ar^1	Ar^2
a	Ph	Ph	**e**	4-$MeOC_6H_4$	Ph
b	Ph	4-MeC_6H_4	**f**	Ph	4-FC_6H_4
c	4-MeC_6H_4	Ph	**g**	Ph	4-BrC_6H_4
d	Ph	4-$MeOC_6H_4$	**h**	Ph	4-$NO_2C_6H_4$

The cycloadducts **216** and **218** are decomposed at elevated temperatures or in alkaline media with the elimination of SO_2 and diethylcyanamide to give 2,3,5-triarylpyrroles **219** and 1-methyl-2,3,5-triarylpyrroles **220,** respectively.[149]



DBU, diazabicycloundecene.

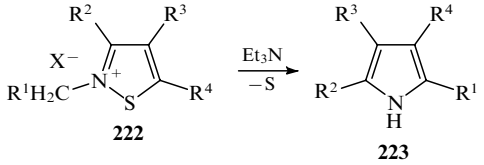
4-Amino-3-carbamoyl-5-(ethoxycarbonyl)isothiazole is used in the synthesis of the isothiazolo[4,5-*d*]pyrimidine derivatives **221**.[150]



R = 2-OMe, 2-Cl, 3-Br, 3-NO_2.

2. Ring transformation reactions

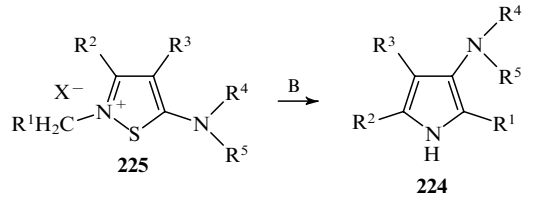
In recent years, some readily available isothiazolium salts have been used in the synthesis of other heterocyclic compounds, pyrrole derivatives, in particular. Thus the reactions of *N*-alkoxycarbonylmethyl- and *N*-cyanomethylisothiazolium **222** salts with triethylamine result in the elimination of sulfur and recyclisation resulting in pyrrole-2-carboxylic acid derivatives **223**.[151]



R^1 = CO_2Me, CO_2Et, CN; R^2 = H, Me, Ph;
R^3 = H, Ph, 2-MeC_6H_4, 4-FC_6H_4, CO_2Et;

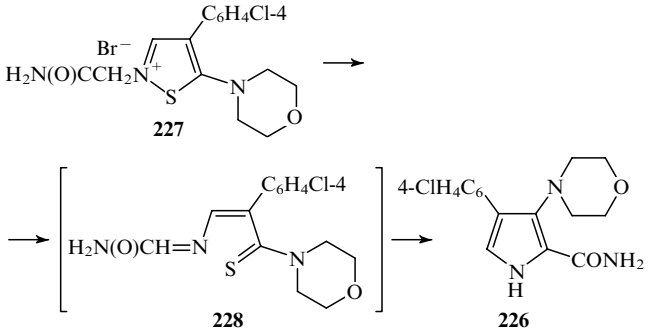
R^4 = Ph, , NHPh, SMe, 4-ClC_6H_4, ; X = Cl, Br.

Aminopyrroles **224** were obtained from isothiazolium salts **225** in a similar way (yields 70%–90%).[152]

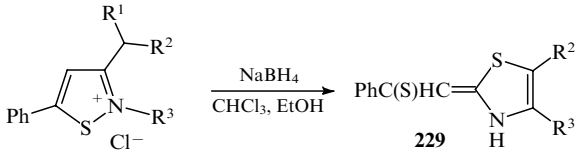


R^1 = H, alkenyl, aryl, NO_2; R^2, R^3 = H, substituted or unsubstituted alkyl, Ar, HetAr; R^4, R^5 = H, heterosubstituted aryl or alkyl;
X = Hal, ClO_4^-, BF_4^-, HSO_4^-, SO_4^{2-}, OH^-, $CF_3SO_3^-$.

The mechanism of formation of 3-aminopyrrole derivatives in the desulfurisation of isothiazolium salts has been studied.[153] It was found that pyrrole **226** is formed from the salt **227** by a cascade of reactions *via* thioamide **228**.[153]

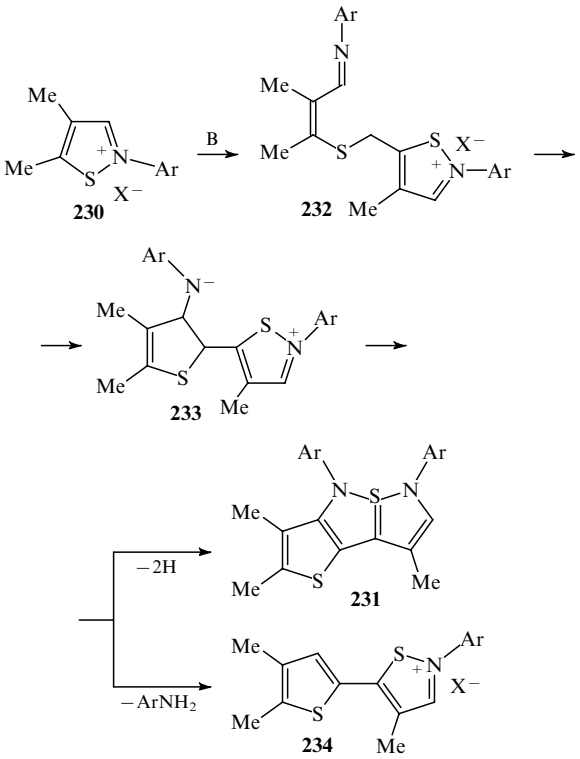


A convenient procedure for the synthesis of 2-phenylthiocarbonylmethylidenedihydrothiazole derivatives **229** from isothiazolium chlorides has been developed.[154]



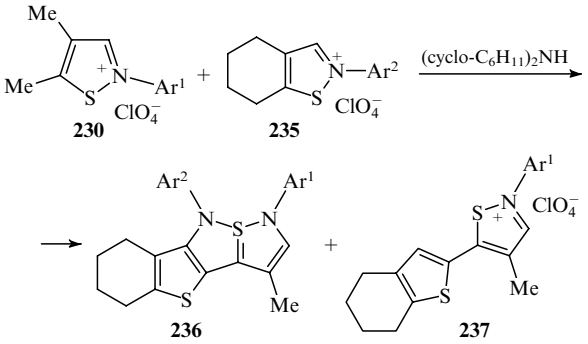
R^1 = Ac, EtCO; R^2 = CO_2Et, CO_2Me; R^3 = Me, Et.

N-Arylisothiazolium salts **230** containing an activated methyl group in position 5 dimerise into thiadiazapentalenes **231** upon treatment with a base. The sulfur atom of one molecule of the salt is attacked by an activated methyl group of another molecule to give the intermediates **232**. Subsequent oxidative closure of the ring *via* zwitterionic intermediates **233** results in thienothiadiazapentalenes **231**. A competing reaction gives 5-(2-thienyl)isothiazolium salts **234** with elimination of aniline.[155]



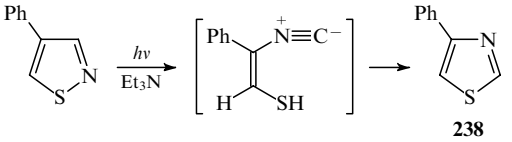
Ar = Ph, 4-MeC$_6$H$_4$; X = Cl$^-$, ClO$_4^-$; B = (cyclo-C$_6$H$_{11}$)$_2$NH.

The reaction between the salts **230** and **235** catalysed by dicyclohexylamine in methanol or DMSO yields 'mixed' thiadiazapentalenes **236** upon oxidative cyclisation and salts **237** upon elimination of aniline.[156, 157]



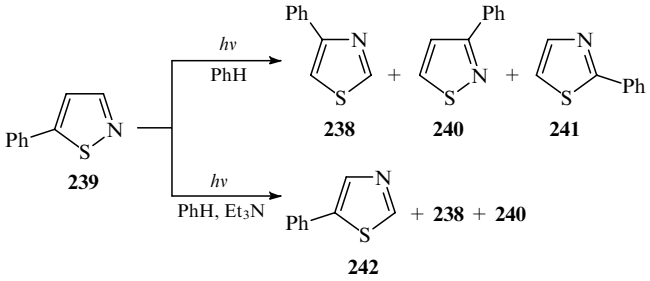
Ar^1 = Ph, 4-MeC$_6$H$_4$; Ar^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$.

Photochemical reactions of several isothiazoles have been studied. Irradiation of 4-phenylisothiazole in benzene yielded small amounts of 4-phenylthiazole (**238**). When the photolysis was carried out in the presence of triethylamine, this rearrangement becomes predominant.[158]



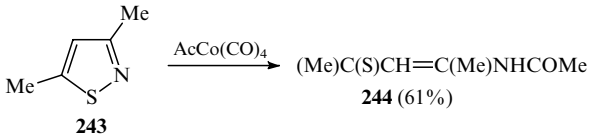
The effect of triethylamine and the solvent polarity on the photochemical reaction of 5-phenylisothiazole (**239**) has been studied.[159] It was found that irradiation in the absence of triethylamine gives 4-phenylthiazole (**238**) as the main product (yield 15%). Other reaction products are represented by 3-phenylisothiazole (**240**) and 2-phenylthiazole (**241**). In the presence of Et$_3$N, 5-phenylthiazole (**242**) is the main product (yield 14%).

Irradiation of 5-phenylisothiazole (**239**) in polar solvents makes this rearrangement more regioselective. The photolysis in methanol in the presence of Et$_3$N gives exclusively compounds **238** and **242** (yields 9% and 34%, respectively). In a more polar solvent (*e.g.*, 2,2,2-trifluoroethanol), only thiazole **241** was identified in the reaction mixture; in the presence and in the absence of Et$_3$N, its yield was 42% and 32%, respectively.[159]



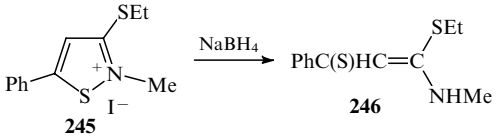
3. Ring opening reactions

Under conditions of phase-transfer catalysis [PhH, H$_2$O, tris(2,6-dioxaheptyl)amine], the reaction of 3,5-dimethylisothiazole (**243**) with acetylcobalttetracarbonyl generated *in situ* from Co$_2$(CO)$_8$, CO and MeI is accompanied by ring opening and *N*-acylation, resulting in thione (**244**) (the ratio of the *E*- and *Z*-isomers is equal to 1 : 10).[160]

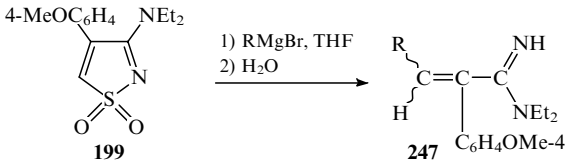


Other *N*-acylated unsaturated thiones are synthesised from isothiazoles in a similar way.

A convenient procedure has been developed for the synthesis of phenylthiocarbonylketene *S*,*N*-acetals (**246**) based on the reaction of 2-alkyl-3-alkylthio-5-phenylisothiazolium salts (*e.g.*, the salts **245**) with sodium borohydride.[161]

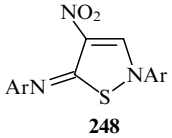


The reaction of 3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide (**199**) with organomagnesium compounds in THF occurs *via* ring opening leading to a mixture of *E*- and *Z*-isomers of 3-substituted 2-arylpropeneamidines **247**.[162]



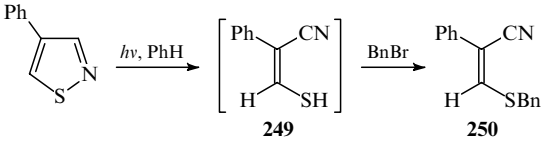
R = Me, Et, Ph, HC≡C, MeC≡C, PhC≡C.

The chemistry of the 4-nitroisothiazole-5(2*H*)-imine derivatives **248**, particularly, their isomerisation and desulfurisation, has been discussed in the papers [163, 164] and a recent review.[165]



It has already been noted (Section III.2) that the photolysis of 4-phenylisothiazole in benzene gives small amounts of 4-phenylthiazole (**238**) as a result of a rearrangement; cyanothiol **249**,

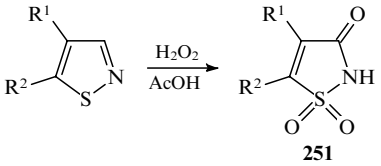
which was trapped as benzyl sulfide **250,** is the main photolysis product in the absence of a base.[158]



249 **250**

4. Miscellaneous reactions of isothiazole derivatives

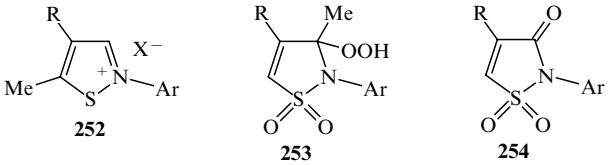
The oxidation of 4,5-disubstituted isothiazoles with hydrogen peroxide results in the corresponding isothiazol-3(2*H*)-one 1,1-dioxides **251**.[166]



251

R^1 = Me, Ph, H; R^2 = Me, Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$.

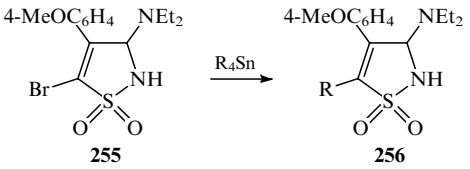
Dioxides **253**, **254** are the oxidation products of the isothiazolium salts **252**.[167]



252 **253** **254**

R = Alk, Ph.

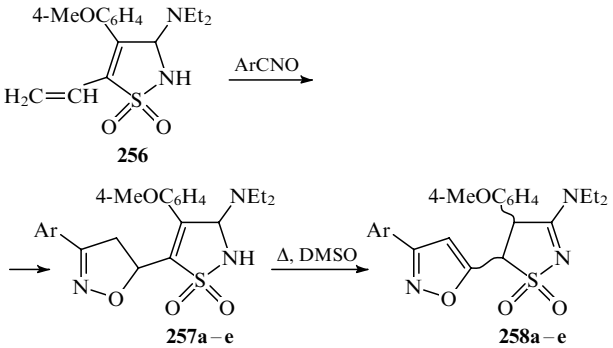
5-Bromo-3-diethylamino-4-(4-methoxyphenyl)-2,3-dihydroisothiazole 1,1-dioxide (**255**) reacts smoothly with various organotin compounds in the presence of palladium catalysts to yield the corresponding 5-substituted derivatives **256**.[168]



255 **256**

R = CH_2=CH, Ph, HetAr, Ar.

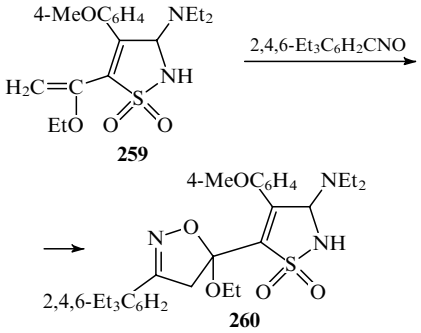
The reaction of the vinyl derivative **256** with nitrile oxides yields the cycloadducts **257a**–**e**, which are rearranged into 4,5-dihydro-5-(isoxazol-5-yl)isothiazole 1,1-dioxides **258a**–**e** (an equimolar mixture of *cis*- and *trans*-isomers) upon heating in DMSO.[169]



256 **257a**–**e** **258a**–**e**

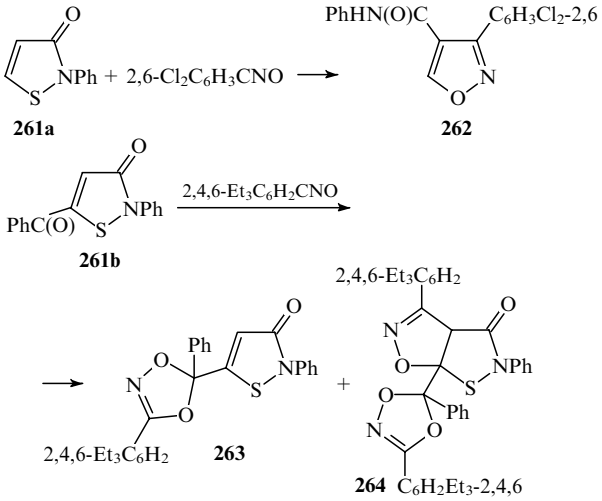
Ar = 3,5-Cl_2-2,4,6-Et_3C_6 (**a**), 2,6-$Cl_2C_6H_3$ (**b**), 4-ClC_6H_4 (**c**), 2,4,6-$Et_3C_6H_2$ (**d**), 4-$NO_2C_6H_4$ (**e**).

3-Diethylamino-2,3-dihydro-5-(1-ethoxyvinyl)-4-(4-methoxyphenyl)isothiazole 1,1-dioxide (**259**) enters into the cycloaddition reaction with 2,4,6-triethylbenzonitrile oxide to give the dihydroisoxazole derivative **260**.[169]



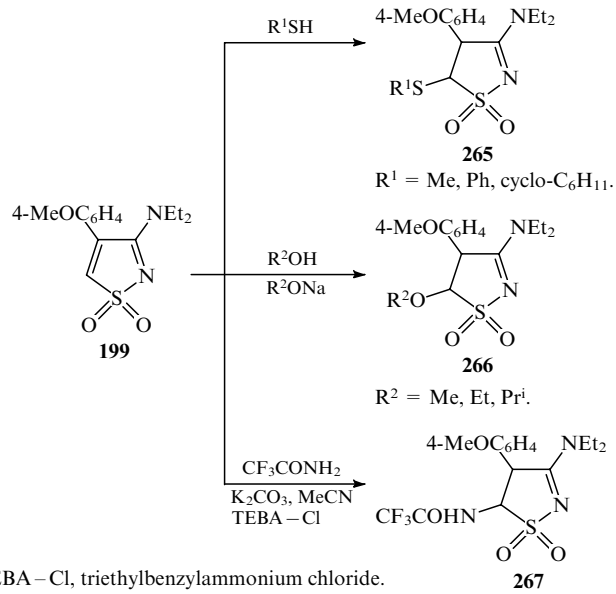
259 **260**

2,6-Dichlorobenzonitrile oxide reacts with isothiazolone (**261a**) at the double bond to give isoxazolecarboxanilide (**262**) as a result of transformation of the primary cycloadducts formed. Contrary to expectations, 2,4,6-triethylbenzonitrile oxide adds to the exocyclic carbonyl group of isothiazolone **261b** to give the monoadduct **263** and the bisadduct **264**.[170]



261a **262** **261b** **263** **264**

An efficient approach based on the Michaelis reaction is used in the synthesis of 5-substituted 3-amino-4-arylisothiazole 1,1-dioxides and their 4,5-dihydro derivatives. The addition of thiols, alcohols and trifluoroacetamide to 3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide (**199**) in the presence of bases



199 **265** **266** **267**

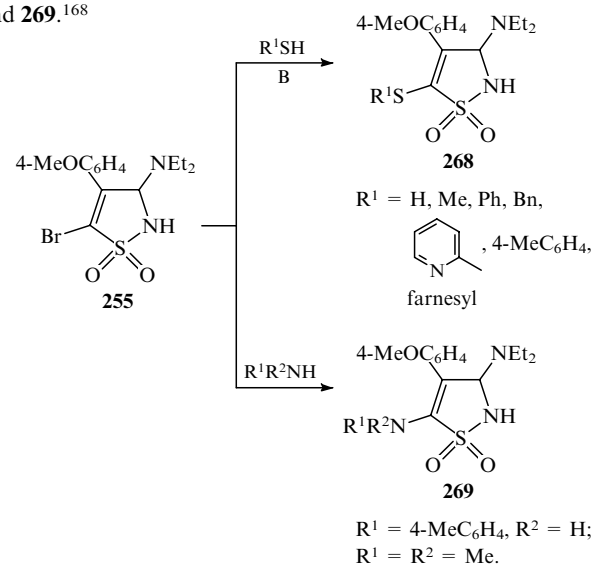
R^1 = Me, Ph, cyclo-C_6H_{11}.

R^2 = Me, Et, Pr^i.

TEBA – Cl, triethylbenzylammonium chloride.

occurs regiospecifically and yields a mixture of (4*S*,5*S*)- and (4*R*,5*S*)-diastereomers of 5-substituted 4,5-dihydroisothiazole 1,1-dioxides **265**–**267**.[171]

The reaction of the 5-bromo-derivative **255** with thiols or amines gives the substituted products of the bromine atom **268** and **269**.[168]

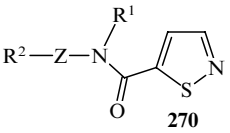


R^1 = 4-MeC_6H_4, R^2 = H;
R^1 = R^2 = Me.

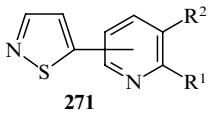
IV. Areas of application of isothiazoles

As noted above, isothiazole derivatives manifest a broad spectrum of useful properties. Back in 1967, isothiazoles were used as starting compounds in the synthesis of highly efficient penicillins and cephalosporins,[2,3] which gave a strong impetus to systematic studies of the biological properties of isothiazole derivatives. In 1988, Mel'nikov who studied the production and application of pesticides and plant growth regulators drew attention to the broad potentialities of isothiazole derivatives.[172] Recent years have been marked by numerous publications (including patents and patent applications) devoted to various applications of isothiazoles as efficient agrochemical and medicinal agents.

It was found that 4-benzoyl- and 4-(hetaroyl)isothiazole derivatives manifest herbicidal activities.[85–88,173] There is evidence of the use of substituted isothiazole-5-carboxamides **270**,[174] isothiazolylpyridines **271** [175] and dihydroisothiazolone derivatives as herbicides.[176]



270

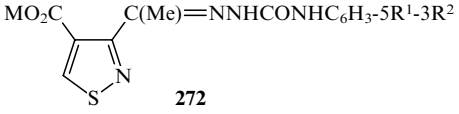


271

R^1 = H, (un)substituted alkyl, (un)substituted acyl;
R^2 = (un)substituted aryl, hetaryl;
Z = (un)substituted C_1–C_4-alkylene.

R^1 = Hal, MeO, FCH_2O, F_3CO;
R^2 = CN, CO_2H, CHO.

When used as herbicides, isothiazole derivatives manifest synergistic effects and are included in various compositions. Thus compounds **272** are auxin transport inhibitors and are used together with other herbicides in order to enhance their action.[10–14]



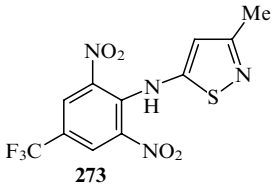
272

R^1, R^2 = H, F, Cl; M = H, Na.

The role of herbicides in these compositions is played by different compounds, *e.g.*, dicamba, glifosat, 2,4-D[10] and herbicides based on phenoxypropionic [11] and phenoxybutyric acids.[14]

Some isothiazoles manifest high insecticidal activities. These include 4,5-dihydro-1*H*-pyrazole derivatives containing various isothiazole substituents in position 4,[177,178] 1,2,3-triazole derivatives containing isothiazole substituents in position 3 ,[179] *etc*. The cyanoisothiazole derivatives **161** manifest high insecticidal activities against termites.[180]

Many isothiazole derivatives, particularly acylated 5-aminoisothiazoles,[94,95] isothiazolecarboxamides,[96–98] 4-cyanoisothiazoles,[112,123,124] 3,4-dichloroisothiazole-5-carboxylic acid and its derivatives,[121] *etc*., manifest fungicidal activities. (3-Methylisothiazol-5-yl)(2,6-dinitro-4-trifluoromethylphenyl)amine (**273**) is used as an agrochemical.[181]



273

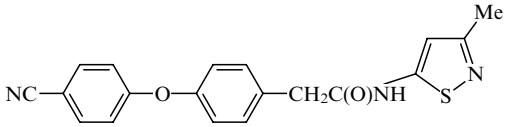
Many heterocyclic and aromatic compounds containing various isothiazole residues [182,183] and 3-isothiazolone derivatives [184–189] in their side chains manifest high fungicidal activities. Isothiazolones are broad-spectrum biocides; they are included in various compositions including commercial ones. They hold great promise for the technology and agriculture being non-harmful to humans, animals and the environment.[20,23,30,190–197]

Isothiazole and isothiazolone derivatives are used in photography,[198–212] cosmetics,[213–215] and as dyes;[216–218] besides, they are components of synergistic bactericidal preparations [219–225] and are used in the chemiluminescent analysis [226,227] of radiographic visualisation.[228] Many of them are antifouling agents.[229–235]

A great number of isothiazole derivatives manifest high antimicrobial activities and are widely used for the protection of natural and technical materials, plants and other objects from harmful microorganisms. These include 3-alkoxyisothiazoles (particularly, compound **122**),[104] allylic ethers **128**–**130**,[106] 5-aminoisothiazoles,[236] 3,5-diaminoisothiazole derivatives **6**,[51] isothiazolecarboxamides [101] and the derivatives **125** and **126**.[105]

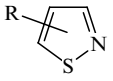
The overwhelming majority of compounds endowed with antimicrobial activities were found among isothiazolone derivatives.[237–265] It was found that the addition of even the simplest isothiazolones to various compositions, *e.g.*, 2-methyl- or 5-chloro-2-methyl-2,3-dihydroisothiazol-3-one, increase markedly their activities.[266–271]

Some isothiazole derivatives manifest different types of biological activities. Thus acylated aminoisothiazoles (compounds **165** [125,272] and **274** [273]) are used as insecticides and acaricides.



274

Compositions possessing bactericidal and fungicidal properties were prepared from some dihydroisothiazolones.[274] Cyanoisothiazoles [112] are used as fungicides and bactericides. Compositions comprising aminoacrylamides and trisubstituted isothiazoles possess insecticidal, fungicidal and herbicidal activities.[275] Compounds **275** have been patented as nematocides, insecticides and acaricides.[276]

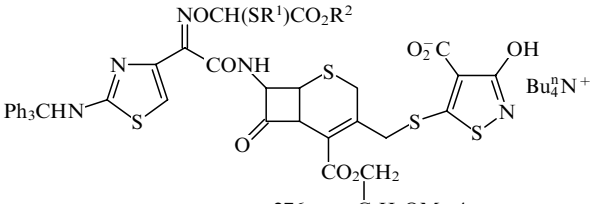


275

R = $CF_2{=}CHCH_2CH_2SO_n$, n = 0–2.

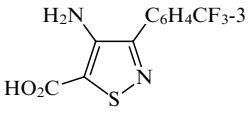
N-Isothiazol-5-ylamides (*e.g.*, compound **110**[92]) manifest an even broader range of pesticidal activities and possess nematocidal, insecticidal, miticidal and fungicidal properties.

An intense search for therapeutic agents among isothiazole derivatives has been carried out over the past decade. Cephalosporins containing a (4-carboxy-3-hydroxyisothiazol-5-yl)thiomethyl group in position 3 (**276**) are used as medicinal drugs possessing a broad spectrum of antibacterial activities, particularly with respect to gram-negative bacteria.[277]



276

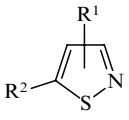
Isothiazolyl aminoalkyl ketones were patented as myorelaxants.[278] 5-Carboxy-3-phenylisothiazoles, particularly 4-amino-3-(3-trifluoromethylphenyl)isothiazole-5-carboxylic acid (**277**), were recommended for use as antiinflammatory agents.[279–281]



277

Dihydroisothiazol-3-one 1,1,-dioxide derivatives inhibit serine proteases. They have been recommended for the treatment of various inflammatory diseases and as antimetastatic agents.[7,8] Some aromatic and heterocyclic compounds containing isothiazole residues inhibit phosphodiesterase and are widely used in the clinical practice as antiasthmatic drugs and in the treatment of diabetes, hypertension, allergic rhinites, nephrites and other diseases.[282,283]

Compounds **278** and their salts have been patented as effective agents for the treatment of Alzheimer's disease.[4]



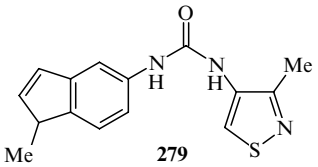
278

R^1 = H, alkyl, cycloalkyl, (un)substituted phenyl;
R^2 = substituted pyrrolidinyl.

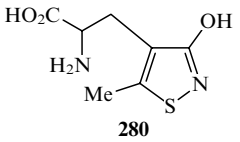
Trisubstituted isothiazole derivatives containing an amino acid or cyclobutene fragment in position 3 were recommended for the treatment of brain ischemia, Huntington's and Parkinson's diseases, epilepsy, Alzheimer's disease, schizophrenia, stress, anxiety and various memory disorders.[284]

5-Hydrazinoisothiazole derivatives act as immunodepressants,[285] whereas 3-isothiazolone derivatives are included in the composition of weight reduction drugs.[286] They are also used for modification of the interleukin-5 receptor.[287]

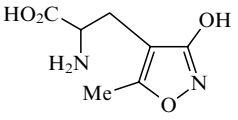
The isothiazole ring is the constituent of various physiologically active compounds. Thus heterocyclic derivatives of urea containing an isothiazole substituent act as antagonists of 5-HT_{2C} and 5-HT_{2B} receptors and are used in the preparation of antidepressant drugs and in the treatment of Alzheimer's disease, schizophrenia, *etc.*[288] Compound **279** is a highly efficient antagonist of 5-HT_{2B} receptors, although its activity is not too high.[289–291] 2-Amino-3-(3-hydroxy-5-methylisothiazol-4-yl)propionic acid (**280**), the isothiazole analogue of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (**281**, AMPA), blocks the activation of glutamate receptors which are crucial for brain ischemia, Alzheimer's disease, hypoglycemia, *etc.*[292,293]



279



280



281

V. Conclusion

As can be seen from the material presented above, new original methods for the synthesis of many isothiazole derivatives have been developed in recent years. These include some previously unknown heterocyclisation reactions (*e.g.*, the syntheses based on α-amino ketones and 2-nitropentachloro-1,3-butadiene), the syntheses of isothiazoles from other, more accessible heterocyclic compounds (particularly, the syntheses based on trithiatriazine trichloride) as well as the syntheses of previously unknown fluoro-substituted isothiazoles. Studies aimed at the functionalisation of isothiazoles, *e.g.*, cross-coupling reactions which made possible the synthesis of previously unavailable derivatives (*e.g.*, isothiazoles containing two acetylene groups) have received further development. The syntheses of biologically active amides, isothiazolones and highly reactive 1,1-dioxides have been carried out. Isothiazoles were used as starting materials for the synthesis of novel, previously unavailable biheterocyclic structures, such as imidazoisothiazoles, diisothiazolopyrazines, isothiazolotriazines, substituted pyrroloisothiazole 1,1-dioxides and other compounds.

Methods for the synthesis of various heterocyclic compounds (pyrazoles, thiadiazapentalenes and other hardly accessible compounds) from readily available isothiazole derivatives have been developed.

High biological activities of isothiazoles is the main impetus for conducting in-depth studies in the field of isothiazole chemistry. More than 50% of work cited in this review are patents devoted to the synthesis and applications of isothiazoles as efficient agrochemical and medicinal preparations.

Obviously, the exceptionally broad spectrum of useful properties of isothiazoles determines the expediency of further studies into their chemistry. We hope that the present review will help attract more attention to this field of chemistry.

References

1. A Adams, R Slask *Chem. Ind. (London)* **42** 1232 (1956)
2. R Raap, R G Micetich *J. Med. Chem.* **11** 70 (1968)
3. US P. 3 268 523; *Chem. Abstr.* **65** 18 597 (1967)
4. US P. 5 409 946; *Chem. Abstr.* **123** 55 872 (1995)
5. US P. 5 411 977; *Ref. Zh. Khim.* 06 O 76P (1997)
6. US P. 5 378 729; *Chem. Abstr.* **123** 33643 (1995)
7. US P. 5 550 139; *Ref. Zh. Khim.* 07 O 152P (1999)
8. WO PCT 95 18 797; *Chem. Abstr.* **123** 340 140 (1995)
9. L Matzen, A Engesgaard, B Ebert, M Didriksen, B Frolund, P Krogsgaard-Larsen, J W Jaroszewski *J. Med. Chem.* **40** 520 (1997)
10. Austr. P. 670 809; *Ref. Zh. Khim.* 22 O 391P (1997)
11. US P. 5 681 793; *Ref. Zh. Khim.* 07 O 394P (2000)
12. US P. 5 888 931; *Ref. Zh. Khim.* 02 O 475P (2000)
13. US P. 5 888 932; *Ref. Zh. Khim.* 04 O 402P (2000)

14. US P. 5 888 937; *Ref. Zh. Khim.* 11 O 431P (2000)
15. Jpn. Appl. 04-270 203; *Chem. Abstr.* **118** 75 364 (1993)
16. US P. 5 591 760; *Ref. Zh. Khim.* 01 O 255P (1998)
17. US P. 5 489 588; *Ref. Zh. Khim.* 02 O 379P (1998)
18. US P. 5 648 086; *Ref. Zh. Khim.* 23 O 385P (1998)
19. US P. 5 559 083; *Ref. Zh. Khim.* 12 O 426P (1999)
20. BRD Appl. 19 548 710; *Chem. Abstr.* **127** 118 601 (1997)
21. US P. 5 661 119; *Chem. Abstr.* **127** 222 242 (1997)
22. US P. 5 922 745; *Ref. Zh. Khim.* 14 O 380P (2000)
23. US P. 5 658 467; *Chem. Abstr.* **127** 224 778 (1997)
24. US P. 5 188 663; *Chem. Abstr.* **119** 88 937 (1993)
25. US P. 5 683 686; *Ref. Zh. Khim.* 17 O 402P (1999)
26. Jpn. Appl. 07-140 620; *Chem. Abstr.* **123** 241 899 (1995)
27. Jpn. Appl. 09-211 786; *Chem. Abstr.* **127** 255 264 (1997)
28. BRD Appl. 4 426 623; *Chem. Abstr.* **124** 204 936 (1996)
29. Br. Appl. 2 335 924; *Ref. Zh. Khim.* 09 N 162P (2000)
30. T Mulligam *Spec. Chem.* **16** 161 (1996); *Ref. Zh. Khim.* 05 O 282 (1997)
31. R Slack, K R H Wooldridge *Adv. Heterocycl. Chem.* **4** 107 (1965)
32. K R H Wooldridge *Adv. Heterocycl. Chem.* **14** 1 (1972)
33. M Hori, H Shimizu *Sulfur Rep.* **4** 313 (1986)
34. D M McKinnon *Sulfur Rep.* **15** 317 (1994)
35. B Iddon *Heterocycles* **41** 533 (1995)
36. J W Pavlik *Mol. Supramol. Photochem. (Organic Photochemistry)* **1** 57 (1997); *Chem. Abstr.* **128** 204 460 (1998)
37. V P Litvinov *Usp. Khim.* **68** 817 (1999) [*Russ. Chem. Rev.* **68** 737 (1999)]
38. Th L Gilchrist *J. Chem. Soc., Perkin Trans. 1* 2849 (1999)
39. M F Ward *Annu. Rep. Prog. Chem., Sect. B* **95** 157 (1999)
40. A R Katrizky, J Lagowski *Heterocyclic Chemistry* (New York: Wiley) (Translated from the English; Moscow: Izd. Inostr. Lit., 1963)
41. L A Paquette *Principles of Modern Heterocyclic Chemistry* (New York: Benjamin, 1968)
42. K Turnbull, in *Heterocyclic Chemistry* Vol. 5 (London: Wiley, 1986)
43. T L Gilchrist *The Chemistry of Heterocyclic Compounds* (Translated from the English; Moscow: Mir, 1996)
44. R F Chapman, B J Peart, in *Comprehensive Heterocyclic Chemistry II* Vol. 3 (Ed. I Shinkai) (Oxford: Elsevier, 1996)
45. P A Bradley, D J Wilkins *Progress in Heterocyclic Chemistry* Vol. 11 (Eds G W Gribble, T L Gilchrist) (Oxford: Pergamon Press, 1999)
46. *Methoden der Organischen Chemie (Houben-Weyl)* Bd. EVIII(III) (Stuttgart: Georg Thieme Verlag, 1993)
47. S D Sokolov *Usp. Khim.* **58** 533 (1979) [*Russ. Chem. Rev.* **58** 289 (1979)]
48. M M Kempbell, in *Comprehensive Organic Chemistry* (Eds D Barton, W D Ollis) (Oxford: Pergamon Press, 1979) Vol. 4
49. A Adams, R Slack *J. Chem. Soc.* 3061 (1959)
50. R E Hackler, K W Burow Jr, S V Kaster, D I Wickiser *J. Heterocycl. Chem.* **26** 1575 (1989)
51. M T Cocco, C Congiu, A Maccioni, V Onnis, M L Schivo, A De Logu *Farmaco* **49** 137 (1994); *Chem. Abstr.* **121** 205 259 (1994)
52. Pol. P. 175 889; *Ref. Zh. Khim.* 01 O 17P (2000)
53. A Kunugi, Md A Jabbar, K Mori, H Uno *Elecrochim. Acta* **44** 4583 (1999)
54. Eur. Appl. 1 053 680; *Ref. Zh. Khim.* 06 O 158P (2001)
55. R V Kaberdin, V I Potkin, Yu A Ol'dekop *Dokl. Akad. Nauk SSSR* **300** 1133 (1988) [a]
56. R V Kaberdin, V I Potkin, Yu A Ol'dekop *Zh. Org. Khim.* **26** 1560 (1990) [b]
57. A I Verenich, A A Govorova, N M Galitskii, V I Potkin, R V Kaberdin, Yu A Ol'dekop *Khim. Geterotsikl. Soedin.* 399 (1992) [c]
58. A N Akopyan, A M Saakyan, Z A Dzhauari *Arm. Khim. Zh.* **21** (5) 414 (1968)
59. M G Voronkov, N S Vyazankin, E N Deryagina *Reaktsii Sery s Organicheskimi Soedineniyami* (Reactions of Sulfur with Organic Compounds) (Novosibirsk: Nauka, 1979)
60. J N Bridson, S B Copp, M J Schriver, S G Zhu, M J Zaworotko *Can. J. Chem.* **72** 1143 (1994)
61. J N Bridson, M J Schriver, S G Zhu *Can. J. Chem.* **73** 212 (1995)
62. M M Krayushkin, M A Kalik, A Ya Kudryavtseva *Izv. Akad. Nauk, Ser. Khim.* 1892 (1992) [d]
63. D K Buffel, L Meerpoel, S M Toppet, G J Hoornaert *Nucleosides Nucleotides* **13** 719 (1994); *Chem. Abstr.* **121** 83 859 (1994)
64. X-G Duan, X-L Duan, C W Rees *J. Chem. Soc., Perkin Trans. 1* 2831 (1997)
65. X-L Duan, Ch W Rees, T-Y Yue *Chem. Commun.* 367 (1997)
66. X-L Duan, R Perrins, Ch W Rees *J. Chem. Soc., Perkin Trans. 1* 1617 (1997)
67. Ch W Rees, T-Y Yue *J. Chem. Soc., Perkin Trans. 1* 2247 (1997)
68. S M Laaman, O Meth-Cohn, Ch W Rees *Synthesis* 757 (1999)
69. X-L Duan, Ch W Rees *J. Chem. Soc., Perkin Trans. 1* 3189 (1997)
70. K Hartke, A Kraska *Arch. Pharm.* **326** (1) 57 (1993); *Chem. Abstr.* **118** 191 686 (1993)
71. B Schulze, U Dietrich, K Illgen, J Siler *Zh. Org. Khim.* **30** 1379 (1994) [b]
72. B Schulze, G Kirsten, S Kirrbach, A Rahm, H Heimgartner *Helv. Chim. Acta* **74** 1059 (1991)
73. S Kirrbakh, K Myetze, R Kempe, R Meizinger, A Kol'berg, B Schulze *Zh. Org. Khim.* **32** 1745 (1996) [b]
74. O Miyato, S Yamakawa, K Muroya, T Naito *Heterocycles* **51** 1513 (1999)
75. Bhavana, S Hastak, B J Ghiya *Ind. J. Heterocycl. Chem.* **2** 133 (1992); *Chem. Abstr.* **118** 212 952 (1993)
76. L Capuano, V Hammerer, V Huch *Liebigs Ann. Chem.* 23 (1994)
77. M R Bryce, S Yoshida, A S Batsanov, J A K Howard *J. Chem. Soc., Perkin Trans. 1* 1157 (1997)
78. K Emayan, R F English, P A Koutentis, Ch W Rees *J. Chem. Soc., Perkin Trans. 1* 3345 (1997)
79. D Clarke, K Emayan, Ch W Rees *J. Chem. Soc., Perkin Trans. 1* 77 (1998)
80. R B Woodword *The Harvey Lecture Series 59* (New York: Academic Press, 1965) p. 31
81. S G Zlotin, P G Kislitsyn, O A Luk'yanov *Izv. Akad. Nauk, Ser. Khim.* 1887 (1997) [d]
82. S G Zlotin, P G Kislitsyn, O A Luk'yanov *Izv. Akad. Nauk, Ser. Khim.* 534 (1998) [d]
83. S G Zlotin, P G Kislitsyn, O A Luk'yanov *Izv. Akad. Nauk, Ser. Khim.* 537 (1998) [d]
84. V I Potkin, N I Nechai, R V Kaberdin *Izv. Akad. Nauk Belarusi, Ser. Khim. Nauk* (4) 85 (1994)
85. WO PCT 97 38 987; *Chem. Abstr.* **127** 346 385 (1997)
86. WO PCT 97 38 996; *Chem. Abstr.* **127** 346 386 (1997)
87. WO PCT 97 38 988; *Chem. Abstr.* **127** 358 855 (1997)
88. BRD Appl. 19 614 859; *Ref. Zh. Khim.* 20 O 483P (1998)
89. Jpn. Appl. 07-196 637; *Chem. Abstr.* **124** 8805 (1996)
90. F Guilloteau, L Miginiac *Synth. Commun.* **25** 1383 (1995)
91. H G Raubenheimer, M Desmet, G J Kruger *J. Chem. Soc., Dalton Trans.* 2067 (1995)
92. WO PCT 95 31 448; *Chem. Abstr.* **124** 202 240 (1996)
93. J G Samaritoni, L Arndt, T J Bruce, J E Dripps, J Gifford, C J Hatton, W H Hendrix, J R Schoonover, G W Johnson, V B Hegde, S Thornburgh *J. Agric. Food. Chem.* **45** 1920 (1997); *Chem. Abstr.* **126** 302 652 (1997)
94. BRD Appl. 19 542 372; *Ref. Zh. Khim.* 23 O 408P (1998)
95. BRD Appl. 19 736 545; *Ref. Zh. Khim.* 12 O 375P (2000)
96. BRD Appl. 4 328 425; *Ref. Zh. Khim.* 14 O 398P (1997)
97. Jpn. Appl. 06-09 313; *Chem. Abstr.* **120** 263839 (1994)
98. Jpn. Appl. 08-277 276; *Chem. Abstr.* **126** 47213 (1997)
99. Jpn. Appl. 08-277 277; *Chem. Abstr.* **126** 47214 (1997)
100. BRD Appl. 19 750 012; *Ref. Zh. Khim.* 09 O 383P (2000)
101. BRD Appl. 19 842 354; *Ref. Zh. Khim.* 03 O 367P (2001)
102. K Burak, Z Machon *Pharmazie* **47** 492 (1992); *Chem. Abstr.* **120** 298 527 (1994)
103. Pol. P. 167 891; *Chem. Abstr.* **125** 58 496 (1996)
104. BRD Appl. 19 712 409; *Ref. Zh. Khim.* 20 O 326P (1999)
105. Eur. Appl. 542 468; *Chem. Abstr.* **119** 139 214 (1993)
106. US P. 5 508 417; *Chem. Abstr.* **125** 58 497 (1996)
107. X-P Yang, Z-M Li, L-X Wang, Y-H Li *Chem. J. Chin. Univ.* **19** 228 (1998); *Ref. Zh. Khim.* 24 O 806 (1998)
108. A Alberola, L Calvo, M T R Rodriguez, M C Sanudo *J. Heterocycl. Chem.* **30** 393 (1993)
109. A Alberola, L Calvo, M T R Rodriguez, M C Sanudo *J. Heterocycl. Chem.* **32** 537 (1995)
110. U Lipnicka, Z Machon *Acta Pol. Pharm.* **50** 235 (1993); *Chem. Abstr.* **121** 35 413 (1994)
111. X-P Yang, Z-M Li, J Lui, H-S Chen *Chin. J. Appl. Chem.* **16** 115 (1999); *Ref. Zh. Khim.* 22 Zh 351 (1999)

112. Can. Appl. 2 152 156; *Chem. Abstr.* **124** 317 143 (1996)
113. BRD Appl. 1 975 0011; *Ref. Zh. Khim.* 11 O 410P (2000)
114. E E Swayze, L B Townsend *J. Heterocycl. Chem.* **30** 1379 (1993)
115. E E Swayze, L B Townsend *J. Org. Chem.* **60** 6309 (1995)
116. C J Shishoo, M B Devani, S Ananthan, V S Bhadti, C V Ullas *J. Heterocycl. Chem.* **25** 759 (1988)
117. S G Zlotin, K S Chunikhin, M O Dekaprilevich *Mendeleev Commun.* 97 (1997)
118. S G Zlotin, A V Bobrov, K S Chunikhin *Izv. Akad. Nauk, Ser. Khim.* 1350 (1999) [d]
119. S G Zlotin, A V Bobrov *Izv. Akad. Nauk, Ser. Khim.* 957 (2000) [d]
120. US P. 3 341 547; *Chem. Abstr.* **68** 114596 (1968)
121. Jpn. Appl. 05-59 024; *Chem. Abstr.* **119** 117 242 (1993)
122. US P. 3 155 678; *Chem. Abstr.* **62** 2778 (1965)
123. US P. 5 484 934; *Ref. Zh. Khim.* 23 O 373P (1997)
124. Eur. Appl. 604 978; *Chem. Abstr.* **121** 134 107 (1994)
125. J G Samaritoni, J M Babcock, M L Schlenz, G W Johnson *J. Agr. Food Chem.* **47** 3381 (1999); *Ref. Zh. Khim.* 08 O 401 (2000)
126. K Ohkata, Y Ohyama, K Akiba *Heterocycles* **37** 859 (1994); *Chem. Abstr.* **121** 57 558 (1994)
127. M Konrad, F Meyer, M Buechner, K Heinze, L Zsolnai *Chem. Ber.-Recl.* **130** 95 (1997)
128. N V Onyamboko, M Renson, C Paulmier *Bull. Soc. Chim. Belg.* **96** 407 (1987)
129. M S Mohamed *Egypt. J. Pharm. Sci.* **35** 427 (1994); *Chem. Abstr.* **123** 285 924 (1995)
130. A V Bobrov, B B Averkiev, S G Zlotin, M Yu Antipin *Izv. Akad. Nauk, Ser. Khim.* 1226 (2001) [d]
131. B Schulze, K Illgen *J. Prakt. Chem., Chem.-Ztg.* **339** 1 (1997); *Chem. Abstr.* **126** 117 919 (1997)
132. J L Marco, S Ingate *Tetrahedron Lett.* **38** 4835 (1997)
133. S T Ingate, J L Marco, M Witvrouw, C Pannecouque, E DeClercq *Tetrahedron* **53** 17795 (1997)
134. J L Marco, S T Ingate, P Manzano *Tetrahedron Lett.* **39** 4123 (1998)
135. J L Marco, S T Ingate, C Jaime, I Bea *Tetrahedron* **56** 2523 (2000)
136. J L Marco, S T Ingate, P M Chinchon *Tetrahedron* **55** 7625 (1999)
137. S G Zlotin, A I Gerasyuto *Izv. Akad. Nauk, Ser. Khim.* 396 (1999) [d]
138. Sh Li, Zh Li *Guangzhou Huagong* **22** 10 (1994); *Chem. Abstr.* **123** 313 798 (1995)
139. BRD Appl. 19 652 531; *Chem. Abstr.* **127** 135 791 (1997)
140. R Glinka, E Zak, K Walczynski *Zesz. Nauk. Politech. Lodz., Technol. Chem. Spozyw.* **708** (53) 51 (1995); *Chem. Abstr.* **124** 86 868 (1996)
141. US P. 5 466 818; *Ref. Zh. Khim.* 24 O 436P (1997)
142. Sh Li, X Tan *Jingxi Huagong (Fine Chem)* **16** 4 (1999); *Ref. Zh. Khim.* 22 O 382 (1999)
143. Jpn. Appl. 06-192 245; *Chem. Abstr.* **121** 280 633 (1994)
144. US P. 5 420 290; *Ref. Zh. Khim.* 10 O 87P (1997)
145. K Hartke, C Ashry *Pharmazie* **51** 638 (1996); *Chem. Abstr.* **125** 300 769 (1996)
146. O Carugo, F Clerici, D Pocar *Tetrahedron* **49** 9117 (1993)
147. F Clerici, F Galletti, D Pocar, P Rowersi *Tetrahedron* **52** 7183 (1996)
148. F Clerici, T Ferrario, M L Gelmi, R Marrelli *J. Chem. Soc., Perkin. Trans. 1* 2533 (1994)
149. P Baggi, F Clerici, M L Gelmi, S Mottadelli *Tetrahedron* **51** 2455 (1995)
150. S Abou El Maaty, M S Mohamed, F El Telebany *Egypt. J. Pharm. Sci.* **33** 441 (1992); *Chem. Abstr.* **121** 57 440 (1994)
151. A Rolfs, J Liebscher *Angew. Chem.* **105** 797 (1993)
152. Eur. Appl. 583 561; *Chem. Abstr.* **120** 244661 (1994)
153. A Rolfs, P G Jones, J Liebscher *J. Chem. Soc., Perkin Trans. 1* 2339 (1996)
154. S H Kim, K Kim *J. Heterocycl. Chem.* **30** 928 (1993)
155. B Friedrich, A Fuks, B Schulze *Zh. Org. Khim.* **30** 1404 (1994) [b]
156. B Schulze, K Rosenbaum, J Hilbig, L Weber *J. Prakt. Chem.-Chem. Ztg.* **334** 25 (1992)
157. B Schulze, U Obst, G Zahn, B Friedrich, R Cimirgalia, H-J Hofmann *J. Prakt. Chem.-Chem. Ztg.* **337** 175 (1995)
158. J W Pavlik, P Tongcharoensirikul, N P Bird, A C Day, J A Barltrop *J. Am. Chem. Soc.* **116** 2292 (1994)
159. J W Pavlik, P Tongcharoensirikul *J. Org. Chem.* **65** 3626 (2000)
160. M de Wang, H Alper *J. Organomet. Chem.* **451** 169 (1993)
161. S H Kim, Y Y Lee, K Kim, J H Kim *Bull. Korean Chem. Soc.* **15** 273 (1994); *Chem. Abstr.* **121** 108 116 (1994)
162. E M Beccalli, F Clerici, M L Gelmi *Tetrahedron* **55** 14975 (1999)
163. D M Argilagos, A Linden, R W Kunz, H Heimgartner *Chimia* **51** 455 (1997); *Ref. Zh. Khim.* 13 Zh 264 (1998)
164. D M Argilagos, M J Trimino, A M Cabrera, A Linden, H Heimgartner *Helv. Chim. Acta* **80** 273 (1997); *Ref. Zh. Khim.* 3 Zh 290 (1999)
165. D M Argilagos, R W Kunz, A Linden, H Heimgartner *Helv. Chim. Acta* **81** 2388 (1998); *Ref. Zh. Khim.* 14 Zh 129 (1999)
166. B Unterhalt, C Langfermann, M Majdrpour, S Kirrbach, A Kolberg, B Schulze *Pharmazie* **53** 764 (1998); *Ref. Zh. Khim.* 9 Zh 264 (1999)
167. B Schulze, A Noack, A Kolberg, in *6-ya Mezhdunarodnaya Konferentsiya 'Khimiya Karbenov i Rodstvennykh Intermediatov' (Programma i Tez. Dokl.), S Peterburg, 1998* [The 6th International Conference 'Chemistry of Carbenes and Related Intermediates' (Programme and Abstracts of Reports), S Petersburg, 1998] p. 137
168. F Clerici, E Erba, M L Gelmi, M Valle *Tetrahedron* **53** 15 859 (1997)
169. F Clerici, M L Gelmi, R Soave, M Valle *Tetrahedron* **54** 11 285 (1998)
170. E Coutouli-Argiropoulou, C Anastasopoulos *J. Heterocycl. Chem.* **33** 731 (1996)
171. E M Beccalli, F Clerici, M L Gelmi *Tetrahedron* **55** 2001 (1999)
172. N N Mel'nikov *Zh. Vses. Khim. O-va im D I Mendeleeva* **33** 602 (1988)
173. BRD Appl. 19 614 858; *Ref. Zh. Khim.* 19 O 386P (1998)
174. Eur. Appl. 761 654; *Chem. Abstr.* **126** 277 469 (1997)
175. US P. 5 438 033; *Chem. Abstr.* **123** 1221 (1995)
176. BRD Appl. 19 620 135; *Ref. Zh. Khim.* 4 O 467P (1999)
177. US P. 5 324 837; *Chem. Abstr.* **121** 205 339 (1994)
178. US P. 5 338 856; *Chem. Abstr.* **121** 300 887 (1994)
179. US P. 6 096 898; *Ref. Zh. Khim.* 11 O 334P (2001)
180. Eur. Appl. 578 246; *Chem. Abstr.* **120** 323 562 (1994)
181. WO PCT 93 19 054; *Chem. Abstr.* **120** 107 030 (1994)
182. Eur. Appl. 538 231; *Chem. Abstr.* **119** 160 256 (1993)
183. WO PCT 93 13 078; *Chem. Abstr.* **119** 271 189 (1993)
184. Eur. Appl. 648 757; *Chem. Abstr.* **123** 55 869 (1995)
185. Zh-M Li, H-S Chen, J Liu, Sh-Ih Lish *Chem. J. Chin. Univ.* **20** 395 (1999); *Ref. Zh. Khim.* 20 Zh 277 (1999)
186. Br. Appl. 2 274 779; *Chem. Abstr.* **121** 295 087 (1994)
187. Br. Appl. 2 304 574; *Ref. Zh. Khim.* 23 O 378P (1997)
188. US P. 5 668 083; *Ref. Zh. Khim.* 11 O 458P (1999)
189. Jpn. Appl. 06-227 912; *Chem. Abstr.* **121** 295 094 (1994)
190. Can. Appl. 2 058 252; *Chem. Abstr.* **118** 141 816 (1993)
191. Can. Appl. 2 069 453; *Chem. Abstr.* **121** 29 268 (1994)
192. US P. 5 430 046; *Ref. Zh. Khim.* 2 O 287P (1997)
193. Jpn. Appl. 08-67 853; *Chem. Abstr.* **125** 36 071 (1996)
194. WO PCT 9614092; *Chem. Abstr.* **125** 95 454 (1996)
195. BRD Appl. 4 344 549; *Ref. Zh. Khim.* 21 O 398P (1997)
196. RF Appl. 96 122 055; *Ref. Zh. Khim.* 19 O 388P (2000)
197. US P. 5 595 575; *Ref. Zh. Khim.* 13 N 162P (1998)
198. Eur. Appl. 712 039; *Chem. Abstr.* **125** 99 942 (1996)
199. Jpn. Appl. 04-194 928; *Chem. Abstr.* **118** 90 712 (1993)
200. Jpn. Appl. 04-152 340; *Chem. Abstr.* **118** 90 693 (1993)
201. Jpn. Appl. 06-03 780; *Chem. Abstr.* **121** 22 412 (1994)
202. Jpn. Appl. 05-333 486; *Chem. Abstr.* **121** 22 406 (1994)
203. Eur. Appl. 508 457; *Chem. Abstr.* **118** 157 782 (1993)
204. Jpn. Appl. 04-177 239; *Chem. Abstr.* **118** 70 018 (1993)
205. Jpn. Appl. 04-128 839; *Chem. Abstr.* **118** 112 860 (1993)
206. Eur. Appl. 529 794; *Chem. Abstr.* **119** 259 396 (1993)
207. Eur. Appl. 549 175; *Chem. Abstr.* **119** 237 893 (1993)
208. Jpn. Appl. 04-260 036; *Chem. Abstr.* **118** 136 118 (1993)
209. US P. 5 514 505; *Chem. Abstr.* **125** 127 644 (1996)
210. Jpn. Appl. 08-201 979; *Chem. Abstr.* **125** 288 680 (1996)
211. Jpn. Appl. 05-331 379; *Chem. Abstr.* **121** 95 875 (1994)
212. Jpn. Appl. 09-133 977; *Chem. Abstr.* **127** 57 952 (1997)
213. R Matissek *GJT-Suppl.* (7) 5; 8 (1987); *Chem. Abstr.* **108** 137 671 (1988)
214. Czech. P. 276 924; *Chem. Abstr.* **121** 163 678 (1994)
215. *Dtsch. Lebensm.-Rundsch.* **89** 181 (1993); *Chem. Abstr.* **121** 163 671 (1994)
216. Eur. Appl. 534 296; *Chem. Abstr.* **119** 162 371 (1993)

217. Eur. Appl. 545 420; *Chem. Abstr.* **119** 162 375 (1993)
218. Jpn. Appl. 09-292 684; *Chem. Abstr.* **128** 68 443 (1998)
219. Jpn. Appl. 07-207 090; *Chem. Abstr.* **123** 230 303 (1995)
220. WO PCT 9 612 407; *Chem. Abstr.* **125** 28 275 (1996)
221. US P. 5 591 759; *Ref. Zh. Khim.* 5 O 404P (1998)
222. US P. 5 523 020; *Ref. Zh. Khim.* 10 O 92P (1998)
223. Eur. Appl. 594 440; *Chem. Abstr.* **121** 258 107 (1994)
224. US P. 5 552 423; *Ref. Zh. Khim.* 9 O 436P (1999)
225. Jpn. Appl. 08-198 714; *Chem. Abstr.* **125** 240 850 (1996)
226. Jpn. Appl. 08-38 195; *Chem. Abstr.* **124** 311 832 (1996)
227. Jpn. Appl. 08-38 196; *Chem. Abstr.* **124** 311 833 (1996)
228. US P. 5 908 931; *Ref. Zh. Khim.* 07 O 47P (2000)
229. Jpn. Appl. 07-196 403; *Chem. Abstr.* **123** 342 819 (1995)
230. Jpn. Appl. 06-40 812; *Chem. Abstr.* **121** 29 270 (1994)
231. Eur. Appl. 706 974; *Chem. Abstr.* **124** 324 873 (1996)
232. Jpn. Appl. 08-20 676; *Chem. Abstr.* **124** 319 797 (1996)
233. US P. 5 670 055; *Chem. Abstr.* **127** 298 502 (1997)
234. W W Bingaman, G L Willingham *Int. Biodeter. Biodegr.* **34** 387 (1994); *Chem. Abstr.* **124** 79 433 (1996)
235. US P. 6 010 693; *Ref. Zh. Khim.* 1 O 377P (2001)
236. BRD Appl. 19 654 147; *Ref. Zh. Khim.* 13 O 436P (1999)
237. Eur. Appl. 542 489; *Chem. Abstr.* **119** 111 272 (1993)
238. Jpn. Appl. 05-163 107; *Chem. Abstr.* **119** 175 864 (1993)
239. Jpn. Appl. 05-170 608; *Chem. Abstr.* **119** 175 869 (1993)
240. Jpn. Appl. 05-286 815; *Chem. Abstr.* **120** 127 766 (1994)
241. US P. 5 288 693; *Chem. Abstr.* **121** 35 595 (1994)
242. Jpn. Appl. 06-87 705; *Chem. Abstr.* **121** 76 166 (1994)
243. Jpn. Appl. 06-148 957; *Chem. Abstr.* **121** 241 882 (1994)
244. Jpn. Appl. 06-227 916; *Chem. Abstr.* **121** 295 095 (1994)
245. Jpn. Appl. 07-258 009; *Chem. Abstr.* **124** 23 925 (1996)
246. Eur. Appl. 686 346; *Chem. Abstr.* **124** 79 443 (1996)
247. Eur. Appl. 686 347; *Chem. Abstr.* **124** 79 444 (1996)
248. W Anker *Microb. Materialzerstoerung Materialschutz* 151 (1995); *Chem. Abstr.* **124** 236 544 (1996)
249. US P. 5 494 588; *Chem. Abstr.* **124** 241 661 (1996)
250. Jpn. Appl. 08-165 206; *Chem. Abstr.* **125** 161 120 (1996)
251. Jpn. Appl. 07-330 520; *Chem. Abstr.* **124** 223 707 (1996)
252. Jpn. Appl. 07-277 910; *Chem. Abstr.* **124** 48 313 (1996)
253. Jpn. Appl. 07-277 911; *Chem. Abstr.* **124** 48 314 (1996)
254. Jpn. Appl. 08-239 694; *Chem. Abstr.* **126** 3076 (1997)
255. US P. 5 670 529; *Chem. Abstr.* **127** 283 428 (1997)
256. Jpn. Appl. 09-209 272; *Chem. Abstr.* **127** 221 913 (1997)
257. Eur. Appl. 834 253; *Chem. Abstr.* **128** 254 064 (1998)
258. Jpn. Appl. 10-27 381; *Chem. Abstr.* **128** 174 208 (1998)
259. Eur. Appl. 827 939; *Chem. Abstr.* **128** 196 442 (1998)
260. US P. 5 703 105; *Chem. Abstr.* **128** 106 408 (1998)
261. Pol. P. 169 519; *Ref. Zh. Khim.* 17 O 376P (1997)
262. Eur. Appl. 774 444; *Chem. Abstr.* **127** 55 587 (1997)
263. Jpn. Appl. 09-263 504; *Chem. Abstr.* **127** 342 912 (1997)
264. BRD Appl. 19 651 351; *Ref. Zh. Khim.* 16 O 440P (1999)
265. BRD Appl. 19 734 244; *Ref. Zh. Khim.* 07 O 138P (2000)
266. Jpn. Appl. 04-290 806; *Chem. Abstr.* **118** 118 948 (1993)
267. Jpn. Appl. 08-193 014; *Chem. Abstr.* **125** 240 846 (1996)
268. Jpn. Appl. 09-151 101; *Chem. Abstr.* **127** 132 269 (1997)
269. Jpn. Appl. 08-183 703; *Chem. Abstr.* **125** 188 330 (1996)
270. Jpn. Appl. 08-183 704; *Chem. Abstr.* **125** 188 331 (1996)
271. Jpn. Appl. 08-253 404; *Chem. Abstr.* **126** 28 030 (1997)
272. J J Sheets, A Schmidt, J G Samaritoni, J M Gifford *J. Agr. Food Chem.* **45** 4826 (1997)
273. BRD Appl. 19 542 372; *Chem. Abstr.* **127** 50 631 (1997)
274. Jpn. Appl. 08-23 136 ; *Chem. Abstr.* **126** 3075 (1997)
275. Jpn. Appl. 08-245 561; *Chem. Abstr.* **126** 31 346 (1997)
276. US P. 5 952 359; *Ref. Zh. Khim.* 09 O 384P (2001)
277. R Hara, E Nakai, H Hisamichi, N Nagano *J. Antibiot.* **47** 477 (1994)
278. US P. 5 338 857; *Chem. Abstr.* **123** 83 354 (1995)
279. Eur. Appl. 578 477; *Chem. Abstr.* **120** 261 340 (1994)
280. WO PCT 9 500 501; *Chem. Abstr.* **124** 55 954 (1996)
281. Eur. Appl. 587 378; *Chem. Abstr.* **120** 290 112 (1994)
282. M J Ashton, D C Cook, G Fenton, J-A Karlsson, M N Palfreyman, D Raeburn, A J Ratcliffe, J E Souness, S Thurairatham, N Vicer *J. Med. Chem.* **37** 1696 (1994)
283. WO PCT 9 815 530; *Chem. Abstr.* **128** 294 695 (1998)
284. Eur. Appl. 0 994 107; *Ref. Zh. Khim.* 19 O 117P (2000)
285. U Lipnicka, Z Machon *Acta Pol. Pharm.* **54** 207 (1997); *Chem. Abstr.* **127** 346 328 (1997)
286. Jpn. Appl. 07-324 007; *Chem. Abstr.* **124** 253 329 (1996)
287. R Devos, Y Guisez, G Plaetinck, S Cornelis, J Tavernier, J van der Heyden, L H Foley, J E Scheffler *Eur. J. Biochem.* **225** 635 (1994)
288. WO PCT 94 14801; *Chem. Abstr.* **121** 179 617 (1994)
289. O N Zefirova, N S Zefirov *Usp. Khim.* **70** 382 (2001) [*Russ. Chem. Rev.* **70** 333 (2001)]
290. I T Forbes, P Ham, D H Booth, R T Martin, M Thompson, G S Baxter, T P Blackburn, A Glen, G A Kennet, M D Wood *J. Med. Chem.* **38** 2524 (1995)
291. I T Forbes, G E Jones, O E Murphy, V Holland, G S Baxter *J. Med. Chem.* **38** 855 (1995)
292. O N Zefirova, N S Zefirov *Zh. Org. Khim.* **36** 1273 (2000) [b]
293. L Matzen, B Ebert, T B Stensbol, B Frolund, J W Jaroszewski, P Krogsgaard-Larsen *Bioorg. Med. Chem.* **5** 1569 (1997)

[a] — *Dokl. Chem. (Engl. Transl.)*
[b] — *Russ. J. Org. Chem. (Engl. Transl.)*
[c] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[d] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*