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SYNTHESIS AND PROPERTIES OF AZOLES CONTAINING BENZO-THIAZOLE SUBSTITUENTS. (REVIEW)

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The results from investigations into the synthesis and properties of five-membered nitrogen-containing heterocycles with several heteroatoms, including benzothiazole fragments, are reviewed.

Keywords: benzothiazole, imidazole, 1,2,4-oxadiazole, 1,3,4-oxa(thia)diazole, pyrazole, tetrazole, 1,2,3- and 1,2,4-triazole, condensation.

In recent decades there has been constant interest in the chemistry of azoles containing benzothiazole fragments as substituents. Among compounds of this type substances with high and varied biological activity and a wide spectrum of practical qualities have been found (polymethine dyes, stabilizers of polymeric materials, antioxidants, optical sensitizers for photographic materials, etc.). Some of them were isolated from natural materials, e.g., the alkaloid luciferin [2-(2-benzothiazolyl)-Δ^2-thiazoline-4-carboxylic acid] and a bioluminescent [2-(5-hydroxy-2-benzothiazolyl)thiazole-4-carboxylic acid].

At the present time a considerable amount of information has accumulated in the literature on the synthesis and practical application of benzothiazolylazoles, requiring systematic classification and critical analysis. During examination of the methods of synthesis we arranged the information not according to the types of benzothiazolylazoles but according to the methods used for their production from derivatives of benzothiazole and various azoles. In our opinion such an approach to systematic classification of the extensive published data gives a clearer idea of the synthetic possibilities of one or the other method.

Compounds with two benzothiazole fragments, which belong to the group of benzothiazole thiacyanine and thiacarbocyanine dyes, are hardly discussed at all in the review. The theory, synthesis, and general character of such dyes were covered in detail in Hamer's monograph [1] and in the reviews [2, 3].

1. METHODS OF SYNTHESIS

1.1. Synthesis of Benzothiazolylazoles by Nucleophilic Substitution and Condensation

Methods for the introduction of benzothiazole fragments into various azoles by nucleophilic substitution and condensation using various functional derivatives (chlorine derivatives, amines, thiols, aldehydes, ketones, and others) of benzothiazole or the corresponding azoles as reagents are discussed in this section. It can

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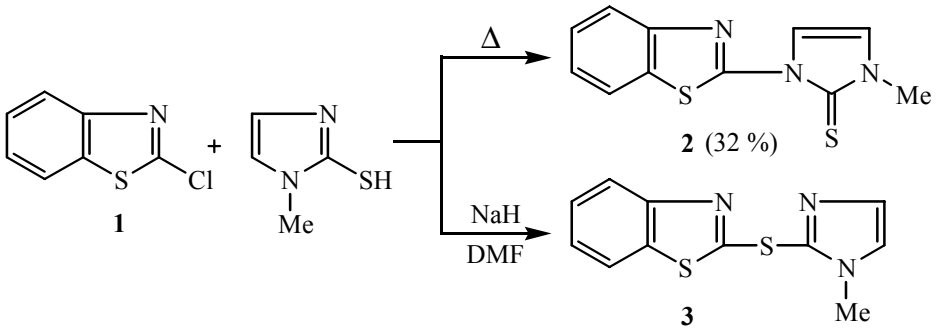
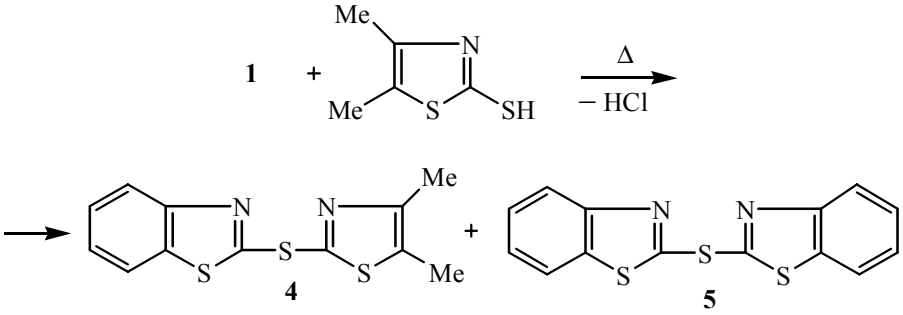
be noted that reagents for such syntheses are at present available. For example, 2-mercaptobenzothiazole is one of the main industrial accelerants for vulcanization and an inhibitor of the aging of rubber [4] and is also a low-toxicity and effective choleretic ("mebetizole") for the treatment of acute and chronic cholangitis and cholecystitis [5].

The structure of the heterocyclic reagents (particularly the capacity for tautomerism) affects the direction of the reactions and frequently leads to the formation of a mixture of compounds. 3-(2-Benzothiazolyl)-1-methylimidazoline-2-thione (**2**) is formed when 2-chlorobenzothiazole (**1**) and 2-mercapto-1-methylimidazole are heated (195°C, 2 h) [6], while 2-(2-benzothiazolylthio)-1-methylimidazole (**3**) is formed during reaction in DMF in the presence of sodium hydride [7].

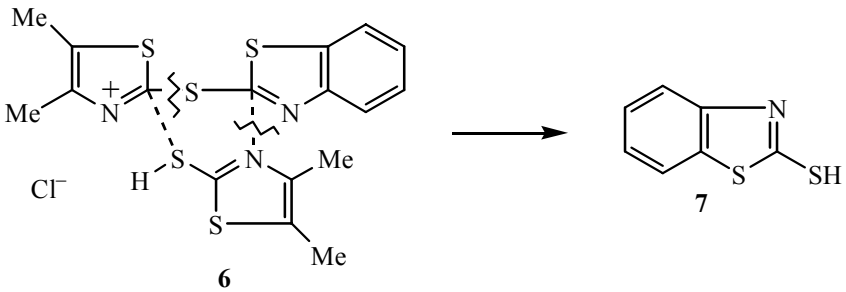


When the chlorine derivative **1** is boiled (5 h) with 2-mercapto-4,5-dimethylthiazole in xylene, di(2-benzothiazolyl) sulfide (**5**) is formed in significant amounts in addition to the expected reaction product 2-(2-benzothiazolylthio)-4,5-dimethylthiazole (**4**) [6].

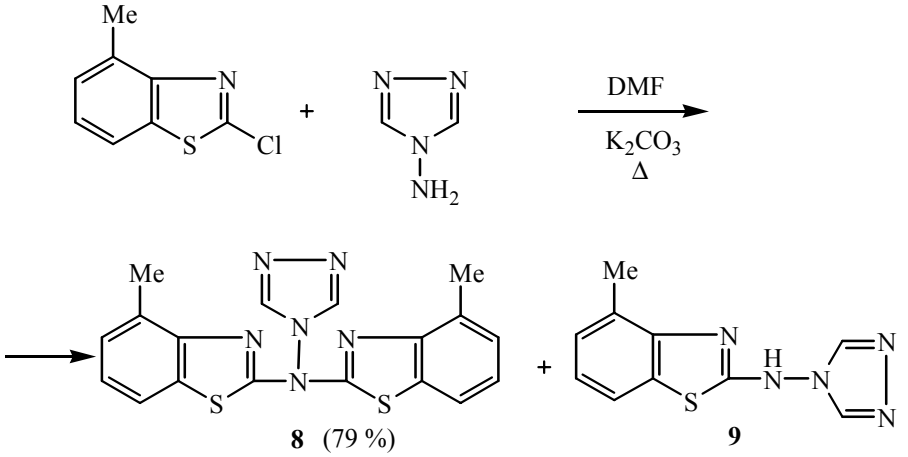


The authors explain the formation of the sulfide **5** by the possible existence of the complex **6** in the transition state. The formation of such a complex is promoted by the increase of the positive charge at the α-carbon atom of the thiazole ring in the sulfide **4** as a result of the formation of a salt with the hydrogen chloride released in the reaction.

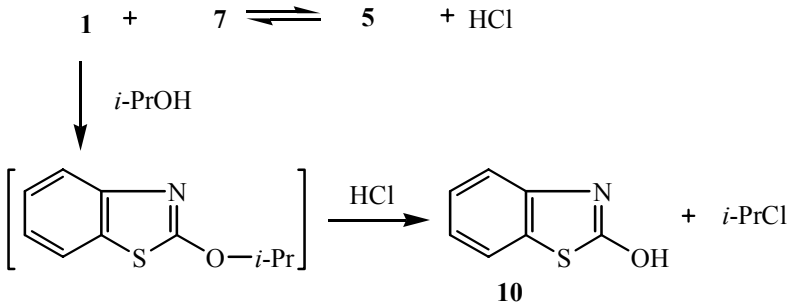
Dissociation of the complex **6** leads to 2-mercaptobenzothiazole (**7**), which reacts with the chloride **1**, forming the sulfide **5**.



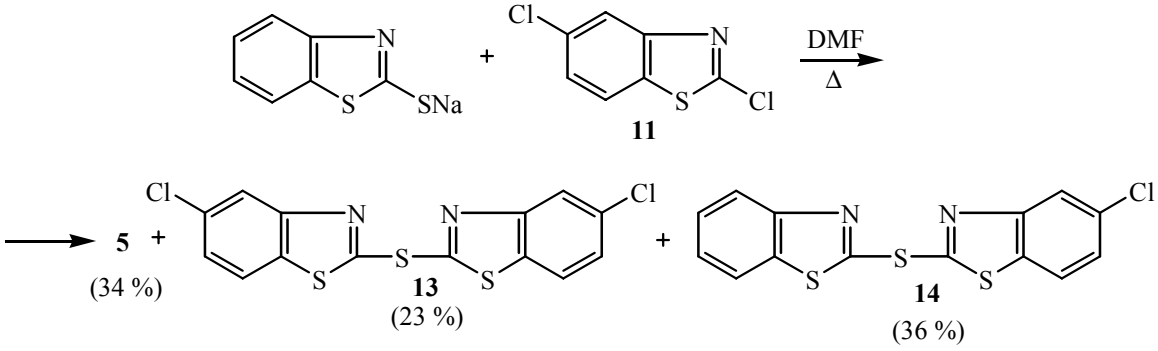
In the reaction of 2-chloro-4-methylbenzothiazole with 4-amino-4H-1,2,4-triazole in the presence of potassium carbonate (molar ratios 1:2:1) in DMF (boiling, 3 h) the main reaction product is 4-[di(4-methyl-2-benzothiazolyl)amino]-4H-1,2,4-triazole (**8**) [8]. Small amounts of the monosubstitution product (the amine **9**) are formed.

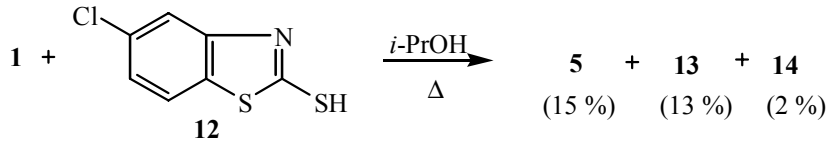


The reaction of the chlorine derivative **1** with the thiol **7** in alcohols is an equilibrium process [9, 10]. For example, in 2-propanol at 82°C equilibrium is reached after 30 min, and the yield of the sulfide **5** here amounts to 72%. Increase of the reaction time to 3 and 5 h reduces the yield of the sulfide **5** to 65 and 56% respectively, and 2-hydroxybenzothiazole (**10**) is formed as side product.



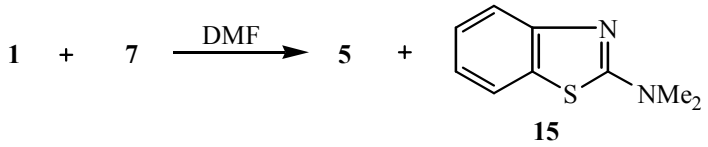
It is interesting to note that the reactions of the sodium derivative of the thiol **7** with 2,5-dichlorobenzothiazole (**11**) in DMF (boiling, 5 h) or of the chloride **1** with 5-chloro-2-mercaptobenzothiazole (**12**) in 2-propanol (boiling, 30 min) lead to the same reaction products, i.e., the sulfide **5**, di(5-chloro-2-benzothiazolyl) sulfide (**13**), and 2-(2-benzothiazolylthio)-5-chlorobenzothiazole (**14**), but in different proportions [11].





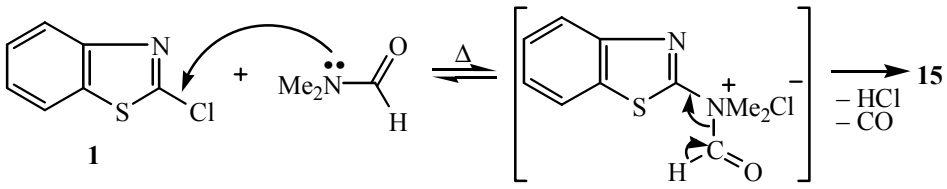
The authors point out that the sulfides **5** and **13** can be synthesized with quantitative yields by heating (140-160°C 5 h) equimolar amounts of the sodium derivatives of the thiols **7** or **12** with 2-chloro- or 2,5-dichlorobenzothiazole (**1**) or (**11**) in DMF or DMSO.

At the same time, depending on the reaction conditions, the reaction of the chloride **1** with the thiol **7** in DMF gives the sulfide **5**, 2-dimethylaminobenzothiazole (**15**), or a mixture of these compounds [9, 11].

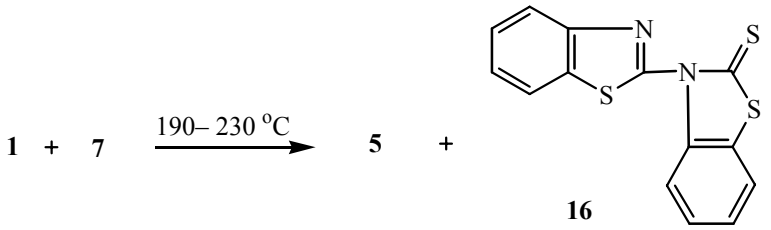


Molar ratio **1**:**7**	Reaction conditions		Composition of reaction products, %		
	T, °C	*t*, h	chloride **1**	sulfide **5**	amine **15**
1:1	80-90	5	—	100	—
1:1	80-90	24	2.6	97.4	—
2:1	80-90	5	18.6	81.4	—
1:1	150-160	5	—	22.3	77
2:1	150-160	5	—	—	100

The authors consider that the amine **15** is the product of the reaction of the chloride **1** with DMF.



In the reaction of the chloride **1** with the thiol **7** or its sodium derivative at 190-230°C (5 h) significant amounts of 2-(2-thioxo-3-benzothiazolinyl)benzothiazole (**16**) are formed in addition to the sulfide **5** [12].

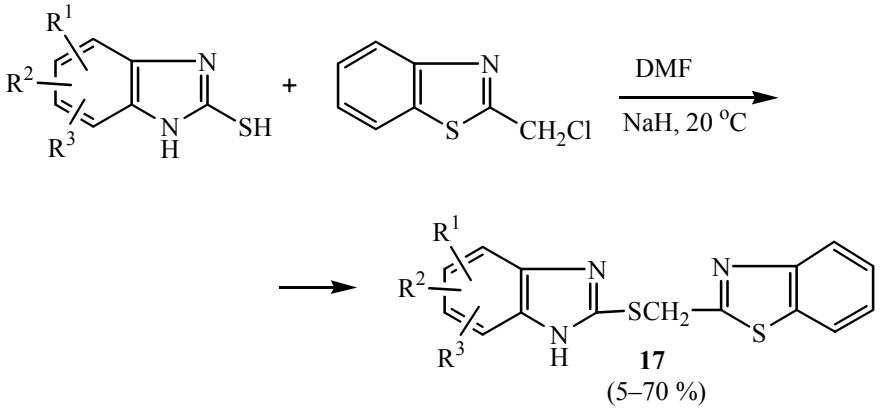


Molar ratio **1**:**7**	Solvent	Reaction temp., °C	Composition of reaction products, %	
			sulfide **5**	thione **16**
1:1.25	–	225-230	23.6	76.4
1:1.35	Decalin	190-200	41.3	58.7
1:1.35*	Decalin	190-200	50.5	49.5
1:1.35	Diglyme	225-230	26.6	73.4

* With the use of sodium mercaptide.

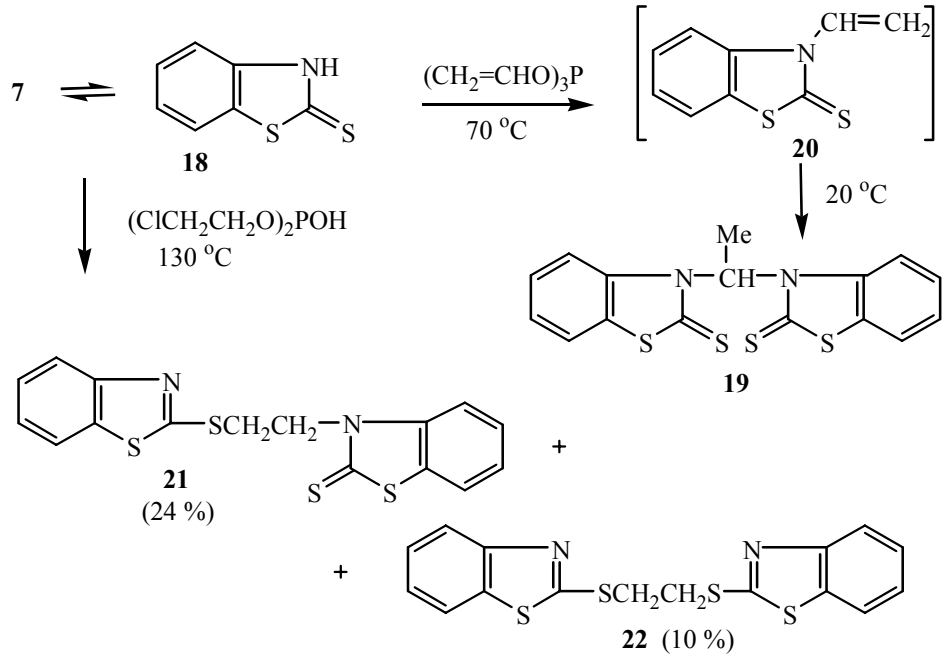
Similarly, a mixture of the sulfide **13** (23%) and 2-(5-chloro-2-thioxo-3-benzothiazolinyl)-5-chlorobenzothiazole was obtained with a yield of 97% from the chloride **11** and the thiol **12** [12].

Alkylation of 2-mercaptobenzimidazole with 2-chloromethylbenzothiazole in DMF in the presence of sodium hydride leads to 2-(2-benzimidazolylthiomethyl)benzothiazoles (**17**) [13].



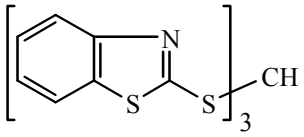
$R^1 – R^3$ = H, Hal, AlkO, Ac

The thiol **7** reacts with trivinyl- and di(β-chloroethyl) phosphite in the tautomeric form of benzothiazoline-2-thione (**18**) [14]. When the latter is heated (70°C) with trivinyl phosphite (molar ratio 3:1) in toluene the only product is 1,1-di(2-thioxo-3-benzothiazolinyl)ethane (**19**), the formation of which the authors explain by addition of the thione **18** to the intermediate 3-vinylbenzothiazoline-3-thione (**20**).

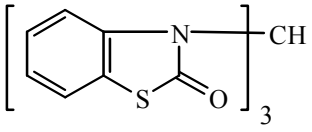


In the reaction of the thione **18** with di(β-chloroethyl) phosphite (molar ratio 1:1, 130°C, 2.5 h) the two isomeric compounds 1-(2-benzothiazolylthio)-2-(2-thioxo-3-benzothiazolinyl)ethane (**21**) and 1,2-di(2-benzothiazolylthio)ethane (**22**) are formed.

The reaction of the thiol **7** with dichlorocarbene, generated from sodium trichloroacetate in anhydrous dioxane (100°C, 8 h), leads to tris(2-benzothiazolylthio)methane (**23**) [15]. From benzothiazol-2-one under analogous conditions tris(2-oxo-3-benzothiazolinyl)methane (**24**) was obtained [16].



23 (40 %)



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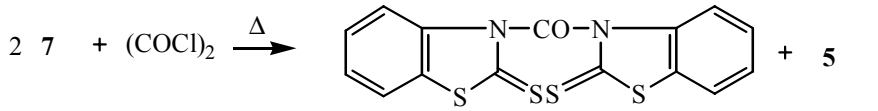
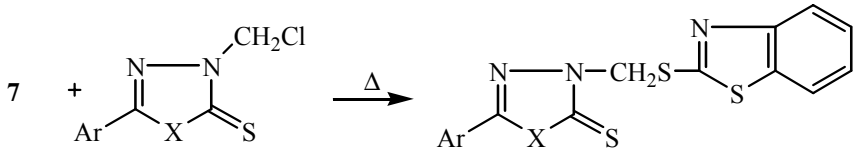
The reaction of the thiol **7** with oxalyl chloride in benzene (boiling, 24 h) leads to the formation of bis(2-thioxo-3-benzothiazolinyl)carbonyl (**25**) together with the sulfide **5**.



25 (19 %) (81 %)

From the thiol **12** under analogous conditions only the sulfide **13** was obtained with a yield of 90% [9].

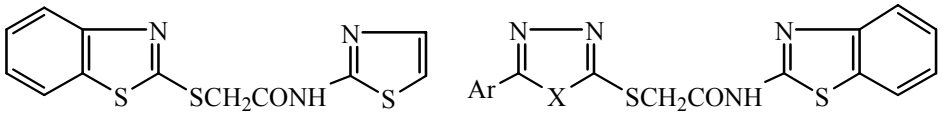
Alkylation of the thiol **7** with 5-aryl-3-chloromethyl-1,3,4-oxa(thia)diazoline-2-thiones in an alcohol solution of alkali (boiling, 20-30 min) gave 5-aryl-3-(2-benzothiazolylthiomethyl)-1,3,4-oxa(thia)diazoline-2-thiones **26a**,**b** [17, 19].



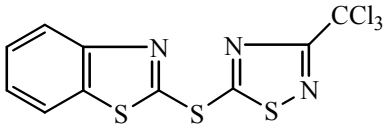
26a,**b** (65–75 %)

a X = O , **b** X = S; Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4

The N-(2-thiazolyl)amide of (2-benzothiazolyl)acetic acid (**27**) was synthesized by the reaction of equimolar amounts of the thiol **7** and the N-(2-thiazolyl)amide of chloroacetic acid in ethanol in the presence of potassium hydroxide [20]. From 5-aryl-1,3,4-oxa(thia)diazoline-2-thiones and the N-(2-benzothiazolyl)amide of chloroacetic acid under analogous conditions the N-(2-benzothiazolyl)amides of (5-aryl-1,3,4-oxa(thia)diazol-2-ylthio)acetic acids **28a**,**b** were obtained [17, 19].



27 (70 %) **28a**,**b**

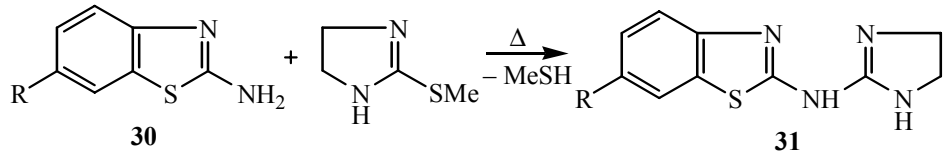


29

a X=O, **b** X=S; Ar = Ph, 4-ClC_6H_4

The synthesis of 5-(2-benzothiazolylthio)-3-trichloromethyl-1,2,4-thiadiazole (**29**) (an analog of the well known product etridiazole) from the thiol **7** and 5-chloro-3-trichloromethyl-1,2,4-thiadiazole in the presence of hydrogen chloride acceptors was described in [21].

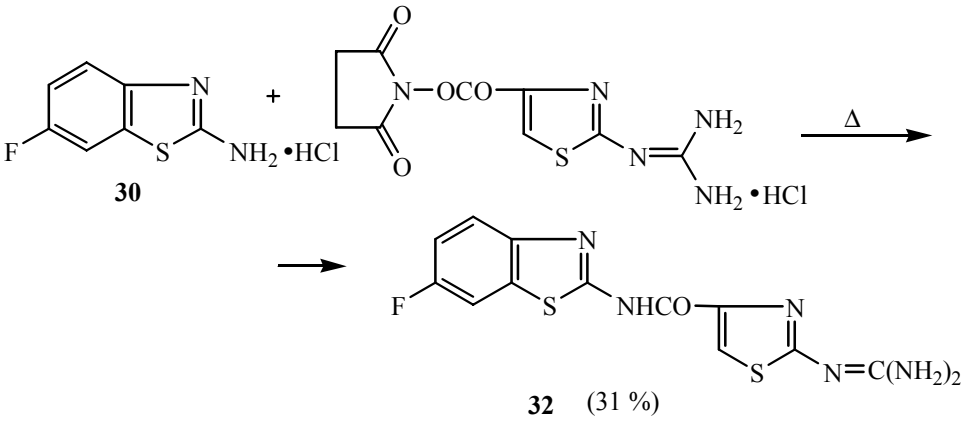
2-(2-Amino-6-R-benzothiazolyl)-Δ^2-imidazolines **31** are formed when 2-amino-6-R-benzothiazoles **30** are boiled with 2-methylthio-Δ^2-imidazoline in ethanol [22].



30 **31** (60–68 %)

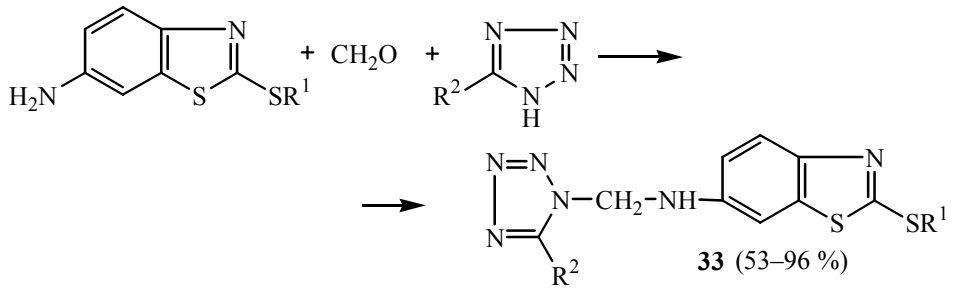
R = H, Cl, Br, MeO, H_2NSO_2

A method was proposed for the synthesis of the N-(6-fluoro-2-benzothiazolyl)amide of 2-guanidinothiazole-4-carboxylic acid (**32**) by the reaction of the hydrochlorides of 2-amino-6-fluorobenzothiazole (**30**) and 2-guanidinothiazole-4-carboxylic ester in N-methylpyrrolidone at 125°C (6 h) [23].



30 **32** (31 %)

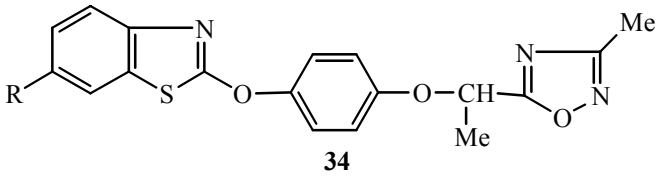
6-(1-Methyl-5-R^2-tetrazolylamino)-2-(R^1-thio)benzothiazoles (**33**) were obtained by the Mannich reaction from 6-amino-2-(R^1-thio)benzothiazoles, 5-R^2-tetrazoles, and 34% formaldehyde in ethanol at 35-40°C [24].



33 (53–96 %)

R^1 = Alk (C_1–C_9), CH_2=$CHCH_2$, $PhCH_2$; R^2 = Ph, 4-$O_2NC_6H_4$, 3,4-$Cl_2C_6H_3$

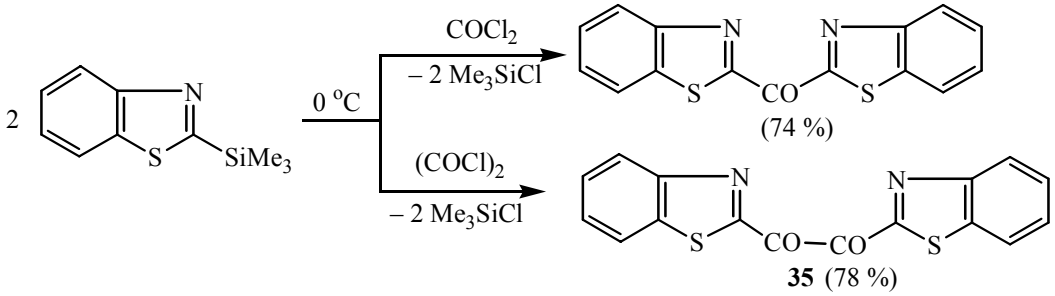
The production of the hydroquinone ethers **34** by the reaction of 2-(4-hydroxyphenoxy)-6-R-benzothiazoles with 5-(1-bromoethyl)-3-methyl-1,2,4-oxadiazole in acetonitrile in the presence of potassium carbonate has been described [25].



34

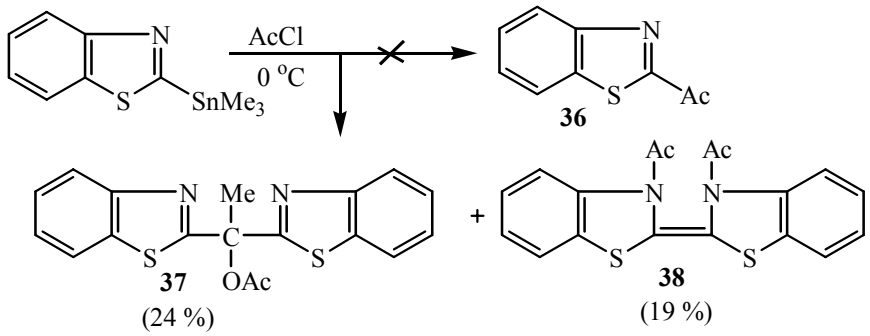
R = H, Cl, Br

Treatment of 2-(trimethylsilyl)benzothiazole with phosgene (molar ratio 2:1) in dichloromethane at 0°C leads to the formation of di(2-benzothiazolyl) ketone [26]. The diketone **35** was obtained under similar conditions from oxalyl chloride.

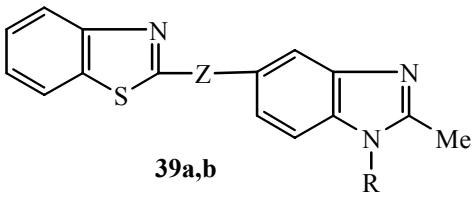


35 (78 %)

At the same time instead of the expected 2-acetylbenzothiazole (**36**) treatment of 2-trimethylstannylbenzothiazole with an equimolar amount of acetyl chloride in carbon tetrachloride at 0°C leads to the formation of two compounds – methyl α,α-di(2-benzothiazolyl)acetate (**37**) and 3,3'-diacetyl-2,2'-dibenzothiazolinylidene (**38**) [26].



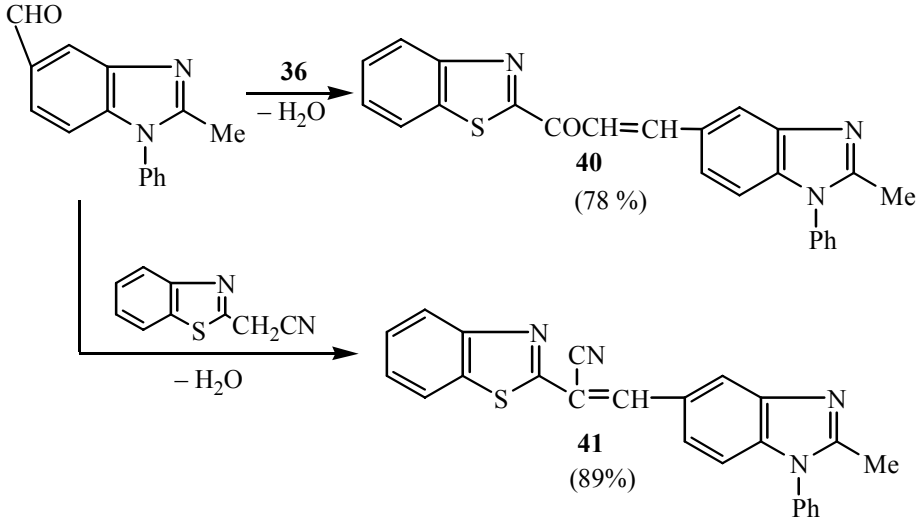
It is known [27, 28] that 1-alkyl(aryl)-2-methylbenzimidazoles with electron-withdrawing substituents at position 5 are used for the production of imidocyanine dyes having specific optical characteristics. In [29] the synthesis of 5-(2-benzothiazolyloxy)-1-ethyl-2-methyl- and 5-(2-benzothiazolyloxycarbonyl)-2-methyl-1-phenylbenzimidazole **39a** and **39b** respectively by the reaction of the chloride **1** with the sodium derivative of 1-ethyl-5-hydroxy-2-methylbenzimidazole in xylene (boiling, 8 h) or of the sodium derivative of 2-hydroxybenzothiazole with 2-methyl-1-phenylbenzimidazole-5-carbonyl chloride in toluene (boiling, 30 min) was described.



39a,b

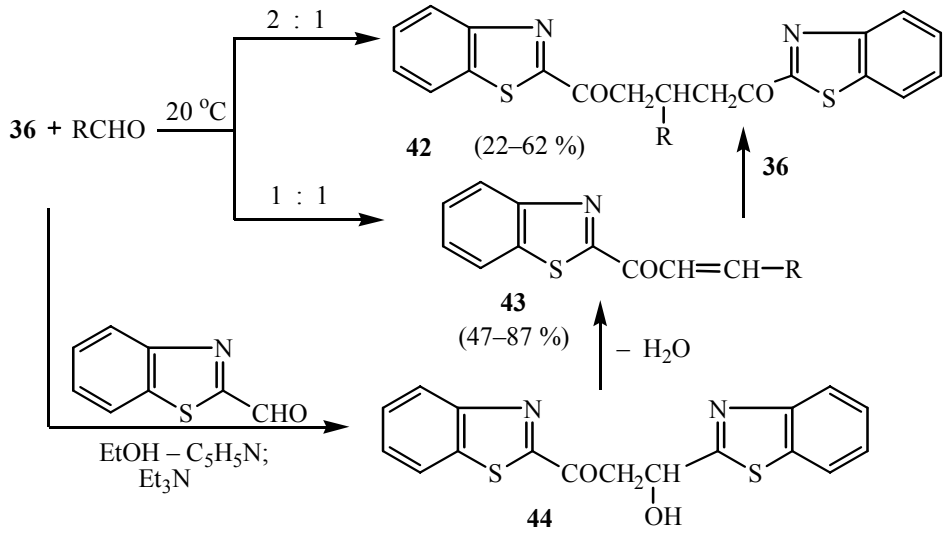
a Z = O, R = Et ; **b** Z = OC(O), R = Ph

The condensation of 5-formyl-2-methyl-1-phenylbenzimidazole with 2-acetylbenzothiazole (**36**) in absolute ethanol in the presence of piperidine or with 2-cyanomethylbenzothiazole in picoline (100°C, 2 h) leads respectively to the 1,3-disubstituted 2-propenone **40** or to α-(2-benzothiazolyl)-β-(2-methyl-1-phenyl-5-benzimidazolyl)acrylonitrile (**41**) [30].



The condensation of the ketone **36** with aromatic and heteroaromatic aldehydes leads to the formation of various products, depending on the reaction conditions [30, 31]. For example, the reaction of the ketone **36** (20°C, 3-20 days) with aldehydes (molar ratio 2:1) in absolute ethanol in the presence of catalytic amounts of piperidine leads to 1,5-di(2-benzothiazolyl)-3-R-pentane-1,5-diones (**42**).

The condensation of equimolar amounts of the ketone **36** and aldehydes under analogous conditions gives 1-(2-benzothiazolyl)-3-R-2-propen-1-ones (**43**), which form the 1,5-diketones **42** when boiled with the ketone **36** in absolute ethanol in the presence of piperidine.



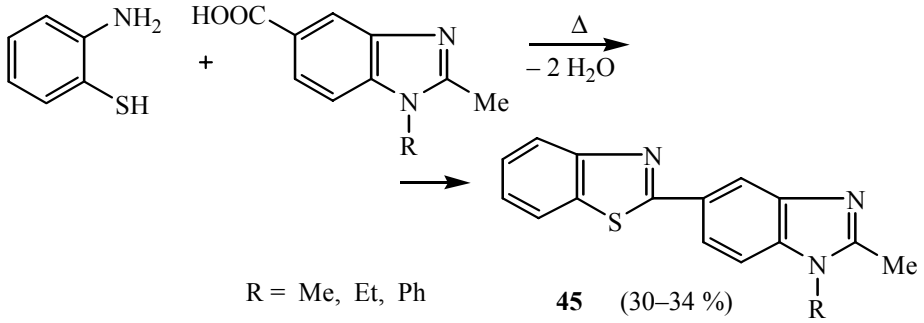
R = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-furyl, 2-thienyl, 2-pyridyl, 2-quinolinyl, 2-benzothiazolyl

The reaction of the ketone **36** (20°C) with 2-formylbenzothiazole (molar ratio 1:1) in a mixture of ethanol and pyridine in the presence of catalytic amounts of triethylamine gave a 41% yield of the aldol condensation product 3-hydroxy-1,3-di(2-benzothiazolyl)propan-1-one (**44**). When boiled in acetic anhydride the product forms the corresponding analog of chalcone **43** (yield 64%).

1.2. Synthesis of Benzothiazolylazoles by Cyclization

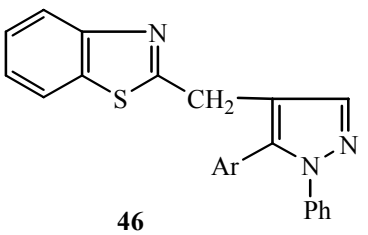
In this section we examine methods for the synthesis of benzothiazolylazoles based on the following approaches: A compound with a benzothiazole fragment is formed during the reaction of reagents containing an azole ring; the reaction of functionally substituted benzothiazoles with suitable reagents leads to the formation of an azole ring.

1.2.1. Cyclization with the Formation of Benzothiazole Fragments. 5-(2-Benzothiazolyl)-1-R-2-methylbenzimidazoles **45** were synthesized by the condensation of 1-R-2-methylbenzimidazole-5-carboxylic acids with *o*-aminothiophenol under pressure at 240°C [32].

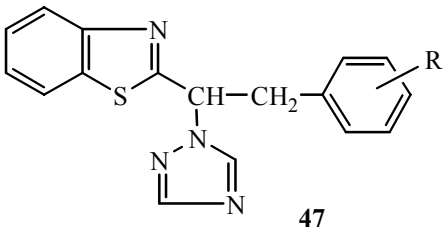


R = Me, Et, Ph **45** (30–34 %)

According to patent data, the condensation of *o*-aminothiophenol with (5-aryl-1-phenyl-4-pyrazolyl)acetyl [33] or β-aryl-α-(1H-1,2,4-triazol-1-yl)propionyl [34] chlorides in N,N-dimethylaniline or toluene leads to the benzothiazoles **46** and 1-(2-benzothiazolyl)-1-(1H-1,2,4-triazol-1-yl)-2-arylethanes (**47**) respectively.



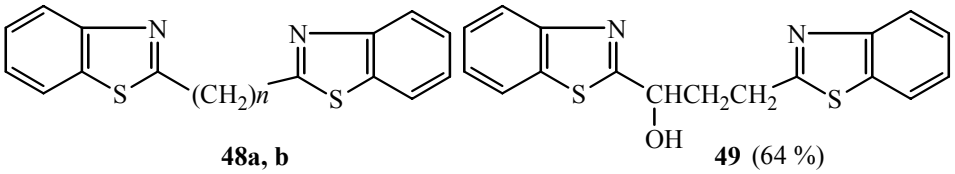
46



47

Ar = Ph, 4-ClC_6H_4; R = H, Hal, Alk, AlkO

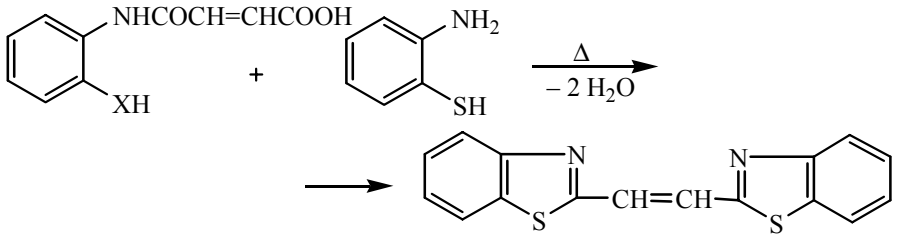
The reaction of *o*-aminothiophenol with malonic ester [27, 35] or with glutaric acid (165-170°C) [36] leads to the formation of di(2-benzothiazolyl)methane (**48a**) and 1,3-di(2-benzothiazolyl)propane (**48b**) respectively. At the same time the reaction of *o*-aminothiophenol with α-hydroxyglutaric acid (molar ratio 2:1) at 160°C under pressure gives 1,3-di(2-benzothiazolyl)-1-propanol (**49**) [37].



48a, b **49** (64 %)

a $n = 1$, **b** $n = 3$

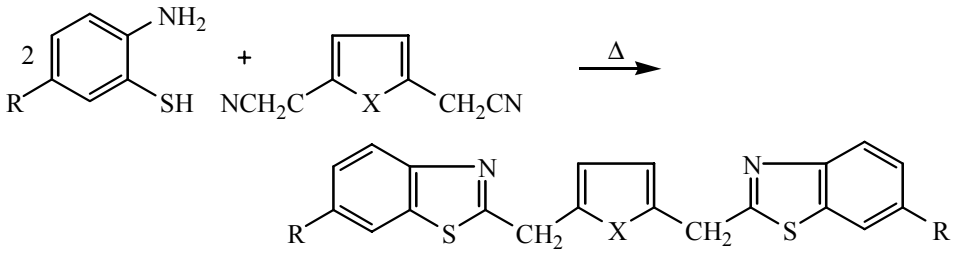
1-(2-Benzothiazolyl)-2-(2-benzothiazolyl)ethylenes **50a-c** were synthesized by the condensation of equimolar amounts of *o*-aminothiophenol and the 2-amino-, 2-hydroxy-, and 2-mercaptophenylmonoamides of maleic acid in polyphosphoric acid at 220-230°C (3 h) [38].



50a–c (50–60 %)

a X = NH, **b** X = O, **c** X = S

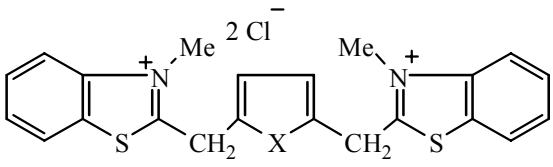
The production of 2,5-disubstituted derivatives of furan and thiophene containing two benzothiazole groups was reported in [39-41]. For example, the derivatives **51** are formed when 2-amino-5-R-thiophenols are heated (190°C, 1 h) with 2,5-di(cyanomethyl)furan or 2,5-di(cyanomethyl)thiophene.



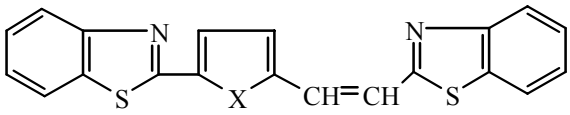
51 (70–79 %)

R = H, EtO, MeOOC; X = O, S

The methodichloride derivatives **52a**,**b** were synthesized by the reaction of *o*-(methylamino)thiophenol with the dichlorides of furan-2,5- and thiophene-2,5-acetic acids in anhydrous ether.



52a,b (22–57 %)

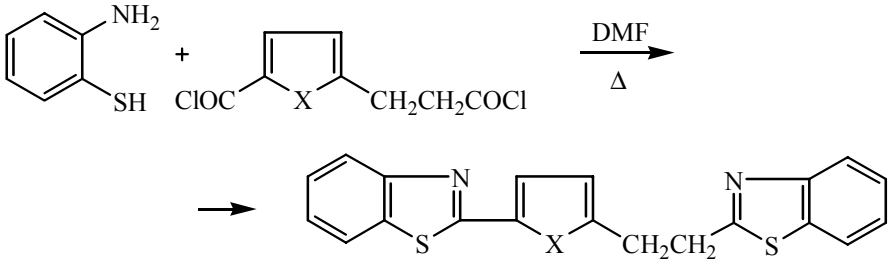


53a (81 %), **b** (62 %)

52, 53 a X = O, **b** X = S

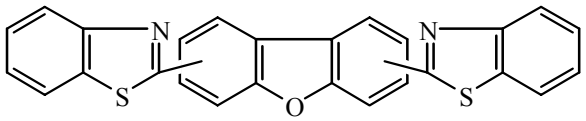
The condensation (130°C, 3 h) of 5-(2-benzothiazolyl)furfural with 2-methylbenzothiazole in the presence of zinc chloride gave 2-(2-benzothiazolyl)-5-[β-(2-benzothiazolyl)vinyl]furan (**53a**). The analogous derivative of thiophene **53b** is formed in the reaction (115°C, 2 h) of *o*-aminothiophene with 2-[β-(2-benzothiazolyl)vinyl]-5-cyanothiophene.

2-(2-Benzothiazolyl)-5-[β-(2-benzothiazolyl)ethyl]furan (**54a**) and the corresponding thiophene derivative **54b** were synthesized with low yields as a result of the condensation of *o*-aminothiophene with the dichlorides of the respective dicarboxylic acids in DMF.

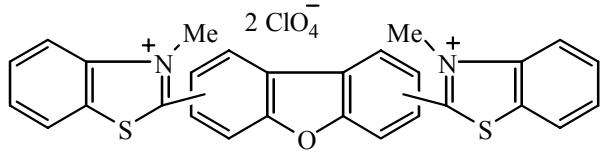


a X = O, **b** X = S **54a**,**b** (10–26 %)

The 2,8- and 4,6-di(2-benzothiazolyl)dibenzofurans **55** were obtained by the condensation of the nitriles or chlorides of the respective dibenzofurandicarboxylic acids with *o*-aminothiophenol, while the quaternary salts **56** were obtained from *o*-(methylamino)thiophenol [42].

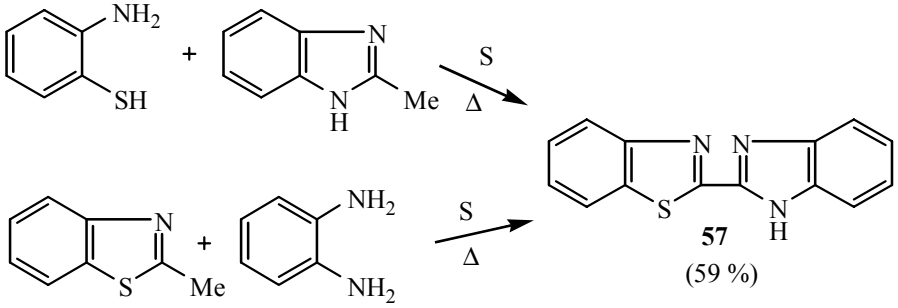


55



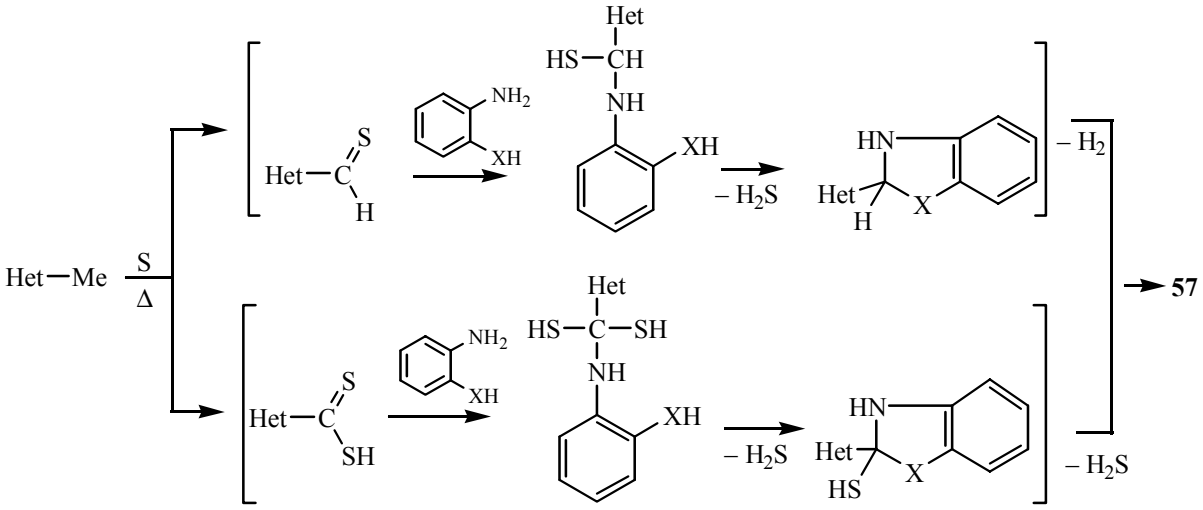
56

The condensation (150-210°C) of 2-methylbenzimidazole with *o*-aminothiophenol and sulfur (molar ratios 1:1:3) leads to 2-(2-benzimidazolyl)benzothiazole (**57**) [43, 44]. The bisheterocycle **57** can also be obtained with a yield of 50% by the reaction of 2-methylbenzothiazole with *o*-phenylenediamine and sulfur under analogous conditions [45, 46].



57
(59 %)

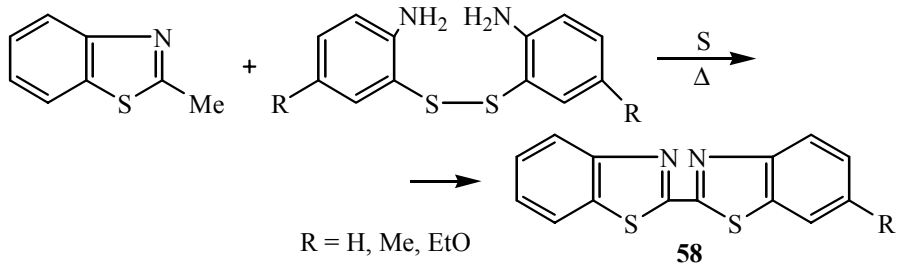
It is suggested that compound **57** is formed by a modified Vilgerodt–Kindler reaction with the intermediate generation of either thioaldehydes or dithiocarboxylic acids [43, 45].



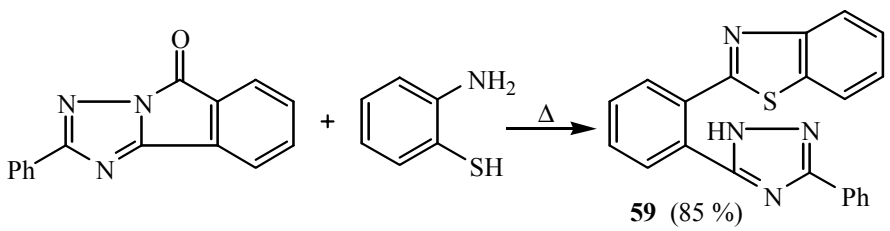
Het = 2-benzimidazolyl, X = S; Het = 2-benzothiazolyl, X = NH

The same bisheterocycle was synthesized with a 50% yield by the reaction of 2-trichloromethylbenzimidazole with *o*-aminothiophenol and triethylamine (molar ratios 1:1:3) in ethanol at 20°C [47].

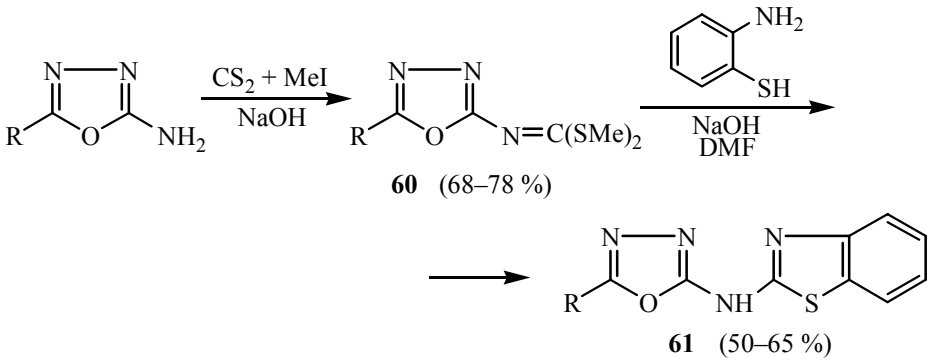
2,2'-Dibenzothiazolyl was obtained with a yield of 34% by the condensation of 2-methylbenzothiazole with *o*-aminothiophenol and sulfur [43, 45]. From 2-methylbenzothiazole, 2,2'-diamino-5,5'-R_2-diphenyl disulfide (molar ratios 1:5:3) under analogous conditions small yields of 6-R-2,2'-dibenzothiazolyls **58** were obtained [43].



When 2-phenyl-5H-1,2,4-triazolo[5,1-*a*]isoindol-5-one is heated (170-180°C, 15-18 h, argon) with *o*-aminothiophenol in PPA the –CO–N< bond is cleaved with the formation of 1-(2-benzothiazolyl)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)benzene (**59**) [48].

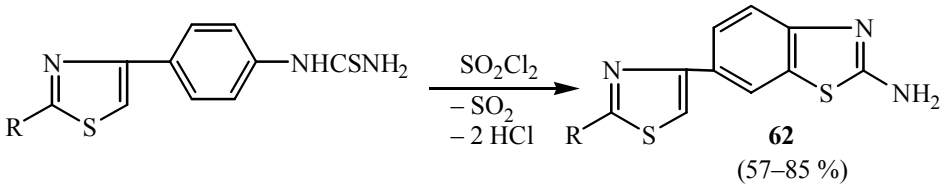


The reaction of 2-amino-5-aryl-1,3,4-oxadiazoles with carbon disulfide and methyl iodide in DMF in the presence of alkali gave di(methylthio)methyleneimines **60**. Condensation of the latter with *o*-aminothiophenol in an alkaline medium (20°C, 30 min, boiling, 5-6 h) led to the formation of 5-aryl-2-(2-benzothiazolylamino)-1,3,4-oxadiazoles **61** [49].



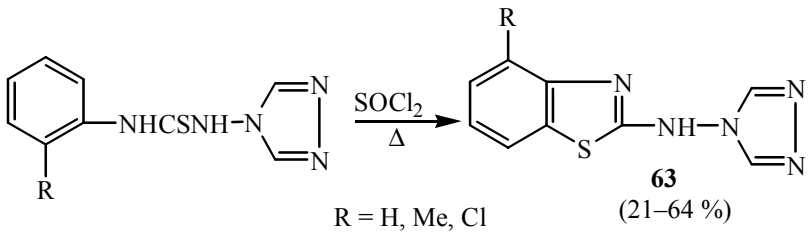
R = 3(4)-MeC_6H_4, 3(4)-ClC_6H_4, 4-$MeOC_6H_4$

2-Amino-6-(2-R-thiazol-4-yl)benzothiazoles **62** were obtained by the cyclization of N-[4-(2-R-thiazol-4-yl)phenyl]thioureas by the action of sulfuryl chloride in chlorobenzene [50].



R = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$

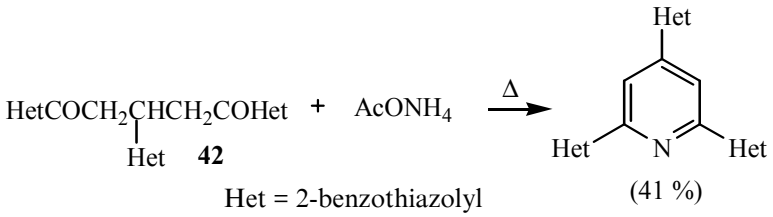
The cyclization of N-(2-R-phenyl)-N'-(4H-1,2,4-triazol-4-yl)thioureas by the action of thionyl chloride at 55°C leads to 2-(4-amino-4H-1,2,4-triazolyl)-4-R-benzothiazoles **63** [8].



R = H, Me, Cl

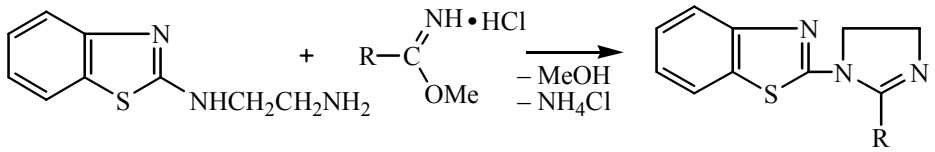
1.2.2. Cyclization Leading to the Formation of Azole Fragments. In these reactions various nitrogen-containing derivatives of benzothiazole (diamines, azides, hydrazines, thioureas, etc.), 1,3-diketones, α,β-unsaturated ketones, α-substituted ketones, and carboxylic acids of the benzothiazole series and their functional derivatives have been used as starting compounds.

2,4,6-Tri(2-benzothiazolyl)pyridine was obtained by melting (190°C, 3 h) 1,3,5-tri(2-benzothiazolyl)pentane-1,5-dione (**42**) with ammonium acetate [31].



Het = 2-benzothiazolyl

The reaction of N-(2-benzothiazolyl)ethylenediamine with the hydrochlorides of carboximidic esters in absolute methanol (0°C, 60°C, 6 h) leads to 1-(2-benzothiazolyl)-2-R-Δ^2-imidazolines **64a-d** [51].

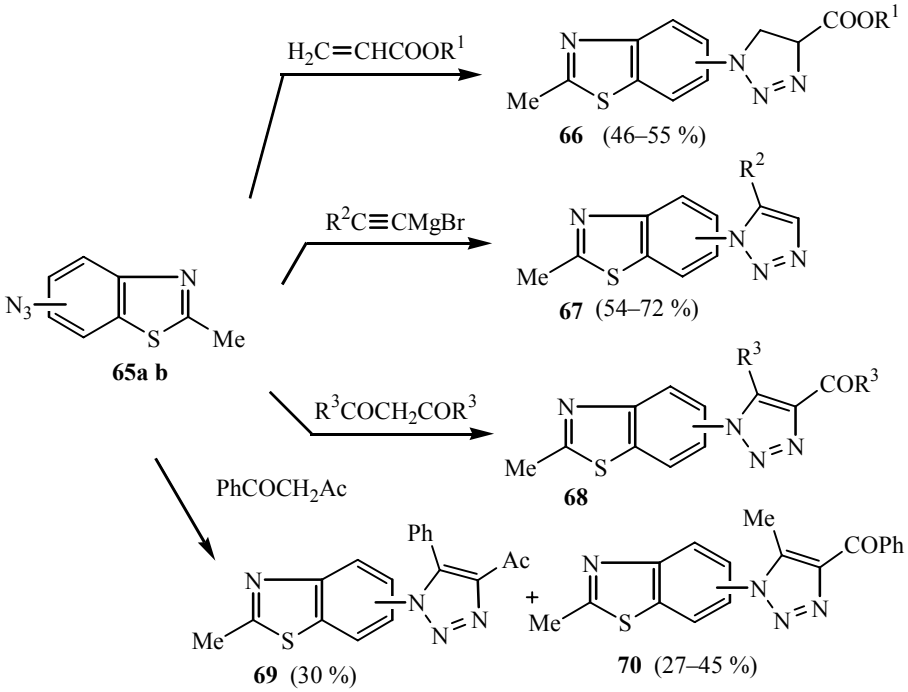


64a–d (56–71 %)

a R = Me, **b** R = Ph, **c** R = $PhCH_2$, **d** R = 5-nitro-2-furyl

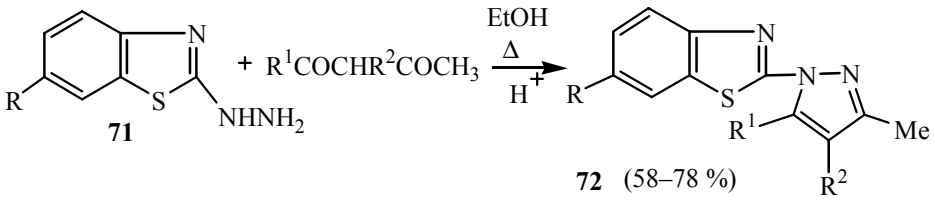
The 1,3-dipolar cycloaddition of 5- and 6-azido-2-methylbenzothiazole **65a** and **65b** to acrylic esters (molar ratio 1:4) at 20°C gives 1-[2-methyl-5(6)-benzothiazolyl]-Δ^2-1,2,3-triazoline-4-carboxylic esters **66** [52, 53].

The reaction of the azides **65a**,**b** with Iotsich complexes in ether takes place regioselectively with the formation of 1,5-disubstituted 1,2,3-triazoles **67** [54]. Condensation of the azides **65a**,**b** with symmetrical 1,3-diketones in the presence of sodium ethoxide (molar ratios 1:2:2) gave good yields of 4-acyl-1-(2-methylbenzothiazolyl)-5-R^3-1,2,3-triazoles **68**. 4-Acetyl-5-phenyl-1,2,3-triazoles **69** and their regioisomers 4-benzoyl-5-methyl-1,2,3-triazoles **70** are formed from the azides **65a**,**b** under analogous conditions.



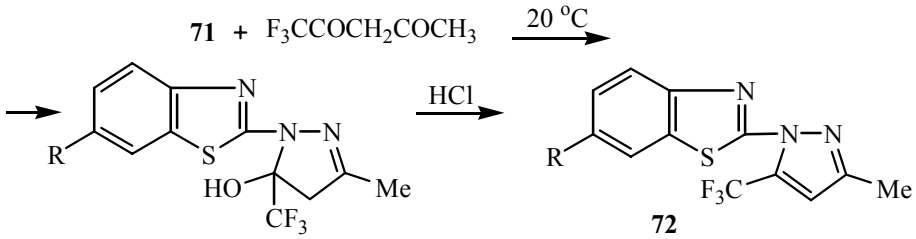
R^1 = Me, Et; R^2, R^3 = Me, Ph

The condensation of 2-hydrazino-6-R-benzothiazoles **71** with 1-R^1-3-R^2-1,3-butanediones in ethanol in the presence of catalytic amounts of acetic acid [55-59] or concentrated hydrochloric acid [60] (boiling, 2-3 h) takes place regioselectively with the formation of 1-(6-R-2-benzothiazolyl)-3-methyl-4-R^2-5-R^1-pyrazoles **72**.

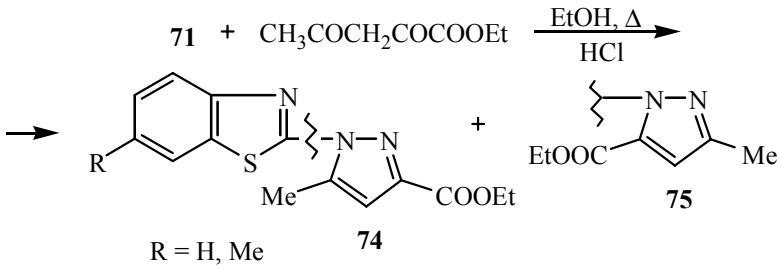


R = H, Cl, F, NO_2, Me; R^1 = Me; R^2 = H, Me, Et, *i*-Pr, Bu, $EtOOCCH_2$;
R^1 = CF_3, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, R^2 = H

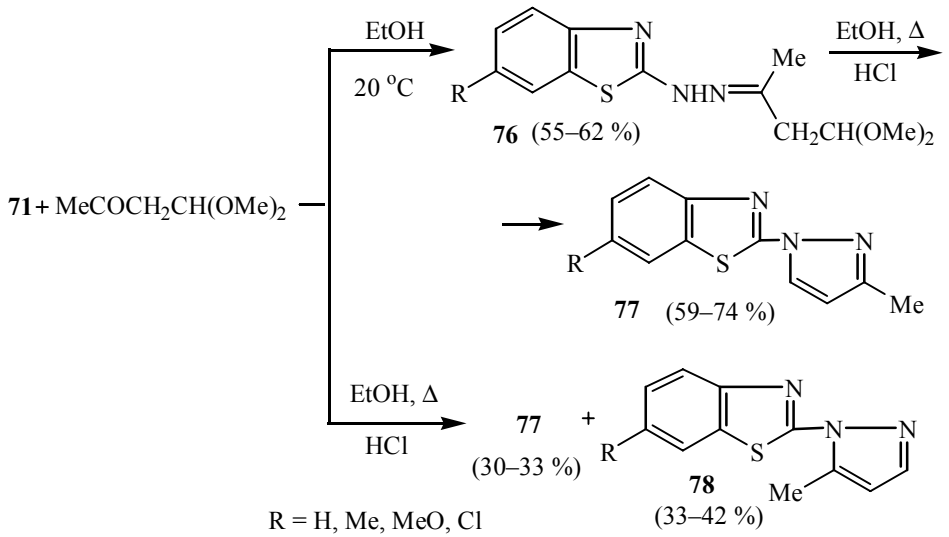
When equimolar amounts of the hydrazines **71** are kept in ethanol at 20°C (12 h) 5-hydroxy-3-methyl-5-trifluoromethyl-Δ^2-pyrazolines **73** are formed. The products are converted by treatment with an alcohol solution of hydrochloric acid into the corresponding pyrazoles **72** [59].



The reaction of the hydrazines **71** with 2,4-dioxopentanoic ester in ethanol in the presence of catalytic amounts of concentrated hydrochloric acid (boiling, 3 h) gives a 3:1 mixture of regioisomers – 5-methyl-3-pyrazolecarboxylic (**74**) and 3-methyl-5-pyrazolecarboxylic (**75**) esters [60].

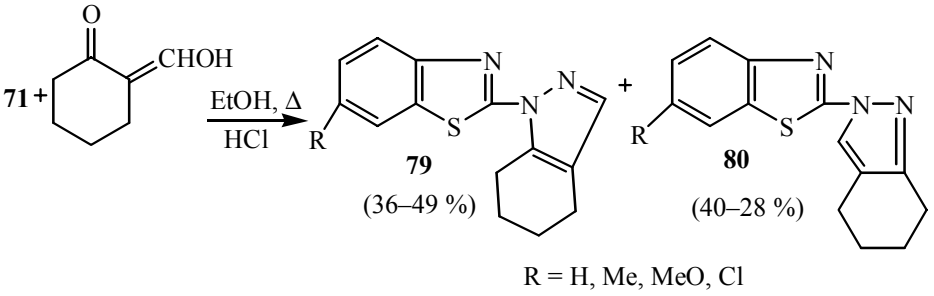


The reaction of equimolar amounts of the hydrazines **71** and β-oxobutyraldehyde dimethyl acetal in ethanol at 20°C leads to the formation of the hydrazones **76**, which undergo cyclization to 1-(6-R-2-benzothiazolyl)-3-methylpyrazoles **77** when boiled in ethanol in the presence of concentrated hydrochloric acid [60]. At the same time the regioisomeric 5-methylpyrazoles **78** are formed together with the pyrazoles **77** when the reagents are boiled in ethanol in the presence of concentrated hydrochloric acid.

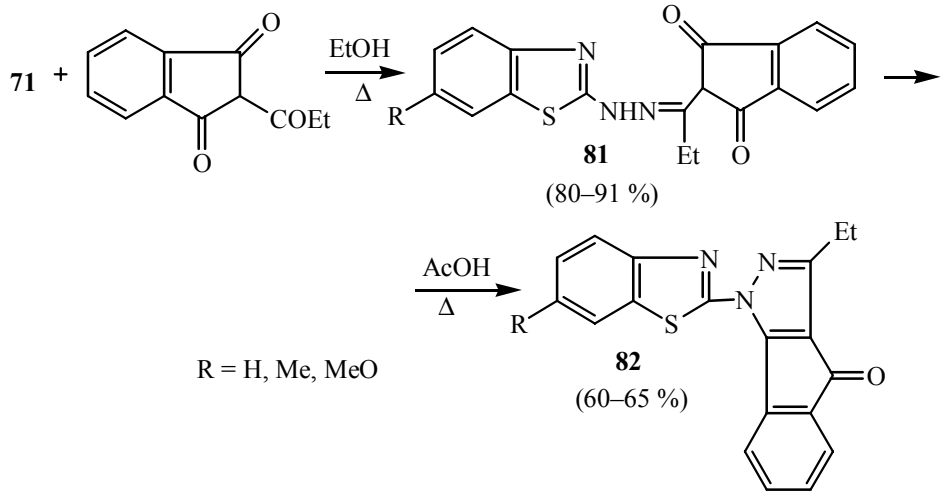


From the hydrazines **71** and malonaldehyde tetramethyl diacetal under analogous conditions 65-69% yields of 1-(6-R-2-benzothiazolyl)pyrazoles are obtained [60].

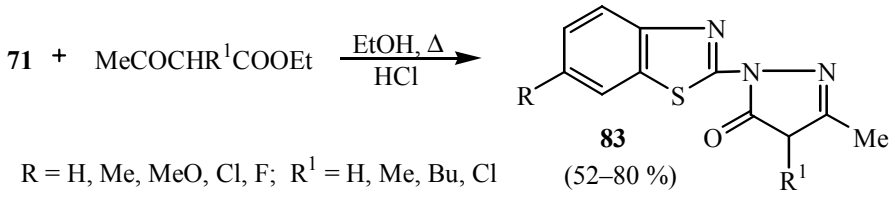
Condensation of the hydrazines **71** with 2-hydroxymethylenecyclohexanone in ethanol in the presence of concentrated hydrochloric acid leads to the isomeric tetrahydroindazoles 1-(6-R-2-benzothiazolyl)-4,5,6,7-tetrahydro-1H-indazoles **79** and 2-(6-R-2-benzothiazolyl)-4,5,6,7-tetrahydro-2H-indazoles **80** [61].



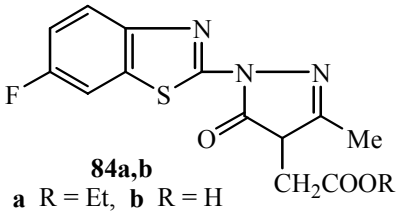
The reaction of equimolar amounts of the hydrazines **71** and 2-propionylindane-1,3-dione in ethanol (boiling, 3 h) gives the hydrazones **81**, which when boiled in acetic acid undergo cyclization to 1-(6-R-2-benzothiazolyl)-3-ethylindeno[1,2-*c*]pyrazol-4-ones **82** [62].



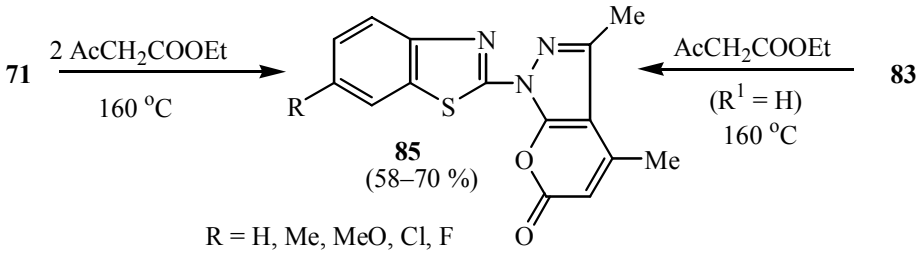
In the reaction of the hydrazines **71** with acetoacetic ester in the presence of concentrated hydrochloric acid (boiling, 4-5 h) the 1-(6-R-2-benzothiazolyl)-3-methyl-4-R'-pyrazol-5-ones **83** were obtained [57, 63].



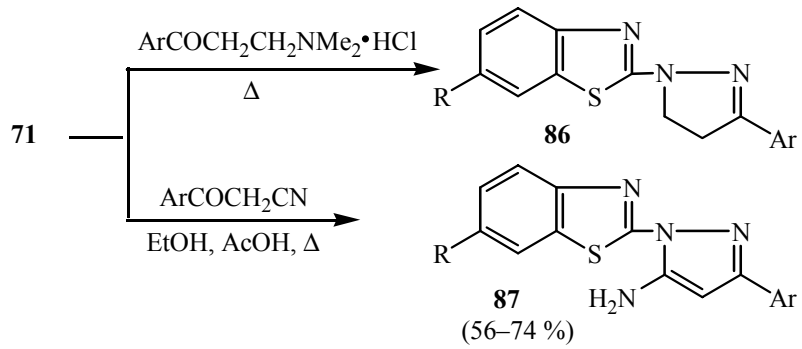
Ethyl 1-(6-fluoro-2-benzothiazolyl)-3-methyl-5-oxo-4H-pyrazolyl-4-acetate (**84a**) was obtained similarly from diethyl acetylsuccinate with a yield of 75%, and its alkaline hydrolysis gave the corresponding acid **84b** [63].



At the same time when the hydrazines **71** were heated (160°C, 1 h) with acetoacetic ester (molar ratio 1:2) the 1-(6-R-2-benzothiazolyl)-3,4-dimethylpyrano[2,3-*c*]pyrazol-6(1H)-ones **85** were obtained [63]. These compounds are also formed when equimolar amounts of the respective 5-pyrazolones **83** (R^1 = H) and acetoacetic ester are heated (160°C).

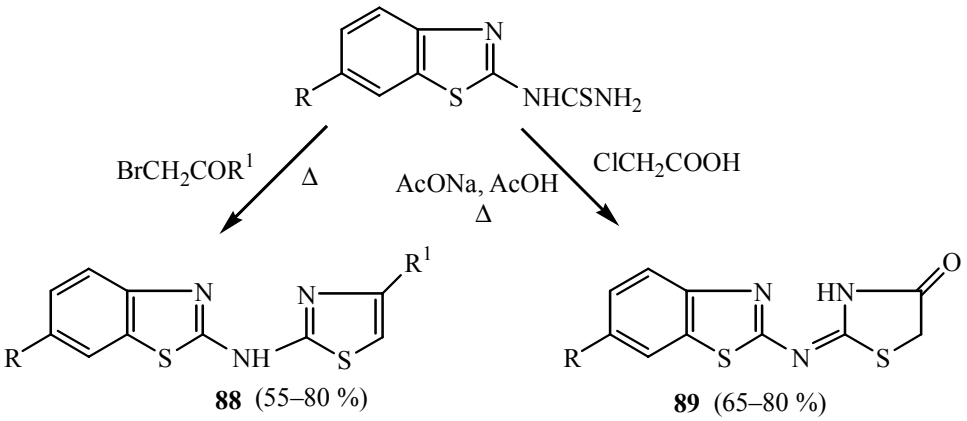


The reaction of the hydrazines **71** with the hydrochlorides of β-dimethylaminopropiophenones leads to 3-aryl-1-(6-R-2-benzothiazolyl)-Δ^2-pyrazolines **86** [64], while boiling (1-2 h) with aroylacetonitriles in ethanol in the presence of acetic acid leads to 5-amino-3-aryl-1-(6-R-2-benzothiazolyl)pyrazoles **87** [65].



R = H, Me, MeO, Cl, NO_2; Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$

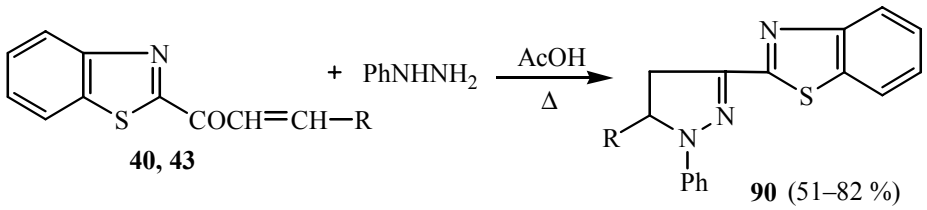
The condensation of N-(6-R-2-benzothiazolyl)thioureas with bromomethyl ketones in ethanol (boiling, 4 h) [66] or with chloroacetic acid and sodium acetate in acetic acid (boiling, 5 h) [67] gave 2-(2-amino-6-R-benzothiazolyl)-4-R^1-thiazoles **88** and 2-(6-R-2-benzothiazolylimino)thiazolidin-4-ones **89** respectively.



88 (55–80 %) **89** (65–80 %)

R = H, Me, MeO, EtO, Cl, NO_2; R^1 = Me, Ar

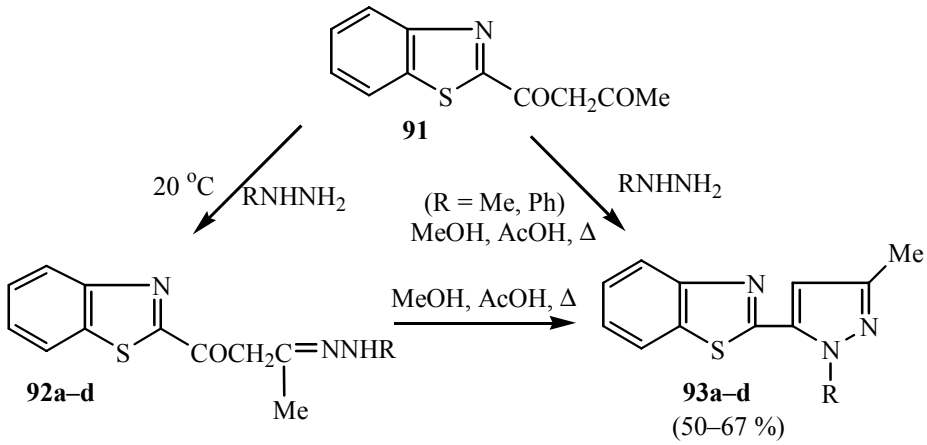
The 5-substituted 3-(2-benzothiazolyl)-1-phenyl-Δ^2-pyrazolines **90** were obtained by the condensation of α,β-unsaturated ketones **40** and **43** with phenylhydrazine in acetic acid (boiling, 2-4 h) [30].



40, 43 **90** (51–82 %)

R = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 2-furyl, 2-thienyl, 2-benzothiazolyl, 2-methyl-5-benzothiazolyl, 2-methyl-1-phenyl-5-benzothiazolyl

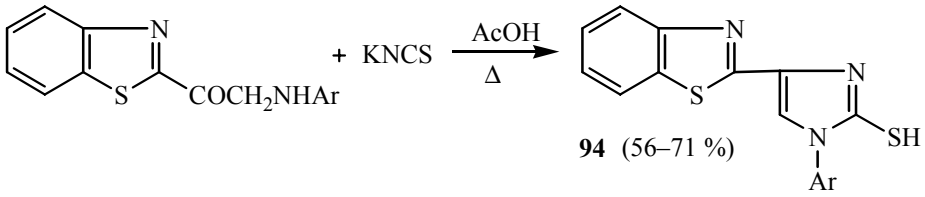
The reaction of 2-acetoacetylbenzothiazole (**91**) with hydrazine and methyl- and arylhydrazines in methanol at 20°C leads to the formation of the monohydrazones **92a-d**, which undergo cyclization to 5-(2-benzothiazolyl)-1-R-3-methylpyrazoles **93a-d** when boiled in methanol in the presence of acetic acid [68].



a R = H, **b** R = Me, **c** R = Ph, **d** R = 4-ClC_6H_4

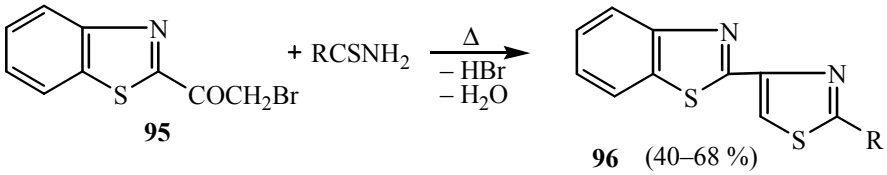
The pyrazoles **93b**,**c** were also synthesized with yields of 66 and 26% respectively by a single-stage method, i.e., by boiling equimolar amounts of the 1,3-diketone **91** and methyl- or phenylhydrazine in methanol in the presence of acetic acid.

The production of 1-aryl-4-(2-benzothiazolyl)-2-mercaptoimidazoles **94** by the Marckwald reaction, i.e., by boiling (5 min) equimolar amounts of 2-(arylaminoacetyl)benzothiazoles and potassium thiocyanate in acetic acid, was reported in [69].



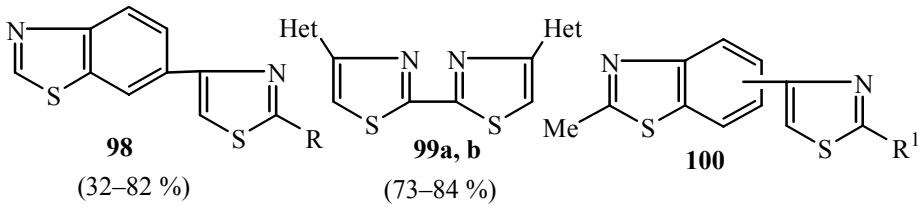
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$HOOCC_6H_4$

The 2-R-4-(2-benzothiazolyl)thiazoles **96** were synthesized by the condensation of 2-(bromoacetyl)benzothiazole (**95**) with the thioamides of carboxylic acids in benzene or ethanol (boiling, 10 min - 3 h) [70-73].



R = H, Me, Ar, $PhCH_2$, 2-thienyl, 4-pyridyl,
3,5-dimethyl-1-pyrazolyl, 1-phenyl-2-methyl, 5-benzimidazolyl

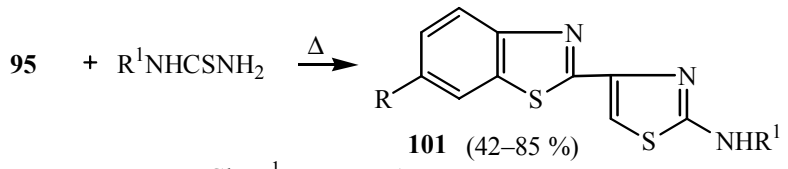
From 2-R-6-(bromoacetyl)benzothiazole **97** (R = H) and thioamides under analogous conditions 2-R-4-(6-benzothiazolyl)thiazoles **98** were synthesized [71].



98 R = H, Me, Ar, $PhCH_2$; **99 a** Het = 2-benzothiazolyl,
b Het = 6-benzothiazolyl; **100** R^1 = H, Me

The condensation of the bromo ketones **95** and **97** with dithioxamide ($H_2NCSCSNH_2$, rubeanic acid) in ethanol (boiling, 6 h) gave 4,4'-di(2-benzothiazolyl)- and 4,4'-di(6-benzothiazolyl)-2,2'-dithiazolyl **99a** and **99b** [71]. The 4-(2-methyl-5-benzothiazolyl)- and 4-(2-methyl-6-benzothiazolyl)-2-R'-thiazoles **100** were obtained by the reaction of 5- or 6-bromoacetyl-2-methylbenzothiazoles with thioformamide or with thioacetamide in toluene (110°C, 2 h) [74].

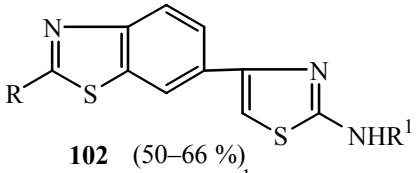
2-(R'-Amino)-4-(6-R-2-benzothiazolyl)thiazoles **101** are produced when equimolar amounts of the bromo ketones **95** and thiourea or N-substituted thioureas are boiled in ethanol [75].



101 (42–85 %)

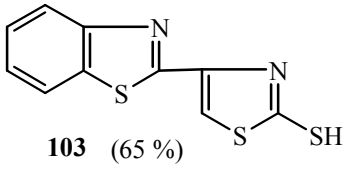
R = H, Me, Cl; R^1 = H, Me, Ar

2-(R'-Amino)-4-(2-R-6-benzothiazolyl)thiazoles **102** were obtained similarly from 2-R-6-(bromoacetyl)-benzothiazoles **97** [76].



102 (50–66 %)

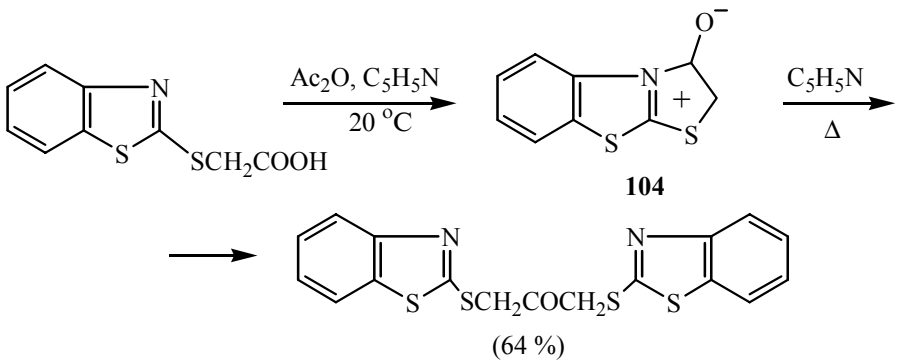
R = H, Me, CF_3; R^1 = H, Ar



103 (65 %)

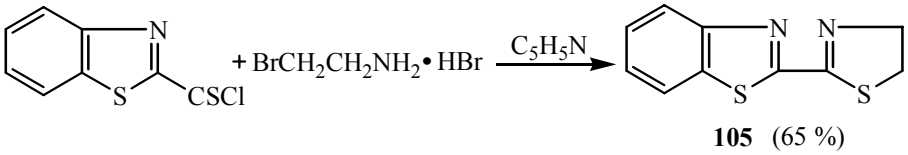
The reaction of the bromo ketone **95** with ammonium dithiocarbamate ($H_2NCSSNH_4$) in ethanol (boiling, 1 h) gives 2-mercapto-4-(2-benzothiazolyl)thiazole (**103**) [77].

Treatment of (2-benzothiazolylthio)acetic acid with a mixture of acetic anhydride and pyridine or triethylamine (20°C) gives the derivative **104**, which is converted by boiling in pyridine (5 min) into 1,3-di(2-benzothiazolylthio)acetone [78].



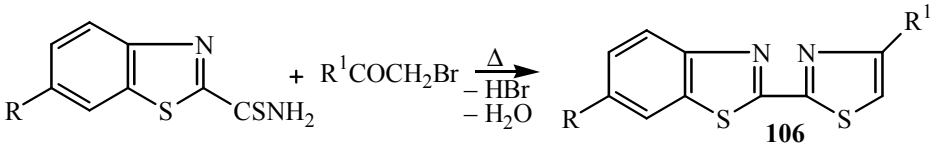
(64 %)

The condensation of 2-benzothiazolylthionyl chloride with 2-bromoethylamine in pyridine gave 2-(2-benzothiazolyl)-Δ^2-thiazoline (**105**), which is a structural analog of luciferin [79].



105 (65 %)

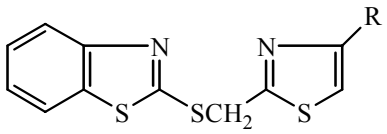
The reaction of equimolar amounts of the thioamides of 6-R-2-benzothiazolecarboxylic acids and α-bromo ketones in ethanol (boiling, 4 h) followed by treatment with aqueous ammonia leads to 2-(6-R-2-benzothiazolyl)-4-R'-thiazoles **106** [80].



106

R = H, Cl; R^1 = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-$O_2NC_6H_4$

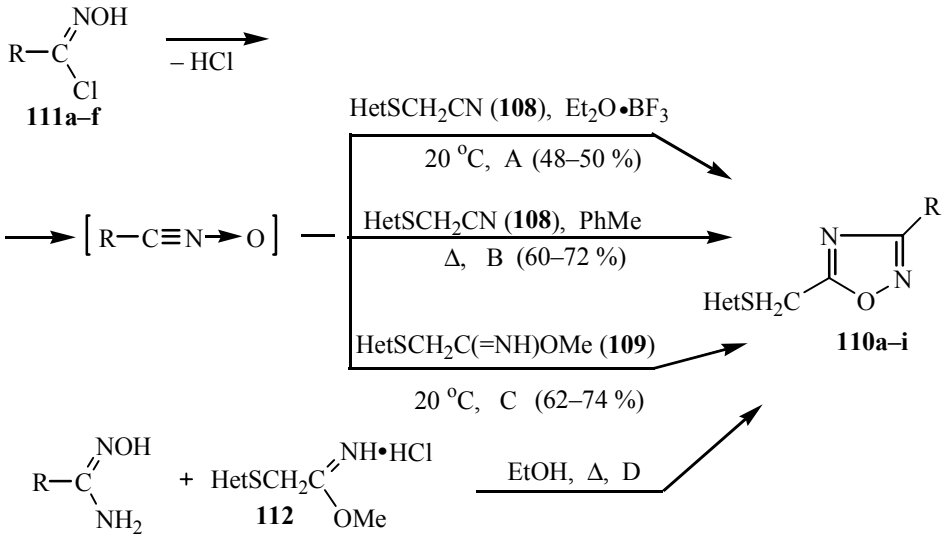
2-(2-Benzothiazolylthiomethyl)-4-R-thiazoles **107** were obtained similarly from the thioamide of (2-benzothiazolylthio)acetic acid [81].



107 (72–80 %)

R = Me, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-thienyl

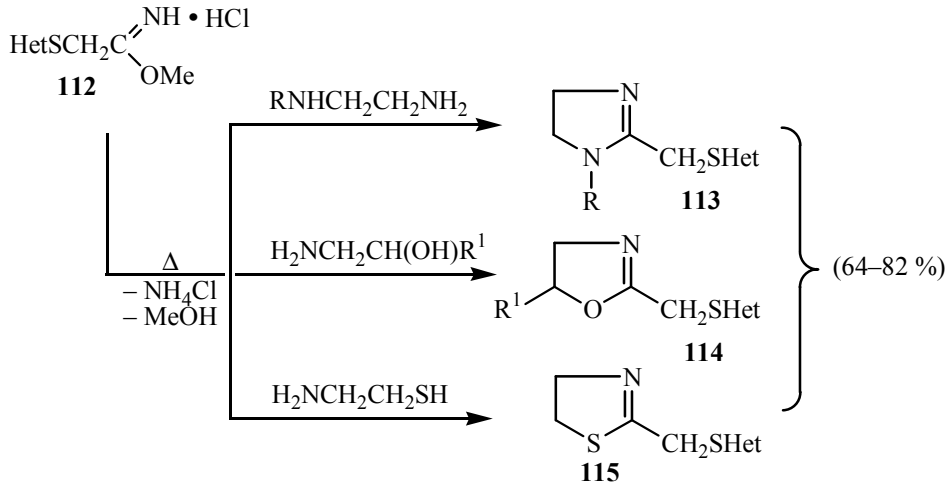
The 1,3-dipolar cycloaddition of the N-oxides of aromatic nitriles with the nitrile **108** or with methyl (2-benzothiazolyl)acetimidate (**109**) resulted in the formation of 3-aryl-5-(2-benzothiazolylthiomethyl)-1,2,4-oxadiazoles **110a-f** [81-83]. The 1,2,4-oxadiazoles **110a-f** were synthesized from the nitrile **108** by two methods: A) by reaction of the acid chlorides **111a-f**, the nitrile **108**, and triethylamine in ether; B) by boiling equimolar amounts of the acid chlorides **111a-f** and the nitrile **108** in toluene until the release of HCl had ceased.



Het = 2-benzothiazolyl; **a** R = Ph, **b** R = 4-$O_2NC_6H_4$, **c** R = 4-ClC_6H_4, **d** R = 4-MeC_6H_4, **e** R = 4-PhC_6H_4, **f** R = 5-nitro-2-furyl, **g** R = 3-pyridyl, **h** R = Me, **i** R = $ClCH_2$

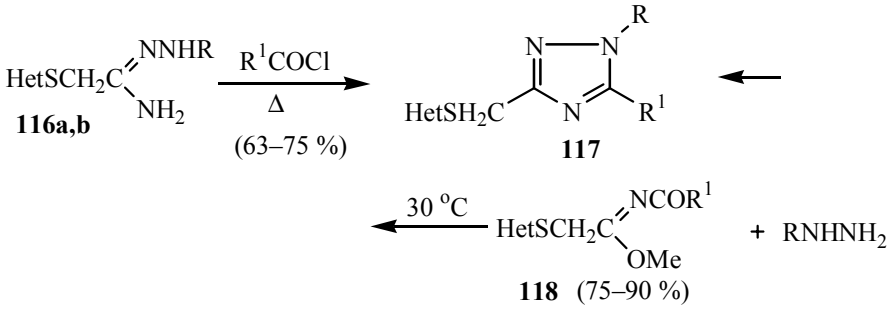
It was shown that the yields of compounds **110a-f** vary between 18-50 (method A) and 60-72 (method B) or 62-74% (method C), depending on the method of synthesis and on the reaction conditions. Average yields (44-65%) of compounds **110a**,**f-i** (method D) were likewise observed in the reaction of equimolar amounts of the amidoximes of carboxylic acids and the hydrochloride of the methyl imidate **112**.

Condensation of the hydrochloride of the imidic ester **112** with ethylenediamine, N-substituted ethylenediamines, β-amino alcohols, and 2-aminoethanethiol in absolute methanol (boiling, 2-6 h) leads respectively to 2-(2-benzothiazolylthiomethyl)-1-R-Δ^2-imidazolines **113**, 2-(2-benzothiazolylthiomethyl)-5-R^1-Δ^2-oxazolines **114**, and 2-(2-benzothiazolylthiomethyl)-Δ^2-thiazolines **115** [81, 84].



Het = 2-benzothiazolyl; R = H, Bu, $C_{12}H_{25}$, $NCCH_2CH_2$, $PhCH_2$, 4-HO-3,5-(t-Bu)$_2C_6H_2(CH_2)_3$, 2-thienylmethyl; R^1 = H, Me

When the N^1-phenyl- and N^1-(3,5-dichloro-2-pyridyl)amidrazones of (2-benzothiazolylthio)acetic acid (**116a**) and (**116b**) are heated (100-120°C, 8-12 h) with acid chlorides in toluene or DMF 1-phenyl- and 1-(3,5-dichloro-2-pyridyl)-3-(2-benzothiazolylthiomethyl)-5-R^1-1H-1,2,4-triazoles **117** are formed [81, 85-88].

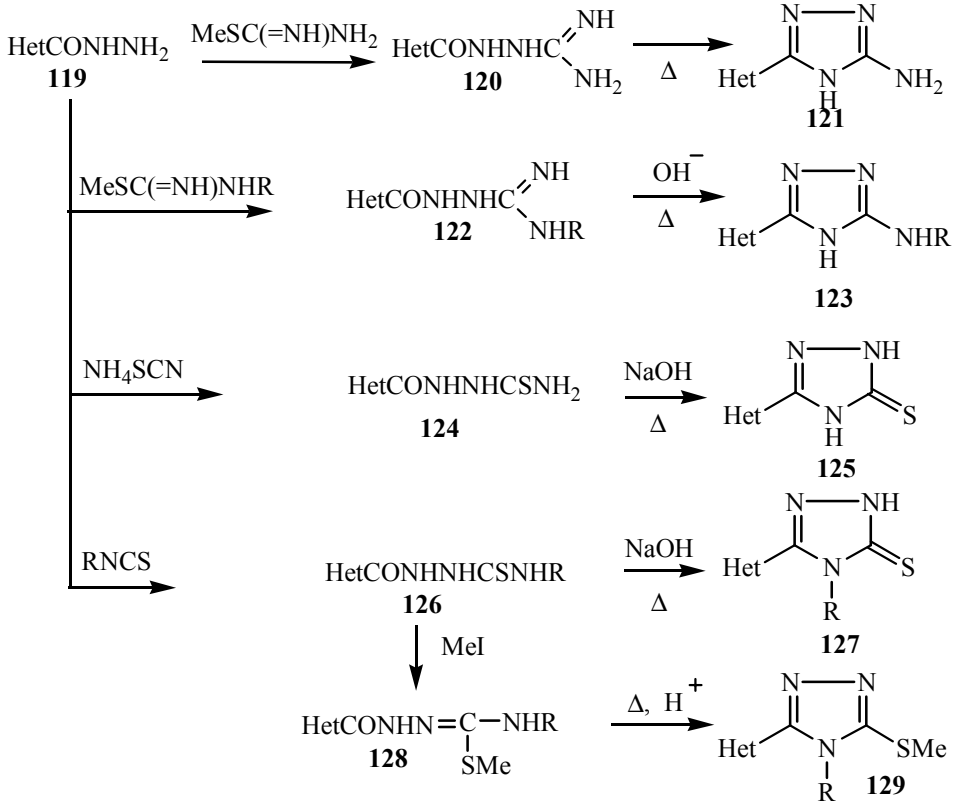


Het = 2-benzothiazolyl; R = Ph, 3,5-dichloro-2-pyridyl; R^1 = Me, $PhCH_2$, Ph, 4-$O_2NC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 5-nitro-2-furyl, 2-thienyl, 3-indolylmethyl, 2-benzothiazolylthiomethyl

The reaction of N-acyl(2-benzothiazolylthio)acetimidic esters **118** with phenyl- or 3,5-dichloro-2-pyridylhydrazine in absolute methanol at 30°C also leads to 1,3,5-trisubstituted 1H-1,2,4-triazoles **117** [81, 85-88].

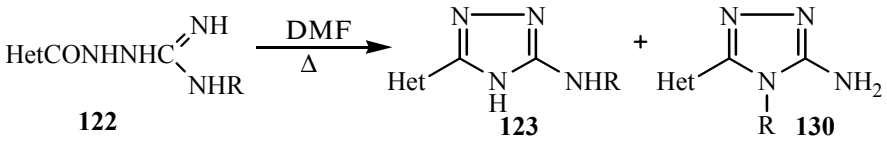
The treatment of 2-benzothiazolecarbohydrazide (**119**) with S-methylisothiourea leads to the formation of 1-(2-benzothiazolylcarbonylamino)guanidine (**120**), the thermolysis of which (250°C, 1 h) leads to 3-amino-5-(2-benzothiazolyl)-4H-1,2,4-triazole (**121**) [89]. During the reaction of the hydrazide **119** with S-methyl-N-alkylisothioureas 4-alkyl-1-acylaminoguanidines **122** are formed. The latter undergo cyclization to 3-alkylamino-4H-1,2,4-triazoles **123** when heated in an aqueous solution of alkali. When the hydrazide **119** is boiled with ammonium thiocyanate in 10% hydrochloric acid 1-(2-benzothiazolylcarbonyl)thiosemicarbazide

(**124**) is formed, and in an alkaline medium the latter undergoes cyclization to 3-(2-benzothiazolyl)-1,2,4-triazoline-5-thione (**125**). 3-(2-Benzothiazolyl)-4-R-1,2,4-triazoline-5-thiones **127** were synthesized similarly from 1-acyl-4-R-thiosemicarbazides **126**, produced by heating equimolar amounts of the hydrazide **119** and thiocyanates in ethanol. 5-Methylthio-4-R-4H-1,2,4-triazoles **129** are formed as a result of the cyclization of S-methylisothiosemicarbazides **128** by boiling in dioxane in the presence of acetic acid [89].



Het = 2-benzothiazolyl; R = Me, Et, CH_2=$CHCH_2$, Ph

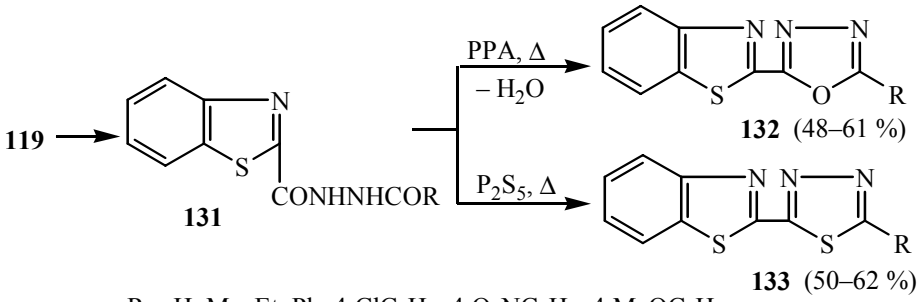
It is interesting to note that when 1-aminoacylguanidines **122** are boiled in DMF (5 h) intramolecular cyclization takes place in two directions with the formation of a mixture of 3-(R-amino)-4H-1,2,4-triazoles **123** and 3-amino-4-R-4H-1,2,4-triazoles **130**.



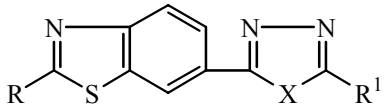
Het = 2-benzothiazolyl

Unfortunately, it is not possible to assess the proposed methods from the preparative standpoint since the authors do not state the yields of the compounds they synthesized.

Acylation of the hydrazide **119** with 90% formic acid or acid chlorides or anhydrides in pyridine gives N-acyl-N'-(2-benzothiazolylcarbonyl)hydrazines **131**, which when heated in polyphosphoric acid (140-150°C, 2 h) are converted into 2-(2-benzothiazolyl)-5-R-1,3,4-oxadiazoles **132** and when heated under vacuum with an excess of phosphorus pentasulfide are converted into 2-(2-benzothiazolyl)-5-R-1,3,4-thiadiazoles **133** [90].



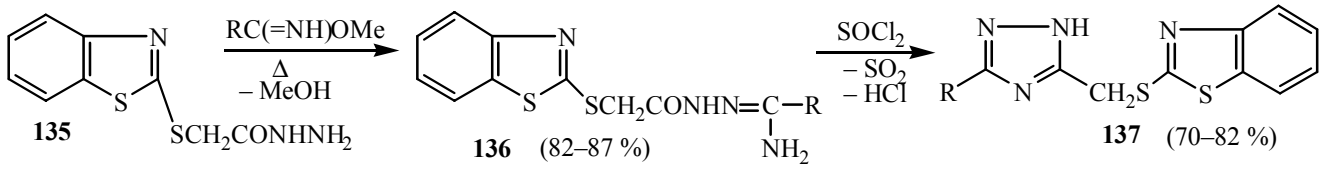
2-(2-R-6-Benzothiazolyl)-5-R^1-1,3,4-oxa(thia)diazoles **134** were synthesized under analogous conditions by the cyclodehydration of N-acyl-N'-(2-R-6-benzothiazolylcarbonyl)hydrazines, produced by the reaction of N-acylhydrazines with 2-R-benzothiazole-6-carbonyl chlorides in pyridine [90]



134 (43–70 %)

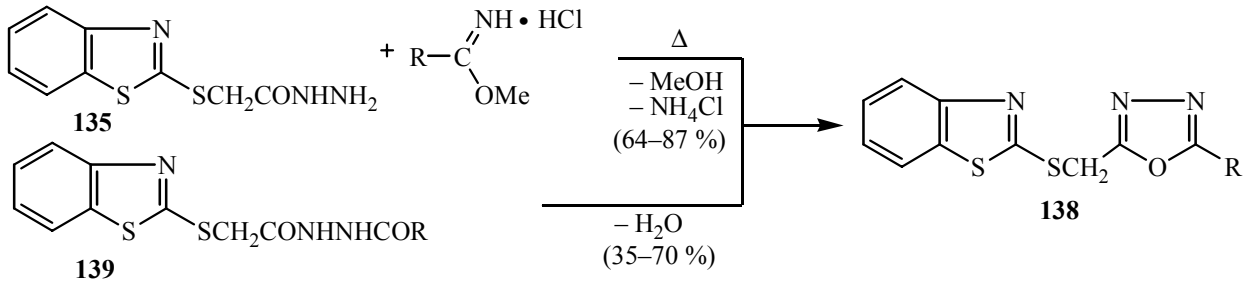
R = H, CF_3; R^1 = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$; X = O, S

The reaction of (2-benzothiazolylthio)acetohydrazide (**135**) with carboximino esters in methanol (boiling, 1 h) leads to N^1-(2-benzothiazolylthioacetyl)amidrazones of carboxylic acids **136**, the cyclodehydration of which by the action of thionyl chloride in anhydrous ether gives 3-R-5-(2-benzothiazolylthiomethyl)-1H-1,2,4-triazoles **137** [81].



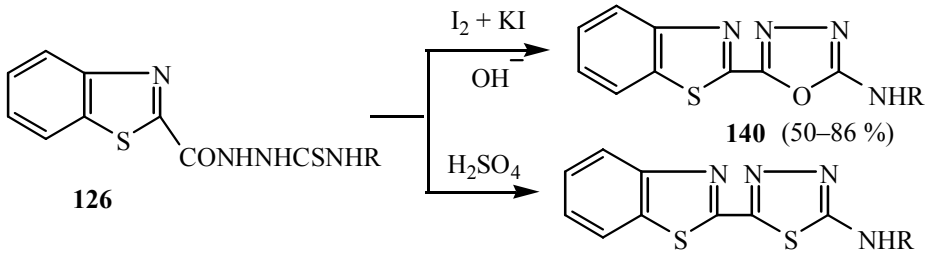
R = C_5H_{11}, Ph, $PhCH_2$, 3-pyridyl, 2-benzothiazolylthiomethyl

At the same time the 2-(2-benzothiazolylthiomethyl)-5-R-1,3,4-oxadiazoles **138** were synthesized by the condensation of the hydrazide **135** with the hydrochlorides of carboximidic esters in ethanol or dioxane (boiling, 1-12 h) [81, 91, 92]. The same compounds were obtained by the cyclocondensation of N-acyl-N'-(2-benzothiazolylthioacetyl)hydrazines **139** by heating with phosphorus oxychloride or by boiling (30 min) with thionyl chloride in anhydrous ether.



R = Me, Pr, $ClCH_2$, $EtOOCCH_2$, $PhCH_2$, 4-$O_2NC_6H_4$, CH_2Ar, 5-nitro-2-furyl, 3-indolyl, 2-benzothiazolylthiomethyl

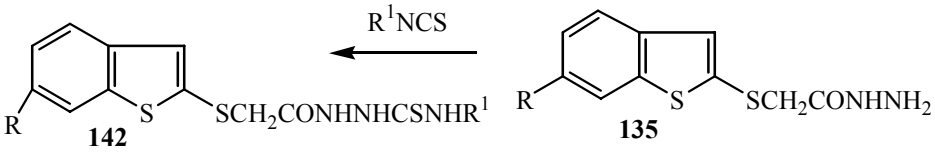
When treated with iodine in a solution of potassium iodide in an alkaline medium at 0-20°C the 1-acyl-4-R-thiosemicarbazides **126** undergo cyclization to 2-(R-amino)-5-(2-benzothiazolyl)-1,3,4-oxadiazoles **140**. Treatment with concentrated sulfuric acid at 0-20°C leads to 2-(R-amino)-5-(2-benzothiazolyl)-1,3,4-thiadiazoles **141** [93].



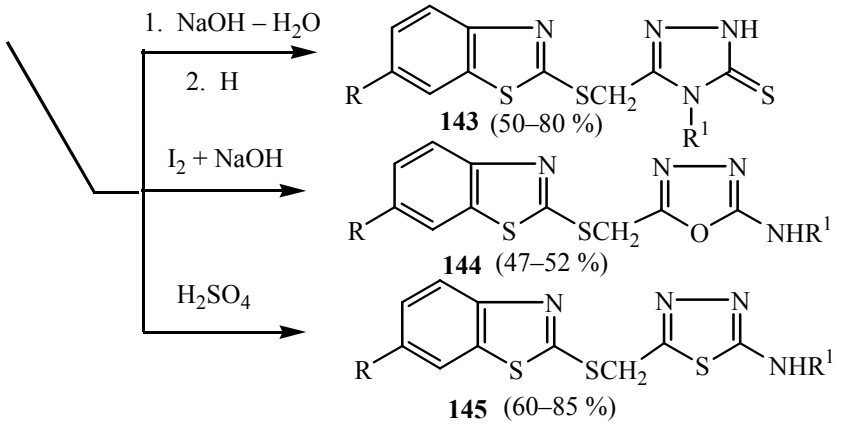
126 **140** (50–86 %) **141** (55–65 %)

R = Me, Et, Pr, Bu, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

The 1-(6-R-2-benzothiazolylthioacetyl)-4-R^1-thiosemicarbazides **142** were synthesized by the reaction of the hydrazides **135** with isothiocyanates. When boiled in an aqueous solution of alkali the products were converted into 3-(6-R-2-benzothiazolylthiomethyl)-4-R^1-1,2,4-triazoline-5-thiones **143**. Treatment with an alcohol solution of iodine in an alkaline medium gave 2-(R^1-amino)-1,3,4-oxadiazoles **144**, while the action of concentrated sulfuric acid at 0°C led to 2-(R^1-amino)-1,3,4-thiadiazoles **145** [81, 93-97].



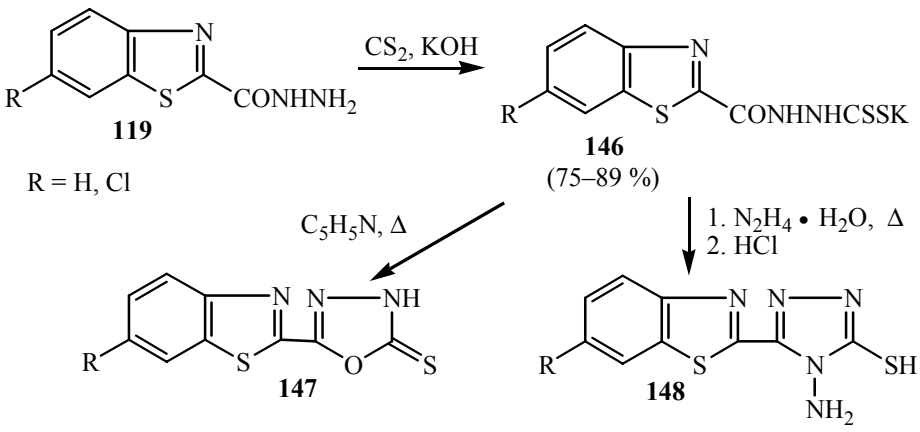
142 **135**



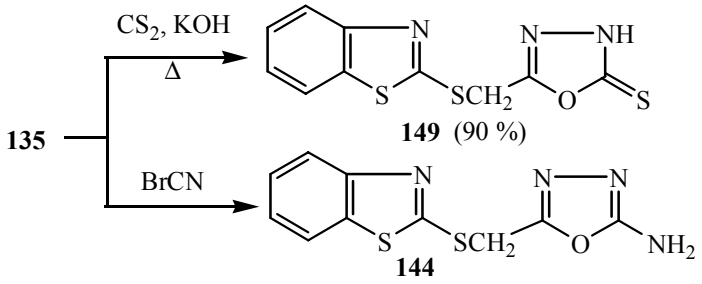
143 (50–80 %) **144** (47–52 %) **145** (60–85 %)

R = H, NO_2; R^1 = CH_2=$CHCH_2$, Ph, 2-MeC_6H_4, 2-$MeOC_6H_4$, $PhCH_2$, 1-$C_{10}H_7$

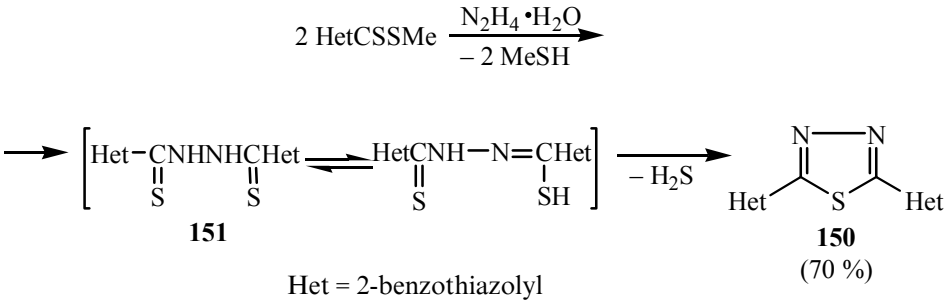
The reaction of 6-R-benzothiazole-2-carbohydrazides **119** with carbon disulfide and potassium hydroxide in ethanol at 20°C gave the potassium salts of dithiocarbazinic acids **146**. When boiled in pyridine the products underwent cyclization to 2-(6-R-2-benzothiazolyl)-1,3,4-oxadiazoline-5-thiones **147**, and when boiled with hydrazine hydrate in ethanol followed by treatment of the reaction mixture with concentrated hydrochloric acid at 0°C they gave 4-amino-3-(6-R-2-benzothiazolyl)-5-mercapto-4H-1,2,4-triazoles **148** [98].



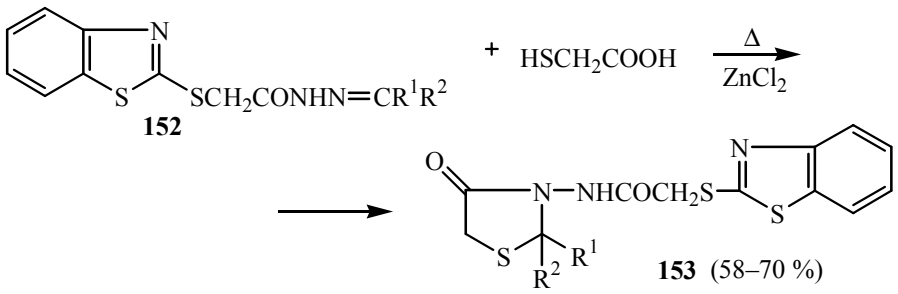
When boiled (18-20 h) with carbon disulfide and potassium hydroxide in ethanol the hydrazide **135** gave 1,3,4-oxadiazoline-5-thione (**149**). In reaction with an equimolar amount of cyanogen bromide in ethanol (60°C, 30 min) it gave 2-amino-5-(2-benzothiazolylthiomethyl)-1,3,4-oxadiazole (**144**) (R = R^1 = H) [95, 99].



Hydrazinolysis of methyl 2-benzothiazolecarbodithioate with 50% hydrazine hydrate (molar ratio 2:1) in ethanol at 40-50°C leads to 2,5-di(2-benzothiazolyl)-1,3,4-thiadiazole (**150**) probably through the formation of the unstable N,N'-dithioacylhydrazine **151** [100].

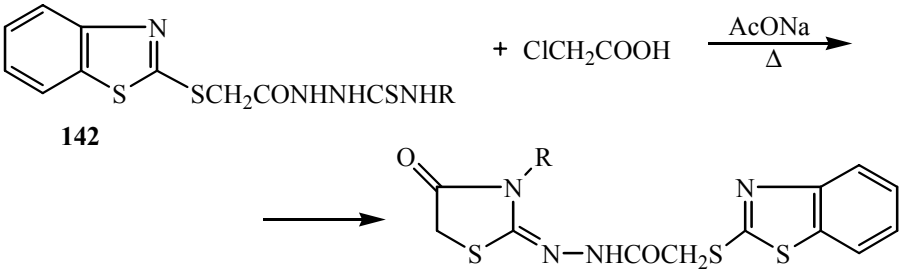


When N-(2-benzothiazolylthioacetyl)hydrazones **152** are boiled (10-12 h) with thioglycolic acid (molar ratio 1:2) in anhydrous benzene or dioxane in the presence of zinc chloride, the 2-substituted 3-(2-benzothiazolylthioacetamido)thiazolidin-4-ones **153** are formed [81, 101-103].



R^1 = *i*-Pr, Ph, 4-HO-3,5-(*t*-Bu)$_2$C$_6$H$_2$, 5-nitro-2-furyl, 3-indolyl;
R^2 = H; R^1 = R^2 = Me

2-(2-Benzothiazolylthioacetylhydrazino)-3-R-thiazolidin-4-ones **154** were synthesized as a result of the reaction of 4-R-thiosemicarbazides **142** with chloroacetic acid and sodium acetate in absolute ethanol (boiling, 6 h) [81, 103].

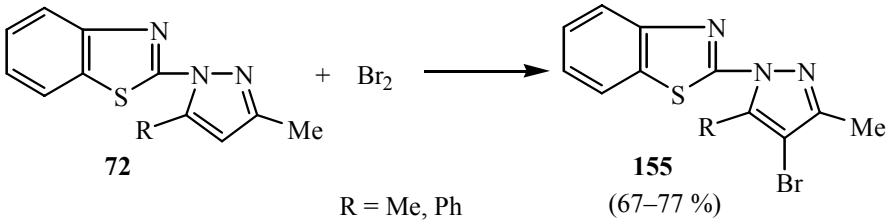


R = CH_2=$CHCH_2$, Ph **154** (64–68 %)

2. CHEMICAL TRANSFORMATIONS OF BENZOTHIAZOLYLAZOLES

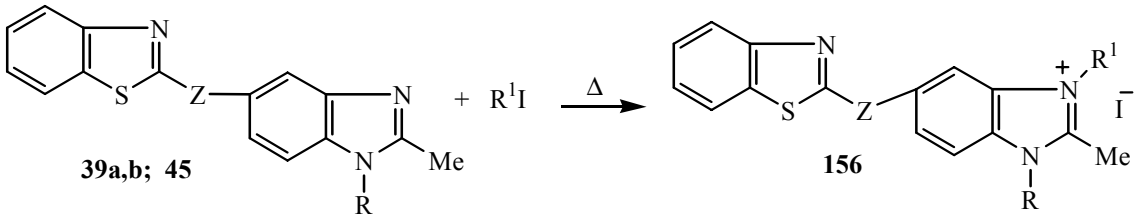
The isolated data on the chemical reactions of such bisheterocycles pertain to substitution in the azole fragments, alkylation at the endocyclic nitrogen atoms, reactions involving functional groups in the heterocyclic fragments and in the side chain, opening of the dihydroazole rings, and recyclization.

For example, the bromination of 1-(2-benzothiazolyl)-3-methyl-5-R-pyrazoles **72** in boiling chloroform [55] or in acetic acid at 20°C [59] takes place regioselectively at position 4 of the pyrazole ring, giving the bromine derivative **155**.



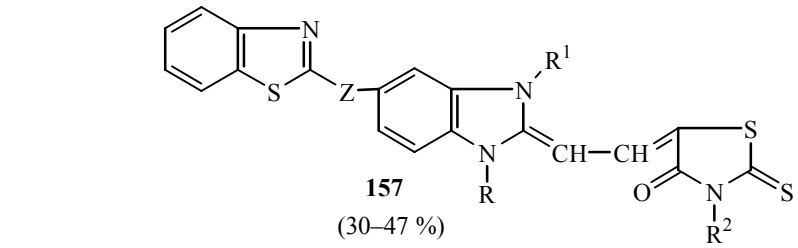
R = Me, Ph (67–77 %)

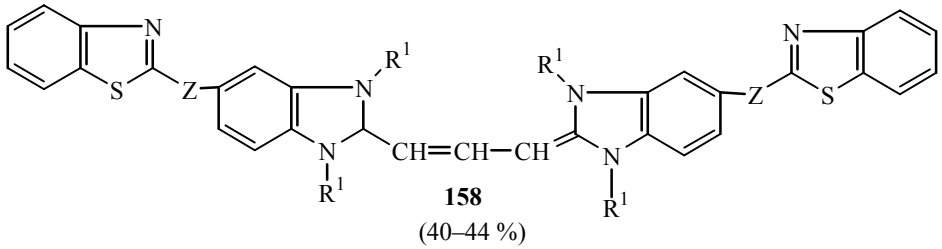
When benzothiazolylbenzimidazoles **39a**,**b** and **45** are heated with an excess of methyl or ethyl iodide in nitrobenzene or under pressure, alkylation takes place only at the nitrogen atom of the benzimidazole fragment, leading to the quaternary salts **156** [29, 32].



Z is absent or Z = O, OC(O); R = Me, Et, Ph; R^1 = Me, Et

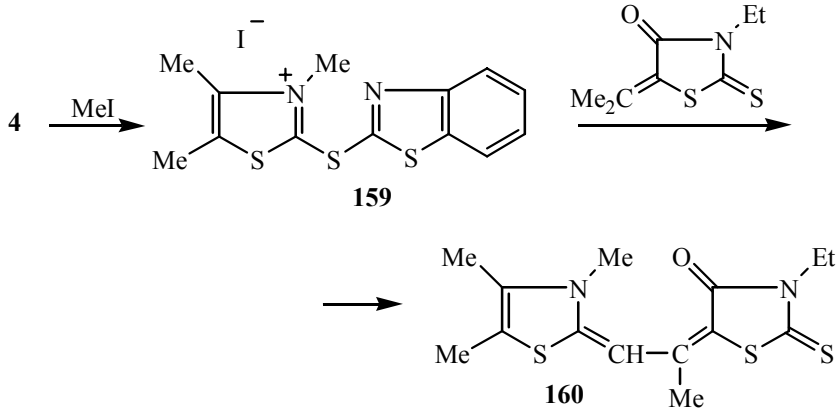
The synthesis of dyes based on benzothiazoles has been described in a series of papers. The reaction of the salts **156** with 3-R^2-anilinomethylenerhodanine in pyridine in the presence of acetic anhydride (boiling, 1-1.5 h) gave the imidadimethine merocyanine dyes **157** while heating with an excess of diethoxymethyl acetate in nitrobenzene gave the imidacarbocyanine dyes **158** [29, 32, 70].



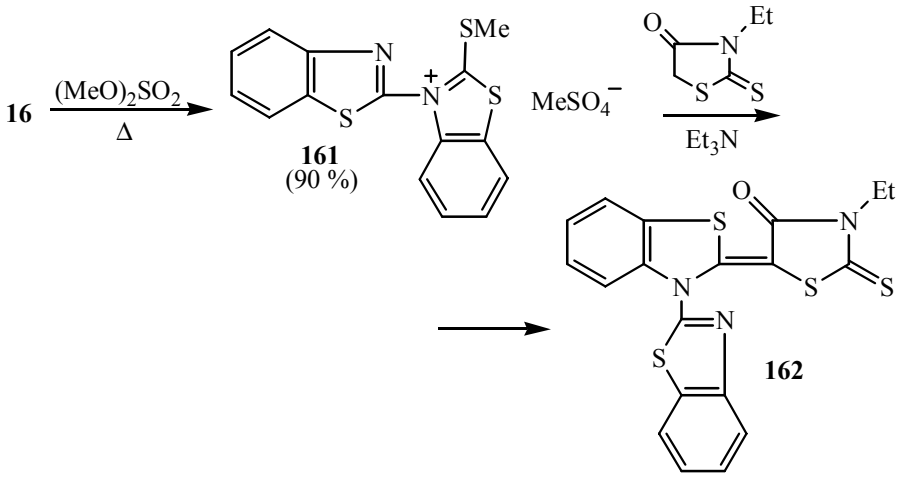


Z is absent or Z = O; R = Me, Et, Ph; R^1 = Me, Et; R^2 = Et

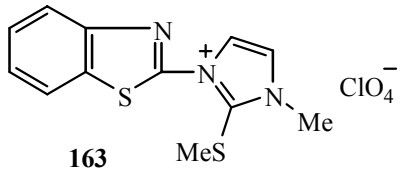
During methylation of the sulfide **4** quaternization takes place at the nitrogen atom of the more basic thiazole fragment with the formation of the quaternary salt **159**, from which the benzothiazolethiol group is easily eliminated [6]. For example, in the reaction of this salt with 3-ethyl-5-isopropylidenerhodanine in DMF in the presence of triethylamine (100°C, 45 min) the merocyanine dye **160** was obtained.



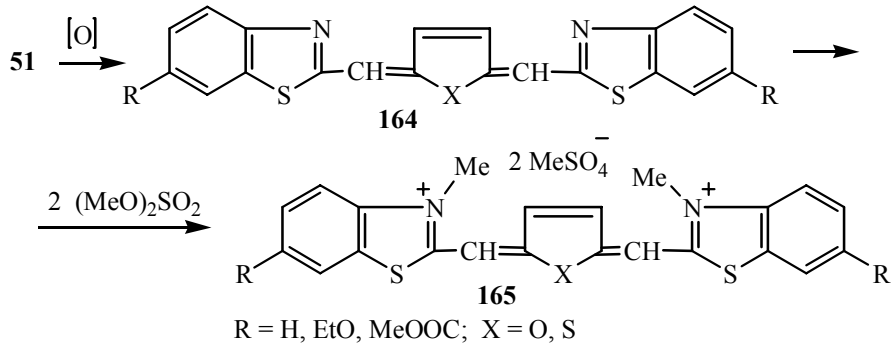
According to data in [6, 11, 12], the sulfide **5** rearranges on heating to 2-(2-thioxo-3-benzothiazolinyl)benzothiazole **16**, which is methylated by the action of dimethyl sulfate only at the thione group, giving 3-(2-benzothiazolyl)-2-methylthiobenzothiazolium methyl sulfate **161**. During the condensation of the latter with 3-ethylrhodanine in absolute ethanol in the presence of triethylamine the zeromethine merocyanine dye **162** is formed [6].



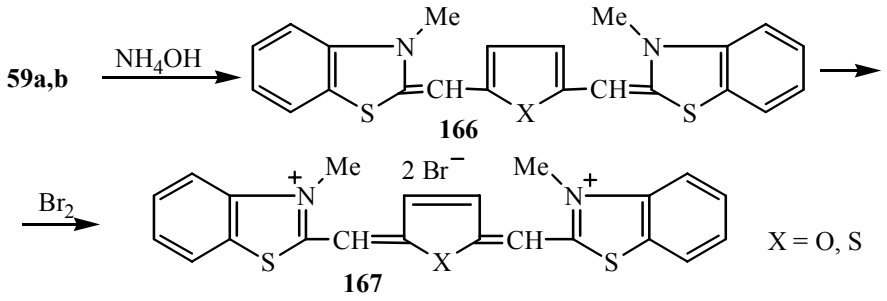
After alkylation with dimethyl sulfate in toluene followed by treatment with sodium perchlorate solution 1-methylimidazoline-2-thione **2** gives 1-methyl-2-methylthioimidazolinium perchlorate **163** [6].



During the oxidation of compounds **51** with N-bromosuccinimide in dioxane orange-colored bases **164** are formed. Their quaternization with dimethyl sulfate leads to the diquaternary salts **165** [39-41].

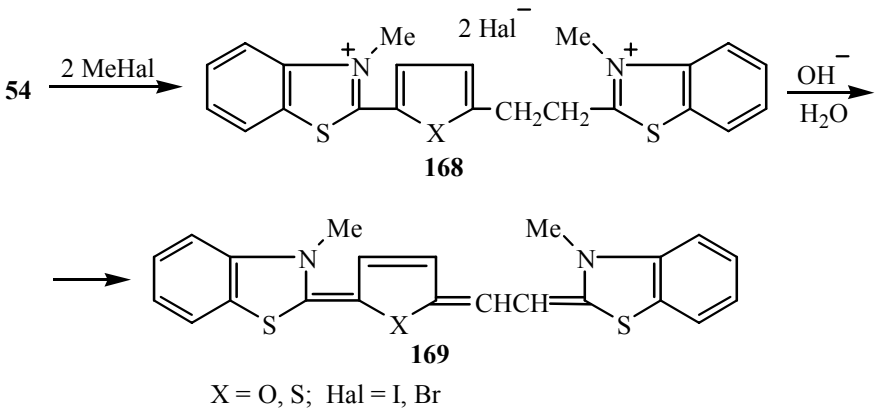


During treatment of the methodichloride derivatives **52a**,**b** with an aqueous solution of ammonia the bismethylene bases **166**, extremely sensitive to atmospheric oxygen, are formed. In solution in carbon tetrachloride they instantly add bromine, forming the stable diquaternary salts **167** [39-41].

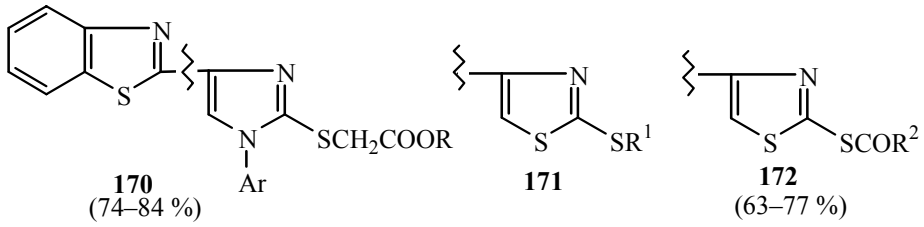


The authors point out that the electronic spectra of compounds **164**, **165**, and **167** are typical of bismethine dyes.

Alkylation of compounds **54a**,**b** with methyl iodide or methyl bromide leads to the dihalides **168**, the treatment of which with an aqueous solution of alkali leads to the formation of unstable intensely colored bismethylene bases **169** [41].



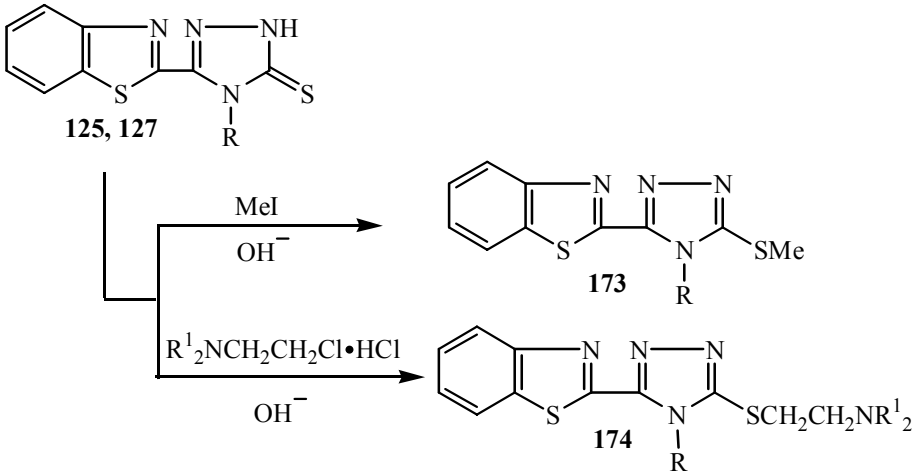
The alkylation and acylation of benzothiazolylazoles at the thiol groups of the azole ring have been described. The alkylation of 2-mercaptoimidazoles **94** with ethyl bromoacetate in ethanol gives 1-aryl-4-(2-benzothiazolyl)-2-imidazolylthioacetic esters **170** [69]. Alkaline hydrolysis of the latter with 10% potassium hydroxide solution in methanol leads to the respective acids, which were also obtained by alkylation of the thiols **94** with chloroacetic acid in the presence of an aqueous solution of alkali.



R = H, Et; R^1 = Me, Et, Pr, *i*-Pr, $AcCH_2$, $HOOC(CH_2)_n$ (*n* = 0, 2), HOOCCHMe, $EtOOCCH_2$; R^2 = Me, Ph

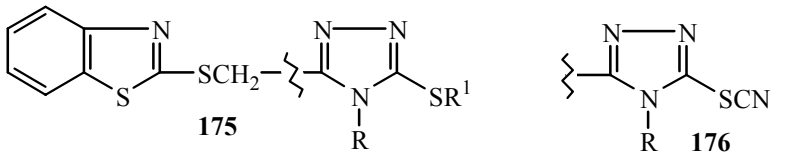
The sulfides **171** were synthesized similarly from 2-mercaptothiazole **103** with yields of 54-94%, while the S-acyl derivatives **172** were obtained during acylation of the acid chlorides in pyridine at 0°C [77].

The alkylation of 4-R-1,2,4-triazoline-5-thiones **125** and **127** with methyl iodide [89] or the hydrochlorides of N,N-disubstituted β-chloroethylamines [104] in an alkaline medium resulted in the production of 3-(2-benzothiazolyl)-4-R-5-methylthio- and 3-(2-benzothiazolyl)-4-R-5-(β-aminoethylthio)-4H-1,2,4-triazoles **173** and **174**.



R = H, Me, Et, CH_2=$CHCH_2$, Ph, $PhCH_2$; R^1 = Me, Et, *i*-Pr;
R^1_2N = pyrrolidino, piperidino, morpholino

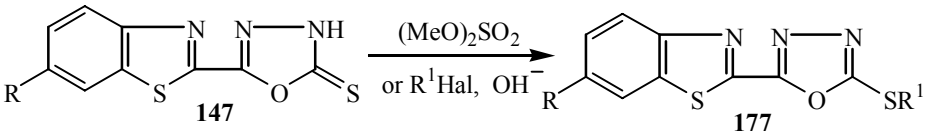
The 3-(2-benzothiazolylthiomethyl)-4-R-5-(R^1-thio)-4H-1,2,4-triazoles **175** were synthesized under analogous conditions from 4-R-1,2,4-triazoline-5-thiones **143**, while treatment of compounds **143** with cyanogen bromide in ethanol in the presence of 5% sodium hydroxide solution gave the thiocyanates **176** [81, 93-97].



(66–70 %)

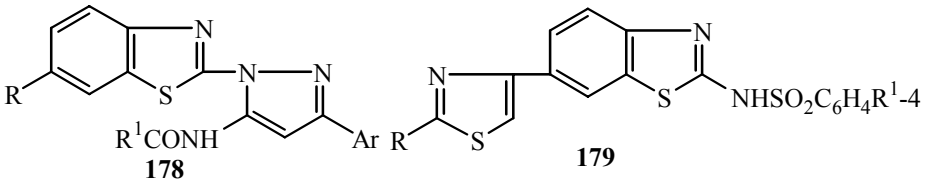
R = H, CH_2=$CHCH_2$, Ph; R^1 = Me, $HOOCCH_2$

Alkylation of 1,3,4-oxadiazoline-5-thiones **147** with dimethyl sulfate or halogen derivatives in ethanol in the presence of alkali leads to 2-(6-R-2-benzothiazolyl)-5-(R^1-thio)-1,3,4-oxadiazoles **177** [98].



R = H, Cl; R^1 = Me, Et, $AcCH_2$, $EtOOCCH_2$, $HOOCCH_2$,
HOOCCHMe; Hal = Cl, Br

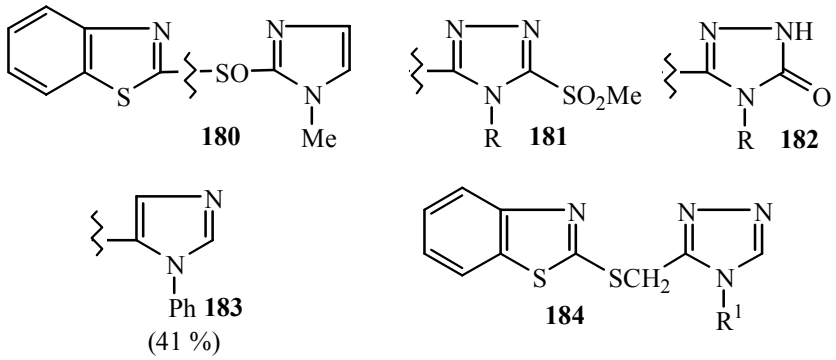
Reactions at an amino group of the azole type also take place according to the usual scheme. Acylation of the 5-aminopyrazoles **87** with acid chlorides in pyridine at 0°C gives good yields of the N-acyl derivatives **178** [65]. The reaction of 2-aminobenzothiazoles **62** with 4-R^1-benzenesulfonyl chlorides in pyridine at 100°C leads to the sulfonyl derivatives **179** [50].



178 R = H, Me, Cl, NO_2; Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^1 = Me, Ph, 3-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$; **179** R = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$; R^1 = Me, AcNH

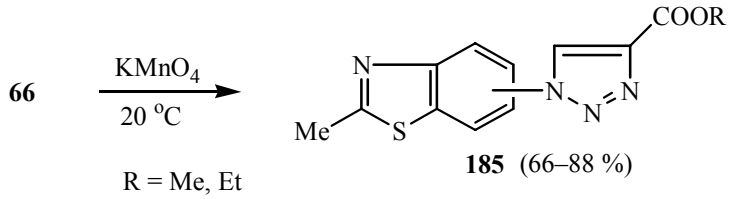
The oxidation of benzothiazolylazoles by various reagents leads to various products, depending on the structure of the initial compounds. The sulfoxide **180** is formed during the oxidation of the sulfide **3** with 3-chloroperbenzoic acid [7], and the methylsulfonyl derivatives **181**, the alkaline hydrolysis of which gives 3-(2-benzothiazolyl)-4-R-1,2,4-triazolin-5-ones **182**, are formed during the oxidation of 4-R-methylthio-4H-1,2,4-triazoles **173** with hydrogen peroxide in acetic acid (boiling, 15 min) [89].

4-(2-Benzothiazolyl)-1-phenylimidazole **183** was synthesized by boiling 2-mercapto-1-phenylimidazole **94** with dilute nitric acid [69], and 3-(2-benzothiazolylthiomethyl)-4-R^1-1,2,4-triazoles **184** were obtained by boiling 1,2,4-triazoline-5-thiones **143** with Raney nickel in alcohol [81].



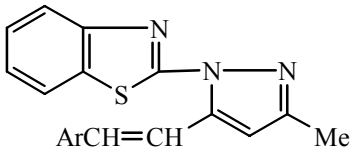
R = Me, Et, CH_2=$CHCH_2$, Ph; R^1 = H, CH_2=$CHCH_2$, Ph

During the oxidation of Δ^2-1,2,3-triazolines **66** with potassium permanganate in acetone at 20°C the corresponding 1,2,3-triazoles **185** were obtained [52, 53].



R = Me, Et

The condensation of 1-hetaryl-3,5-dimethylpyrazoles **72** with aromatic aldehydes in an alkaline medium takes place only with the participation of the Me group at position 5 and leads to 1-(2-benzothiazolyl)-3-methyl-5-styrylpyrazoles **186** [58]. 5-Arylidene-2-(R-2-benzothiazolylimino)thiazolidin-4-ones **187** were synthesized similarly from 4-thiazolidinones **89** [67].



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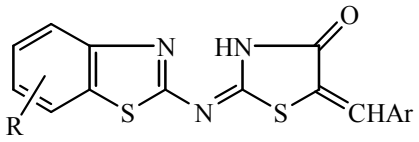
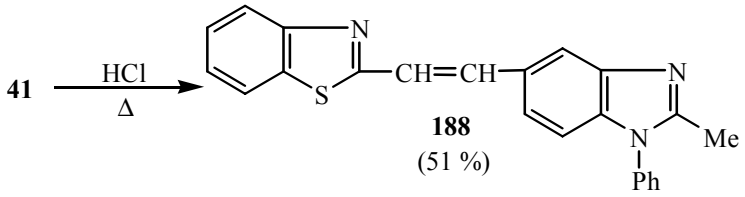


187 (40–60 %)

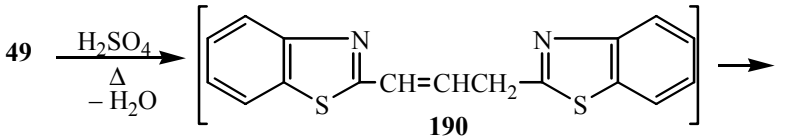
Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 2-HOC_6H_4;
R = H, 6-Me, 6-Cl, 6-NO_2, 6-MeO, 4-Cl

The α,β-Dihetarylacrylonitrile **41** is converted into α-(2-benzothiazolyl)-β-(1-phenyl-2-methyl-5-benzimidazolyl)ethylene (**188**) when heated (150°C, 1 h) in a sealed tube with hydrochloric acid [30].

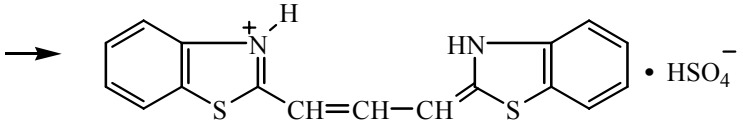


188
(51 %)

The simplest northiacarbocyanine dye 2-[3-(2-benzothiazolinylidene)-1-propenyl]benzothiazolium sulfate (**189**) was obtained by heating (190-200°C, 7 min) the alcohol **49** with concentrated sulfuric acid [37]. The author supposes that the dehydration product 1,3-dihetaryl-1-propene (**190**) is formed intermediately.

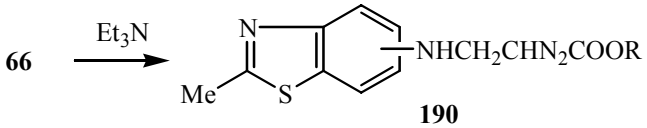


190



189

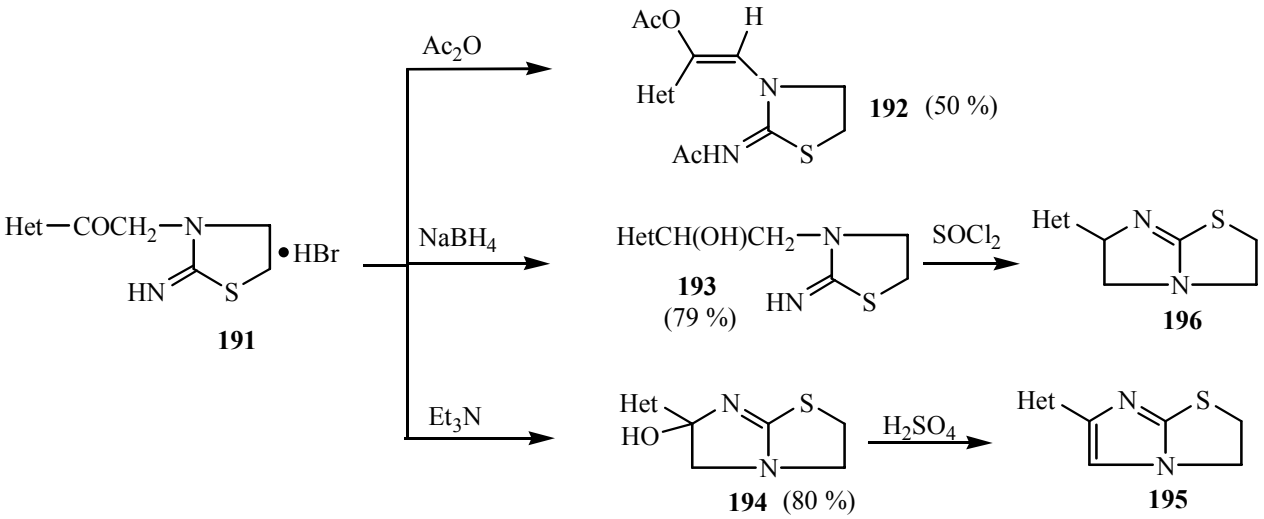
When the Δ^2-1,2,3-triazoline-4-carboxylic esters **66** are treated with triethylamine in benzene the dihydroazole ring is opened, and the α-diazo-β-(2-methylbenzothiazolylamino)propionic esters **190** are formed [52, 53].



190
(80–95 %)

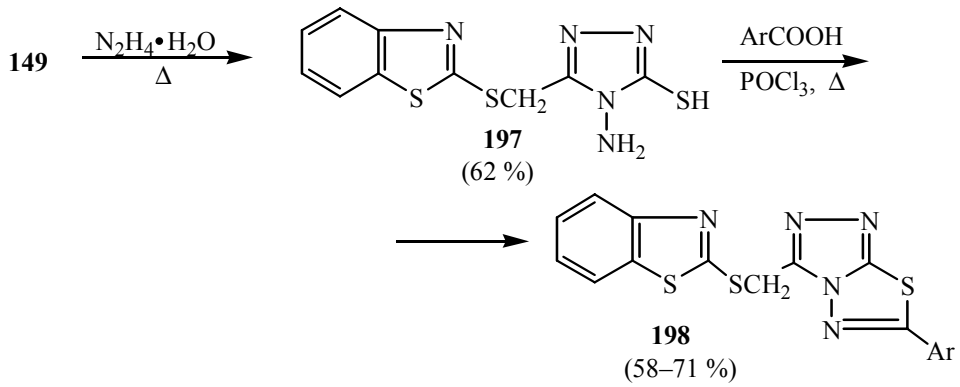
R = Me, Et

The acylation of 2-[(2-imino-3-thiazolidinyl)acetyl]benzothiazole hydrobromide (**191**), which is the product from condensation of the α-bromo ketone **95** with 2-amino-Δ^2-thiazoline, by acetic anhydride in pyridine at 20°C gives 1-acetoxy-2-(2-acetylimino-3-thiazolidinyl)-1-(2-benzothiazolyl)ethylene (**192**), while reduction with sodium borohydride in methanol at 0°C gives 1-(2-benzothiazolyl)-2-(2-imino-3-thiazolidinyl)ethanol (**193**) [105].



Treatment of the hydrobromide **191** with two equivalents of triethylamine in chloroform at 20°C leads to the formation of 6-(2-benzothiazolyl)-6-hydroxy-2,3,5,6-tetrahydroomidazo[2,1-*b*]thiazole (**194**), which is easily dehydrated by the action of concentrated sulfuric acid to 2,3-dihydroimidazo[2,1-*b*]thiazole (**195**). 2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole (**196**) was obtained from the alcohol **193** as a result of intramolecular cyclodehydration by the action of thionyl chloride at 20°C.

4-Amino-3-(2-benzothiazolylthiomethyl)-5-mercapto-4H-1,2,4-triazole (**197**) was synthesized by boiling 1,3,4-oxadiazoline-5-thione **149** with hydrazine hydrate. When heated with aromatic acids in phosphorus oxychloride it formed 6-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **198** [99].



Ar = Ph, 3(4)-$O_2NC_6H_4$, 2(4)-ClC_6H_4, 2(4)-$NH_2C_6H_4$, 4-HOC_6H_4

3. PRACTICAL APPLICATION OF BENZOTHIAZOLYLAZOLES

Compounds with high and varied biological activity have been found in the series of azoles containing benzothiazole fragments described above.

High anti-inflammatory activity is exhibited by 1-(6-fluoro-2-benzothiazolyl)-3-methyl-5-oxo-4H-pyrazole-4-acetic acid **84b** [63], pyrano[2,3-*c*]pyrazol-6(1H)-ones **85** [63], 2-(2-amino-6-R-benzothiazolyl)-4-R^1-thiazoles **88** [66], and 1-aryl-2-imidazolylthioacetic acids **170** [69]. 2-(R^1-Amino)-4-(2-R-6-benzothiazolyl)thiazoles **102** exhibit anti-inflammatory activity at the level of the familiar product

phenylbutazone but are less active than 2-(R^1-amino)-4-(6-R-2-benzothiazolyl)thiazoles **101** [75, 76]. Moderate anti-inflammatory activity was found in 2-isopropylthio- and 2-acetonylthio-4-(2-benzothiazolyl)thiazole (**171**) [77], and also in 5-(acylamino)pyrazoles **178** [65].

The thiazolylbenzothiazoles **96** and **98** and also 4,4'-dibenzothiazolyl-2,2'-dithiazoles **99a**,**b** exhibit moderate analgesic and antidepressant activity together with high anti-inflammatory activity with low toxicity (LD_{50} >> 800 mg/kg) [70-73].

According to patent data [33], 5-aryl-4-(2-benzothiazolylmethyl)-1-phenylpyrazoles **46** exhibit high analgesic activity. 1,3,4-Oxa(thia)diazoline-2-thiones **26a**,**b** [17-19], 5-aryl-2-(2-benzothiazolylthiomethyl)-1,3,4-oxadiazoles **138** [106], sulfamide derivatives of 2-amino-6-(2-R-4-thiazolyl)benzothiazoles **179** [50], and 5-arylidenethiazolidin-4-ones **187** [67] are effective antibacterial agents.

N-Substituted 2-amino-Δ^2-imidazolines **31** [22] and 2-amino-5-aryl-1,3,4-oxadiazoles **61** [49] exhibit high antibacterial activity together with antitubercular and fungicidal activity. 6-(5-Phenyl-1-tetrazolylmethyl)amino-2-ethylthiobenzothiazole **33** showed high antibacterial activity against *M. tuberculosis* INH-67 at a concentration of 25 mg/ml and high antiviral activity at a concentration of 50-100 mg/ml [24]. High antimicrobial activity is exhibited by 1,2,4-oxadiazole **110f**, 1,3,4-oxadiazoles **138**, and 3-(2-benzothiazolylthioacetamido)thiazolidin-4-ones **153**, containing 5-nitrofuryl or 4-hydroxy-3,5-di-*tert*-butylphenyl fragments [81].

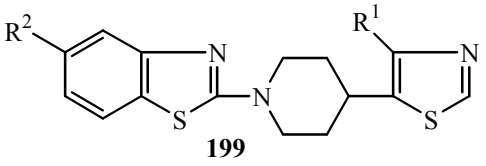
The N,N-Disubstituted 5-(2-aminoethylthio)-1,2,4-triazoles **174** were patented as highly effective antihypertensive products [104], while the 2-(2-benzothiazolylmethylthio)benzimidazoles were patented as effective inhibitors of lipoxygenase [13].

In 1991 the N-(5-fluoro-2-benzothiazolyl)amide **32** (GTC) was proposed by American scientists [23] as a selective antitumor product.

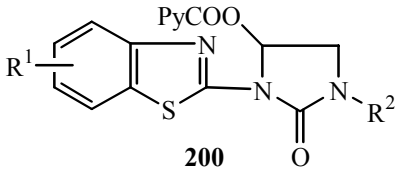
The thiocyanate **176** and 3-allylthiazolidin-4-one **154** exhibit high choleretic activity and significantly surpasses the familiar product mebetizole (2-mercaptobenzothiazole) in its effectiveness. Δ^2-Thiazoline **115** and 2-(4-hydroxy-3,5-di-*tert*-butylphenyl)thiazolidin-4-one **153** at a dose of 300 mg/kg exhibit radioprotective activity, while 1,2,4-oxadiazole **110g**, the hydrochlorides of 1-R-2-(2-benzothiazolylthiomethyl)-Δ^2-imidazolines **113**, and 2-(2-benzothiazolylthiomethyl)-5-(4-nitrobenzyl)-1,3,4-oxadiazole **138** at doses of 5.4-9.8 mg/kg possess considerable curare-like activity [81].

In the series of 6-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **198** there are products with high antihelminthic activity [99].

According to patent data [107], 2-[4-(4-R^1-5-imidazolyl)piperidino]-5-R^2-benzothiazoles **199** can be used as ligands for 5-HT receptors.



199



200

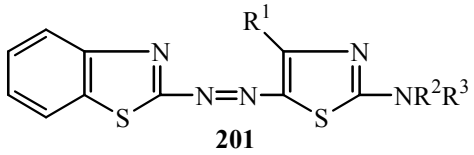
199 R^1 = H, cycloalkyl; R^2 = H, F; **200** R^1 = 5-Me, 5-F, 5-F_3C, 6-Cl, 7-Br, 4-MeO; R^2 = Me, Et, CH_2=$CHCH_2$, $HCCCH_2$; Py = 2(3,4)-pyridyl, 2-chloro-3-pyridyl, 3-methyl-4-pyridyl, 6-fluoro-2-pyridyl, 4,5-dimethyl-3-pyridyl

High and selective herbicidal activity is exhibited by the ethers of hydroquinone **34** [25] and the ethers of 1-(R^1-2-benzothiazolyl)-3-R^2-oxoimidazolidin-5-ol (**200**) [108]. The N-substituted 1H-1,2,4-triazole **47** [34], the thiazoles **96** [71, 72], and the sulfoxide **180** [7] possess clearly defined fungicidal activity.

In the literature [109, 110] there are data on the possibility of using 1-(2-benzothiazolyl)-2-R-Δ^2-imidazolines **64a-d** as antimicrobial additives to rocket fuels. It was established that the most active in this series of compounds was 2-(5-nitro-2-furyl)-Δ^2-imidazoline **64d**, which fully suppress the growth of microorganisms at concentrations of 0.005-0.010 wt.%.

3-(2-Benzothiazolyl)-Δ^2-pyrazolines **90** are of interest as substances that possess strong luminescence in solutions and also as intermediates for the production of cyanine dyes [30]. 4-[2-methyl-5(6)-benzothiazolyl]thiazoles **100** can be used for the same purposes [74].

The azo derivatives **201** have been patented as light-fast azo dyes for polyester fibers [111].



201

R^1 = alkyl, alkanoyl, aryl, heteryl, HO; R^2, R^3 = alkyl, alkenyl, cycloalkyl, aryl
R^2R^3N = morpholino, piperidino

1-R-2-(2-Benzothiazolylthiomethyl)-Δ^2-imidazolines **113** are effective antioxidant and polyfunctional additives for lubricating oils [81, 84, 112]. The thiazoles **107**, 3,5-disubstituted 1H-1,2,4-triazoles **137**, 1,3,4-oxadiazoles **138**, and 5-(R^1-thio)-4H-1,2,4-triazoles **175**, containing 2-benzothiazolylthiomethyl fragments, were proposed for use as light and heat stabilizers for polymeric composites [113] and cellulose-containing textile materials [114]. 2-(2-Benzothiazolylthiomethyl)-5-R-1,3,4-oxadiazoles **138** are also highly effective in the inhibition of the thermal polymerization of styrene and 2-methyl-5-vinylpyridine [115].

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