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Heterocyclization Reactions Involving Thiols

I.V. Koval'

Ukrainian State University of Chemical Technology, Dnepropetrovsk, 49005 Ukraine

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Abstract—Information on the syntheses of sulfur-containing heterocycles involving thiols is systematized and generalized. Data on biological action of some among these systems are mentioned.

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1. INTRODUCTION

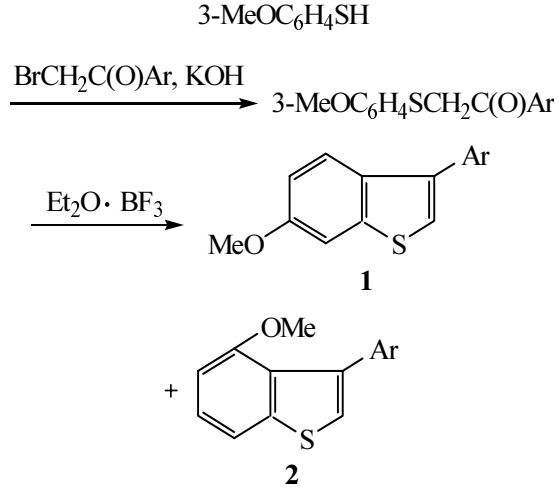
A promising line in the thiol chemistry that is extensively developed nowadays is involving the compounds into heterocyclization to produce substances that often possess practically useful properties. The heterocyclization is due to the presence of a thiol group whose cleavage can result in various highly reactive intermediates, first of all, in thiolate anions capable to take part in the nucleophilic substitution, oxidation, and other processes that commonly underlie the ring closure. In these processes are involved as a rule dithiols and bifunctional thiols containing alongside the SH group also other reactive functional groups (NH_2, CO_2H, CO_2R etc.). The monofunctional thiols are used in the synthesis of sulfur-containing heterocycles considerably more seldom. The heterocyclization with thiols participation was described in some sections of reviews [1–3], but since publication of the latter appeared a lot of new results requiring generalization. Just these data are analyzed in the present review.

Ivan Koval' was born in 1942 in a settlement Podgornoe, Dnepropetrovskaya oblast'. In 1967 he graduated from Dnepropetrovsk Institute of Chemical Technology, Candidate of Sciences since 1970, Doctor of Sciences since 1987, Academician of the Ukrainian Tecnological Academy since 1995. I.V.Koval' heads the Chair of the Chemical Technology of Macromolecular Compounds of the Ukrainian State University of Chemical Technology.

The field of scientific interests: the organoelement chemistry and the chemistry of macromolecular compounds. The main scientific achievements are the discovery, development of generation methods, and detailed investigation of characteristics of α-sulfenyl-N-anions. He is author of over 200 scientific publications, among them 20 reviews on the modern problems of the organoelement chemistry.

2. HETEROCYCLIC SYSTEMS BASED ON MONOFUNCTIONAL THIOLS

The building up of heterocyclic systems starting with monofunctional thiols consists in selecting reagents with functional groups capable to react with the SH group and with another reaction site present in the thiol molecule. A good example of this procedure is the synthesis of 3-aryl-substituted benzothiophenes based on 3-methoxythiophenol and aliphatic-aromatic σ-bromoketones [4]. In the first stage the nucleophilic substitution of the bromine with arylthio group gave rise to the corresponding sul-

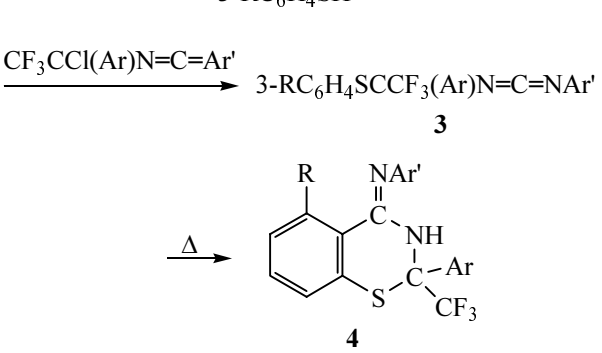


1 + **2**, 81–95%

Ar = Ph, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2,4-$(MeO)_2C_6H_3$, 2-MeO-5-MeC_6H_3, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-BrC_6H_4.

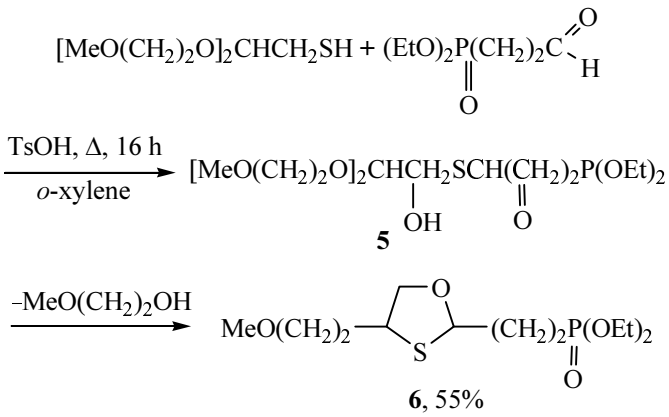
fides that in the second stage underwent cyclization under the action of boron trifluoride etherate involving one of the *ortho*-positions of the thiol benzene ring and the carbonyl group in an enol form. This synthesis gives as products 3-aryl-6- and 4-methoxy-benzothiophenes **1**, **2** in a ratio (6–10):1.

Similarly sulfides **3** produced in reaction of thiophenols with halocarbodiimides underwent cyclization at heating involving one of the *ortho*-positions of the thiol benzene ring and the carbon atom from the carbodiimide group [5]. Here the reaction products were 1,3-benzothiazine dihydro derivatives **4**.

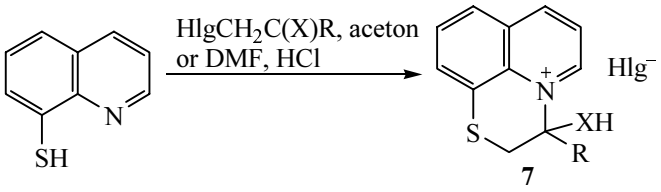


R = Me, MeO; Ar = Ar' = Ph, 4-MeC_6H_4

In the course of preparation of a presumable anti-HIV agent analogs of cytidine were synthesized; one stage of the synthesis contained the condensation of 2-di(2-methoxyethoxy)-1-ethanethiol with 3-diethoxyphosphanopropanal resulting in a diastereomers mixture (1:1) of 2-diethylphosphonoethyl-5-(2-methoxyethoxy)-1,3-oxathiolane **6** [6]. In the first stage of the condensation the reaction of the thiol and aldehyde group afforded a hemithioacetal **5** which underwent cyclization eliminating methoxyethylhydroxy group.

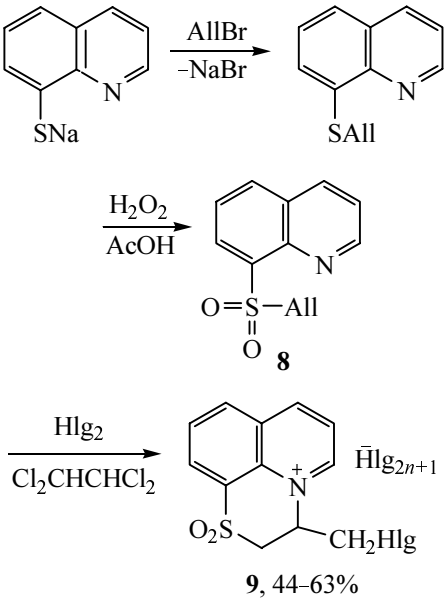


In 8-mercaptoquinoline a nitrogen atom served as a second reaction site converted at the heterocyclization into an onium state **7** [7–9].



R = H, Me; X = O, S; Hlg = Cl, Br.

8-Mercaptoquinoline sodium salt afforded with allyl bromide sulfone **8** which was further halogenized with subsequent heterocyclization into salts **9** [10].



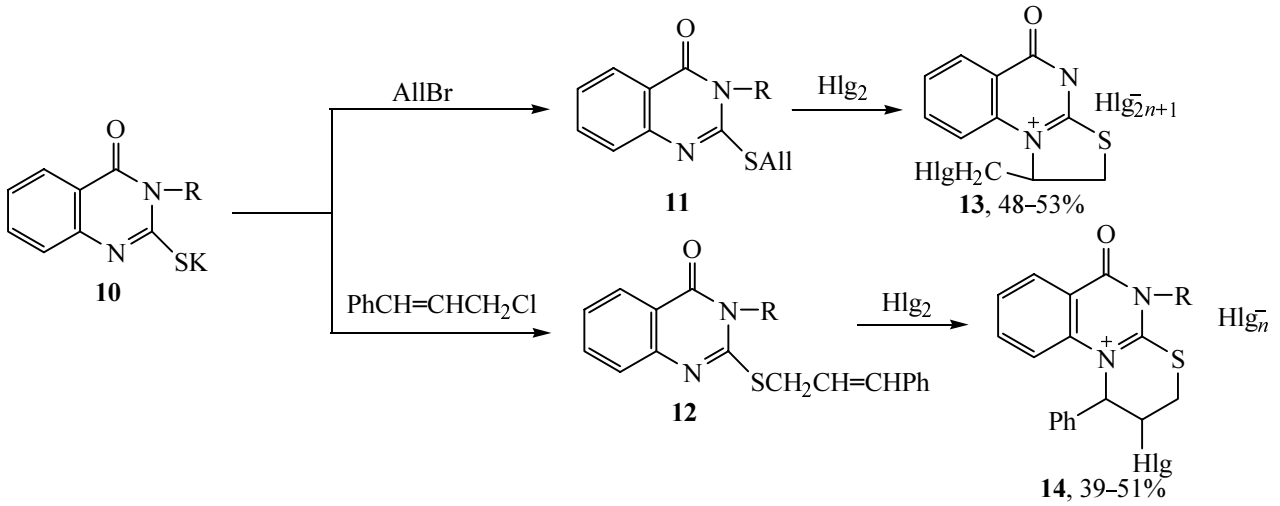
Hlg = I, n = 0, 1; Hlg = Br, n = 0; X = I, n = 0, 1; X = Br, n = 1.

In the same way halocyclization occurred with 2-(2-propenylthio)-3-R-(4*H*)-quinazolin-4-ones **11**, **12**, obtained by alkylating potassium salt of 2-mercapto-3-R-1*H*-quinazolin-4-ones **10** with allyl halides (Scheme 1) [11].

In some instances the sulfide obtained in the first stage was subjected to modification to create a new functional group taking part in the heterocyclization, for example, in the synthesis of heterocyclic system **15** based on allylthiol and 2-chloro-3-formyl-R-quinolines (Scheme 2) [12].

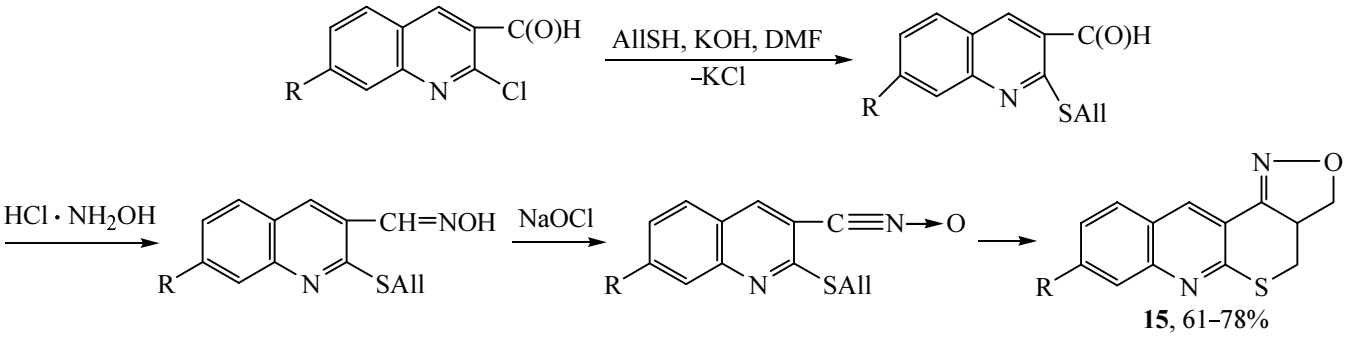
In the synthesis of a crown thioether **17** bissulfide **16** obtained in the first stage was further subjected to reductive cyclization (Scheme 3) [13].

Scheme 1.



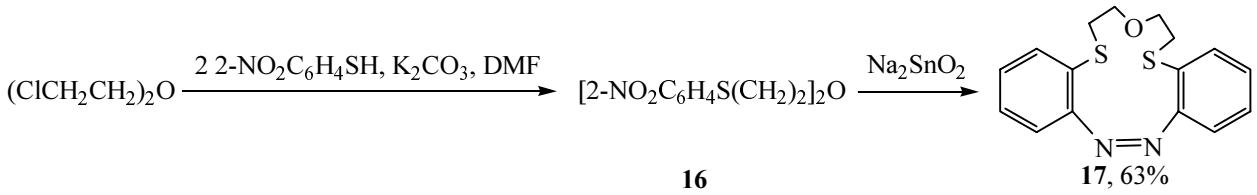
R = Me, Ph; Hlg = I, Br; n = 3, 5.

Scheme 2.



R = H, Me, Cl.

Scheme 3.



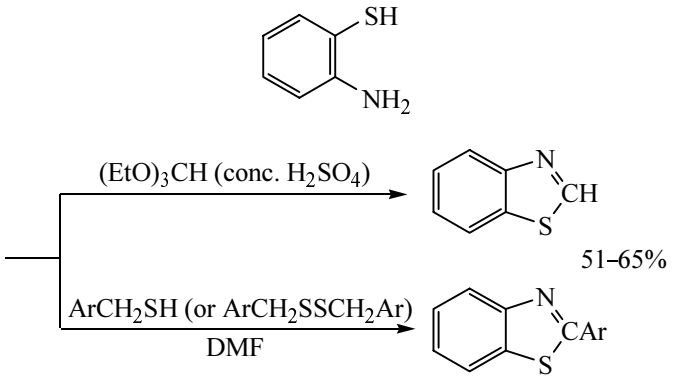
3. HETEROCYCLIC SYSTEMS BASED ON BIFUNCTIONAL THIOLS

3.1. *Heterocyclic Systems Based on 2-Aminothiophenol*

The wide application of 2-aminothiophenol to the syntheses of sulfur-containing heterocyclic systems is due to the presence of a fragment with S and N atoms attached to the *ortho*-positions of the benzene ring which is present in the structures of 1,3-benzothiazole, 1,4-benzothiazine, 1,5-benzothiazepine, 9,10-phenothiazine. To build up these rings the second reagents are selected including the second fragment of the ring; they should contain functional groups capable to react with thiol and amino groups of the 2-aminothiophenol.

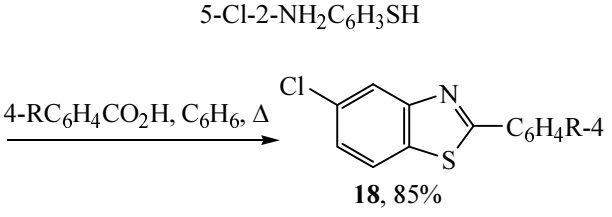
Synthesis of 1,3-benzothiazole and its derivatives. 1,3-Benzothiazole ring forms by introducing one carbon atom that should be linked to sulfur and nitrogen. There-

fore the cyclocondensation with 2-aminothiophenol is carried out with reagents capable to furnish this carbon atom. These compounds should contain at one carbon atom labile readily departing fragments of functional groups (for instance, triethyl orthoformate applied to the synthesis of 1,3-benzothiazole, and phenylmethanethiols used to prepare 2-aryl-1,3-benzothiazoles in 51–65% yields [14]). Several versions of this condensation mechanism were suggested, among them one involving anion-radical formation [14].



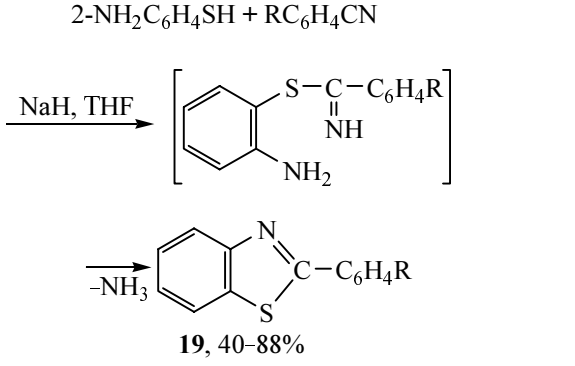
Ar = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$

Into the reaction with 2-aminothiophenol and its derivatives in the synthesis of 1,3-benzothiazole more frequently the reagents are brought containing at the same carbon atom functional groups simultaneously reacting with the thiol and amino functions, for instance, like in the synthesis of 2-aryl-1,3-benzothiazoles **18** possessing antiarthritis action [15]. The formation of 2-(2-aminophenyl)-1,3-benzothiazoles was observed in the reaction of 2-aminothiophenol with isatoic anhydride [16].

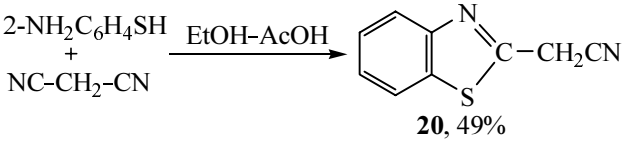


R = H, Me

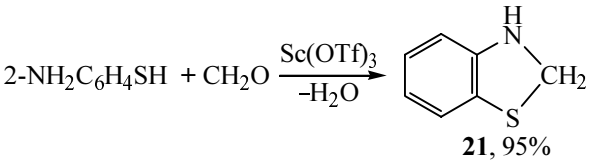
In the synthesis of 2-aryl-1,3-benzothiazoles **19** nitriles of aromatic acids were brought into the cyclocondensation with 2-aminothiophenol [17]. The cyclocondensation of 2-aminothiophenol with malononitrile occurred involving one of the cyano groups of the latter affording nitrile **20** [18].



R = 2-F, 4-F, 2-CF_3, 3-CF_3, 3,5-F_2, 2-Cl, 3-Cl, 4-Cl, 2-MeO, 3-MeO, 4-MeO.



Starting with 2-aminothiophenol and carbonyl compounds 2,3-dihydro-1,3-benzothiazole and a number of its derivatives are obtained. For instance, 2,3-dihydro-1,3-benzothiazole **21** was prepared by cyclocondensation of 2-aminothiophenol with formaldehyde [19].

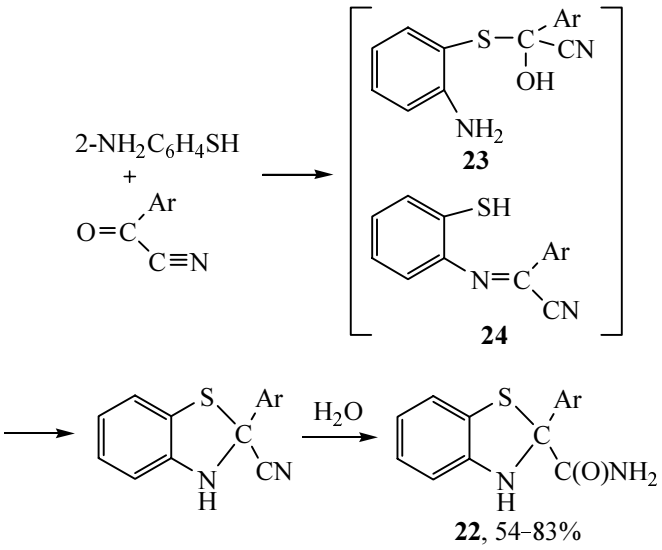


The heterocyclization of arylketoacids nitriles with 2-aminothiophenol also involves the carbonyl group and finally results in 2-aryl-2-carbamoyl-2,3-dihydrobenzothiazoles **22** [20]. Here two pathways are possible: either with formstion of hemithioacetals **23** or Schiff bases **24** (Scheme 4).

The 2,3-dihydrobenzothiazole derivatives **25** and **26** also formed in the reaction of 2-aminothiophenol with methyl benzyl ketone [21]; therewith the ratio of compounds **25** and **26** equaled 6:1 (Scheme 5).

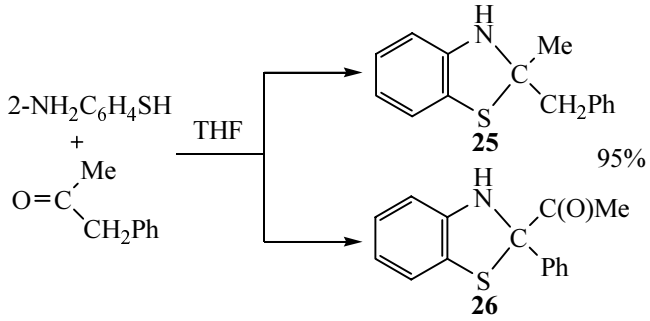
Compound **26** originated apparently from the reaction of the enol form of the methyl benzyl ketone occurring with the reaction center transfer. A cyclocondensation of 2-aminothiophenol with 3,4-diamino-2,5-diethoxy-

Scheme 4.

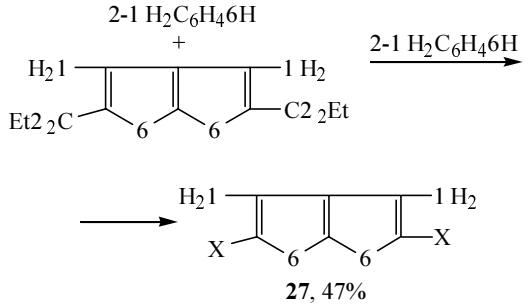


22, 54–83%

Scheme 5.



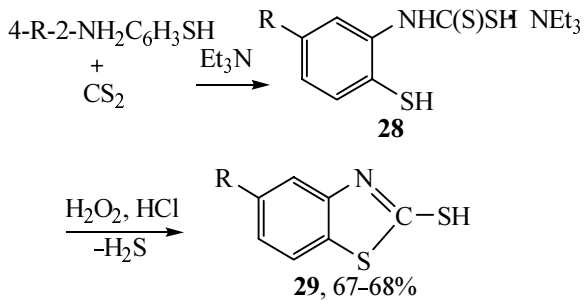
carbonylthieno[2,3-*b*]thiophene in the presence of polyphosphoric acid was described furnishing thieno[2,3-*b*]-thiophene derivative **27** containing two benzothiazole fragments [22].



27, 47%

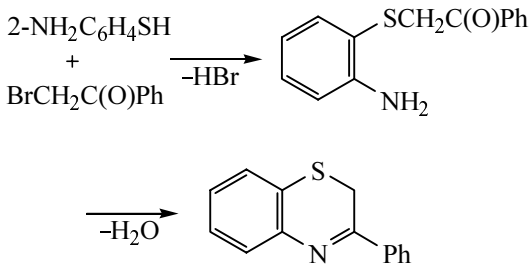
X = 2-benzothiazol-1-yl.

The reactions of 2-aminothiophenol and its derivatived with the carbon disulfide in the presence of triethylamine followed by treating the arising dithiocarbamates **28** with 30% H_2O_2 and concn. HCl resulted in 2-mercaptobenzothiazole **29** and its derivatives [23].



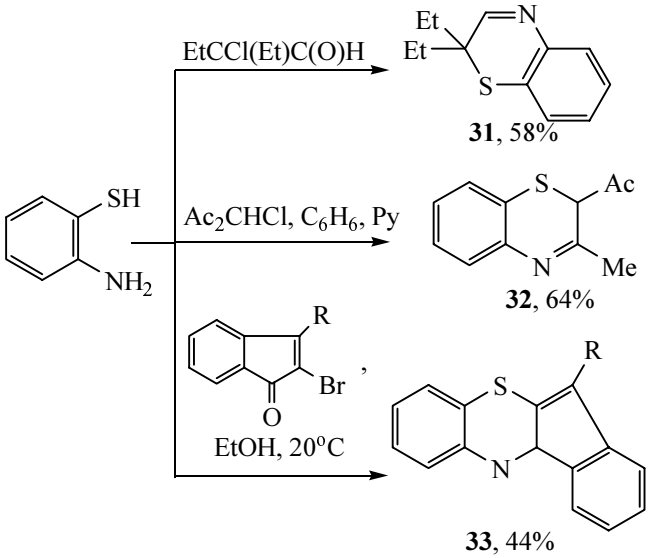
R = H, Cl.

Synthesis of 1,4-benzothiazines. The building of benzothiazines starting with 2-aminothiophenol requires the choice of reagents containing functional groups at two vicinal carbons, and one of these groups should react with thiol, and another with amino group, like in the synthesis of 3-phenyl-3*H*-1,4-benzothiazine **30** from 2-aminothiophenol and bromoacetophenohe [24].



30, 86%

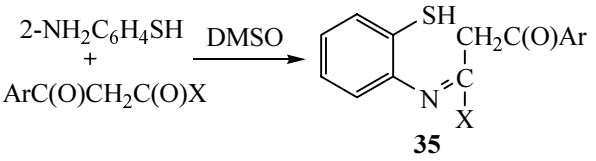
In the same fashion the 2-aminothiophenol reacted with 2-chloro-2-ethylbutanal [25], diacetylchloromethane [26],



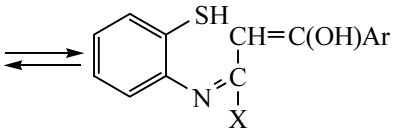
R = H, Me.

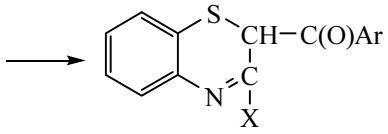
and 3-R-2-bromo-1-indenone [27] to give derivatives of 1,4-benzothiazine **31–33**.

The oxidative condensation of 2-aminothiophenol with diketones gave rise to 1,4-benzothiazine derivatives **34** [28]. Apparently the reaction of the amino group with the carbonyl first affords intermediate **35** which suffers cyclization in an enol form involving the SH group. Therewith the cyclization product is oxidized in the presence of dimethyl sulfoxide.



35





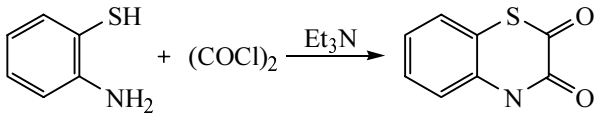
34, 57–70%

Ar = 4-ClC_6H_4, 4-$MeOC_6H_4$; X = 4-Me-2-(4-RC_6H_4)-5-thiazolyl (R = H, Cl, OMe).

The cyclocondensation of 2-aminothiophenol with carbazole-1,4-dione occurs by addition of the mercapto group to the C=C bond and by reaction of the amino group with a carbonyl; as a result forms a mixture of two isomers of 1,4-benzothiazine derivatives **36** and **37** (Scheme 6)[29].

Starting with 2-aminothiophenol derivatives of 2,3-dihydro-1,4-benzothiazinone **38** [30] and were also obtained **39** [31]. The formation of compound **38** resulted from amino group acylation with maleic anhydride and mercapto group addition across the C=C bond. Compound **39** originated presumably from the mercapto group benzoylation followed by cyclization of the arising compound in the enol form (Scheme 7). The corresponding benzothiazinones were also obtained by reaction of 2-aminothiophenol with 1-aryl-(alkyl)-5,6,7,8-tetrafluoro-3-ethoxysalylcinnolones [32].

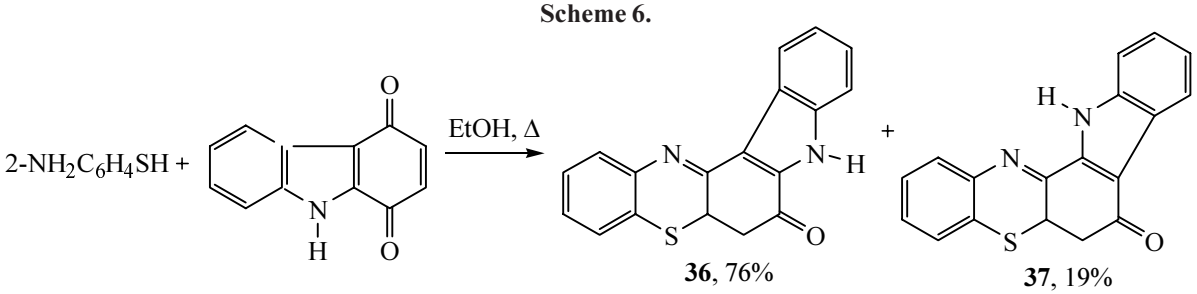
The synthesis of 1,4-benzothiazine-2,3-dione **40** was carried out by reacting 2-aminothiophenol with oxalyl chloride in the presence of triethylamine [33].



40, 83%

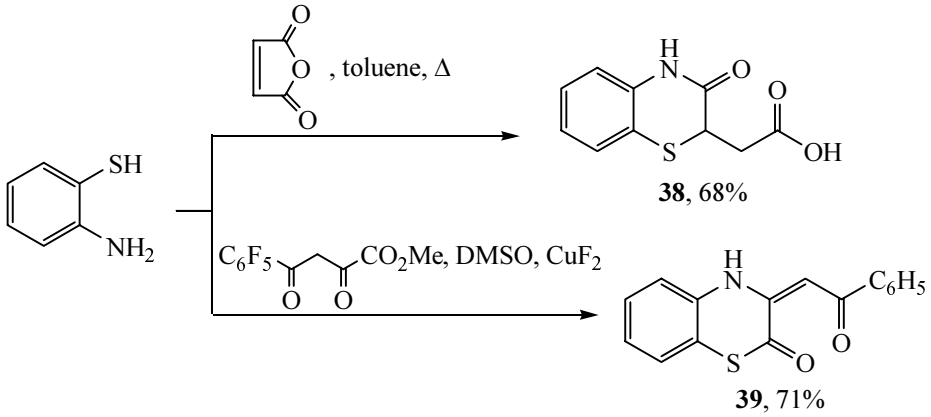
The preparation of 1,5-benzothiazepines based on the 2-aminothiophenol consists in addition thereto of a frag-

Scheme 6.



36, 76% **37**, 19%

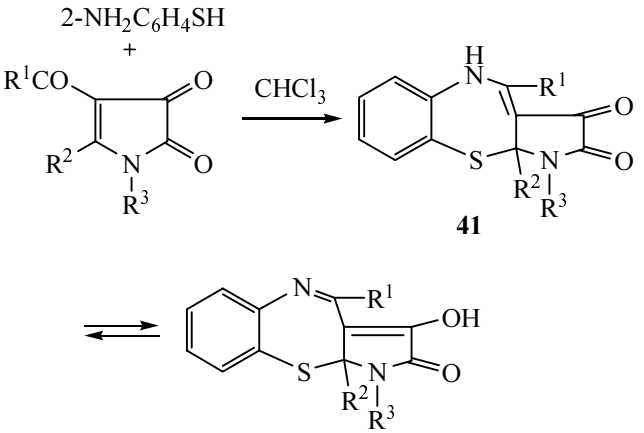
Scheme 7.



38, 68%

39, 71%

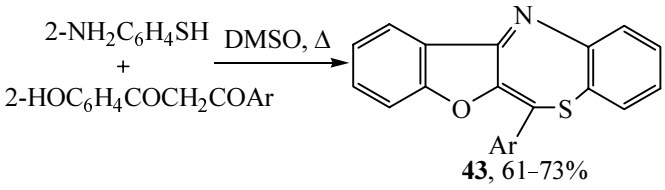
ment containing three carbon atoms. As a rule donors of such fragments are dicarbonyl compounds, unsaturated ketones and acids, and their derivatives. For instance, the reaction of the 2-aminothiophenol with 4-acyl-2,3-dihydro-2,3-pyrrolidones starting by the nucleophilic addition of the mercapto group to the C=C bond followed by the reaction between the amino group and the carbonyl from the acyl moiety led to substituted 1,2,3,10*a*-tetrahydro-5*H*-pyrrolo(2,3-*b*)-1,5-benzothiazepine-2,3-diones **41** that isomerized into alcohols **42** [34].



42, 80–99%

R^1 = *i*-Pr, Ph, 4-BrC_6H_4, 4-ClC_6H_4; R^2 = MeCOO, Ph; R^3 = Ph, 4-$EtOC_6H_4$, $PhCH_2$.

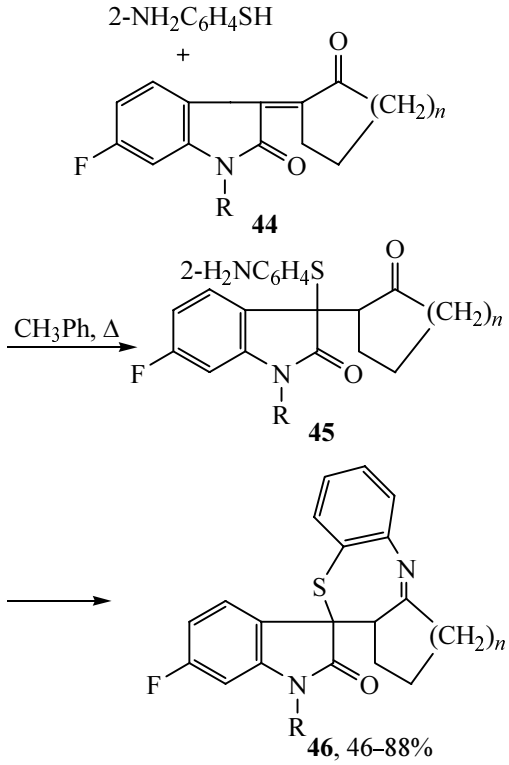
The oxidative cyclocondensation of the 2-aminothiophenol with aromatic diketones containing a hydroxy group in the *ortho*-position proceeded in a more complicated fashion [35]. In this case alongside the 1,5-benzothiazepine ring arose also a dihydrocoumarin ring.



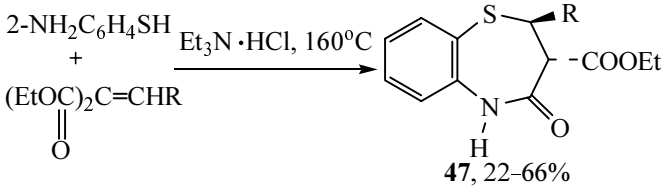
43, 61–73%

In reaction of the 2-aminothiophenol with unsaturated cyclic ketones **44** first the thiol group adds to the C=C bond to yield sulfides **45** whose condensation affords 2,3-dihydro-1,5-benzothiazepines **46** [36].

The cyclocondensation of the 2-aminothiophenol with diethyl R-methylenemalonates occurs in the same way and affords 2-R-3-ethoxycarbonyl-2,5-dihydro-1,5-benzothiazepin-4-ones **47** [37].

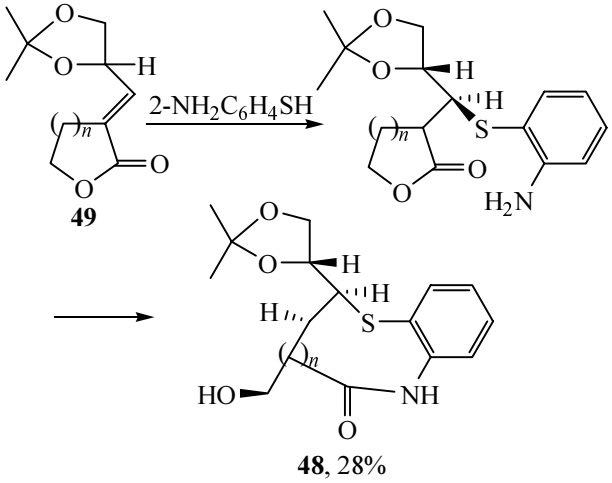


R = H, Me; *n* = 1, 2



R = 2-thienyl, 3-thienyl, 5-methyl-2-thienyl.

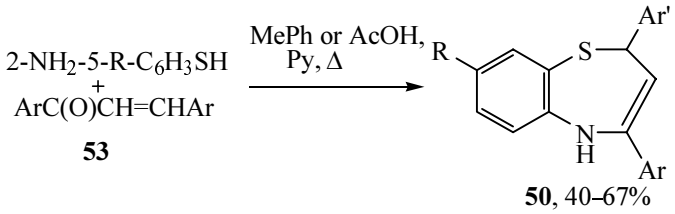
A stereoselective synthesis of optically active 1,5-benzothiepin-4-ones **48** is based on the addition of



n = 1, 2.

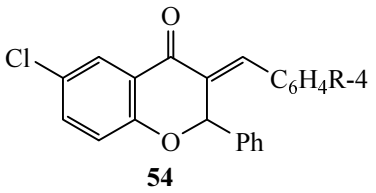
2-aminothiophenol to chiral lactones **49** with subsequent transformation of the ring [38].

The derivatives of dihydro-1,5-benzothiazepine **50**–**52** were obtained by reaction of the 2-aminothiophenol or its derivatives with chalcones **53** [39–42], flavones **54** [43], or with benzofuran derivatives **55** [44].



53 **50**, 40–67%

R = H, Cl, Br, F, Me, OMe, OEt; Ar = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4; Ar' = Ph, 4-FC_6H_4, 4-$Me_2NC_6H_4$, 2-ClC_6H_4.



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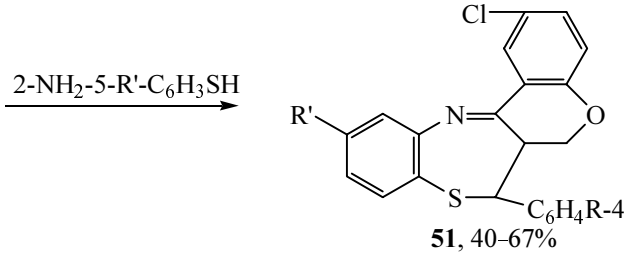
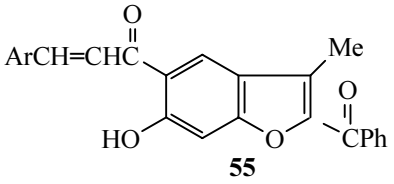


51, 40–67%

R = Cl, MeO; R' = F, Cl, Br, Me, MeO, EtO.



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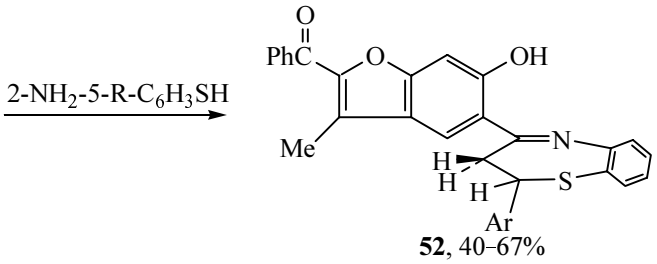
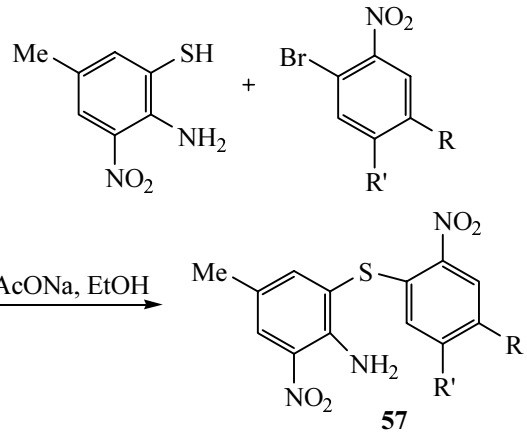


52, 40–67%

Ar = 4-MeC_6H_4, 2-ClC_6H_4, 3,4-$(NO_2)_2C_6H_3$.

Synthesis of phenothiazines and their analogs. The formation of a phenothiazine ring from the 2-aminothiophenol requires addition of sulfur and nitrogen atoms to the *ortho*-carbons of the aromatic ring. The addition of sulfur occurs as a rule by nucleophilic substitution of an activated halogen. The arising sulfides in the second stage of the synthesis undergo cyclization involving the amino group and the position *2* of the second aromatic ring. When the position contains labile substituents (halogen atoms or a nitro group), the cyclocondensation cleanly proceeds in the alkaline medium or in the presence of potassium amide in liquid ammonia. When this position is free, the chemical modification of the amino group is required to perform the cyclocondensation: Into the amino group are introduced easily departing fragments, like in the synthesis of 3-methyl-1-nitro-7-R-8-R'-phenothiazines **56** [45]. Sulfides **57** obtained in the first stage were formylated and then were subjected to cyclocondensation followed by Smiles rearrangement.



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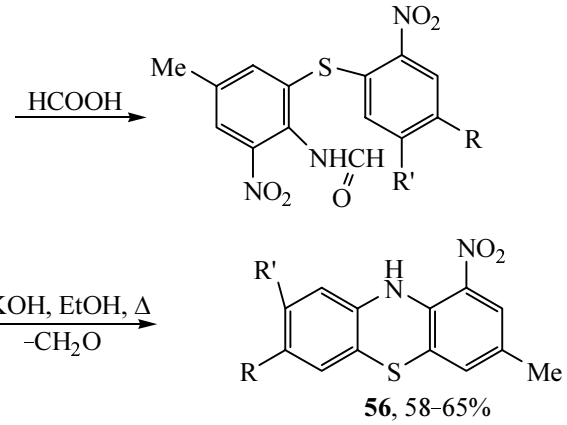
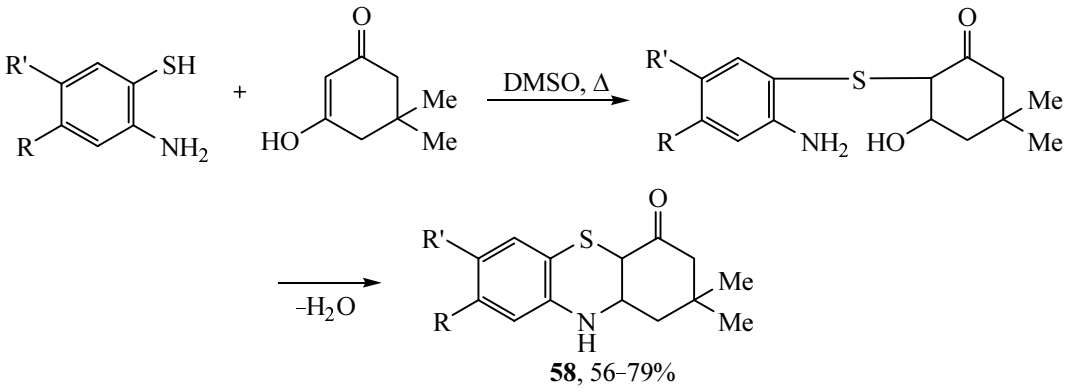


56, 58–65%

R = H, Me, Cl; R' = H, Br.

Cyclocondensations of 2-aminothiophenol and its homologs with dimedone gave rise to 2,3-dihydro-1*H*-phenothiazin-4(10*H*)-ones derivatives **58** (Scheme 8)[46]. In

Scheme 8.



58, 56–79%

R = H, Me; R' = H, Br, Cl, EtO, Me.

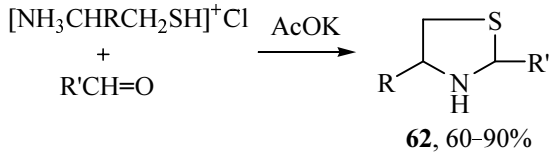
the first stage of this synthesis the enol form of dimedone takes up the thiol group furnishing sulfides **50** which suffer further cyclization involving NH_2 and OH groups.

The syntheses of heterocyclic systeme involving only the amino group of the 2-aminothiophenol are scarce. Among these should be mentioned the synthesis of 1-(2-mercaptophenyl)-6-arylpyramidine-2(1*H*)-thiols with the use of isothiocyanates [47] and of 1-[2-(R-methylthio)-phenyl]pyrroles using benzyl chloride and dimethoxytetrahydrofuran [48].

3.2. *Heterocyclic Systems Based on Other Aminothiols*

Among the other aminothiols the 2-aminoethanethiol is the most extensively used compound in the synthesis of heterocycles [49–56]. The building up of the heterocyclic systems is similar to the processes involving the 2-aminothiophenol. As in the synthesis of 1,3-benzothiazoles for the introduction of a single carbon atom into the ring in the preparation of 1,3-thiazolidine derivatives the reagents used contain at one carbon atom labile groups like thioacetyl, hydroxy group etc. For instance, in the synthesis of 2-aroylmethylene-1,3-thiazolidines **60** [51] these reagents were dithioacetals, and in the synthesis of 1,3-thiazolidine-2-carboxylic acid **61** [52], dihydroxyacetic acid (Scheme 9).

The condensation of 2-aminoethanethiol hydrochloride and its homologs with aldehydes afforded 1,3-thiazolidines **62** [55].

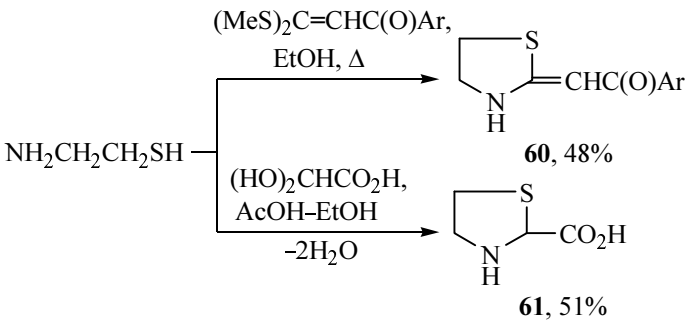


62, 60–90%

R = H, CO_2Et, CO_2Me; R' = H, Me.

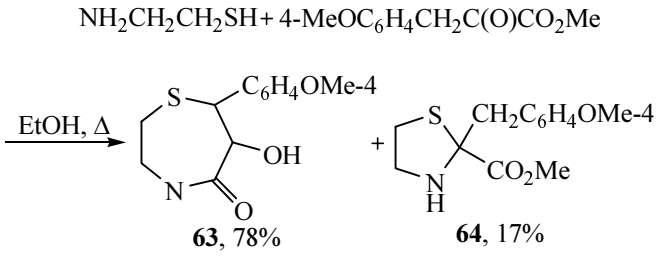
The reaction of the 2-aminoethanethiol with methyl 3-(4-methoxyphenyl)pyruvate furnished a derivative of *cis*-1,4-thiazepinone **63** (prevailing product) and thiazolidine derivative **64** [53]. Compound **63** apparently originates from the reaction of the enol form of the methyl ester with participation in the cyclocondensation of the C=C bond and the ester group. Compound **64** was ob-

Scheme 9.



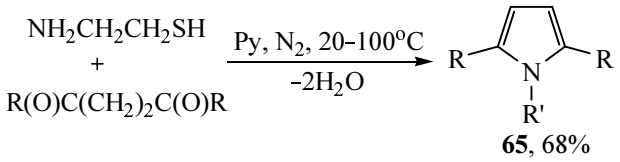
60, 48%

61, 51%



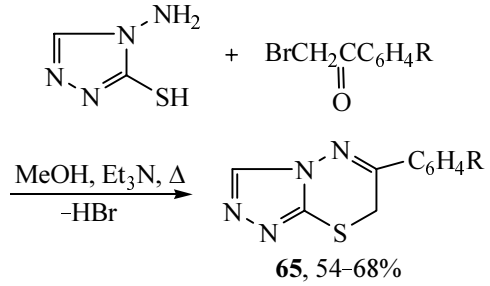
tained in the reaction of the keto form of the methyl ester involving the carbonyl group.

The condensation of the 2-aminoethanethiol with diketones in the presence of pyridine may occur involving only the amino group affording N-substituted pyrroles **65** [57].



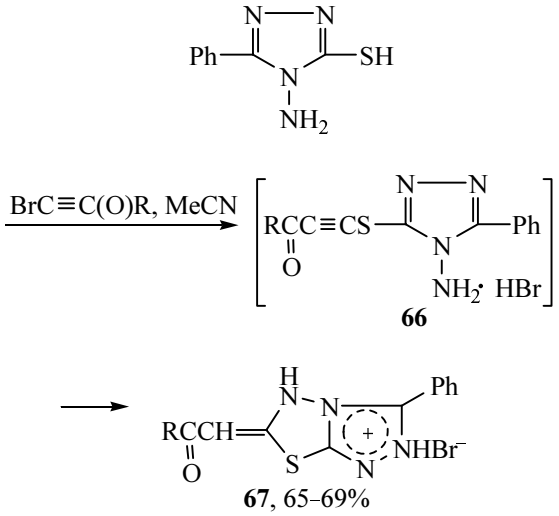
R = Me; R' = CH_2CH_2SH.

Fused heterocyclic systems were obtained from aminomercaptotriazoles [58–66] analogously to the above considered syntheses of heterocycles bazed on the 2-aminothiophenol. In reactions with aminomercaptotriazoles most often halocarbonyl compounds are used. For instance, the cyclocondensation of 4-amino-3-mercapto-1,2,4-triazole with bromomethyl aryl ketones resulted in heterocycles **65** [58].



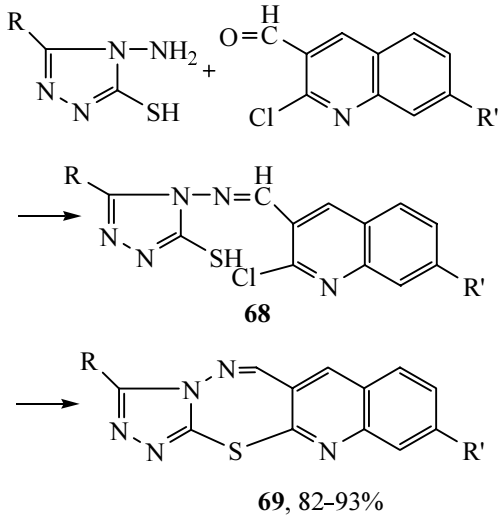
R = H, 4-MeO, 4-EtO, 4-Br, 4-Cl, 4-NO_2, 2-OH-5-NO_2.

The reaction of 5-phenyl-4-amino-3-mercapto-1,2,4-triazole with bromoethynyl ketones took another route [59]. The reaction of thiol group with the bromoethynyl one gave sulfides **66** owing to the amino group addition to the C≡C bond; the sulfides underwent cyclization into 1,3,4-thiadiazolo-[2,3-*d*]-1,2,4-triazolium bromides **67**.



R = Ph, 2-thienyl.

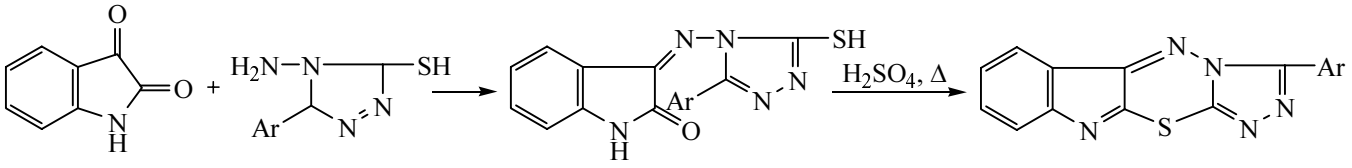
In the condensation of 3-R-4-amino-5-mercapto-1,2,4-triazoles with 2-chloro-3-formyl-7-R-quinolines first the amino group reacted with formyl giving thiols **68**, and the latter underwent cyclization by reaction of the thiol group with the chlorine atom affording compounds **69** [60].



R = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4; R' = H, Me, Cl.

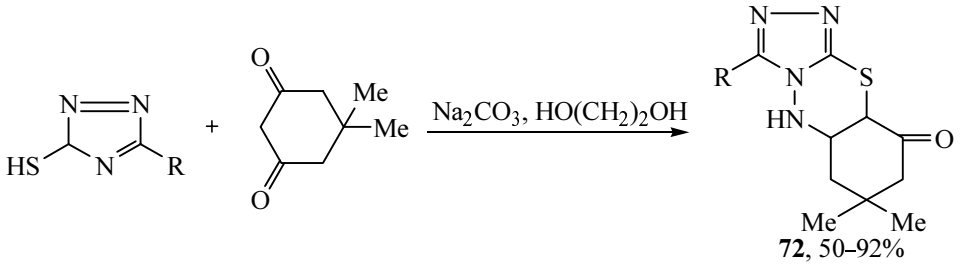
The condenation of 4-amino-5-aryl-3-mercapto-1,2,4-triazoles with isatin also started with the reaction of the amino group. Thus forming imines **70** were converted into compounds **71** exhibiting fungicidal activity [61].

The cyclocondensation of 4-amino-3-R-5-mercapto-1,2,4-triazoles with dimedone gave rise to heterocycles **72** [62]. The dimedone reacted here in the enol form.



70 **71**, 23–68%

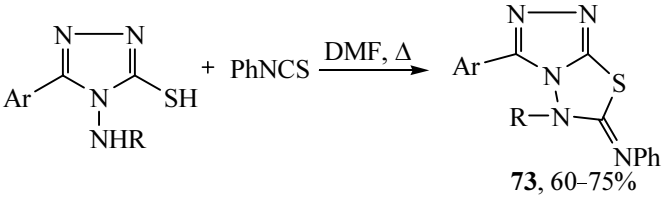
Ar = Ph, 2-ClC_6H_4, 2-$MeOC_6H_4$, 4-MeC_6H_4, 2,4-$Cl_2C_6H_3$.



72, 50–92%

R = H, Ph, 2-quinolyl.

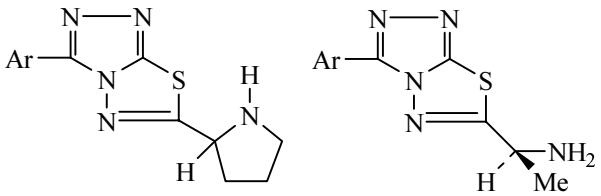
The cyclocondensation of 3-aryl-5-mercapto-4-(4-pyridylcarbonylamino)-1,2,4-triazoles with phenyl isothiocyanate afforded compounds **73** [63].



73, 60–75%

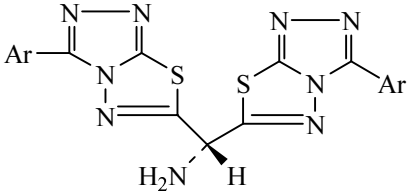
R = 4-pyridylcarbonyl; Ar = Ph, 4-ClC_6H_4.

The cyclocondensation of 4-amino-3-aryl-5-mercapto-1,2,4-triazoles with (*L*)-proline, (*L*)-alanine, and (*L*)-aspartic acid in the presence of $POCl_3$ yielded respectively heterocyclic systems **74–76** possessing microbicidal activity [64].



74, 62%

75, 75%



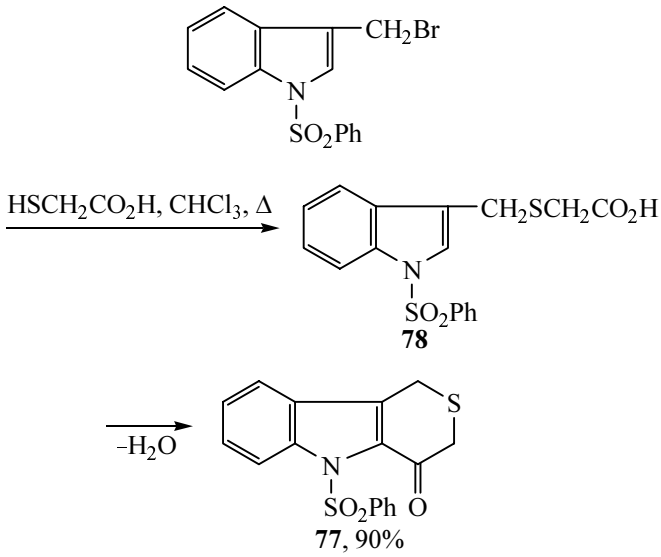
76, 55%

Ar = $PhCH_2$, Ph, 2-$MeOC_6H_4$

4-Amino-5-mercapto-3-(4-*tert*-butylphenyl)-1,2,4-triazole by concensation with cyanogen bromide furnished 6-amino-3-(4-*tert*-butylphenyl)-*sym*-triazolo[3,4-*b*]-1,3,4-thiadiazole in a 82% yield [65].

3.3. *Heterocyclic Systems Bazed on Mercaptoacids*

Heterocyclic systems based on mercaptoacetic acid and its derivatives. The mercaptoacid most frequently used in syntheses of heterocyclic compounds is the mercaptoacetic acid apparently due to the presence of three reactive sites participating in the heterocyclization. The building up of heterocyclic systems starting with the mercaptoacetic acid includes the choice of compounds capable to react with one of the functional groups (com-

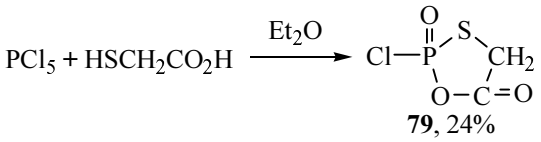


78

77, 90%

monly with the thiol group) affording intermediate compounds which further suffer cyclization involving the second functional group. In the synthesis of 1-oxo-9-phenylsulfonyl-1,2,3,4-tetrahydro-3-thiacarbazole **77** the intermediately arising sulfide **78** undergoes further cyclodehydration in the presence of polyphosphoric ester with the participation of the carboxy group [66].

The cyclocondensation of mercaptoacetic acid with PCl_5 led to 2,5-dioxo-2-chloro-1,2,3-oxothiophospholane **79** [67].



79, 24%

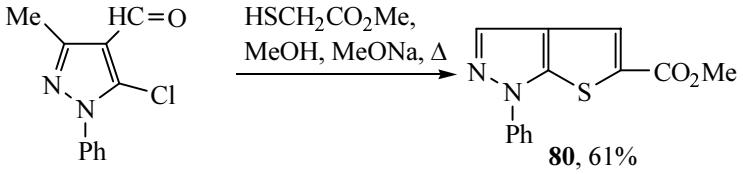
A similar reaction product was obtained by treating the mercaptoacetic acid esters with PCl_3 [68] but in both cases the formation mechanism is obscure.

When in the reagent a halogen atom was adjacent to a carbonyl or cyano group this compound underwent cyclocondensation with mercaptoacetic acid esters involving the methylene group of the latter, as in the synthesis of heterocyclic systems **80** [69], **81** [70], **82** [71], and **83** (Schemes 10, 11)[72].

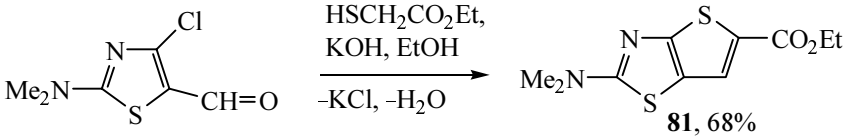
In aromatic carbonyl compounds and aromatic carbonitriles not only halogen atoms but also other functional groups can undergo substitution. For instance, in the synthesis of naphtho[1,2-*b*]thiophene **84** [73] and benzo(*b*)-thiophene **86** [75] derivatives the substitution occurred respectively at dimethylamino and nitro groups (Scheme 12).

The intermediate sulfides can form also by nucleophilic addition of the thiol group to the bonds C≡N of nitriles, C=N of Schiff bases and hydrazones, and C=O of carbonyl compounds. For instance, the addition of the mercaptoacetic acid to the C≡N bond of the cyanoacetamide afforded sulfide **87** which by reaction of the carboxy group with the imino group underwent cyclization into thiazolone derivative **88** [76].

Scheme 10.

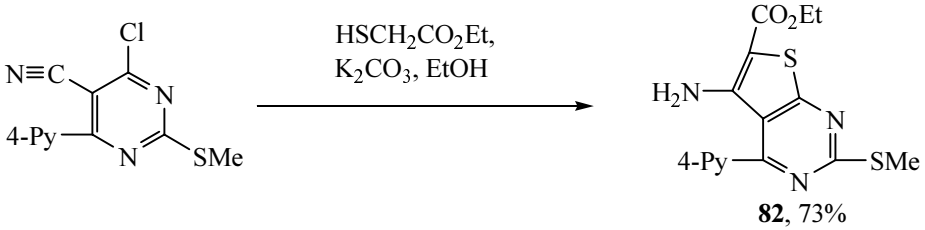


80, 61%

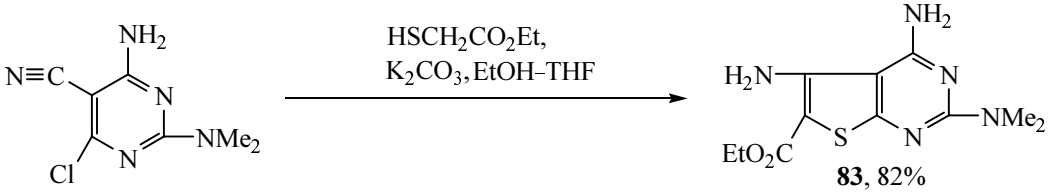


81, 68%

Scheme 11.

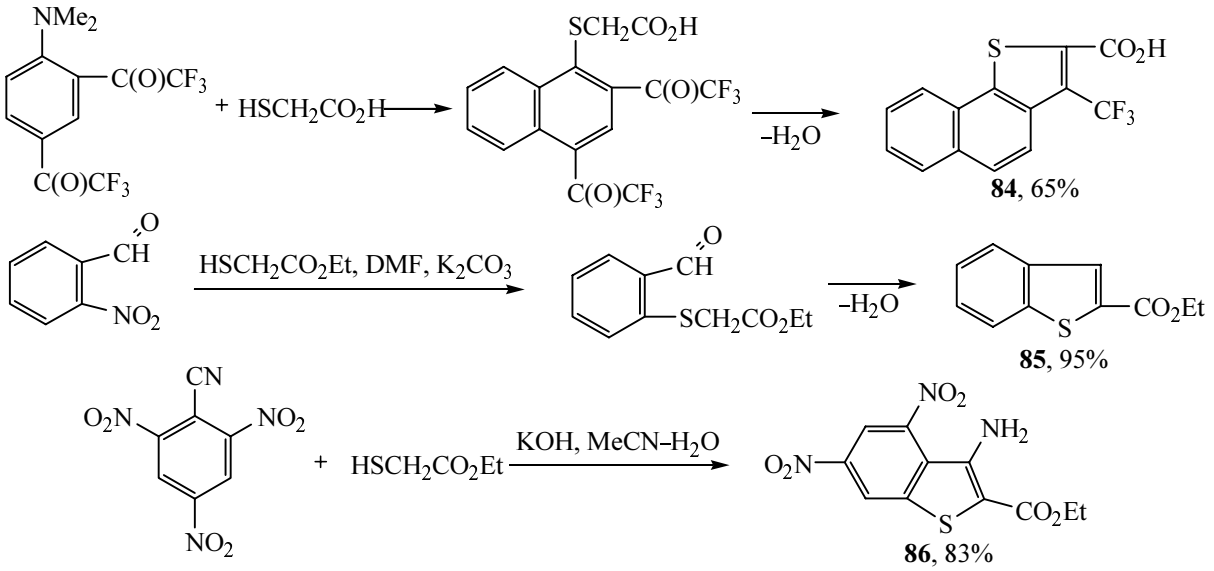


82, 73%

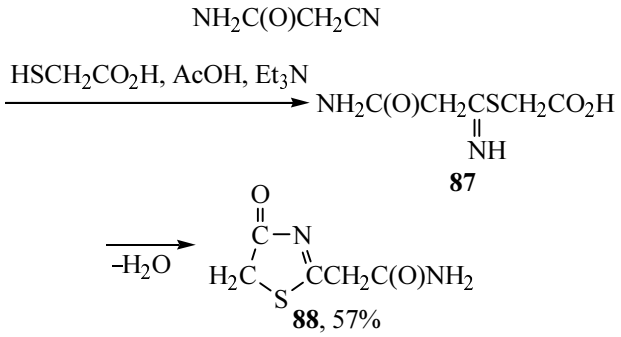


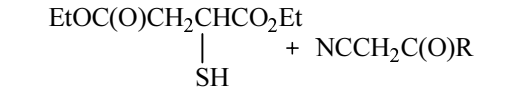
83, 82%

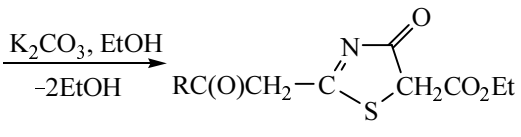
Scheme 12.



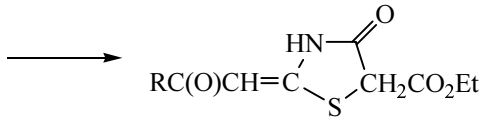
Similarly except for alcohol elimination occurred the cyclocondensation of oxonitriles with diethyl 2-mercaptosuccinate resulting in the derivatives of 4-oxothiazolidine **89** [77].







R = Alk, Ar.

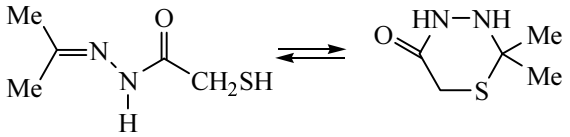


89, 82–93%

From the mercaptoacetic acid and Schiff bases a number of derivatives of 4-oxothiazolidine **90** were prepared containing in positions *2* and *3* aryl [78–80] and heterocyclic [81] substituents and exhibiting microbicidal activity, and also a number of spirocyclic systems **91** [82], **92** [83] with the oxothiazolidine ring. The building up of this ring in both cases occurred by the reaction of CO_2H and NH groups in the intermediate sulfides (Scheme 13).

Sometimes reaction of mercaptoacids is carried out not with Schiff bases, but with amines and carbonyl compounds [84–87]. This synthetic procedure was used in the preparation of heterocyclic systems **93** [85], **94** [86], and **95** [87] possessing antibacterial activity (Scheme 14).

The thiol group relatively easily added to the C=N bond of hydrazones. Therewith as mentioned in [88] the acetone mercaptoacetylhydrazone in solutions is subject to the ring-chain tautomerism between the thiadiazine and hydrazone forms.



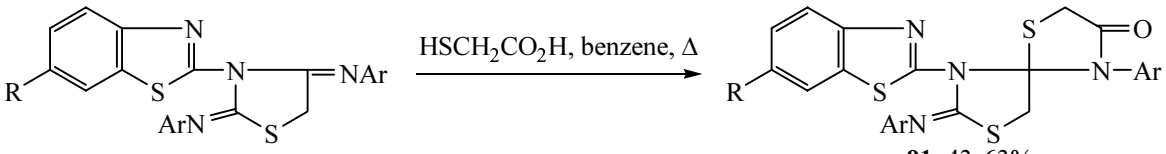
From hydrazones and mercaptoacetic acid was synthesized a series of heterocyclic systems **96** having oxothiazolidine ring [89–92]; some compounds among them possessed fungicidal activity.

Oxothiazolidines **97** prepared from the mercaptoacetic acid and hydrazones were subjected to further con-

Scheme 13.

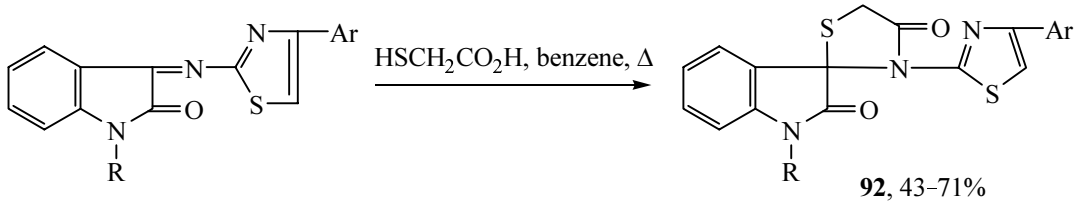
90, 50–79%

R = Ar, Ht; Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4.



91, 43–63%

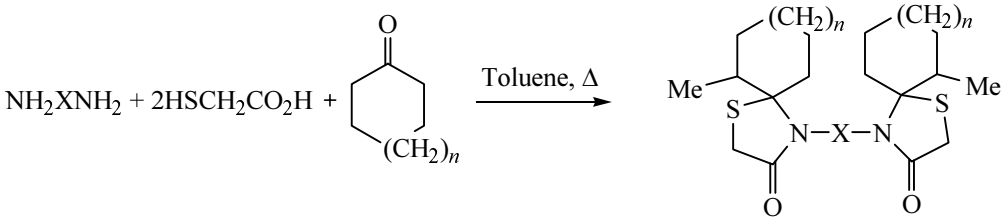
R = 4-$NO_2C_6H_4S$; Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4.



92, 43–71%

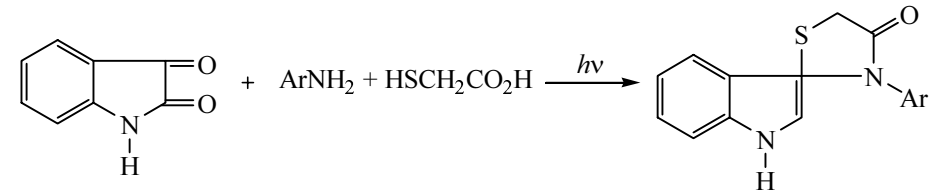
R = H, Me; Ar = Ph, 2-FC_6H_4, 4-FC_6H_4, 4-F-3-MeC_6H_3, 4-F-3-ClC_6H_3, 4-F-2-ClC_6H_3, 4-F-3-MeC_6H_3

Scheme 14.

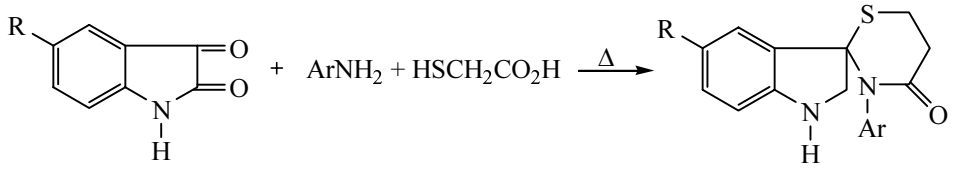


93, 38–82%

X = C_6H_4, $(CH_2)_2$; n = 1, 2.



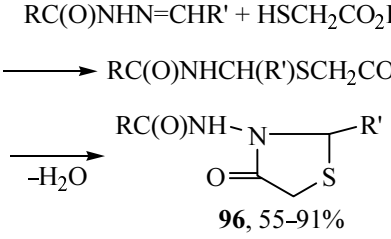
94, 41–68%



95, 44–71%

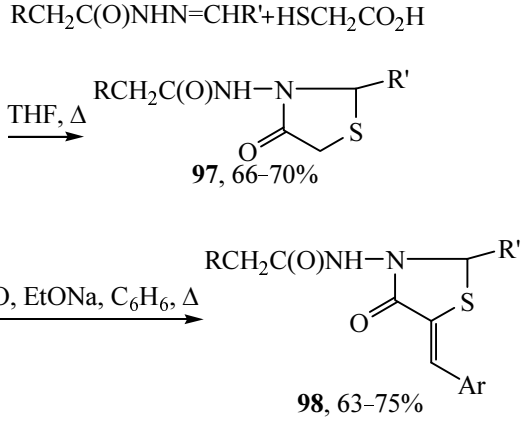
R = H, F; Ar = 2-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3-$CF_3C_6H_4$.

densation with aldehydes in order to convert them into compounds **98** exhibiting anticancer, fungicidal, and anticonvulsant action [93, 94].



96, 55–91%

R = 4-[3,4,5-$(MeO)_3C_6H_2C(O)NH]C_6H_4$, $PhOCH_2$, 2-$ClC_6H_4OCH_2$, 4-$ClC_6H_4OCH_2$, 2-$MeOC_6H_4OCH_2$, 4-$MeOC_6H_4OCH_2$, 2,4-$Cl_2C_6H_3OCH_2$; R' = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-HOC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 3-MeO-4-HO-5-BrC_6H_2, 2-furyl.

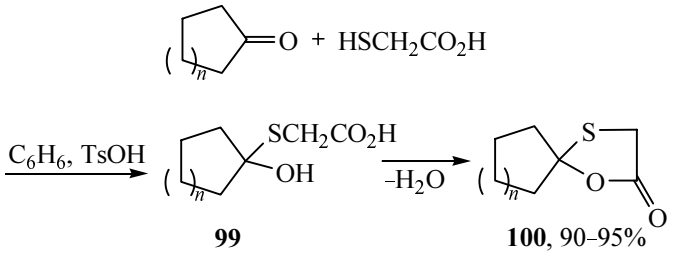


97, 66–70%

98, 63–75%

R = carbazol-9-yl, 2-chlorophenothiazin-10-yl; R' = Ar = 2-ClC_6H_4, 4-ClC_6H_4, 2-$MeOC_6H_4$, 2-$NO_2C_6H_4$.

Quite a number of heterocyclic systems was synthesized starting with mercaptoacetic acids, its derivatives, and carbonyl compounds. Depending on the structure of carbonyl compounds various versions of cyclocondensation are used. One of them consists in addition of the mercaptoacetic acid to the C=O bond of cyclic ketones [95]. Hemithioacetals **99** forming in this case were subjected

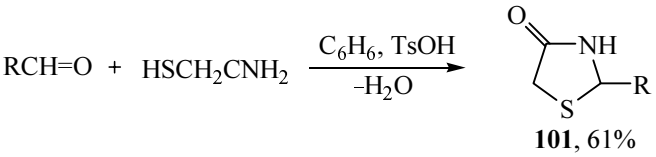


99 **100**, 90–95%

n = 1, 2.

to dehydration in the presence of *p*-toluenesulfonic acid to furnish compounds **100**.

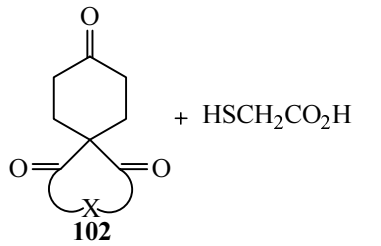
In similar fashion but involving the amide group occurred the cyclocondensation of mercaptoacetamide with aliphatic aldehydes affording 2-R-4-oxothiazolidine **101** [96].



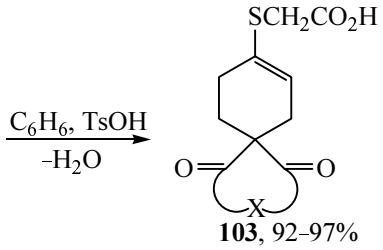
101, 61%

R = $TrO(CH_2)_2$.

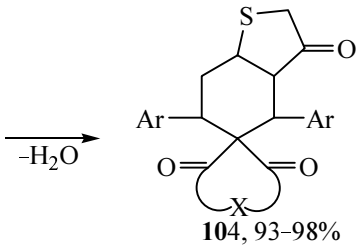
The addition of mercaptoacetic acid across the C=O bond of cyclic ketones **102** occurred with dehydration of the arising hemithioacetals into unsaturated sulfides **103** that suffered cyclodehydration in the presence of *p*-toluenesulfonic acid giving compounds **104** in a quantitative yield [97].



102



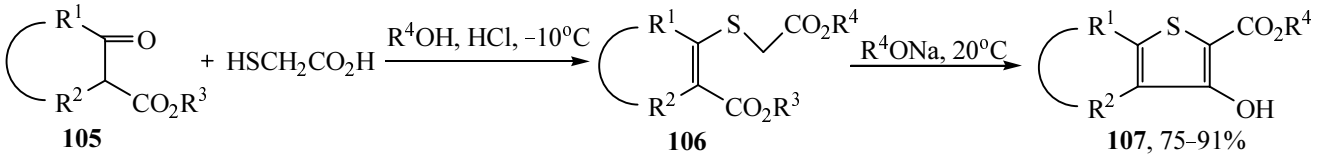
103, 92–97%



104, 93–98%

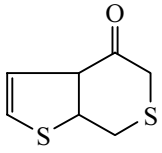
X = NH, O, NHC(O)NH; Ar = Ph, 4-$MeOC_6H_4$.

The mercaptoacetic acid with cyclic β-oxoesters **105** form sulfides **106** which under the action of alcoholates undergo cyclodehydration yielding thiophenes **107** [98]. In this case the cyclocondensation involves the methylene and the ester groups.



R^1, R^2 = $(CH_2)_5$, $(CH_2)_6$, CH(Me)$(CH_2)_2$, CH(Me)$(CH_2)_3$; R^3, R^4 = Me, Et.

A multistage synthesis was described of 7*H*-thieno-[2,3-*c*]thiopyran-4(5*H*)-one **108** based on methyl mercaptoacetate and 2-thiophenecarbaldehyde [99]. The



108, 64%

synthesis involved the addition of the mercapto group across the C=O bond of the aldehyde followed by the reduction of hemithioacetal with pyridineborane in the presence of the trifluoroacetic acid, the hydrolysis of methoxycarbonyl group by KOH in methanol, and conversion of the carboxy group into acyl chloride by treatment with $SnCl_4$ in carbon disulfide.

A synthesis was reported of 2-amino-5-aryl-5*H*-thiazolo-[4,3-*b*]-1,3,4-thiadiazoles based on mercaptoacetic acid, thiosemicarbazide, and aromatic aldehydes [100]; however these data were disproved later [101]: In this reaction formed presumably only aromatic aldehydes thiosemicarbazides.

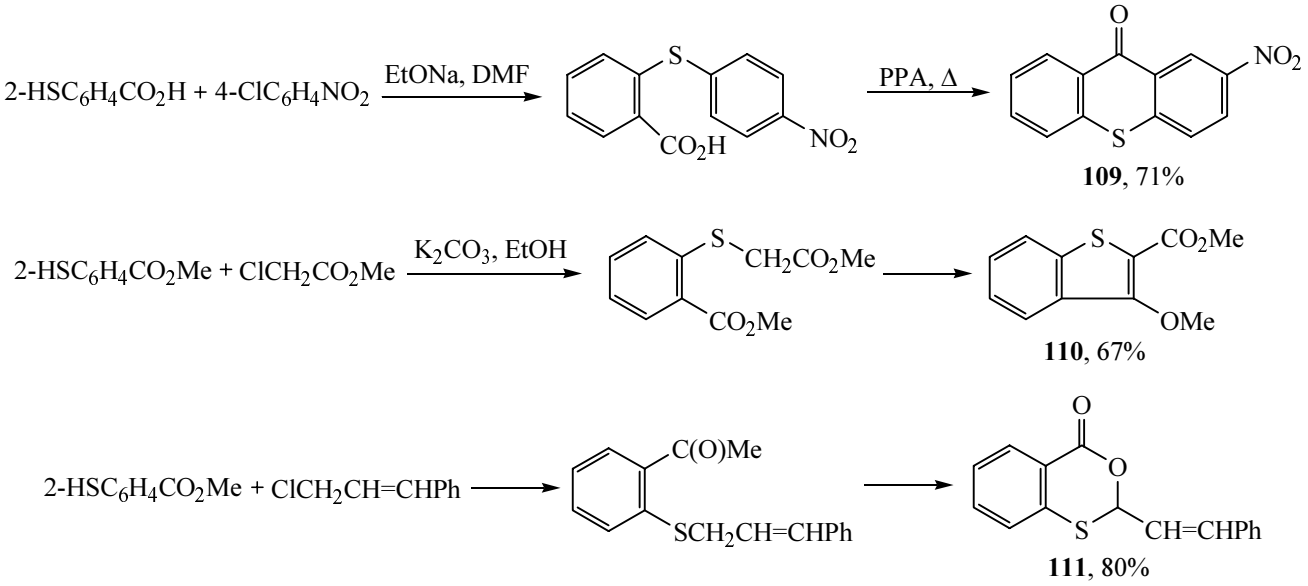
Heterocyclic systems based on 2-mercaptobenzoic acid and its derivatives. A series of fused heterocyclic systems was obtained starting with 2-mercapto-benzoic acid and its derivatives. The 2-mercaptobenzoic acid or its esters are commonly converted into sulfides by arylation, alkylation, or acylation with subsequent cyclocondensation of the sulfides involving carboxy or ester group as for example in the synthesis of heterocyclic systems **109** [102], **110** [103], and **111** [104] (Scheme 15).

In the multistage synthesis of 4-hydroxy-3-ethoxycarbonylthiocoumarin-2-one **112** [105] alongside the conversion of the thiol group into a sulfide was also performed successive transformation of the carboxy group into an acyl chloride and keto group (Scheme 16).

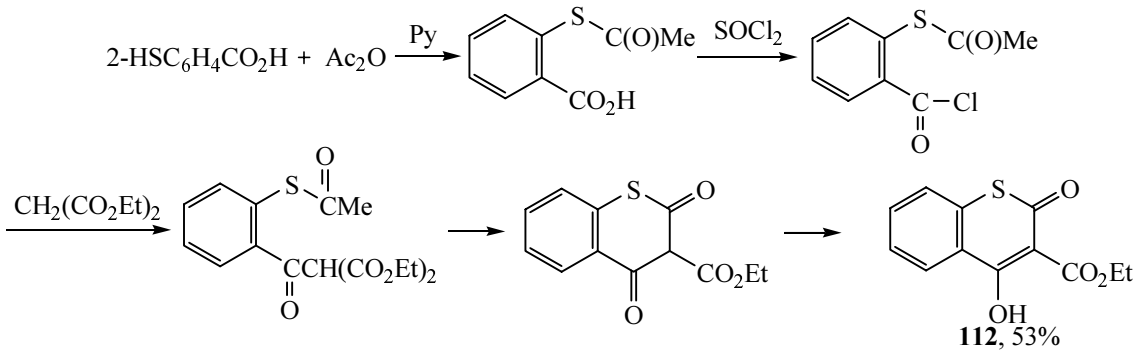
In the synthesis of 5-R-6-R'-1,2-benzisothiazolin-3-ones **113** from disubstituted esters of 2-mercaptobenzoic acid the initial esters were converted by the hydroxyl-amine-O-sulfonic acid into sulfenylamides **114** which underwent cyclization into the final products (Scheme 17) [106].

The cyclocondensation of the 2-mercaptobenzoic acid with thiolacetic acid in the presence of H_2SO_4 afforded 3*H*-1,2-benzodithiol-3-one **115** [107].

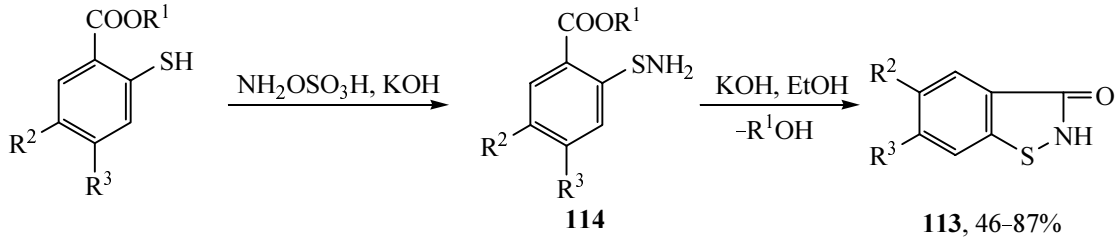
Scheme 15.



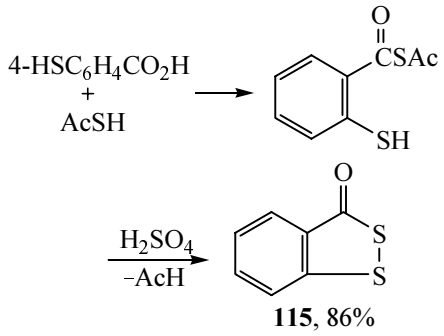
Scheme 16.



Scheme 17.

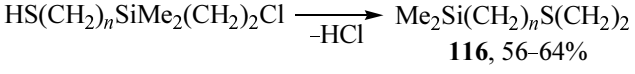


R^1 = Me, Et; R^2 = H, Cl, MeO; R^3 = H, Cl, MeO.

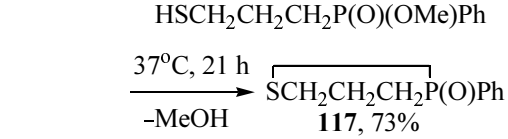


The synthesis of sulfur-containing heterocyclic systems is far less often performed applying other mercaptoacids, in particular, 3-mercaptopropanoic acid. A cyclocondensation was reported of the 3-mercaptopropanoic acid with benzothiophen-3(2*H*)-one affording 3,4-dihydrothiopyrano-[3,2-*b*]benzothiophen-4(2*H*)-one [108]. The application of the 3-mercaptopropanoic acid to the synthesis of 4-oxothiazolidine derivatives of 2-methyl-1*H*-benzimidazole exhibiting microbicidal action was also described [109]. A synthesis of 2,3-dihydrothiopyrano-[2,3-*b*]pyridin-4(4*H*)-one from 2-mercaptopyridine-3-carboxylic acid was reported in [110].

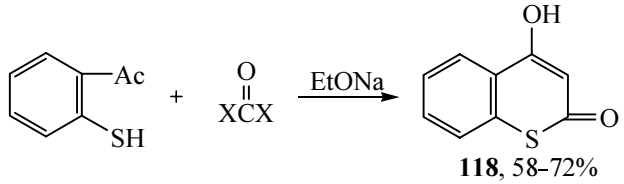
Heterocyclic systems based on other bifunctional thiols. Organosilicon alkanethiols containing a chlorine atom at the chain end under UV irradiation suffer an intramolecular cyclization into thiasilacycloalkanes **116** [111]. An intramolecular cyclization in the presence of acids occurs also with alkanethiols containing a terminal methoxyphosphonate group furnishing compounds **117** [112].



n = 1, 2.



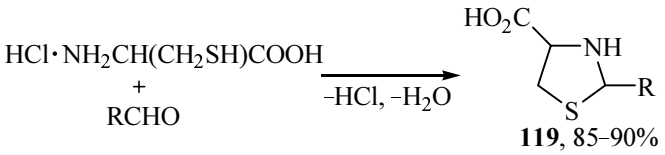
A new synthesis of 4-hydroxythiocoumarin-2-one **118** was developed consisting in reaction between 2-acetyl-



X = Cl, MeO, EtO.

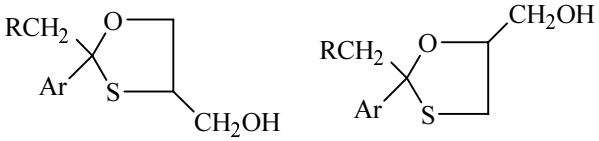
thiophenol and phosgene (or alkyl carbonate) in toluene in the presence of bases [113].

A cyclocondensation of cysteine hydrochloride with aldehydes led to 2-R-1,3-thiazolidine-4-carboxylic acids **119** [114].



119, 85–90%

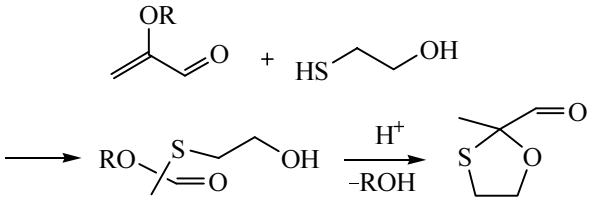
The reaction of 3-mercapto-1,2-propylene glycol with aliphatic-aromatic ketones in benzene in the presence of *p*-toluenesulfonic acid gave rise to a mixture of 1,3-oxathiolane derivatives **120** and **121** [115].



120, 48–63% **121**, 37–51%

R = H, 4-MeC_6H_4; Ar = Ph, 4-MeC_6H_4.

The formation of 1,3-oxathiolane derivatives **122** was also observed in reaction of 2-mercaptoethanol with 2-alkoxypropenals [116]. The following scheme of 1,3-oxathiolane derivatives formation was suggested in this case.



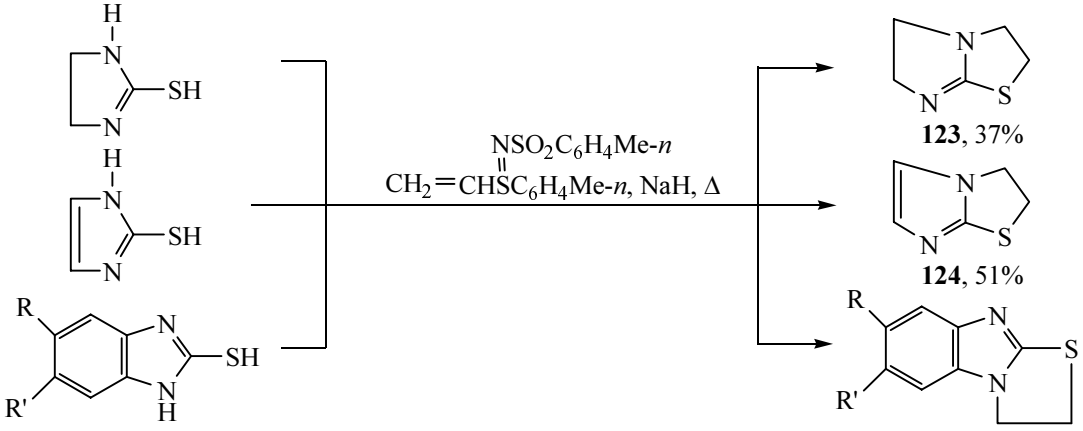
122, 64%

An ingenious synthesis was described of sulfur-containing fused heterocyclic systems **123–125**. The method consisted in reaction of 2-mercaptoimidazole, 2-mercaptoimidazoline, or 2-mercaptobenzimidazoles with S-vinyl-S-*p*-tolyl-*N*-*p*-toluenesulfonylsulfinylimine in the presence of sodium hydride (Scheme 18) [117].

A number of fused heterocyclic systems was prepared starting with mercapto-1,2,4-triazoles derivatives [118–121]. For instance, a synthesis was described of heterocyclic systems **126–129** based on 3(4-amino-5-mercapto-1,2,4-triazol-3-yl)quinoxalin-2(1*H*)-one and, respectively, on aryl bromomethyl ketone, 2,3-di-chloroquinoxaline, benzoin, and chloroacetic acid (Scheme 19) [118].

The addition of 3-mercapto-5-R-1,2,4-triazoles to 2-phenyl-4-(R-benzylidene)oxazol-5(4*H*)-ones with sub-

Scheme 18.



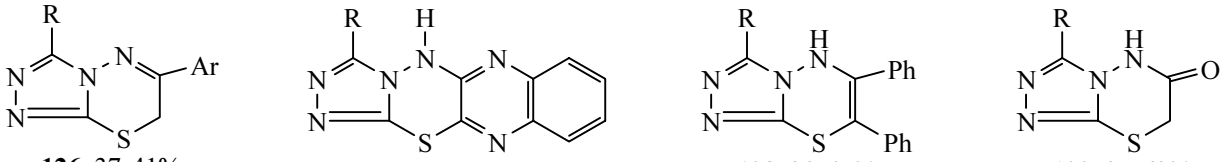
123, 37%

124, 51%

125, 28–62%

R = H, Me, MeO, NO_2; R' = H, Me, MeO, NO_2, Cl.

Scheme 19.



126, 37–41% **127**, 32–50% **128**, 28–47% **129**, 25–62%

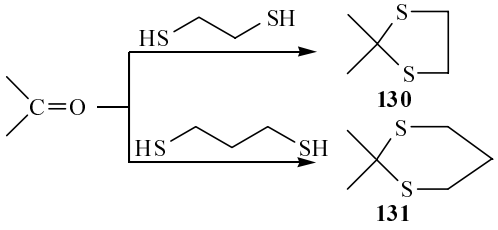
R = 2-oxo-1*H*-quinoxalyl-3-yl; Ar = Ph, 4-ClC_6H_4.

sequent transformation of the ring in the intermediate obtained afforded in 73–80% yields 2-(R-phenyl)benzamido-6-R-2,3-dihydro-*sym*-triazolo-[3,4-*b*]-1,3-thiazin-4(4*H*)-ones (R = Ph, 3-ClC_6H_4) [119].

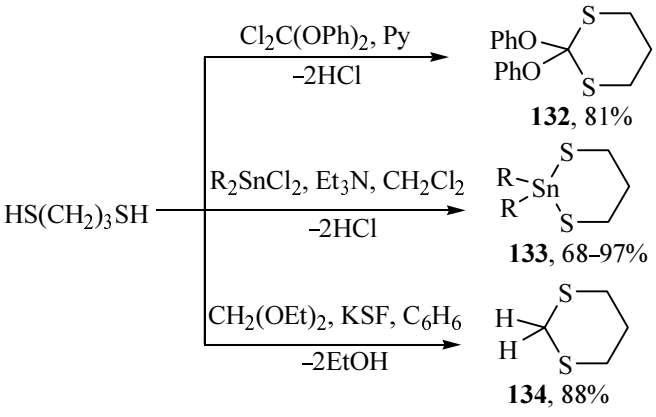
By reaction of 3-mercapto-5-(aryloxymethyl)-1,2,3-triazoles with (1-phenylethyl)amine and CH_2O in the presence of HCl were synthesized in 50–95% yields chiral derivatives of *sym*-triazole (S)-3-(1-phenylethyl)-5-(aryloxymethyl)-2,3-dihydro-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazines (Ar = Ph, 2-$MeOC_6H_4$, 3-MeC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4) [120].

4. HETEROCYCLIC SYSTEMS BASED ON DITHIOLS

Dithiolanes, dithianes, and other heterocyclic systems containing two sulfur atoms. Reactions of 1,2- or 1,3-dithioglycols with carbonyl compounds give rise to 1,3-dithiolanes **130** [122–130] or 1,3-dithianes **131** [123–136] which depending on the character of the initial compounds can contain various groups and substituents in position *2*, including also fragments of natural substances.

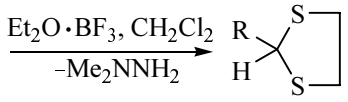


The cyclocondensation occurred with a quantitative yield in anhydrous organic solvents (CH_2Cl_2, $CHCl_3$, MeOH, THF etc.) at 0–40°C in the presence of catalysts like $BF_3{\cdot}OEt_2$ [122–131], Bu_4NF [132], KSF [134], HCl [131], $ZnCl_2$ [129], Et_3N [135], and $LiClO_4$ [136]. The catalyst activated the carbonyl group and took part in dehydration of the intermediate hemithioacetals. Since the C–S bond are highly labile compounds **130** and **131** are frequently used as protecting groups in the multistage syntheses of various naturally occurring compounds [112, 125, 126, 128–139]. The formation of dithiane (**132** and **134**) and dithiole (**135**) ring occurs also in reactions of 1,2- or 1,3-dithioglycols with geminal dihalo derivatives [137, 138], hydrazones [139], and diethoxymethane [140].



R = Me, C_6H_{13}.

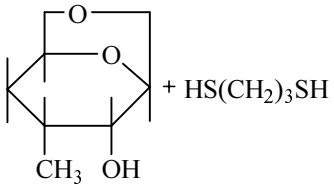
$HS(CH_2)_2SH + RCH{=}NNMe_2$

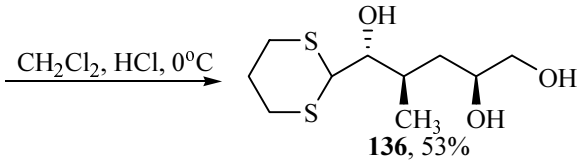


135, 82–89%

R = 4-$NO_2C_6H_4$, 4-ClC_6H_4, C_5H_{11}, PhCH=CH.

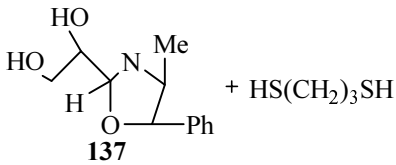
1,3-Dithianes formed also in reactions of 1,3-dithiols with compounds containing a latent carbonyl group. For instance, the thiolysis of 1,6-anhydro-3,4-bisdeoxy-3-C-methyl-β-*D*-allopyranose resulted in a derivative of 1,3-dithiane **136** [141].



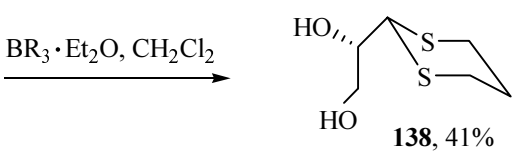


136, 53%

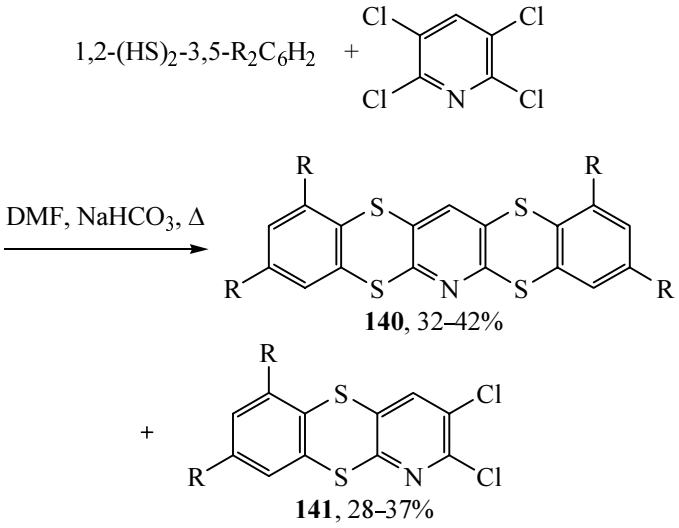
Similarly occurred thiolysis of 1,3-oxazolidine derivative **137** involving a ring opening and resulting in formation of a cyclic reaction product **138** [142].



137



138, 41%

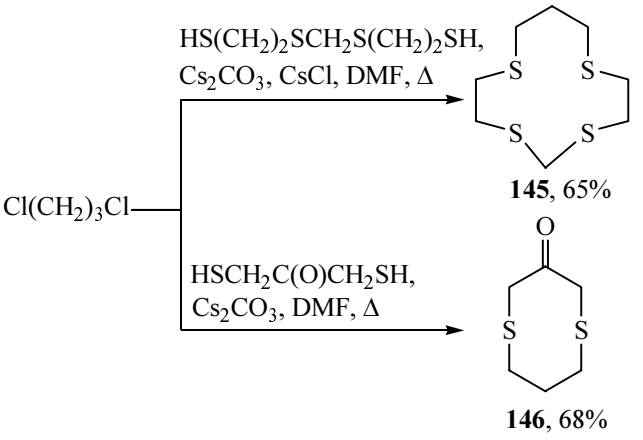


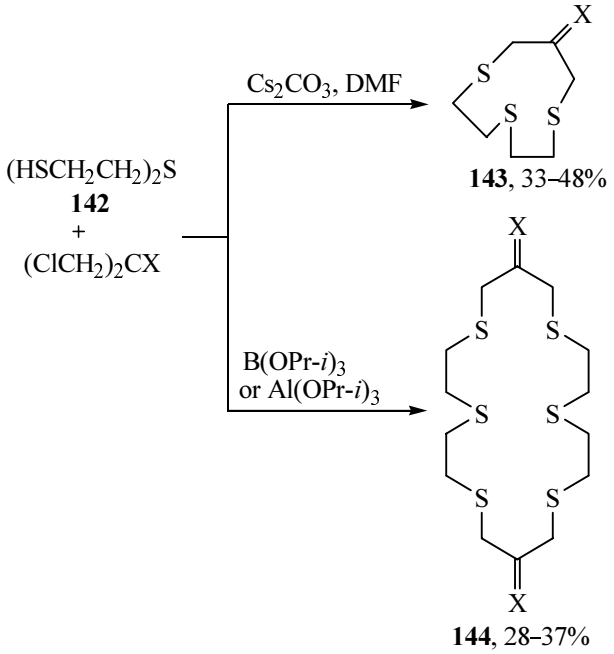
A series of 1,3-dithiolane **139** analogs was obtained by reaction of geminal dimercapto compounds sodium salts with 2,3-dichloro-1,4-naphthoquinone [143]. Similar compounds formed also in reaction of geminal dimercapto compounds with haloacetylenes [144].

From 1,2-dithiophenols with 2,3,5,6-tetrachloropyridine under an argon atmosphere a mixture of compounds **140** and **141** was obtained [145].

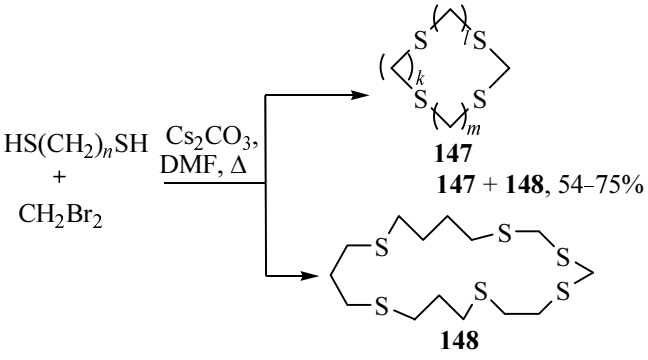
Crown thioethers and other macroheterocyclic systems. The synthesis of crown thioethers consists in selection of reagents with functional groups readily reacting with thiol groups with macroring formation. As these reagents the terminal dihalo derivatives are often applied. To suppress the side reactions the processes are carried out at a high dilution. The condensation can involve both a single molecule of each initial reagent and two or even three of each. Consequently these condensation types are designated as [1+1]-, [2+2]-, and [3+3]-cyclocon-densation [2]. The occurrence of the certain cyclocon-densation type depends on the reaction conditions and especially on the nature of the catalyst used. For instance, the reaction of 3-thiapentane-1,5-dithiol with dichloro derivatives **142** in the presence of Cs_2CO_3 afforded crown thioethers **143**, whereas in the presence of $B(OPr\text{-}i)_3$ and $Al(OPr\text{-}i)_3$ crown thioethers **144** were formed [146].

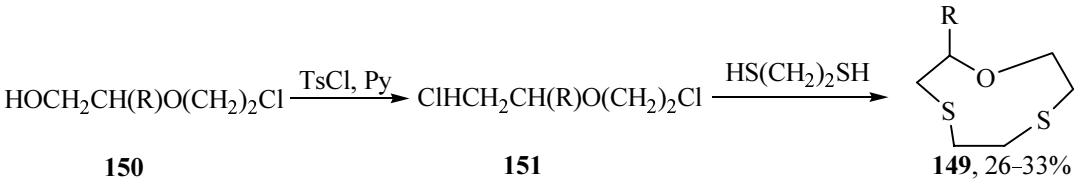
Cs_2CO_3 catalyzed also the reactions between 3,5-dithiaheptane-1,7-dithiol [147] and 1,3-dimercapto-2-propanone [148] with 1,3-dichloropropane yielding crown thioethers **145** and **146** respectively.





The cyclocondensation of ethane- and propanedithiols with dibromomethane in the presence of Cs_2CO_3 furnished a mixture of crown thioethers **147** and **148** [149].



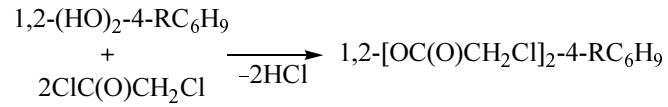


150 **151** **149**, 26–33%

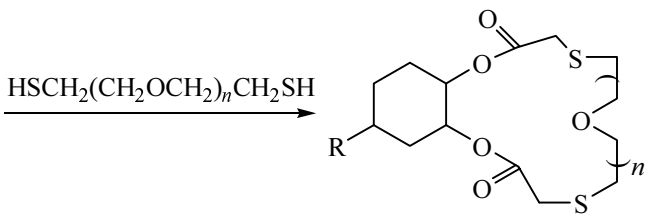
R = Me, Et, Ph.

In the synthesis of crown thioethers **149** based on derivatives of chlorohydrin **150** the latter was first converted into a chloro derivative **151** that further reacted with 1,2-ethanedithiol [150].

Syntheses were described of a series of *trans*-cyclohexano-crown thioethers **152** and **153** from dihydroxycyclohexanes that were transformed into chlorine-containing esters **154** and **155** and reacted with dithiols [151].

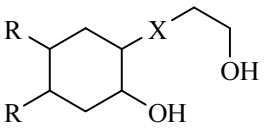


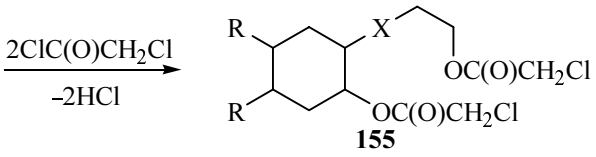
154



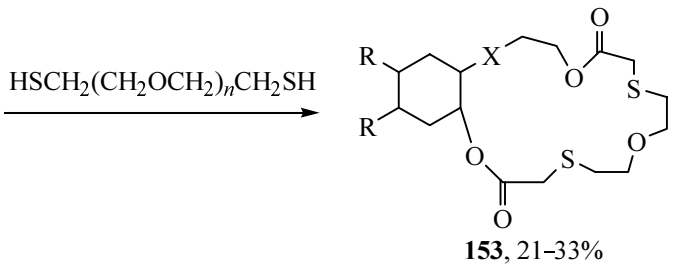
152, 23–34%

R = H, Me, Bu; *n* = 1, 2.





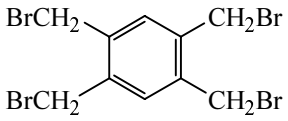
155

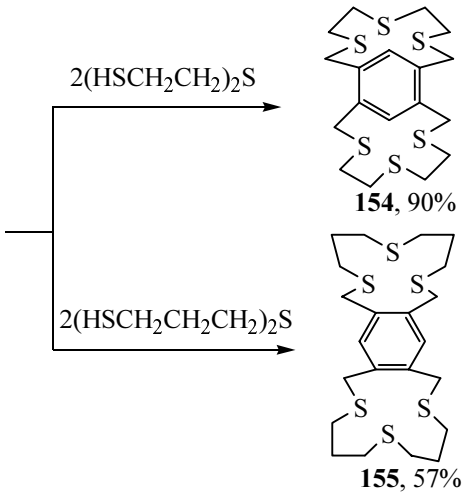


153, 21–33%

R = H, COOEt; X = O, S.

In the synthesis of crown thioethers aliphatic-aromatic compounds are also used containing halogen atoms or thiol groups in a side chain. For instance, a regioselective cyclocondensation was reported of 1,2,4,5-tetra(bromomethyl)benzene with 3-thiapentane-1,5-dithiol and with 4-thiaheptane-1,7-dithiol under high dilution that afforded biscrown thioethers **154** and **155** [152].





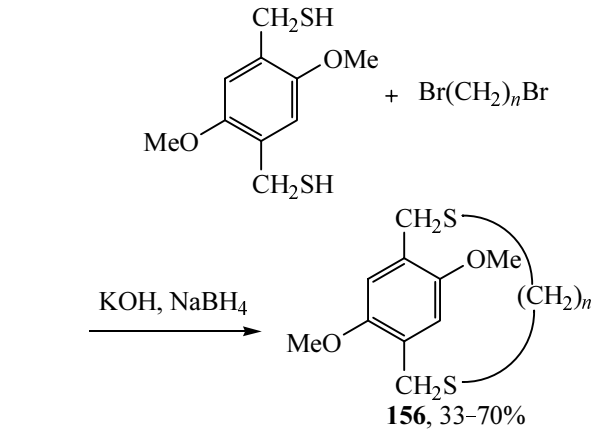
154, 90%

155, 57%

A synthesis of a number of paracyclophanes **156** was described based on 2,5-dimethoxy-1,4-di(mercaptomethyl)benzene and terminal dibromoalkanes [153].

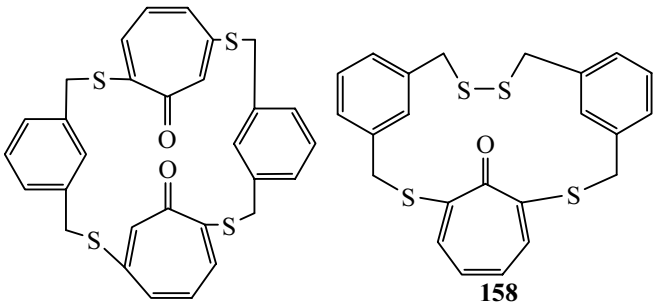
The reaction of 1,3-bis(mercaptomethyl)benzene with 2,7-dibromotropone in *t*-BuOH or DMF in the presence of *t*-BuOK yielded at the ratio of the reagents 1:1 crown thioethers **157**, and at the ratio 2:1, crown thioethers **158** [154].

A [2+2]-cyclocondensation was described of 4-amino-3,5-dimercapto-1,2,4-triazole dipotassium salt with termi-



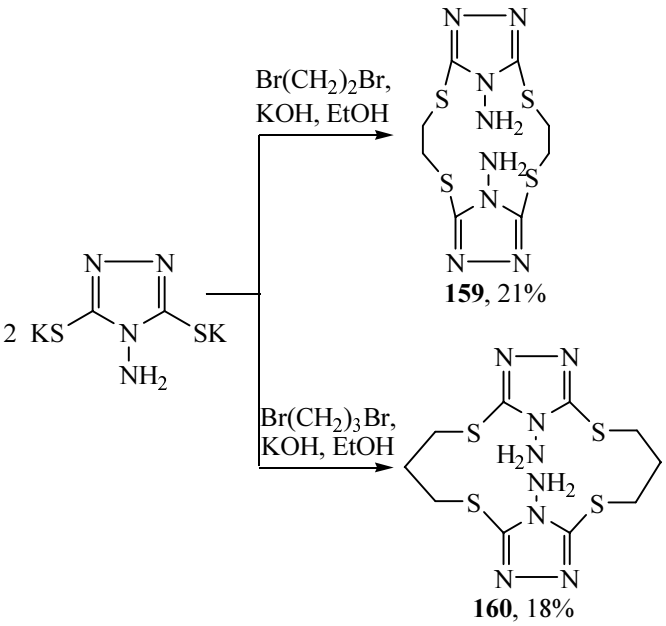
156, 33–70%

$n = 2, 3$.



157 **158**

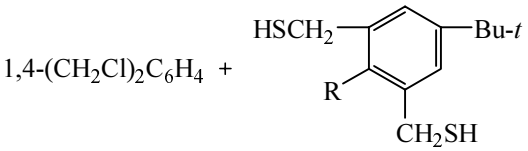
nal dibromoalkanes resulting in crown thioethers **159** and **160** [155].

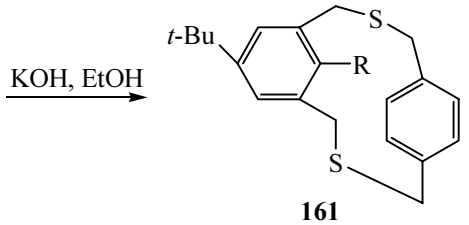


159, 21%

160, 18%

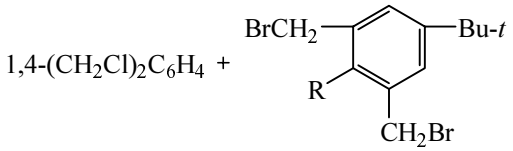
Under high dilution the synthesis of cyclophanes **161**, **162** [156], **163** [157], and **164** was performed [158].

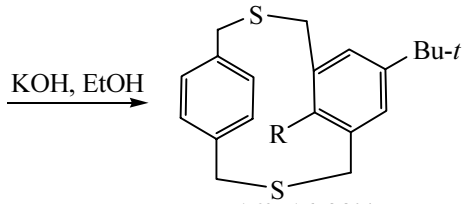




161

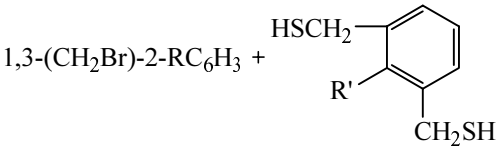
R = Me, MeO.

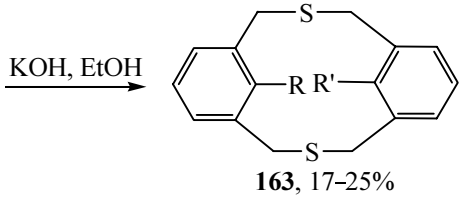




162, 16–28%

R = H, Me, MeO, Br.



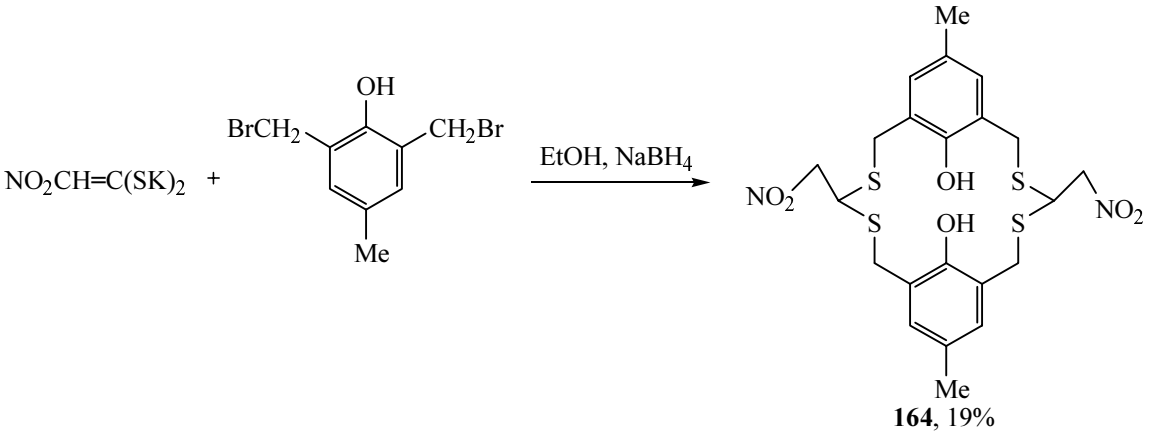


163, 17–25%

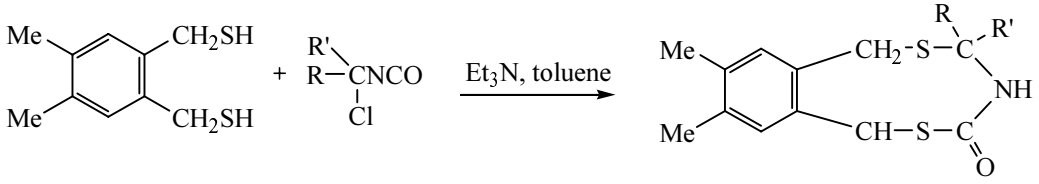
R = NO_2; R' = H, NO_2.

Sometimes the cyclocondensation with dithiols occurs with participation of other functional groups beside halogens, for instance, isocyanate group in the synthesis of 3-R-3-R'-9,10-dimethyl-4-aza-2,6-dithiabenzocyclononan-5-ones **165** [159]. A synthesis was reported of 6-mercapto-6-phenyltetrahydro- thiopyran-2-one based on 2,2-dimercapto-1-chloro-2-phenylethane and 3-aminopropionic acid [160].

Complex heterocyclic systems were obtained from unsaturated dithiols. For instance, a synthesis was de-

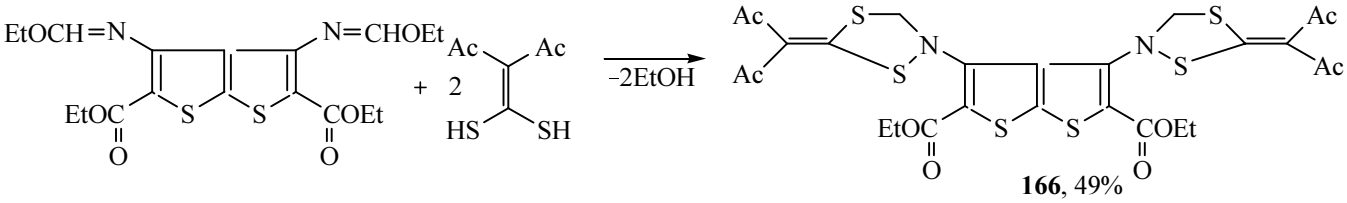


164, 19%

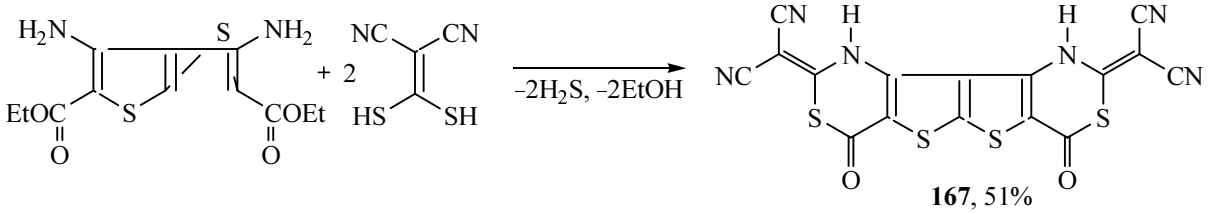


165, 70–86%

R = CF_3; R' = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$.



166, 49%



167, 51%

scribed of fused thieno[2,3-*b*]thiophenes **166** and **167** proceeding from 1,1-dimercapto-2,2-di-acetylethylene and 1,1-dimercapto-2,2-dicyanoethylene [161].

5. CONCLUSION

One among the promising development lines of thiol chemistry is the synthesis of heterocyclic systems based on thiols taking into account the high reactivity of the thiol group. In this connection the synthesis of heterocyclic systems from thiols should include the following: Thiol selection should be performed with consideration of the structure of the heterocyclic system and the structure of the fragment supplied by thiol; therewith the thiol alongside the SH group must contain also other functional groups or reaction sites; the choice of reagents for reaction with the thiol should take into account the structure of the heterocyclic system and the structure of the fragment supplied by the reagent; the reagent must contain functional groups easily reacting with the thiol group and the other reaction sites.

Considering the relative availability of thiols this line in the thiols chemistry apparently will develop further in future.

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