Chemistry of Heterocyclic Compounds, Vol. 42, No. 2, 2006

SYNTHESIS OF CONDENSED THIAZOLES. (REVIEW)

N. G. Smirnova, I. V. Zavarzin, and M. M. Krayushkin

Data on the synthesis of thiazoles systems condensed with heterocycles are classified. The principal directions in the practical application of these substances are briefly discussed.

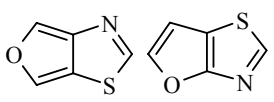
Keywords: condensed thiazoles, isoxazolothiazoles, pyrazolothiazoles, pyrrolothiazoles, thiazoloisothiazoles, thiazolopyridines, thiazolothiazoles, thienothiazoles, furothiazoles.

The chemistry of thiazole and most of its derivatives has been well studied [1-3]. However, the chemistry of condensed thiazoles (with the exception of benzothiazoles) is still essentially in the development stage. The number of publications on this subject is relatively small, and they have almost all appeared in the last three decades. At the same time it has been demonstrated that such condensed products are biologically active substances [2, 3], have been widely investigated as potential drugs [3-7], and have found use in medicine [3, 4]. Condensed thiazoles have also been used as the components of photographic materials [8-11] and semiconductors [12-14].

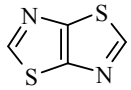
Reviews have been published on the synthesis and biological activity of benzothiazoles [3, 15] and thiazolopyridines [3]. In the present work we examine thiazole systems condensed with five-membered heteroaromatic rings and also present new data on thiazolopyridines.

1. THIAZOLE SYSTEMS CONDENSED WITH FIVE-MEMBERED HETEROAROMATIC RINGS

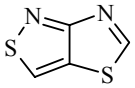
The following thiazole systems condensed with five-membered heteroaromatic rings have been described in the literature: Furothiazoles, thiazolothiazoles, thiazoloisothiazoles, pyrazolothiazoles, isoxazolothiazoles, pyrrolothiazoles, thienothiazoles.



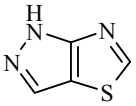
Furothiazoles



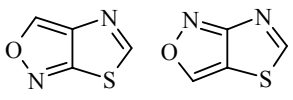
Thiazolothiazoles



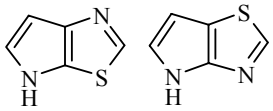
Thiazoloisothiazoles



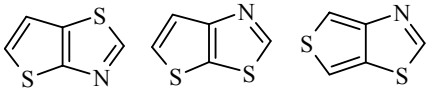
Pyrazolothiazoles



Isoxazolothiazoles



Pyrrolothiazoles



Thienothiazoles

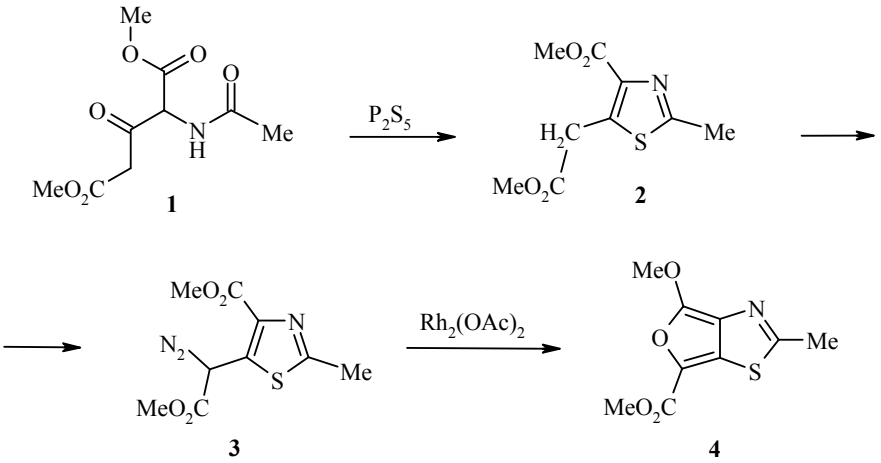
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow; e-mail: mkray@ioc.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 167-190, February, 2006. Original article submitted November 28, 2005.

 0009-3122/06/4202-0144

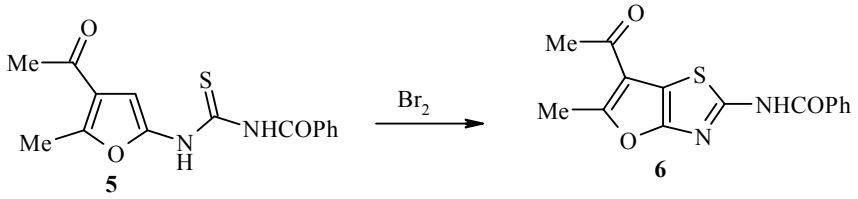
The obvious mutually complementary paths for the synthesis of such systems include construction of the thiazole ring from the five-membered heterocycle or creation of the heterocycle from thiazole.

Furothiazoles

Both methods have been used in the synthesis of furothiazines. Thus, furo[3,4-*d*]thiazole (**4**) was obtained by a multistage scheme from dimethyl α-nitroacetonedicarboxylate, the nitro group of which is reduced and then acylated with acetic anhydride. The obtained amide **1** is converted by treatment with phosphorus pentasulfide into the thiazole **2**. Diazotization of the latter and boiling the diazo compound **3** with $Rh_2(OAc)_2$ in dichloroethane lead to the formation of furo[3,4-*d*]thiazole (**4**). The yield on the initial amide **1** amounts to 17% [16].



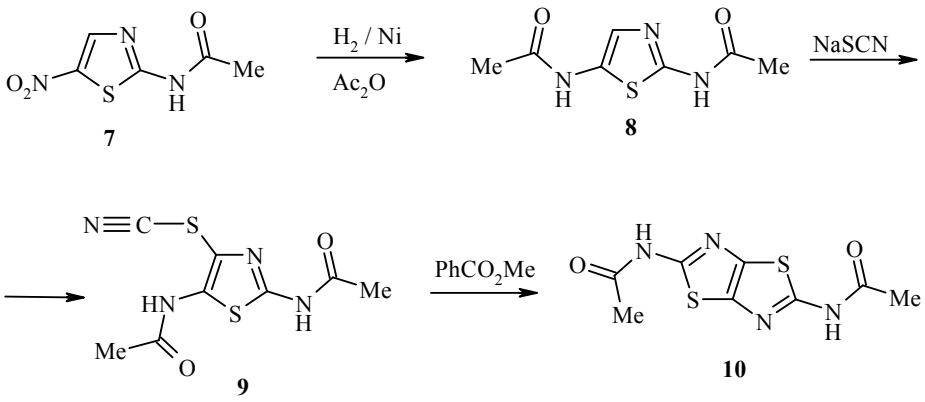
An alternative approach to the synthesis of furo[2,3-*d*]thiazole (**6**) was realized from furylthiourea (**5**) by the action of bromine in acetic acid or in trimethyl phosphate with a yield of 47-60%, calculated on the initial thiourea [17].



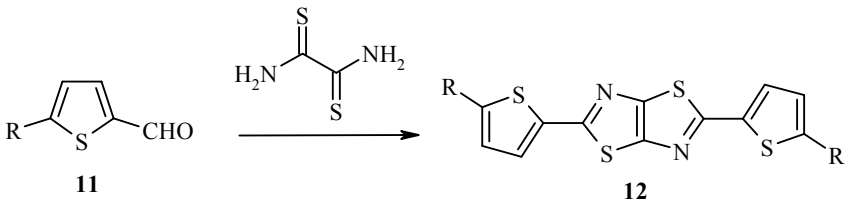
Thiazolothiazoles

Of the compounds examined in the present review the thiazolothiazoles are in greatest demand. They have found use in optical recording materials, as lightness accelerators, in silver-halide photographic materials [18-20], and also as semiconductors [12-14].

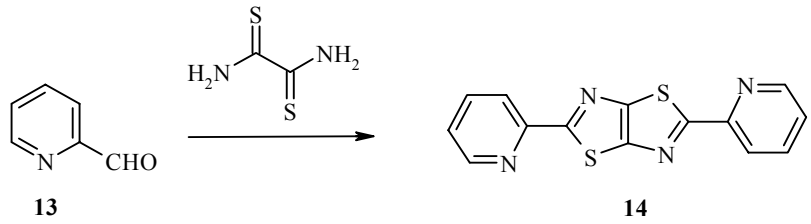
The synthesis of symmetrical di(acetylamino)thiazolothiazole (**10**) from 2-(acetylamino)-5-nitrothiazole (**7**) includes reduction of the nitro group followed by acylation of the obtained amine with acetic anhydride, subsequent thiocyanation of which leads to the thiazole **9**. The latter is converted into the product **10** when heated in phenyl methyl ketone at 120°C for 2 h. The overall yield of the thiazolothiazole **10**, calculated on the initial compound **7**, amounts to 9% [4].



Thiophene-containing and pyridine-containing thiazolothiazoles are used as semiconductors [12-14]. They are produced by the reaction of 2-thiophenecarbaldehyde (**11**) or 2-pyridinecarbaldehyde (**13**) with dithiooxamide. The yields of the final products **12** and **14** vary in the range of 24-46%, calculated on the initial aldehydes **11** and **13** [12-14].

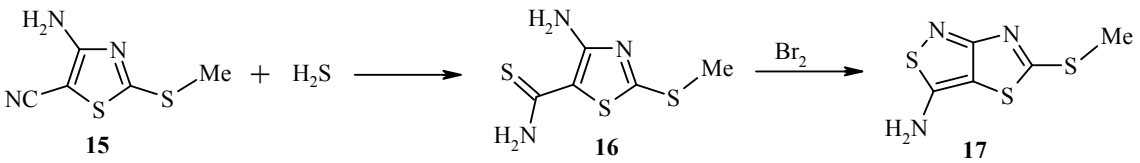


R = H, 2-thienyl, 4-*n*-hexyl-2-thienyl



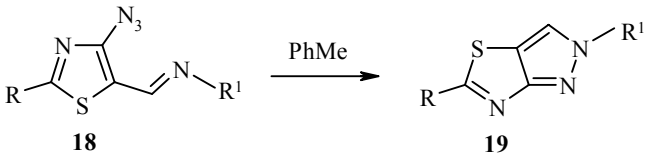
Thiazoloisothiazoles

5-Methylthio[1,3]thiazolo[4,5-*c*]isothiazol-3-ylamine (**17**) is obtained by the reaction of 4-amino-5-cyanothiazole (**15**) with hydrogen sulfide followed by cyclization of the thioamide **16**, leading to the thiazoloisothiazole **17** [21].



Pyrazolothiazoles

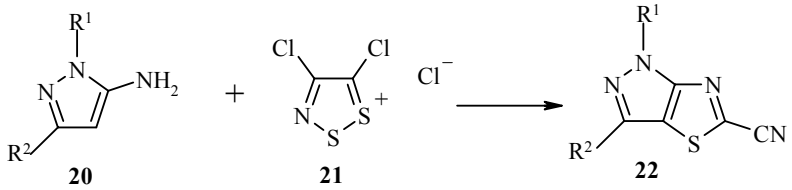
Pyrazolopyrazoles are used as antiviral agents and inhibitors of sialidosis [4]. The most general method for their synthesis is probably the cyclization of geminal azido imines **18**. Thus, pyrazolo[3,4-*d*]thiazoles **19** were synthesized with yields of 80% by heating in toluene the Schiff bases **18**, which were in turn obtained by the reaction of the corresponding 4-azidothiazolecarbaldehydes with various substituted anilides [22, 23].



18 **19**

R = H, SMe, Ph; R^1 = Ph, *p*-tolyl

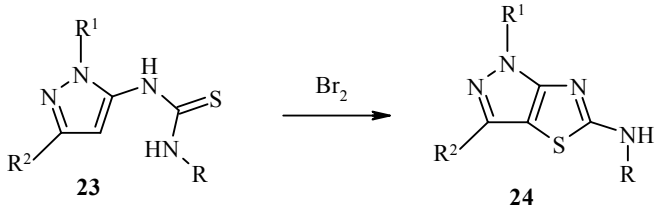
An interesting but probably special method is the reaction of 5-aminopyrazoles **20** with Appel's salt (**21**) at room temperature, giving the pyrazolo[3,4-*d*]thiazoles **22** with yields of 40-81% [24].



20 **21** **22**

R^1, R^2 = Me, Ph

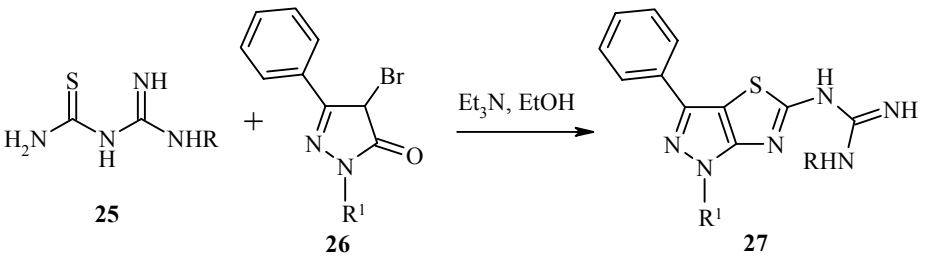
When treated with bromine in acetic acid or chloroform the pyrazolylthioureas **23** obtained from aminopyrazole give good yields of pyrazolo[3,4-*d*]thiazoles **24** [25, 26]. This approach to the construction of condensed systems has already been demonstrated during the synthesis of compound **6** [17] and is clearly one of the most convenient.



23 **24**

R = H, Alk, Ar, COPh, CSNHAr; R^1, R^2= Alk, Ar

The pyrazolothiazolylguanidines **27** are obtained by a similar method with a yield of 74% by the reaction of carbamidinoylthioureas **25** with 4-bromo-5-phenyl-2,4-dihydropyrazol-3-one (**26**) [27].

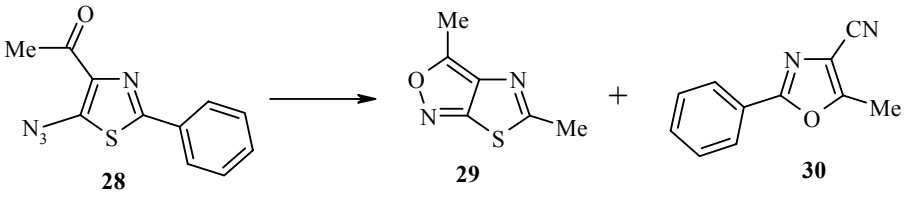


25 **26** **27**

R = Ar; R^1 = Me, Ph

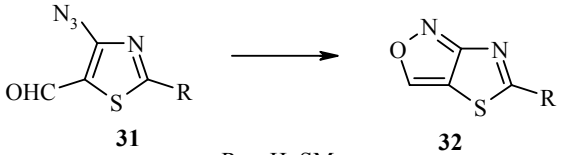
Isoxazolothiazoles

The synthesis of isoxazolothiazoles from the azido derivative of thiazole **28** is familiar. On heating intramolecular cyclization occurs at the azido and acyl functions, leading to the formation of the isoxazolothiazole **29** with a yield of 50% [28]. The oxazole **30** is formed as side product.



28 **29** **30**

Similarly, the isoxazolo[3,4-*d*]thiazole **32**, unstable in air, is formed with a 61% yield when 5-thiazolecarbaldehyde **31** is heated in boiling toluene [22].



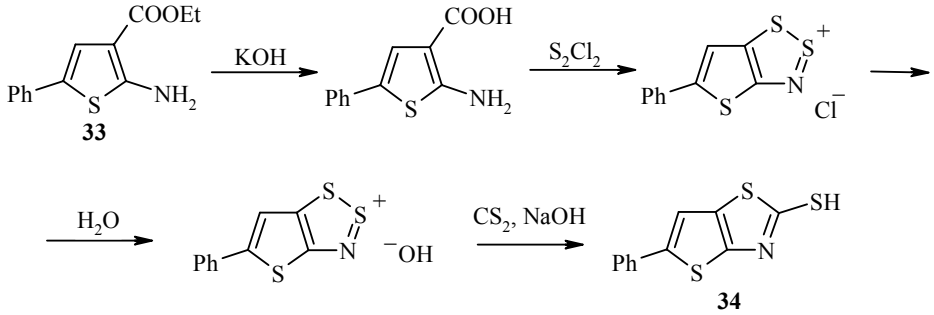
31 **32**

R = H, SMe

Thienothiazoles

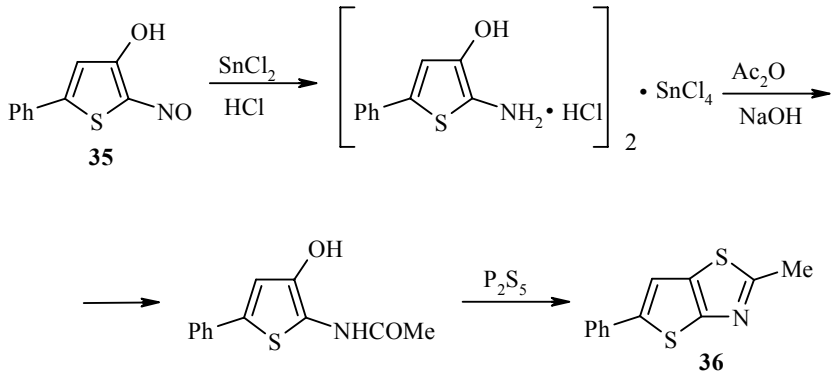
Thienothiazoles are spectral sensitizers for photographic materials and silver-halide emulsions [8, 9]. Their derivatives are used as sensitizers in photofilms for medical radiograms [10] and also in volume photography [11].

2-Mercaptothieno[2,3-*d*]thiazole (**34**) was synthesized by a multistage scheme from 2-amino-3-ethoxycarbonyl-5-phenylthiophene (**33**) with an overall yield of 10% [8].

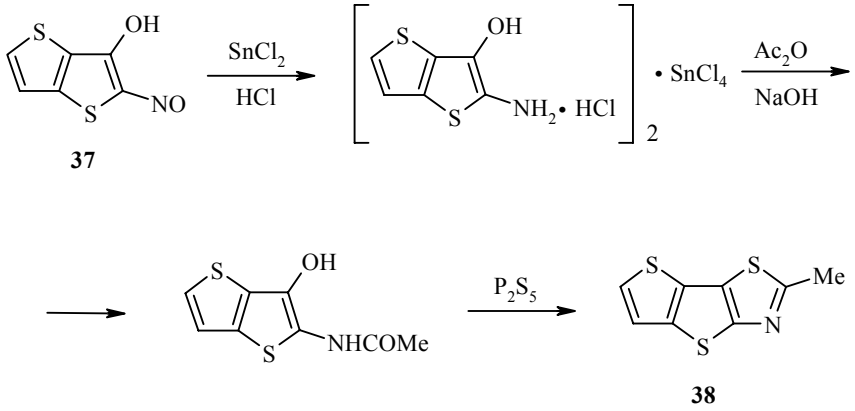


33 **34**

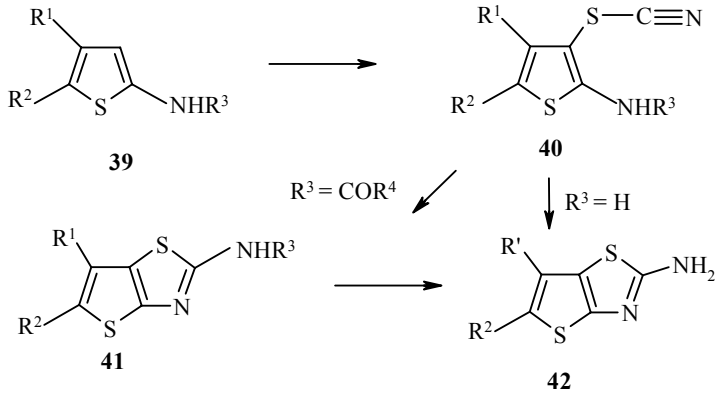
Methylthieno[2,3-*d*]thiazole was obtained with an overall yield of 7% from 3-hydroxy-2-nitroso-5-phenylthiophene (**35**) according to the following scheme [9].



2-Methylthieno[3,2-*b*]thieno[2,3-*d*]thiazole (**38**) was obtained by a similar scheme also with a yield of 7% from 2-nitrosothieno[3,2-*b*]thiophen-3-ol (**37**) [29].

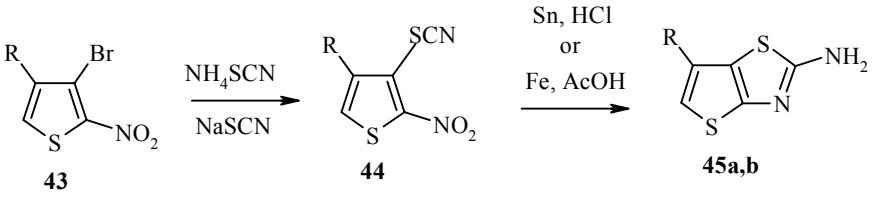


The thienothiazole structure **42** was obtained by thiocyanation of 2-aminothiophenes **39** [30] or 2-(acylamino)thiophenes **39** [31] followed by intramolecular cyclization of the thiocyanatothiophenes **40** with the formation of the thieno[2,3-*d*]thiazole (**41**) with yields of 48-75%. Hydrolysis of the latter gave the amine **42** (65-77%) [31]. In the case of R^3 = H the reaction does not stop at the formation of the thiocyanation product **40** but leads to further cyclization with the formation of the condensed aminothienothiazole **42**.



R^1, R^2 = Me, $(CH_2)_4$, Ph; R^4 = Alk, Ar

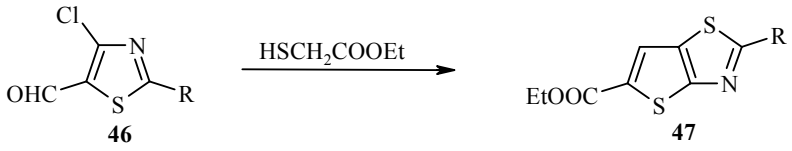
The thiocyanate derivatives of thiophene **44** are formed readily during the reaction of the bromides **43** with ammonium thiocyanate in alcohol [32] or sodium thiocyanate in DMSO [32]. The nitro group is reduced by the action of tin in hydrochloric acid [32], iron in acetic acid [33], or by reduction in an alkaline medium ($FeSO_4$ and ammonia) [34]. Subsequent intramolecular cyclization gave the 2-aminothieno[2,3-*d*]thiazole (**45a**) (R = H) with a yield of 17% [32] and methyl 2-aminothieno[2,3-*d*]thiazolecarboxylate (**45b**) (R = CO_2Me) with a yield of 87% calculated on the initial bromides [33].



43 **44** **45a,b**

45 a R = H, **b** R = CO_2Me

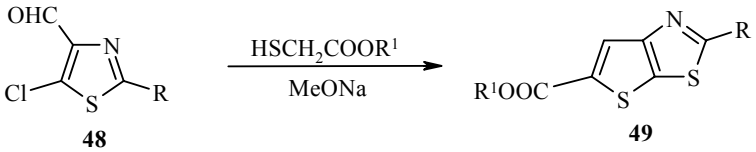
By reaction with ethyl 2-mercaptoacetate in ethanol in the presence of sodium ethoxide 4-chloro-5-formylthiazole **46** was converted into the thieno[2,3-*d*]thiazole-5-carboxylate (**47**) [22]. Other derivatives were obtained in the same way [35]. The yields of the final compounds were ~50% calculated on the initial 4-chlorothiazole.



46 **47**

R = H, Cl, SMe

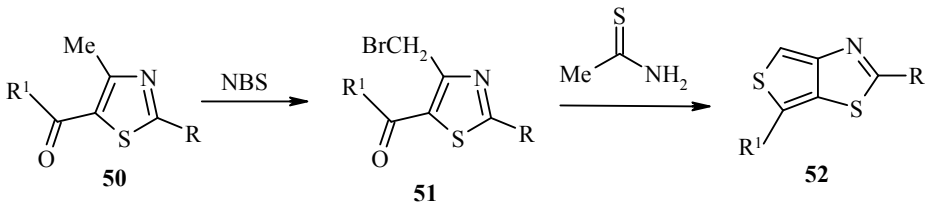
The isomeric phenylthieno[3,2-*d*]thiazole (**49**) was synthesized in a similar way from 5-chloro-4-formyl-2-phenylthiazole (**48**) and thioglycolic acid in the presence of sodium methoxide with a yield of 38% [36]. 2-Acetylaminothieno[3,2-*d*]thiazole was obtained similarly [37].



48 **49**

R = Ph, NHCOMe; R^1 = H, Me

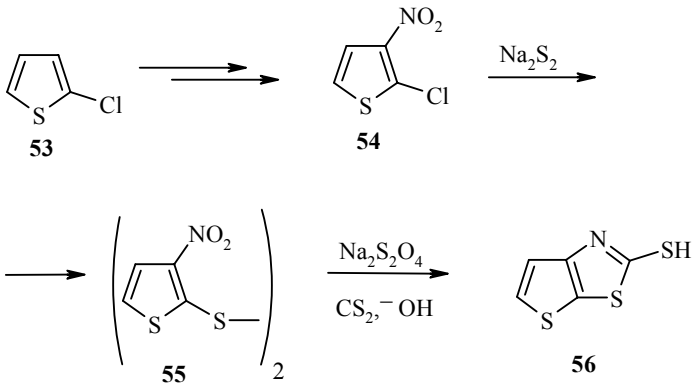
The isomeric thieno[3,4-*d*]thiazoles **52** were synthesized from the corresponding thiazoles **50** through the formation of the intermediate bromomethyl derivatives **51** with yields of 42-64% on the initial thiazole **50** [38, 39].



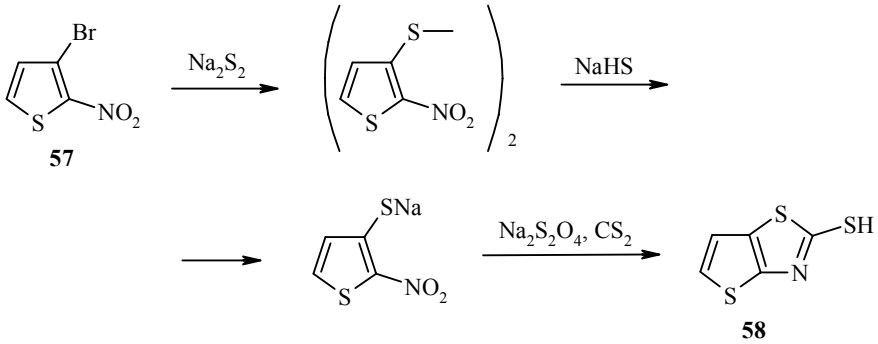
50 **51** **52**

R = Me, Ph; R^1 = Ar

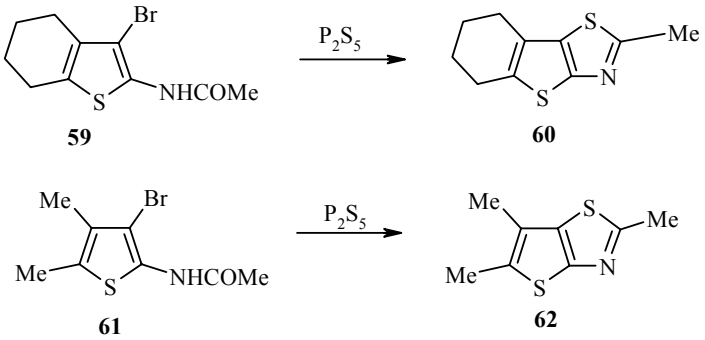
2-Mercaptothieno[3,2-*d*]thiazole (**56**) was synthesized from 2-chlorothiophene (**53)** by a multistage synthesis with the intermediate production of the chloronitrothiophene **54** and subsequent reduction of the disulfide **55** with a yield of 9% on the initial chlorothiophene **53** [40].



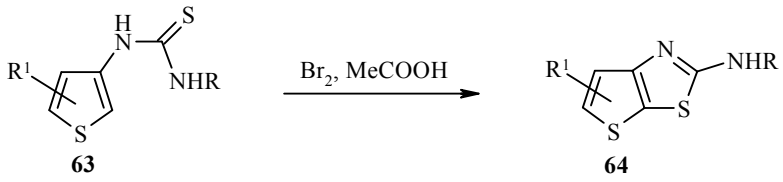
The isomeric 2-mercaptothieno[2,3-*d*]thiazole (**58**) was obtained in a similar way from bromonitrothiophene **57** (15%) [41].



The cyclization of 2-acetylamino-3-bromothiophene derivatives **59** and **61** by the action of phosphorus pentasulfide was used for the production of 2-methylthienothiazoles **60** (36%) [42] and **62** (42%) [43].



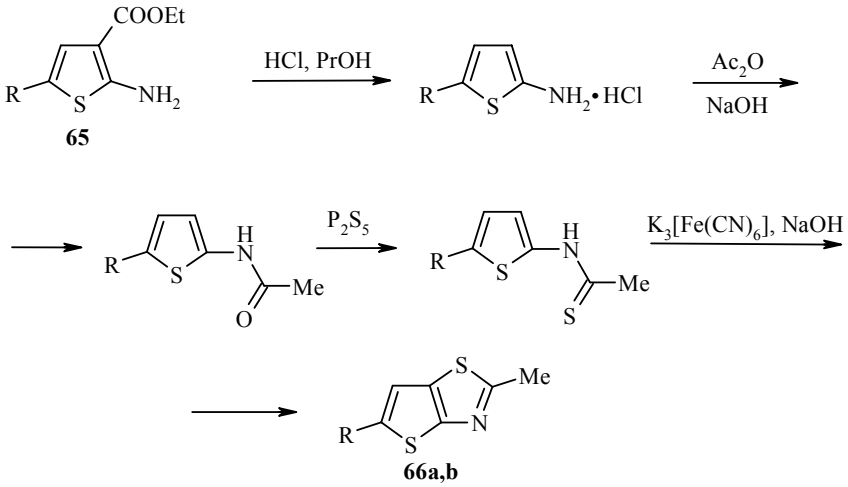
Above, it was mentioned for the case of the synthesis of the derivatives **6** and **24** that hetarylthioureas can undergo cyclization in the presence of oxidizing agents, forming condensed thiazoles with fairly good yields. Similar transformations to thieno[3,2-*d*]thiazoles **64** from the thioureas **63** with yields of 35-71%, calculated on the initial amine, were described in [37, 44].



63 **64**

R = H, COMe, COOEt, COPh; R^1 = H, Alk

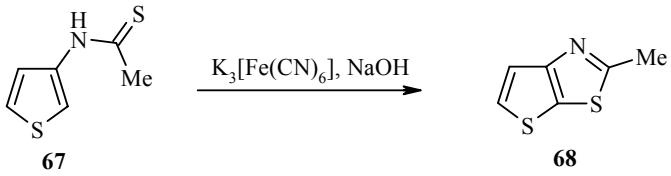
In [42, 45] the oxidation of thioamides of the thiophene series was realized with potassium hexacyanoferrate. Methylthieno[2,3-*d*]thiazole (**66a**) and methylphenylthieno[2,3-*d*]thiazole (**66b**) were obtained by this method. The yields in these reactions were small and amounted to 5% on the initial aminothiophene **65**.



65 **66a,b**

a R = H, **b** R = Ph

The methylthieno[32-*d*]thiazole **68** was synthesized in a similar way from the thioamide **67** with a small yield [46].



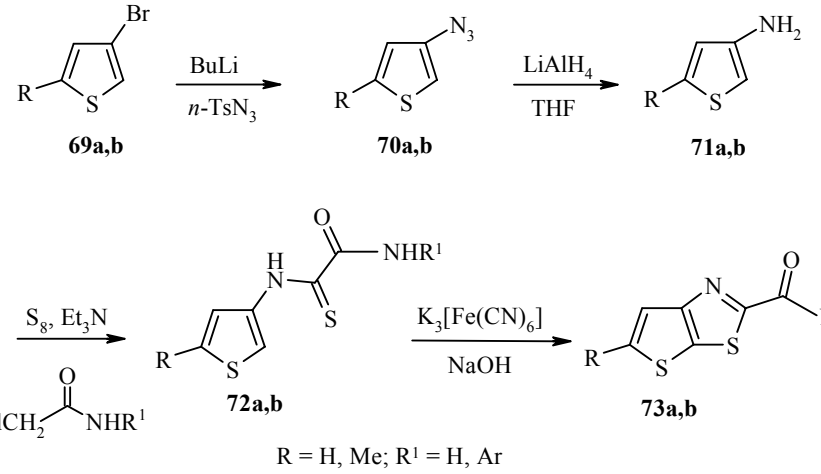
67 **68**

As seen from the data presented in the literature [42, 45, 46], the oxidative cyclization of thioamides of the thiophene series takes place under stringent conditions. The production of thienothiazoles is an extremely laborious process, and the yields of the thienothiophenes are small. Thus, for example, the overall yield of 2-methylthieno[3,2-*d*]thiazole (**68**) is not higher that 1.5% calculated on the initial thiophene [47, 48].

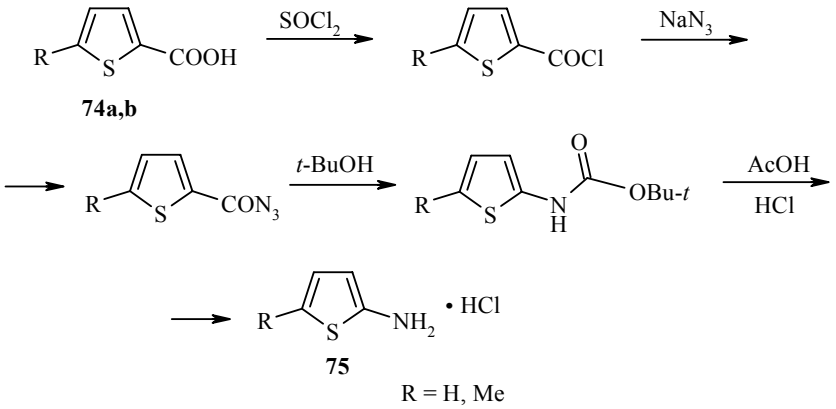
This method was realized with much greater success for the production of condensed products from heterocycles with monothiooxamide fragments. The latter are easily obtained during the reaction of a wide range of amines with chloroacetamides and sulfur in the presence of triethylamine by a modification of the procedure in [49-55].

Some examples of such syntheses from aminothiophenes are given below. The production of 3-aminothiophene (**71a**) and 4-amino-2-methylthiophene (**71b**) was realized by a two-stage scheme from the readily obtainable 3-bromothiophene (**69a**) and 4-bromo-2-methylthiophene (**69b**) [56]. The bromides **69a**,**b**

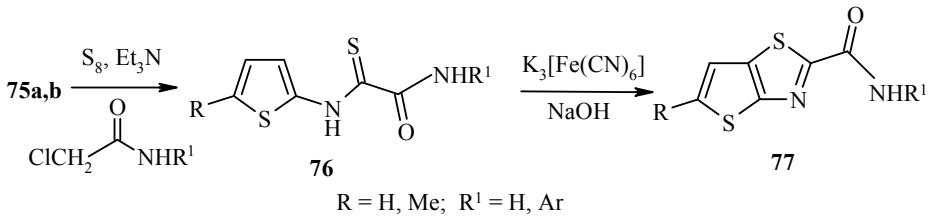
were treated with *n*-BuLi in ether, and *p*-toluenesulfonyl azide was then added at -70°C. The 3-azidothiophene (**70a**) and 4-azido-2-methylthiophene (**70b**) formed here were reduced with lithium aluminum hydride in THF. The cyclization of the monothiooximes **72** to the thiazole system in alkaline aqueous solutions by the action of $K_3[Fe(CN)_6]$ at 20°C led to good yields of the 2-carbamoylthieno[3,2-*d*]thiazoles **73** [57].



The synthesis of isomeric carbamoylthieno[2,3-*d*]thiazoles **77** from 2-carboxythiophene (**74a**) and 5-carboxy-2-methylthiophene (**74b**), including the production of the intermediate 2-aminothiophenes **75** [79], was likewise described in [58].



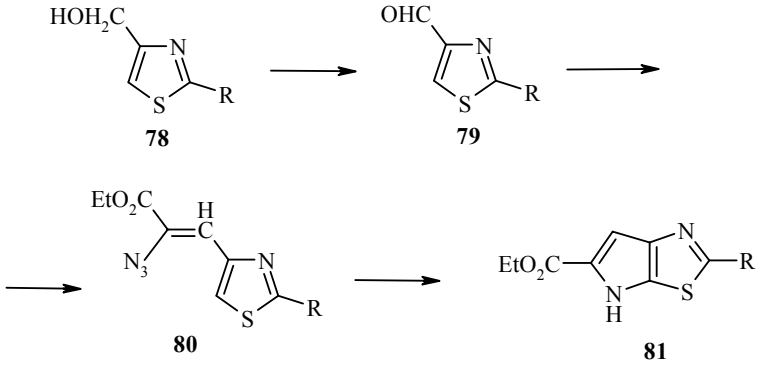
The authors point out that the cyclization of the monothiooximes **76** to the thiazole system takes place at 0°C in a 2% solution of sodium hydroxide, and the 2-carbamoylthieno[2,3-*d*]thiazoles **77** are formed with satisfactory yields [58].



Pyrrolothiazoles

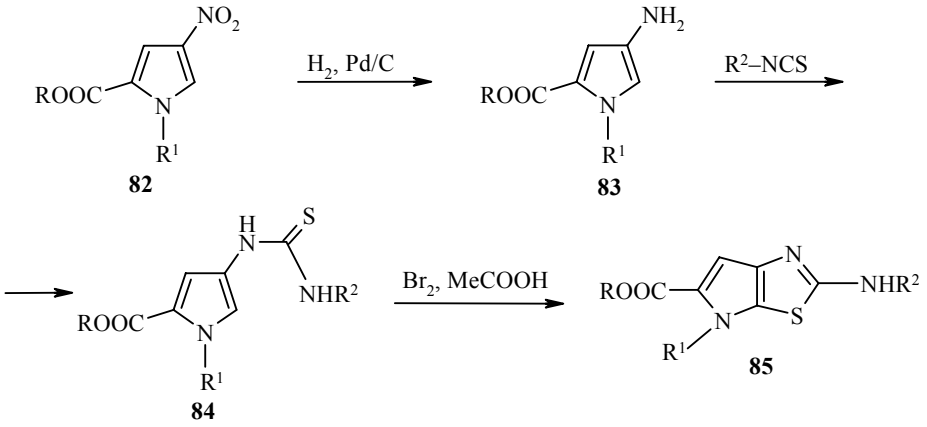
Pyrrolothiazoles are widely used as biologically active substances. They have been used as anti-inflammatory agents and immunomodulators [5], and also as anticoagulants, inhibitors of factor X_a, and for the prevention and treatment of thrombosis and embolism [6, 7]. They are also used as components of photographic films and papers [60].

The synthesis of substituted pyrrolo[3,2-*d*]thiazoles includes a stage involving oxidation of 4-hydroxymethylthiazoles **78** with manganese dioxide and condensation of the obtained formyl derivative **79** with ethyl azidoacetate. Heating of the azidoacrylate **80** formed here in xylene leads to the pyrrolothiazole **81** with an overall yield of 9% [61].



R = H, Me, Ph

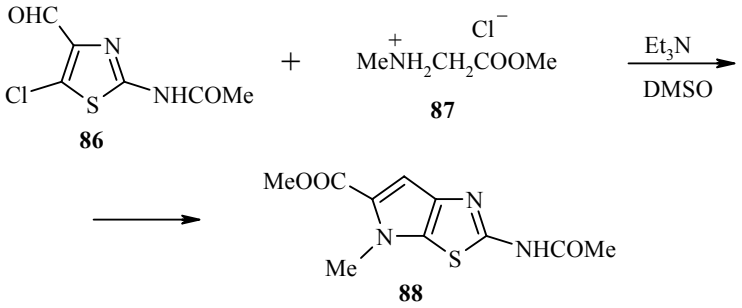
The aminopyrrole **83**, obtained by reduction of the nitropyrrole **82**, was transformed into the pyrrolothiourea **84**, subsequent cyclization of which gave the condensed system **85** with a yield of about 50% calculated on the initial nitro compound **82** [62].



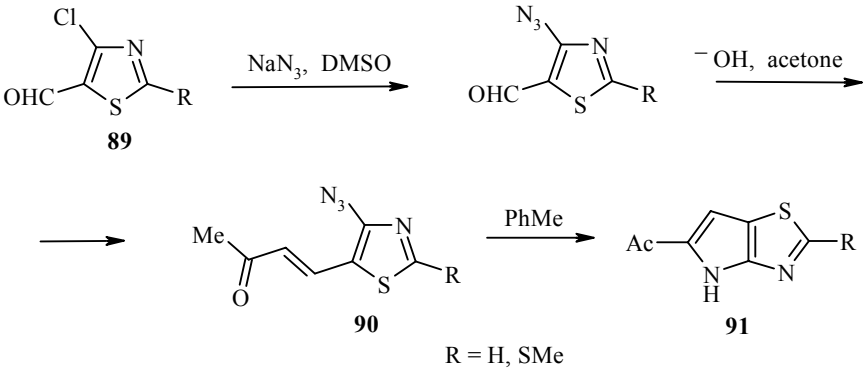
R = Alk; R^1 = H, Me; R^2 = H, COAlk, COPh

Pyrrolo[2,3-*d*]thiazoles and pyrrolo[3,4-*d*]thiazoles were obtained in the same way [62].

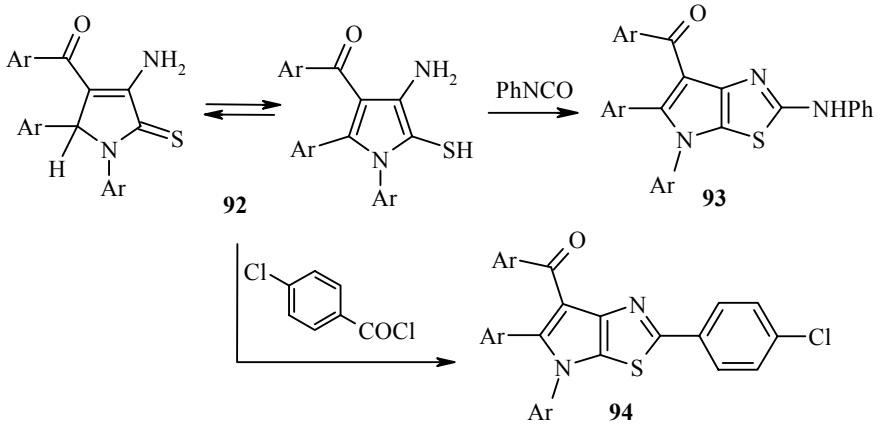
The production of the pyrrolo[3,2-*d*]thiazole **88** with a yield of 32% from the product of the condensation of thiazolecarbaldehyde **86** with methyl sarcosinate hydrochloride **87** was described in [62].



The pyrrolo[2,3-*d*]thiazoles **91** were obtained from *trans*-alkenylazidothiazole **90** by heating in toluene with an overall yield of 40%, calculated on the initial thiazole **89** [28].



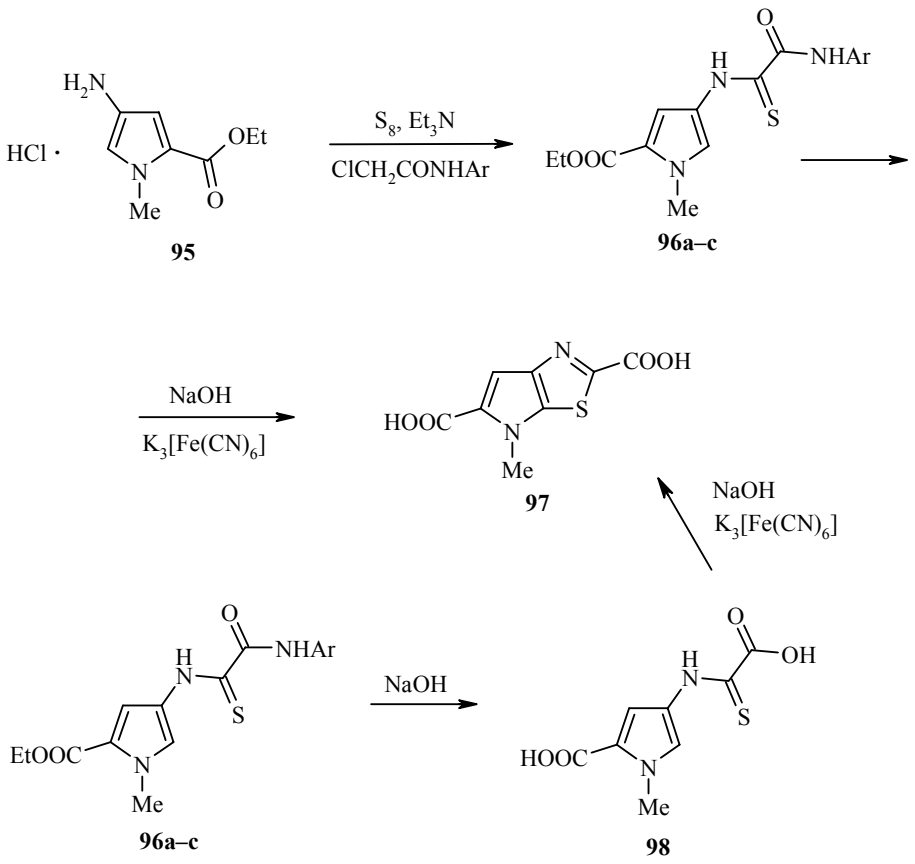
The synthesis of pyrrolothiazines **93** and **94** with good yields (80%) from mercaptopyrrole **92** with phenyl isocyanate and *p*-chlorobenzoyl chloride has also been used [63].



As also in the case of thienothiazoles [57, 58], one of the most attractive general methods for the synthesis of pyrrolothiazines is the oxidation of the corresponding monothiooxamides with $K_3[Fe(CN)_6]$ in alkaline solutions. This method was used for the creation of a thiazole ring based on aminopyrroles.

Thus, ethyl 4-amino-1-methyl-1H-pyrrole-2-carboxylate hydrochloride (**95**) [64, 65] was transformed with good yields into monothiooxamides **96**, the oxidative cyclization of which with the formation of a thiazole system takes place under the influence of $K_3[Fe(CN)_6]$ in 20% sodium hydroxide solution at 20°C. The cyclization here is accompanied by hydrolysis of the ester groups and the formation of 4-methyl-4H-pyrrolo-[3,2-*d*][1,3]thiazole-2,5-dicarboxylic acid (**97**) [66].

The process probably takes place with the formation of the intermediate diacid **98**, which can in a number of case be isolated from the reaction mixture. This acid also forms the acid **97** under the conditions of oxidative cyclization.



2. THIAZOLE SYSTEMS CONDENSED WITH SIX-MEMBERED HETEROAROMATIC RINGS

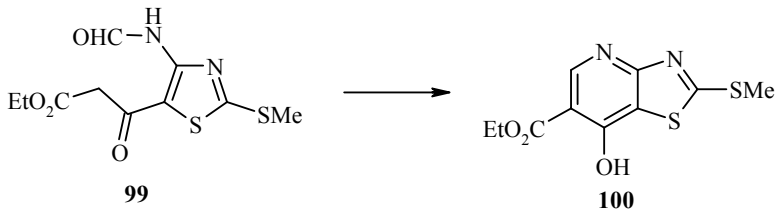
Thiazolylpyridines

Derivatives of thiazolopyridine exhibit biological activity, including analgesic, antipyretic, antiinflammatory, and antifungal activity [3, 67], are drugs such as inhibitors of integrally bound kinase and therapeutic agents for hyperproliferative and other disorders [68-70], for the treatment of diabetes and other diseases [71], sexual dysfunction [72], and as antibacterial preparations [73].

Recently great attention has been paid to the synthesis of compounds containing pyridine and 2-carbamoylthiazole fragments and their biological activity. Thus, on the basis of thiazolopyridines tetrahydropyridine derivatives were created for use as antithrombotic agents [74-76].

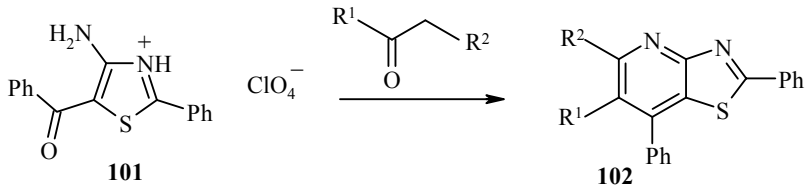
Several methods for the synthesis of thiazolopyridine are known. First we will consider methods for the construction of the pyridine ring on the basis of thiazole.

The cyclization of 5-acyl-4-amino-substituted thiazoles **99** both with bases and with acetic acid leads to 7-hydroxy-2-(methylsulfanyl)thiazolo[4,5-*b*]pyridine (**100**) with a yield of 70% [77].



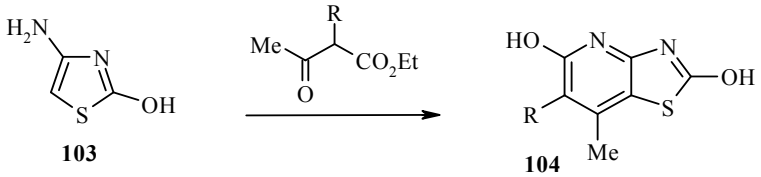
99 **100**

During the condensation of 4-amino-5-benzoyl-2-phenylthiazole (**101**) with ketones at 130-150°C thiazolo[4,5-*b*]pyridines **102** are formed with yields of 46-64% [78].



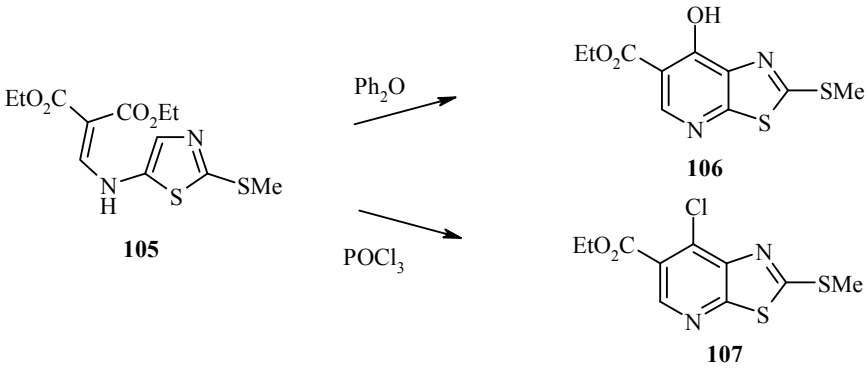
101 **102**

Heating of 4-aminothiazol-2-ol (**103**) with derivatives of acetoacetic ester in methanol in the presence of sodium methoxide gives 7-methylthiazolo[4,5-*b*]pyridine-2,5-diols **104**. The yields vary in the range of 79-100% [79].



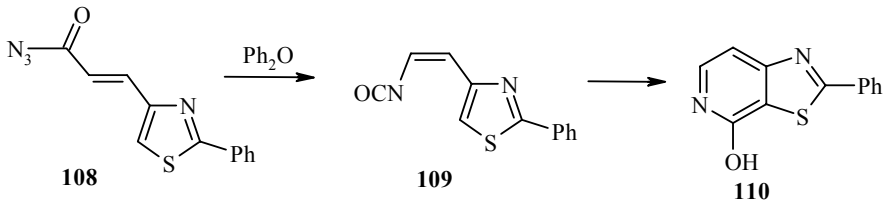
103 **104**

5-Aminothiazoles with an unsubstituted position 4 react with diethyl ethoxymethylenemalonate, forming the intermediate **105**, which undergoes cyclization on heating to the thiazolopyridine **106** (90%); in reaction with phosphorus oxychloride the chlorine derivative **107** is obtained with a yield of 53% [80].



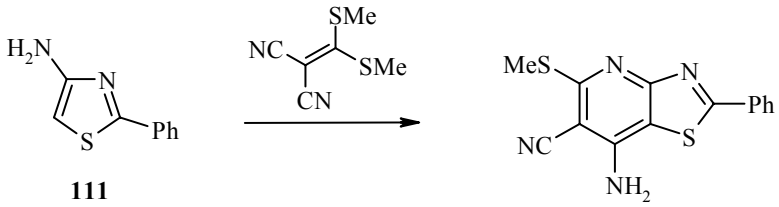
105 **106** **107**

When heated in diphenyl ether (2*E*)-3-(2-phenyl-1,3-thiazol-4-yl)acryloyl azide (**108**) gives the isocyanate **109**, which then undergoes cyclization to the phenylthiazolopyridin-4-ol (**110**) with a yield of more than 90% [81].



108 **109** **110**

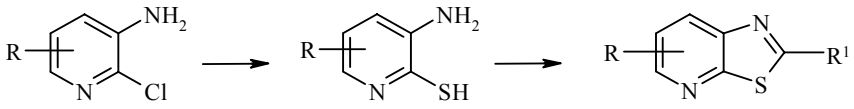
The thiazolopyridine **112** was obtained by the reaction of bis(methylthio)methylenemalononitrile with 4-amino-2-phenylthiazole (**111**) [82].



111 **112**

A fairly large number of publications have also been devoted to the construction of the thiazole ring by cyclization of functional groups in the pyridine.

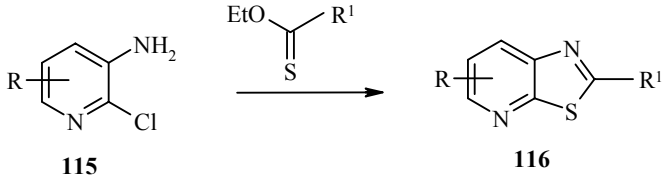
The reaction of aminopyridine-2-thiols **113** with acids or their anhydrides leads to the thiazolopyridines with yields of 60-70% [83, 84].



113 **114**

R^1 = Ph, Me, Et, CF_3, $CHCl_2$, CCl_3,CH_2Cl, COOEt, H

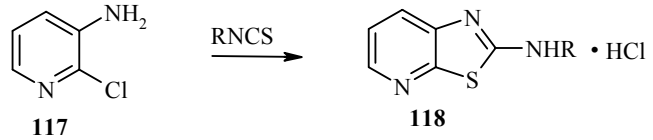
In the reactions of amino-2-chloropyridines **115** with the esters of O-alkylthiocarboxylic acids the amino group is initially activated by N-metallation with ethylmagnesium bromide, butyllithium, or sodium hydride, after which it is treated with the thioesters. The yields of the thiazolopyridines **116** amount to 70% [85-87].



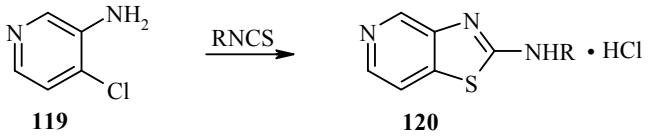
115 **116**

R^1= Ph, *p*-tolyl, Me, styryl, SH

The thioureas obtained from aminochloropyridines **117** and **119** and alkyl-, aryl-, or ethoxycarbonylisothiocyanates undergo further cyclization with substitution of the chlorine. The yield of the final thiazolopyridines **118** and **120** amounts to 60-70% [88-90].



117 **118**



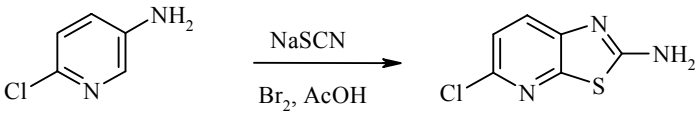
119 **120**

R = Alk, Ar, COOEt

The thiazolopyridine derivative **122** was also obtained from a thiourea of the pyridine series **121** by treatment with HBr in DMSO [91].

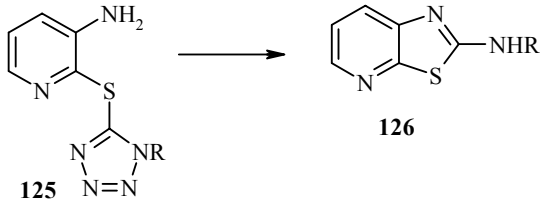
121 **122**

5-Amino-2-chloropyridine (**123**) was converted into 2-aminothiazolopyridine **124** with a yield of 91% by reaction with sodium thiocyanate in the presence of bromine in acetic acid [92].



123 **124**

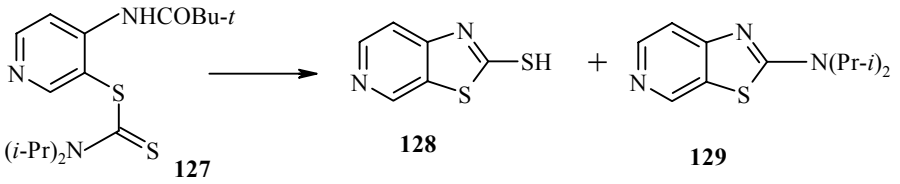
The treatment of 3-amino-2-(1H-thiazol-5-ylsulfanyl)-substituted pyridines **125** with hydrochloric acid in ethanol leads to thiazolo[5,4,-*b*]pyridin-2-amines **126** with yields of 40-80% [90].



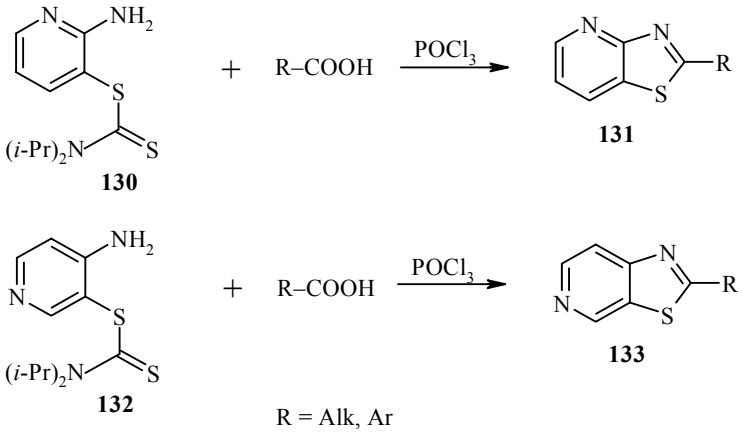
125 **126**

R = Alk, Ar

The cyclization of pyridinedithiocarbamate **127** with alkali in ethanol gives a mixture of thiazolopyridinethiol **128** (86%) and N,N-diisopropylthiazolopyridine-2-amine (**129**) (14%) [93, 94].

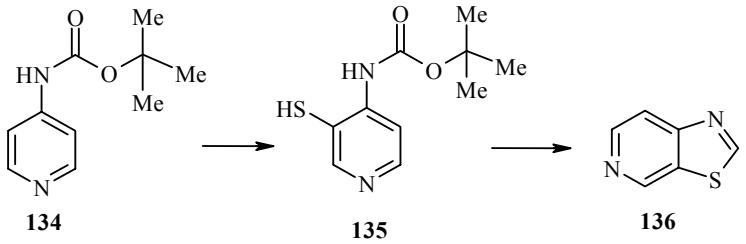


Treatment of *ortho*-amino(diisopropyldithiocarbamato)pyridines **130** and **132** with a carboxylic acid in the presence of phosphorus oxychloride leads to the formation of thiazolopyridines **131** and **133** with moderate yields [67].

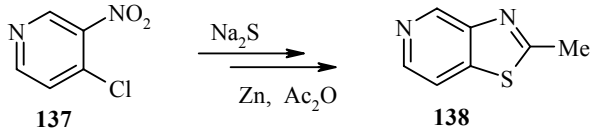


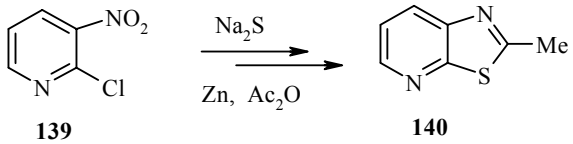
2-Substituted thiazolo[4,5-*b*]pyridines are obtained similarly by the treatment of *ortho*-amino(diisopropyldithiocarbamato)pyridines with acid chlorides in dichloromethane in the presence of triethylamine followed by boiling in hydrochloric acid [95].

Thiazolo[5,4-*c*]pyridine (**136**) was obtained by a multistage reaction from *tert*-butoxycarbonylaminopyridine **134**. Cyclization of the amide **135** was realized with a yield of 20% by heating in formic acid [96].



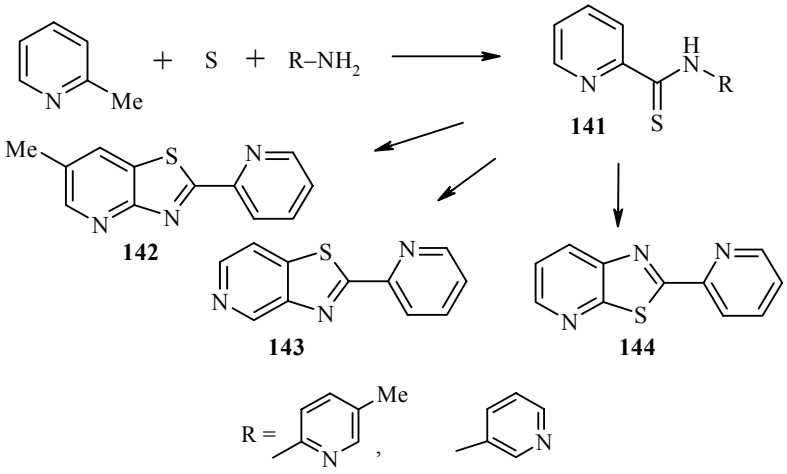
2-Methyl[1,3]thiazolo[5,4-*b*]- and 2-methyl[1,3]thiazolo[4,5-*c*]pyridines (**138**) and (**140**) were obtained from *ortho*-nitrochloropyridines **137** and **139** [97-99]. The reaction takes place through the formation of a disulfide and its subsequent reduction with zinc. The yields of the pyridines **138** and **140** amounted to ~50%.





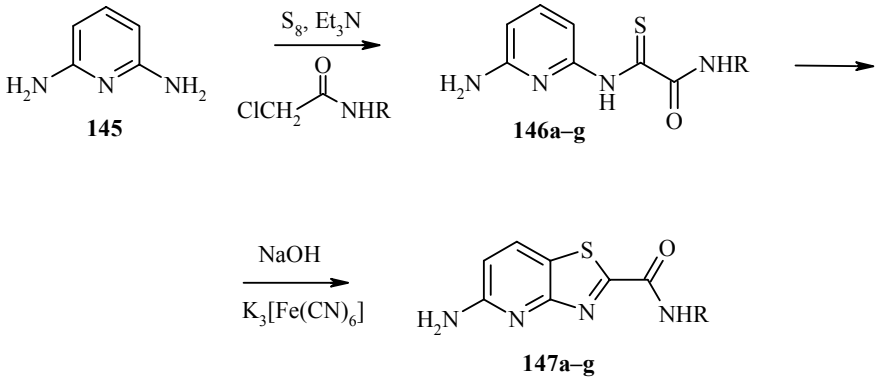
139 **140**

The thiazolopyridines **142-144** were obtained by oxidation of the pyridine **141** with potassium hexacyanoferrate in an alkaline medium [100].



As in the case of the synthesis of thienothiazoles [57, 58], this method can be applied more successfully to the cyclization of monothiooxamides of the pyridine series. Thus, it was used for the production of thiazolo[4,5-*b*]- and thiazolo[5,4-*b*]pyridine-2-carboxamides.

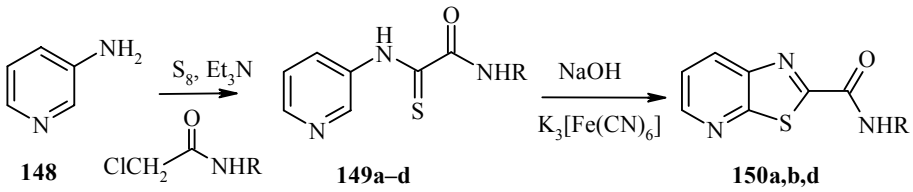
It was demonstrated that oxidation of the monothiooxamides **146** and **149**, obtained from the corresponding aminopyridines **145** and **148**, chloroacetamides, and sulfur in the presence of triethylamine, with $K_3[Fe(CN)_6]$ takes place at 50°C and leads with high yields to 5-aminothiazolo[4,5-*b*]pyridine-2-carboxamides **147** and to thiazolo[5,4-*b*]pyridine-2-carboxamides **150** [101, 102].



145 **146a–g**

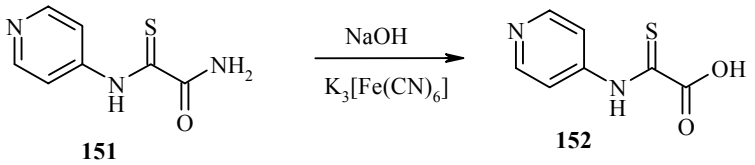
147a–g

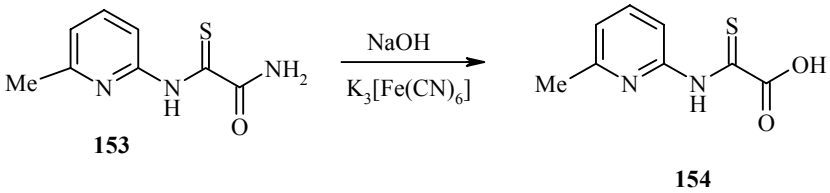
146, 147 a R = Ph, **b** R = 4-BrC_6H_4, **c** R = 4-ClC_6H_4, **d** R = 4-FC_6H_4, **e** R = 4-MeC_6H_4, **f** R = 4-$MeOC_6H_4$, **g** R = 2-FC_6H_4



149, 150 **a** R = Ph, **b** R = 4-FC_6H_4, **c** R = 2,6-$(Me)_2C_6H_3$, **d** R = 4-BrC_6H_4

The authors of [101] mention that the nature of the substituent in the pyridine ring has a deciding effect on the course of the reaction. Thus, the formation of thioxazole rings was not observed in the case of the monothiooxamides obtained from the product **151** or methylpyridine **153**. The unsubstituted amides were saponified under alkaline conditions to the corresponding acids, and the main reaction products were the N-pyridylthiooxamic acids **152** and **154**.





It can be supposed that the methods for the synthesis of thiazolopyridines described in this section will prove useful also for the synthesis of condensed thiazoles with other six-membered aromatic heterocycles.

REFERENCES

1. D. Kikelj and U. Urleb, in: *Science of Synthesis*, Georg Thieme Verlag (2002), Vol. 11, p. 627. *Chem. Abstr.*, **139**, 6779 (2003).
2. G. Pattenden, *J. Heterocycl. Chem.*, **29**, 607 (1992).
3. H. Ulrich, in: *Science of Synthesis*, Georg Thieme Verlag (2002), Vol. 11, p. 835. *Chem. Abstr.*, **139**, 52895 (2003).
4. G. Seybold and H. Eilingsfeld, *Liebigs Ann. Chem.*, 1271 (1979).
5. J. Barker, J. G. Kettle, and A. W. Faull, PCT Int. Appl. WO 9940914; *Chem. Abstr.*, **131**, 170342 (1999).
6. T. Ota, S. Komoritani, T. Yoshino, K. Uoto, Y. Nakamoto, H. Naito, A. Mochizuki, T. Nagata, H. Kanno, N. Haginoya, K. Yoshikawa, M. Nagamochi, and S. Kobayashi, Japan Kokai Tokkyo Koho JP 2003183286; *Chem. Abstr.*, **139**, 85363 (2003).
7. T. Ohta, S. Komoriya, T. Yoshino, K. Uoto, Y. Nakamoto, H. Naito, A. Mochizuki, T. Nagata, H. Kanno, N. Haginoya, K. Yoshikawa, M. Nagamochi, S. Kobayashi, and M. Ono, PCT Int. Appl. WO 0316302; *Chem. Abstr.*, **138**, 205076 (2003).

8. P. I. Abramenko, T. K. Ponomareva, and G. I. Priklonskikh, *Khim. Geterotsikl. Soedin.*, 477 (1979).
9. P. I. Abramenko and V. G. Zhiryakov, *Khim. Geterotsikl. Soedin.*, 1624 (1970).
10. V. R. Berdnikov, L. Ya. Kaplun, N. V. Pospelova, E. A. Silaev, and L. V. Formina, Russ. Patent RU 2195011; *Chem. Abstr.*, **139**, 141038 (2003).
11. E. B. Lifshits, A. V. Medvedeva, V. N. Podlesnykh, E. A Silaev, M. N. Ushomirskii, and L. V. Formina, Russ. Patent RU 2184387; *Chem. Abstr.*, **138**, 262613 (2003).
12. J. A. Zampese, F. R. Keene, and P. J. Steel, *Dalton Transactions*, 4124 (2004).
13. S. Ando, J. Nishida, Y. Inoue, S. Tokito, and Y. Yamashita, *J. Mater. Chem.*, **14**, 1787 (2004).
14. S. Ando, J. Nishida, E. Fujiwara, H. Tada, Y. Inoue, S. Tokito, and Y. Yamashita, *Chem. Lett.*, **33**, 1170 (2004).
15. V. Sutoris, *Agrochemia (Bratislava)*, **30**, No. 1, 15 (1990).
16. S. Reck, C. Nather, and W. Friedrichsen, *Heterocycles*, **48**, 853 (1998).
17. L. Grehn, *Chem. Scripta*, **11**, 199 (1977).
18. S. Hirabayashi and Y. Nagaoka, Japan Kokai Tokkyo Koho JP 03230158; *Chem. Abstr.*, **116**, 162453 (1992).
19. Y. Nagaoka and S. Hirabayashi, Eur. Pat. Appl. EP 407206; *Chem. Abstr.*, **116**, 31206 (1992).
20. Y. Oguchi and K. Arahara, Jpn. Patent JP 61228988; *Chem. Abstr.*, **106**, 224569 (1987).
21. H. Eilingsfeld and G. Swybold, Ger. Offen 2713573; *Chem. Abstr.*, **90**, 23035 (1978).
22. S. Athmani, M. F. Farhat, and B. Iddon, *J. Chem. Soc.*, *Perkin Trans. 1*, 973 (1992).
23. E. Ceulemans, K. Vercauteren, L. K. Dyall, D. Buelens, and W. Dehaen, *Tetrahedron*, 9657 (1997).
24. G. L'Abbe, B. D'Hooge, and W. Dehaen, *J. Chem. Soc, Perkin Trans. 1*, 2379 (1995).
25. H. Eilingsfeld and R. Niess, Ger. Offen 2429195; *Chem. Abstr.*, **84**, 135649 (1976).
26. P. Bounaud and A. Vaino, PCT Int. Appl., WO 2005068473, http://www.espacenet.com.
27. M. S. Chande and P. V. R. Carvalho, *Indian J. Chem.*, **43B**, 378 (2004).
28. E. Ceulemans, L. K. Dyall, and W. Dehaen, *Tetrahedron*, **55**, 1977 (1999).
29. P. I. Abramenko and V. G. Zhiryakov, *Khim. Geterotsikl. Soedin.*, 1039 (1976).
30. V. K Gewald, M. Hentschel, and R. Heikel, *J. Prakt. Chem.*, **315**, 539 (1973).
31. V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1204 (1974).
32. N. I. Astrakhantseva, V. G. Zhiryakov, and P. I. Abramenko, *Zh. Vses. Khim. Obshch.*, **21**, 219 (1976).
33. P. Stanetty, T. Dvorak, and M. D. Mihovilovic, *ARKIVOC*, 1128 (2001)
34. C. Paulmier and F. Outurquin, *J. Heterocycl. Chem.*, **20**, 113 (1983).
35. S. Athmani and B. Iddon, *Tetrahedron*, **48**, 7689 (1992).
36. I. Ya. Kvitko, R. V. Khozeeva, N. S. Fedorova, V. A. Smirnova, and A. V. El'tsov, *Khim. Geterotsikl. Soedin.*, 474 (1979).
37. L. Grehn, *J. Heterocycl. Chem.*, **15**, 81 (1978).
38. Shafiee, A. Shafaati, and B. Habibi-Khameneh, *J. Heterocycl. Chem.*, **26**, 709 (1989).
39. Shafiee and A. Mazloumi, *J. Heterocycl. Chem.*, **15**, 1455 (1978).
40. N. I. Astrakhantseva, V. G. Zhiryakov, and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 1607 (1975).
41. N. I. Astrakhantseva, V. G. Zhiryakov, and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 1355 (1976).
42. L. D. Pinkin, V. G. Dzyubenko, P. I. Abramenko, and I. S. Shpileva, *Khim. Geterotsikl. Soedin.*, 410 (1987).
43. P. I. Abramenko, T. K. Ponomareva, and G. P. Priklonskikh, *Zh. Vses. Khim. Obshch.*, **23**, 711 (1978).
44. M. I. A. Moneam and A. M. K. El-Dean, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **178**, 2639 (2003).
45. V. G. Zhiryakov and I. I. Levkoev, *Dokl. Akad. Nauk*, **120**, 1035 (1958); *Chem. Abstr.*, **52**, 20128 (1958).
46. V. G. Zhiryakov, *Khim. Nauka i Prom.*, **4**, 680 (1959).
47. Hill, M. De Vleeschauwer, K. Houde, and M. Belley, *Synlett*, 407 (1998).
48. V. G. Zhiryakov, *Khim. Nauk i Prom.*, **4**, 573 (1959).

49. V. N. Yarovenko, F. M. Stoyanovich, O. Yu. Zolotarskaya, E. I. Chernoburova, I. V. Zavarzin, and M. M. Krayushkin, *Izv. Akad. Nauk. Ser. Khim.*, 136 (2002).
50. V. Zavarzin, V. N. Yarovenko, A. Yu. Martynkin, and M. M. Krayushkin, in: *The 18th International Symposium on the Organic Chemistry of Sulfur (13-18 July 1998), Abstracts*, Florence, Italy, p. 106 (1998).
51. V. Zavarzin, V. N. Yarovenko, A. V. Shirokov, N. G. Smirnova, A. A. Es'kov, and M. M. Krayushkin, *ARKIVOC*, 205 (2003).
52. V. N. Yarovenko, S. A. Kosarev, I. V. Zarvarzin, and M. M. Krayushkin, *Izv. Akad. Nauk. Ser. Khim.*, 753 (1999).
53. V. N. Yarovenko, S. A. Kosarev, I. V. Zarvarzin, and M. M. Krayushkin, *Izv. Akad. Nauk. Ser. Khim.*, 1708 (2002).
54. V. N. Yarovenko, S. A. Kosarev, I. V. Zarvarzin, and M. M. Krayushkin, *Izv. Akad. Nauk. Ser. Khim.*, 1387 (2002).
55. V. N. Yarovenko, S. A. Kosarev, A. V. Shirokov, I. V. Zavarzin, and M. M. Krayushkin, *Izv. Akad. Nauk. Ser. Khim.*, 1487 (2000).
56. Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein, and B. V. Lopatin *Zh. Obshch. Khim.*, **34**, 969 (1964).
57. V. N. Yarovenko, N. G. Smirnova, V. N. Bulgakova, I. V. Zavarzin, and M. M. Krayushkin, *Zh. Org. Khim.*, **39**, 1232 (2003).
58. I. V. Zavarzin, N. G. Smirnova, V. N. Yarovenko, and M. M. Krayushkin, *Zh. Org. Khim.*, **40**, 146 (2004).
59. Binder, G. Habison, and C. R. Noe, *Synthesis*, 255 (1977).
60. T. Nakamura, T. Hioki, K. Ohzeki, and N. Hanaki, US Patent Appl. Publ. US 2002 58216; *Chem. Abstr.*, **136**, 393179 (2002).
61. Shafiee, A. Mazloumi, and V.I. Cohen, *J. Heterocycl. Chem.*, **16**, 1563 (1979).
62. L. Grehn, *Chem. Scripta*, **13**, 78 (1979).
63. El-Sharief, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **148**, 117 (1999).
64. B. Eldon, *J. Am. Chem. Soc.*, **118**, 6141 (1996).
65. V. A. Ryabinin and A. N. Sinyakov, *Biorganich. Khimiya*, **24**, 601 (1998).
66. N. G. Smirnova, I. V. Zavarzin, V. N. Yarovenko, and M. M. Krayushkin, in: *I Youth Conference, Institute of Organic Chemistry, Russian Academy of Sciences. Abstracts* [in Russian], Moscow (2005), p. 118.
67. G. A. El-Hiti, *Monatsh. Chem.*, **134**, 837 (2003).
68. Z. Zhang, T. S. Daynard, S. Wang, X. Du, G. B. Chopiuk, J. Yan, J. Chen, and S. V. Sviridov, PCT Int. Appl. WO 2004 11460; *Chem. Abstr.*, **140**, 163862 (2004).
69. Parlati, U. V. Ramesh, R. Singh, D. G. Payan, R. Lowe, and G. C. Look, Patent WO2005037845, http://www.espacenet.com.
70. M. Hemmerling and T. Klingstedt, Patent WO2004099204, http://www.espacenet.com.
71. Yasuda, K. Morimoto, S. Kanan, M. Hikota, T. Matsumoto, and K. Arakawa, Japan Kokai Tokkyo Koho 2004 2368; *Chem. Abstr.*, **140**, 71039 (2004).
72. M. D. Cowart, PCT Int. Appl. WO 03101994; *Chem. Abstr.*, **140**, 27845 (2004).
73. Brooks, D. T. Davies, G. E. Jones, R. E. Markwell, and N. D. Pearson, PCT Int. Appl. WO 03087098; *Chem. Abstr.*, **139**, 337959 (2003).
74. N. Haginoya, S. Kobayashi, S. Komoriya, T. Yoshino, M. Suzuki, T. Shimada, K. Watanabe, Y. Hirokawa, T. Furugori, and T. Nagahara, *J. Med. Chem.*, **47**, 5167 (2004)
75. N. Haginoya, S. Kobayashi, S. Komoriya, T. Yoshino, T. Nagata, Y. Hirokawa, and T. Nagahara, *Bioorg. Med. Chem.*, **12**, 5579 (2004).
76. N. Haginoya, S. Kobayashi, S. Komoriya, Y. Hirokawa, T. Furugori, and T. Nagahara, *Bioorg. Med. Chem. Lett.*, **14**, 2935 (2004).

77. Hayakawa and Y. Tanaka, *Heterocycles*, **22**, 1697 (1984).
78. Schäfer, H. Hartmann, and K. Gewald, *J. Prakt. Chem.*, **316**, 19 (1974).
79. I. D. Komaritsa, *Khim. Geterotsikl. Soedin.*, 1547 (1989).
80. D. C. Leysen, A. Haemers, and W. Bollaert, *J. Heterocycl. Chem.*, **21**, 401 (1984).
81. Shafiee and H. Ghazar, *J. Heterocycl. Chem.*, **23**, 1171 (1986).
82. El-Desoky and Aboul-Fetouh, *J. Chem. Technol. Biotechnol.*, **67**, 153 (1996).
83. T. Y. Shen, R. L. Clark, A. A. Pessolano, B. E. Witzel, and T. J. E. Yanza, Ger. Patent DE 2330109 (1974); *Chem. Abstr.*, **80**, 95916 (1974).
84. N. Suzuki and R. Dohmori, *Chem. Pharm. Bull.*, **27**, 410 (1979).
85. Couture, P. Grandclaudon, and E. Huguerre, *J. Heterocycl. Chem.*, **24**, 1765 (1987).
86. Couture, E. Huguerre, and P. Grandclaudon, *Synth. Commun.*, **19**, 713 (1989).
87. Zhu, M. Zhang, and M. Dai, *J. Heterocycl. Chem.*, **42**, 727 (2005).
88. D. G. Kulkarni, S. R. Lokhande, and B. G. Khadse, *Indian J. Pharm. Sci.*, **43**, No. 2, 37 (1981); *Chem. Abstr.*, **95**, 169055 (1981).
89. W. Altlang and G. A. Molander, *J. Heterocycl. Chem.*, **14**, 129 (1977).
90. W. Altlang, *J. Org. Chem.*, **41**, 3395 (1976).
91. R. D. Norcross, US Patent US2005065151, http://www.espacenet.com.
92. Tsuruoka and Y. Kaku, *Chem. Pharm. Bull.*, **46**, 623 (1998).
93. Smith, C. M. Lindsay, and J. K. Morris, *Chem. Ind. (London)*, 302 (1988).
94. Eunsook Ma, *Molecules*, **8**, 678 (2003).
95. Smith, D. Anderson, and I. Matthews, *Sulfur Lett.*, **18**, 79 (1995).
96. N. Haginoya, S. Komoriya, K. Osanai, T. Yoshino, T. Nagata, M. Nagamochi, R. Muto, M. Yamaguchi, T. Nagahara, and H. Kanno, *Heterocycles*, **63**, 1555 (2004)
97. T. Takahashi and H. Saikashi, *J. Pharm. Soc. Japan*, **64**, 201 (1944).
98. S. G. Fridman, *Zh. Obshch. Khim.*, **26**, 613 (1956).
99. S. G. Fridman, *Zh. Obshch. Khim.*, **26**, 864 (1956).
100. Kramberger and P. Lorencak, *J. Heterocycl. Chem.*, **12**, 337 (1975).
101. I. V. Zavarzin, N. G. Smirnova, V. N. Yarovenko, and M. M. Krayushkin, *Izv. Akad. Nauk. Ser. Khim.*, 1299 (2004).
102. I. V. Zavarzin, N. G. Smirnova, V. N. Yarovenko, and M. M. Krayushkin, *Zh. Org. Khim.*, **42**, 288 (2006).