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HETEROCYCLIZATION OF THIOAMIDES CONTAINING AN ACTIVE METHYLENE GROUP (REVIEW)

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Data from the last six years on the heterocyclization of thioamides containing an active methylene group are analyzed and classified.

Keywords: thioamides, thiolactams, active methylene group, heterocyclization, multicomponent reactions, recyclization.

At the present time there has been a considerable increase in the number of publications on the chemistry of thioamides, and this is explained by the value of the compounds as initial reagents for further transformations and particularly for the synthesis of various sulfur- and nitrogen-containing heterocycles [1-8]. The enormous practical significant of the latter is common knowledge – they have found application as drugs, pesticides, dyes, and preservatives.

Thioamides with an active methylene group are attractive synthesis units for the production of heterocycles. These polyfunctional compounds can be represented by the formula $R^3–CH_2CS–NR^1R^2$ (where R^1, R^2 = H, Alk, Ar; R^3 is an electron-withdrawing group such as CN, AlkCO, ArCO, $(AlkO)_2PO$, $AlkSO_2$, $ArSO_2$, NO_2). The presence of another reaction center (the methylene group) makes it possible to use them as N–C–C and S–C–C components for various condensations [1-8]. A special feature of such substrates is the ability to react both with dinucleophilic and with dielectrophilic and dipolar reagents. As a rule the products of these heterocyclizations contain functional groups, which makes it possible to achieve their modification or annelation. Such characteristics of thioamides with an active methylene group substantially increase their synthetic potential and extend the range of accessible heterosystems, while the use of modern physical methods of investigation (X-ray crystallographic analysis and 1D and 2D NMR spectroscopy) makes it possible to establish the structure of the obtained compounds unambiguously. The presence of biological activity in the products of these transformations also attracts investigators to this subject [5-8].

The reason for the appearance of this review was the increasing need for generalization and classification of new information on the heterocyclization of such thioamides that had not been included in previous reviews [2-5] and also to define the trends in the study of these processes. Since one of the most important reports in this field is the review [1] we undertook an analysis of the literature that has appeared in the last six years.

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1. THE ACIDITY OF THIOAMIDES CONTAINING AN ACTIVE METHYLENE GROUP

Before examining the actual heterocyclization of such thioamides it is necessary to pay attention to their acidity since this factor is directly related to the ability of the substrates to generate ambident anions [9], which in reactions with electrophilic reagents frequently determines the direction of reaction. Due attention has not previously been paid to this aspect – existing data on the ionization constants of thioamides are fragmentary and unsystematic [10, 11]. It should be noted that the acidity of thioamides is approximately 10-100 times higher than the acidity of structurally similar amides [10], and it is this which determines the ease of the occurrence of the reactions of thioamides with electrophiles in the presence of bases.

Recently [12] the pK_a values of thioacetamides in 1:1 DMSO–H_2O were determined by pH-metric titration. The experimental data indicated that thioamides containing acetyl or aroyl groups at position 2 are more acidic than thioamides with a phenylsulfonyl or cyano group (pK_a 7.04-8.53 and 8.59-11.56 respectively). For comparison the pK_a values of such classical CH acids as malononitrile and diethyl malonate amount to 11.19 and 13.3 respectively [13]. The increased acidity of 3-oxopropanethioamides is probably explained by stabilization of their anions as a result of the delocalization of electron density between the S, N, and O atoms.

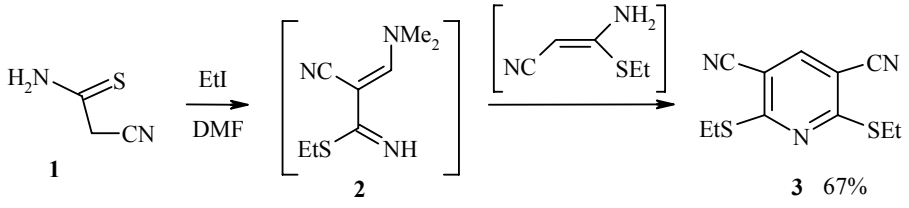
2. HETEROCYCLIZATION

The heterocyclic transformations of thioamides containing an active methylene group can be classified according to such criteria as the topology of the ring structure, the reaction mechanism, and the nature and structure of the initial reagents. Since the nature of the substituents at position 2 of the above-mentioned thioamides has a substantial effect on the direction of their cyclization it is in our opinion most convenient to classify the reactions according to the structure of the initial thioacetamides and the topology of the cyclocondensations.

2.1. Heterocyclization of N-R-2-Cyanothioacetamides (R = H, Alk, Ar)

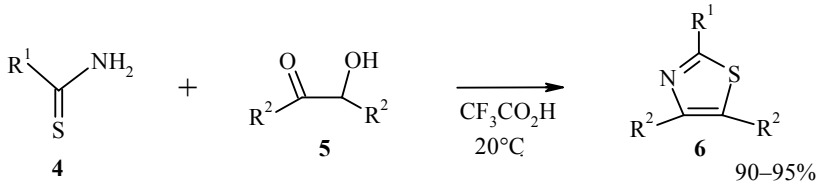
2-Cyanothioacetamide is one of the most readily obtainable thioamides with an active methylene group and has moreover a fairly high acidity (pK_a 9.46 [12]). For the indicated reasons the reactions are extremely varied, as was echoed in the reviews [1, 4-8, 14-17]. In these articles information on methods for the synthesis of cyanothioacetamide was classified [6, 8], and data on the use of (thio)amides of cyanoacetic acid in fine and combinatorial synthesis [5-8, 14-17], including use of the methodology of multicomponent condensation [5-8, 14], were analyzed.

2.1.1. Cyclocondensation of Cyanothioacetamide with 1,1-Dielectrophiles. The alkylation of cyanothioacetamide **1** with ethyl iodide in dimethylformamide, accompanied by [3+2+1] cyclization to 3,5-dicyano-2,6-diethylthiopyridine **3**, can be included among such reactions [18]. The dimethylformamide here fulfills the function of "supplier" of the methine fragment. The cyclization probably takes place through the intermediate **2**.



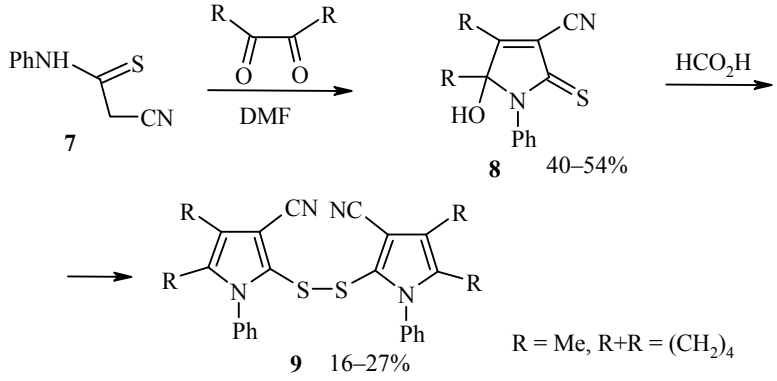
2.1.2. [3+2] Cyclocondensation of N-R-2-Cyanothioacetamides with 1,2-Dielectrophiles. Examples of [3+2] cyclizations of N-R-2-cyanothioacetamides with 1,2-dielectrophilic reagents were presented in [19-22], where the above-mentioned thioamides were used as N,C,S [19, 20], N,C,C [21], and S,C,C components [22].

4,5-Bis(2',5'-dimethylthiophen-3-yl)-2-R-thiazoles **6** were obtained with quantitative yields by reaction of the thioamides **4** with 2-hydroxy-1,2-bis(2,5-dimethyl-3-thienyl)ethan-1-one **5** [19].

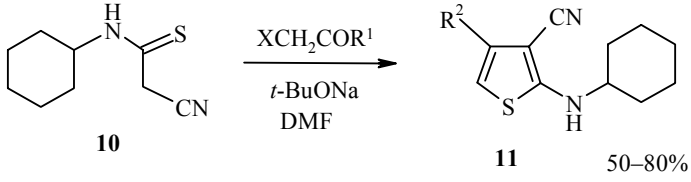


R^1 = Me, NH_2, Ph, CH_2CN; R^2 = 2,5-dimethylthien-3-yl

The products from the cyclization of N-phenyl-2-cyanothioacetamide **7** and 1,2-diketones are 5-hydroxy-γ-thiolactams **8**, which are transformed in reaction with formic acid into di(2-pyrrolyl) disulfides **9** [21].



The effect of steric factors on the direction of cyclization of N-cyclohexylcyanothioacetamide **10** with α-halocarbonyl compounds was investigated in [22]. It was found that on account of presence of the bulky cyclohexyl substituent at the N atom the thioacetamide **10** reacts with halo ketones and ethyl bromoacetate with the formation not of thiazoles, as expected, but of 2-(N-cyclohexylamino)-3-cyano-4-R-thiophenes **11**.



R^1 = Me, 4-$MeOC_6H_4$, OEt; R^2 = Me, 4-$MeOC_6H_4$, OH; X = Br, Cl

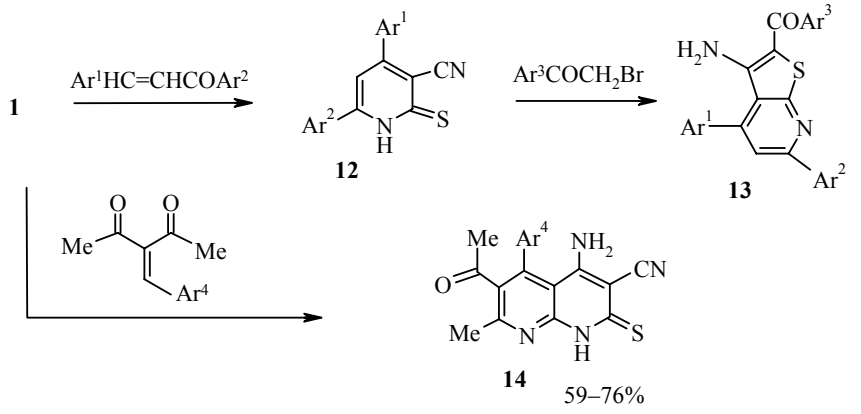
2.1.3. [3+3] Cyclization of Cyanothioacetamide with 1,3-Dielectrophiles.

2.1.3.1. Condensation with Acyclic Reagents. Of synthetic importance is the group of reactions based on the reaction of 2-cyano-thioacetamide as the N,C,C component with derivatives of α-unsaturated ketones [23-28] and carboxylic acids [29, 30]. They take place by a [3+3] cyclization mechanism and provide a general method for the production of derivatives of 3-cyanopyridine-2-thione. In all probability the reactions are realized through the products from Michael or Knoevenagel addition, which in some cases can be isolated and characterized [5-8].

Chalcones [23-25], β-enaminocarbonyl compounds [26-28], and derivatives of 2-methylenecyanoacetic acid [29, 30] were used as starting synthesis units. On account of the presence of the vicinal reaction groups the synthesized pyridine-2-thiones are usually employed in further transformations, including annelation to polycyclic hetero compounds [23, 24, 26, 27, 29].

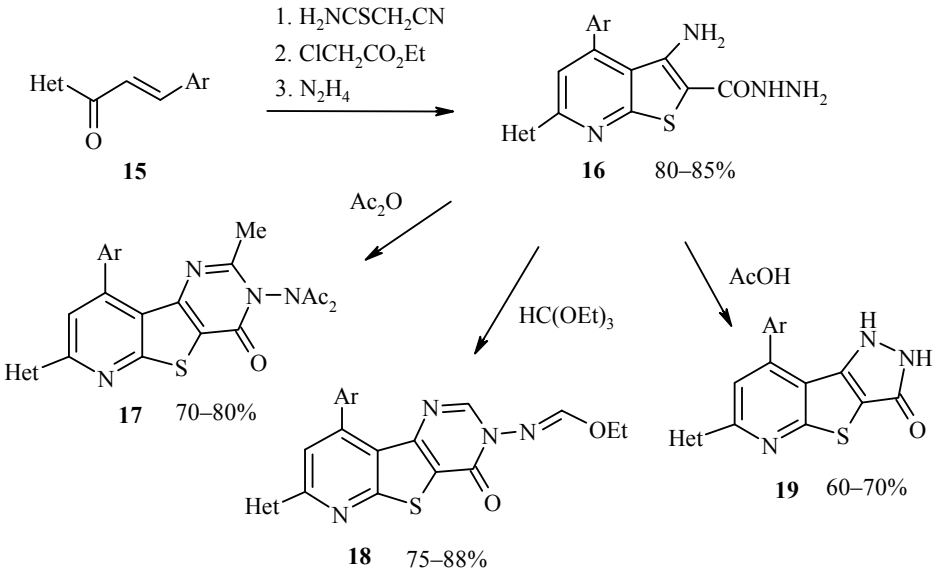
3-Cyanopyridine-2(1H)-thiones **12** were obtained by the reaction of cyanothioacetamide **1** with chalcones, and their treatment with α-halo ketones provided a suitable method for the synthesis of 3-amino-2-aroylthieno[3,2-*b*]pyridines **13** [23].

A single-stage method for the production of the bicyclic structure of 1,2-dihydro[1,8]naphthiridine-2-thiones **14** from a chalcone and the thioamides **1** looks promising [24].



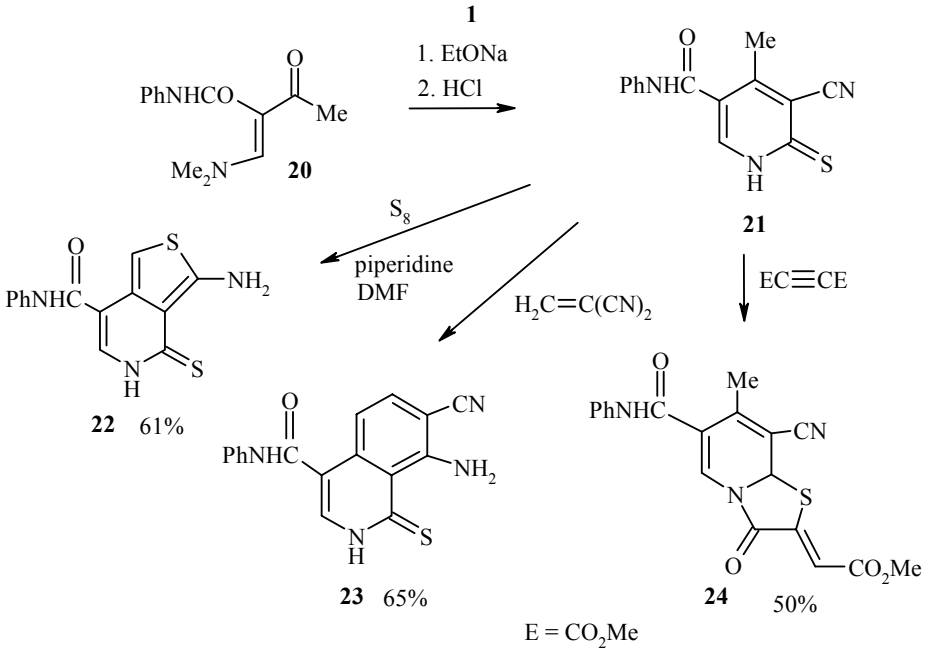
Ar^1 = 1- naphthyl, 2- naphthyl; Ar^2 = Ph, 4-MeC_6H_4; Ar^3 = Ph, 4-ClC_6H_4;
Ar^4 = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

3-Cyanopyridine-2-thiones, isolated during the cyclization of cyanothioacetamide with the chalcones **15**, proved to be valuable starting materials for the synthesis of condensed bi- and tricyclic heterocycles **16**-**19** [25].

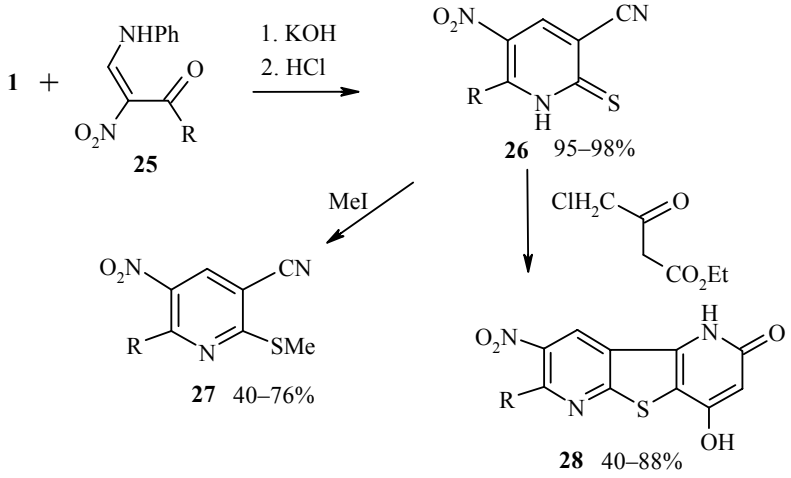


Ar = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4; Het = 2-thienyl

5-Arylcarbamoyl-3-cyano-4-methylpyridine-2-thiones **21**, obtained from cyanothioacetamide **1** and 2-(N,N-dimethylaminomethylene)-3-oxobutyranilide **20**, have found use for transformation into condensed bicyclic heterosystems **22**-**24** [26].



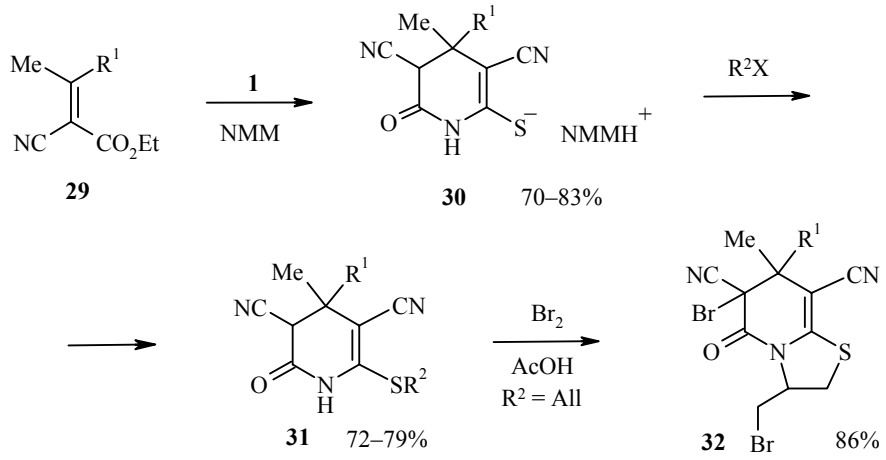
A preparative synthesis of 3-cyano-5-nitro-6-R-pyridine-2(1H)-thiones **26**, involving the cyclocondensation of cyanothioacetamide **1** with 2-nitro-3-phenylamino-1-R-prop-2-en-1-ones **25**, was described in [27]. Compounds **26** are alkylated selectively in an alkaline medium with the formation of the thioethers **27** and also enter into reaction with ethyl 4-chloro-3-oxobutyrate. The products of the last reaction are substituted pyridine[2',3';4,5]thieno[2,3-*b*]pyridin-2(1H)-ones **28**.



R = EtO, OH, Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4

Cyanothioacetamide and 2-benzoyl-1-(phenylamino)ethene in acetic acid were used for the synthesis of 3-cyano-6-phenylpyridine-2(1H)-thione [28].

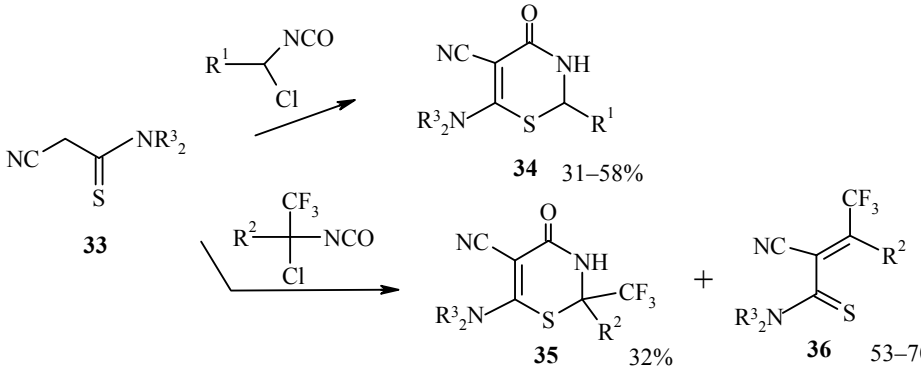
N-Methylmorpholinium 6-oxo-1,4,5,6-tetrahydropyridinethiolates **30**, produced by the condensation of cyanothioacetamide **1** with ethyl 2-cyano-3-methyl-3-R-2-propenoates **29**, were transformed into 2,3,6,7-tetrahydro-5H-[1,3]thiazolo[3,2-*a*]pyridin-5-ones **32** [29].



R^1 = Me, Et; R^2 = Me, Et, CH_2–CH=CH_2, CH_2–C(Me)=CH_2; X = Cl, Br;
NMM = N-methylmorpholine

1-Amino-2,4-dicyanobuta-1,3-diene-1-thiolates and 6-amino-3-cyanopyridine-2-thiones, used as initial reagents for the synthesis of thiazoles by the Hantsch method and 6-amino-2-alkylthio-3-cyanopyridines respectively, were obtained by the cyclization of cyanothioacetamide with derivatives of ethoxymethylene-cyanoacetic acid under the conditions of base catalysis [30].

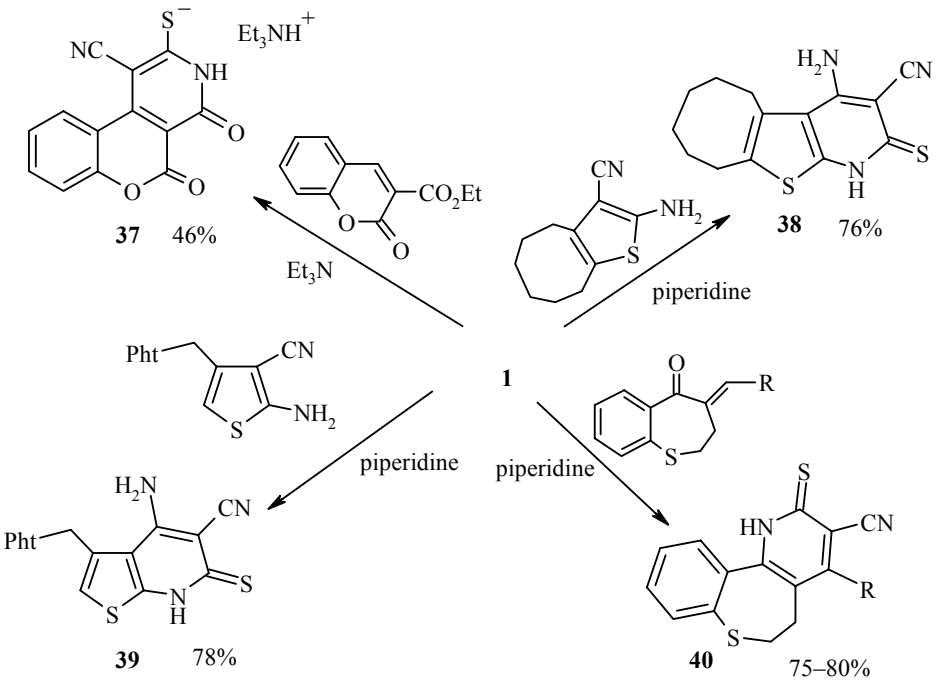
The products from the reaction of N,N'-disubstituted cyanothioacetamides **33** with 1-chlorobenzyl isocyanates are 2,3-dihydro-4H-1,3-thiazin-4-ones **34** [31], whereas the direction of the cyclocondensation of 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates with the substrates **33** depends on the nature of the substituent in the initial isocyanates. In the case of the 4-tolyl and 4-anisyl derivatives 3-aryl-2-cyano-3-trifluoromethyl-acrylothioamides **36** and cyanuric acid were isolated from the reaction solution, whereas use of the 4-trifluorophenyl reagent led to the formation of a mixture of compounds **35** and **36**.



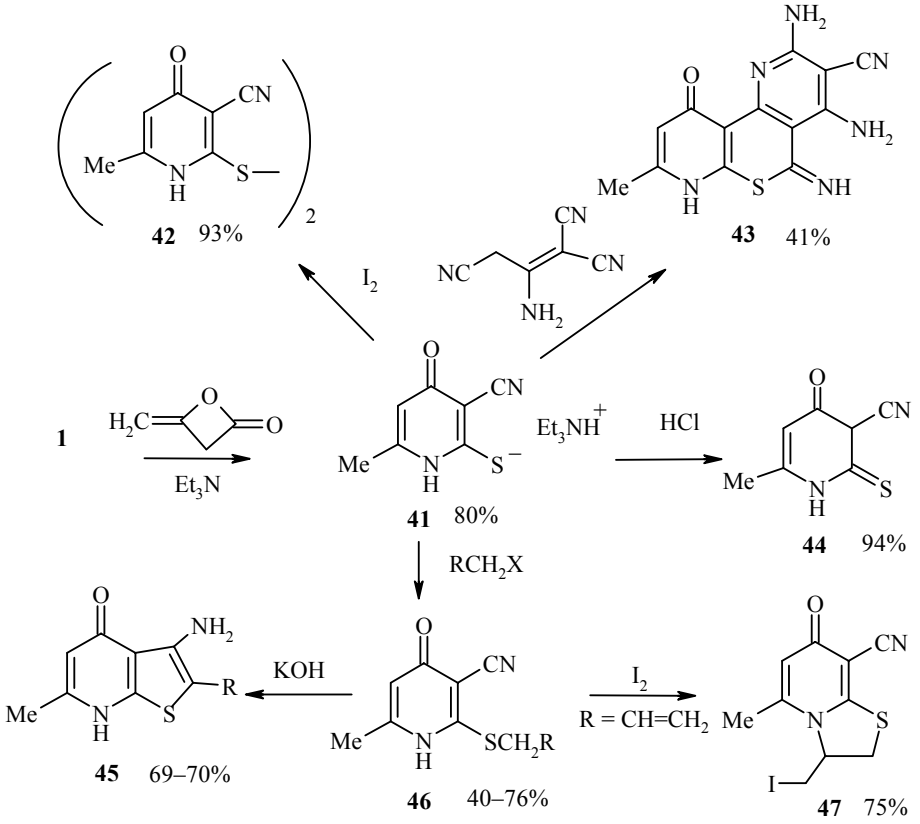
R^1 = 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3,4-$Cl_2C_6H_3$; R^2 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CF_3C_6H_4$;
$R^3 + R^3$ = $(CH_2)_4$, $(CH_2)_2O(CH_2)_2$

2.1.3.2. Annelation of Heterocycles by Cyanothioacetamide. Cyanothioacetamide has found use for the annelation of heterocycles, which can be regarded as a method for "making up" the 3-cyano-2-thioxo-pyridine ring to structures containing vicinal amino and cyano groups [32, 33], or an activated double bond

[34, 35]. As a result of the transformations triethylammonium 1-cyano-4,5-dioxo-3,4,5,6-tetrahydro[1]benzopyrano[3,4-*c*]pyridine-2-thiolates **37** [34], 6,7-dihydrothieno[2,3-*b*]pyridines **38** [33] and **39** [32], and 4-aryl-3-cyano-5,6-dihydro-1-benzothiepino[5,4-*b*]pyridine-2(1H)-thiones **40** [35] were obtained.

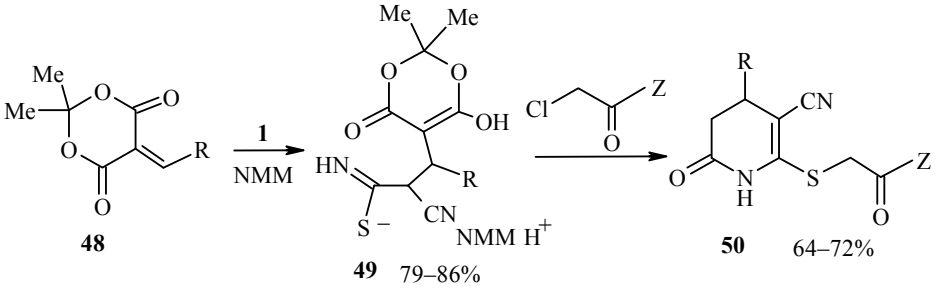


Pht = phthalimido; R = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4



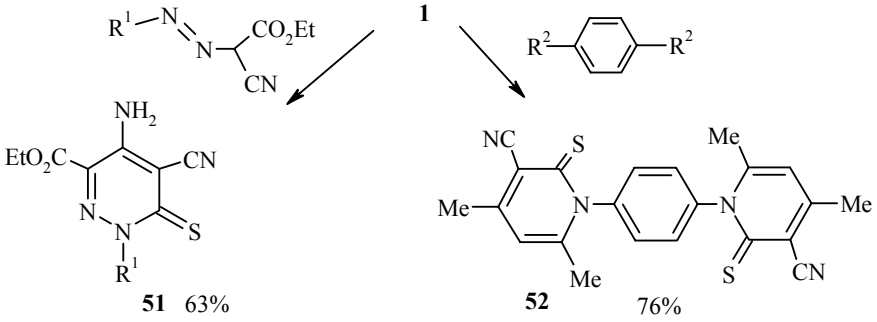
2.1.3.3. Recyclization as a Method for the Synthesis of Derivatives of 3-cyanopyridine-2-thione. The cycloacylation of cyanothioacetamide **1** with diketene can be regarded formally as recyclization. It takes place regiospecifically and is a preparative method for the synthesis of triethylammonium 3-cyano-6-methyl-4-oxo-1,4-dihydropyridine-2-thiolate **41** [36]. The latter serves as the initial reagent for subsequent reactions, including the production of thieno[2,3-*b*]pyridines **45** and thiazolo[3,2-*a*]pyridines **47** and also the new heterosystem 5H-pyrido[2',3':4,5']thiopyrano[2,3-*b*]pyridine **43**.

During the reaction of cyanothioacetamide **1** and aryl(heteryl)methylene derivatives of Meldrum's acid **48** the products **49** from Michael addition were isolated [37], and their regiospecific alkylation with α-halocarbonyl compounds gave 6-alkylthio-1,2,3,4-tetrahydropyridines **50**.



R = Ph, 2- thienyl, 4-HO-3-EtOC$_6$H$_3$; Z = PhCH$_2$O, 4-BrC$_6$H$_4$

2.1.4. [4+2] Cyclization of Cyanothioacetamide with 1,4-Dielectrophilic Reagents. Such reactions include the reaction of cyanothioacetamide **1** with the azo derivative of cyanoacetic ester, leading to the formation of substituted 1,6-dihydropyridazine-6-thiones **51** [38], and the synthesis of the phenylenedipyridine-2-thione derivative **52** [39].

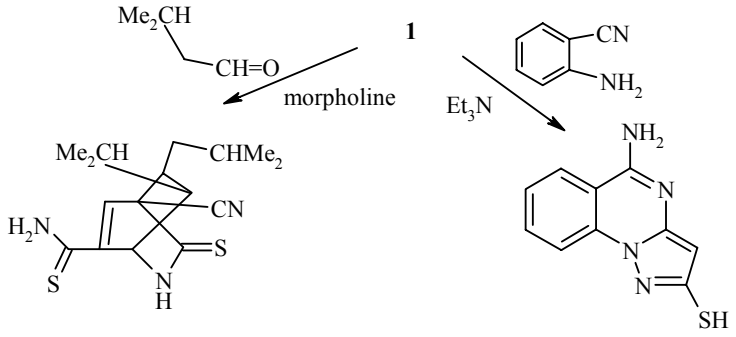


R^1 = 3-aminocarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl;
R^2 = MeC(OH)=CH–C(Me)=N

2.1.5. Unusual Two-Component Heterocyclizations of Cyanothioacetamide. For some reactions the cyclization scheme is more complicated than [3+2], [3+3], or [4+2] cyclocondensation. At the same time these transformations cannot be rated as multicomponent syntheses in so far as only two initial reagents take part in them [40-43]. Nevertheless the products of these reactions are hetero framework [40], polycyclic [41, 42], and spiro compounds [43] with unexpected structures. In view of the complexity of a faithful interpretation of the results of spectral investigations the structure of the products described in [40, 41, 43] was confirmed by X-ray crystallographic analysis. In further investigations the mechanisms of these reactions need to be substantiated.

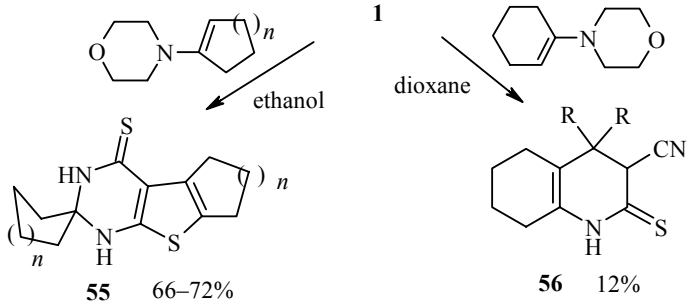
An example of the simultaneous use of cyanothioacetamide **1** as N,C,C and C,C components was described in [40]. The product from its condensation with isovaleraldehyde is the 2-azabicyclo[2.2.2]oct-5-ene-3-thione derivative **53**.

The reaction of the thioacetamide **1** with 1-amino-2-cyanobenzene provides a method for the production of 5-amino-2-mercaptopyrazolo[1,5-*a*]quinazoline **54** [42].



53 71% **54** 92%

In [41] a convenient method was developed for the synthesis of the spiro-substituted heterosystem of the thieno[2,3-*d*]pyrimidine-4-thione derivative **55** by the reaction of the thioamide **1** with N-(1-cycloalkenyl)-morpholines in ethanol. If the ethanol is replaced by dioxane the reaction of the cyanothioacetamide **1** with twice the amount of 1-(4-morpholino)cyclohex-1-ene leads to the formation of the previously undescribed 3-cyano-4-cyclohexanespiro-1,2,3,4,5,6,7,8-octahydroquinoline-2-thione **56** [43].

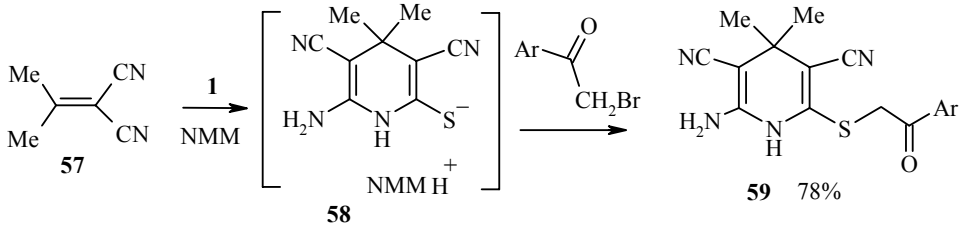


55 66–72% **56** 12%

R + R = $(CH_2)_5$; *n* = 1, 2

2.1.6. One-Pot Multicomponent Heterocyclizations of Cyanothioacetamide. The multicomponent (cascade, tandem) reactions of cyanothioacetamide, the order of their stages, and the proposed mechanisms were analyzed earlier in the reviews [1, 5-8, 14]. On account of the experimental convenience and technological effectiveness multicomponent reactions were developed further in [44-62]. The advantages of the condensations include the possibility of producing derivatives of 3-cyanopyridine-2-thione [44-52], polysubstituted thiazoles [52] and thiophenes [53], and polycyclic heterosystems containing a pyridine ring [54-61] in one pot.

It was established [44] that 1,1-dicyano-2,3-dimethylethene **57** reacts with the thioacetamide **1** and 4-methoxyphenyl bromomethyl ketone with the formation of 6-amino-2-(4-methoxybenzoylmethylthio)-4,4-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile **59**.

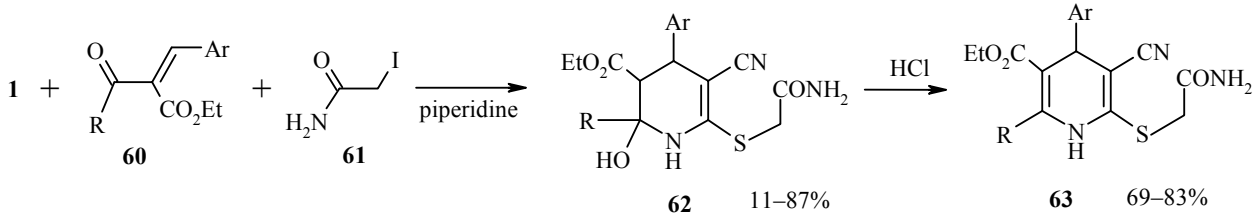


57 **58** **59** 78%

Ar = 4-$MeOC_6H_4$

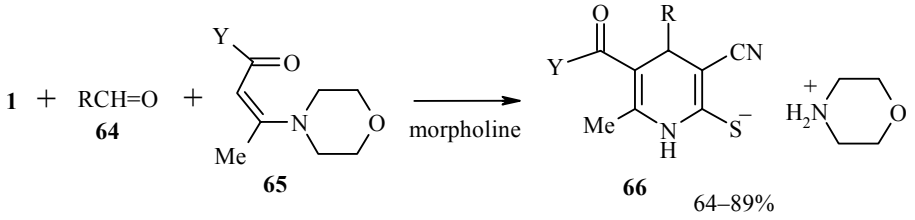
The authors of [45] developed a rapid method (5-8 min) for the synthesis of 6-amino-4-aryl-3,5-dicyano-pyridine-2(1H)-(thi)ones involving three-component condensation of cyano(thio)amide with arylaldehydes and malononitrile in a microwave oven.

The pyridine-3-carbonitriles **62** and **63** were obtained by the multicomponent reaction of compounds **1**, **60**, and **61** [46-49], and their cardiovascular activity [48] and electrochemical oxidation [47-49] were investigated. It was found that the derivatives of 1,4,5,6-tetrahydropyridine **62** are as a rule oxidized more readily than the corresponding 1,4-dihydropyridines **63**.



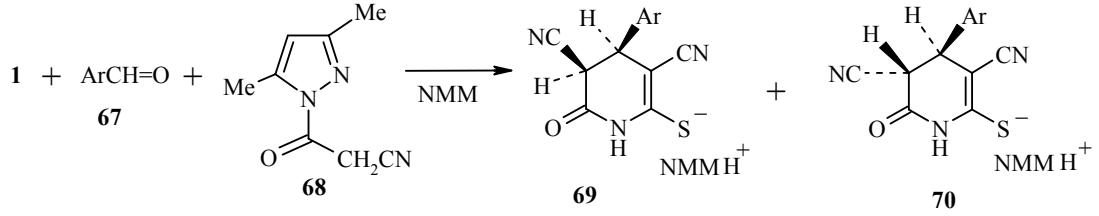
Ar = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$; R = Me, Ph, 4-$O_2NC_6H_4$

In [50] a new method was described for the synthesis of morpholinium 1,4-dihydropyridine-2-thiolates **66**, based on the cyclization of cyanothioacetamide **1** with aldehydes **64** and enamines **65**. The structure of compounds **66** was proved both by spectroscopic methods and by alkylation at the S atom with 1,2-dibromo-ethane, allyl bromide, and chloroacetonitrile.



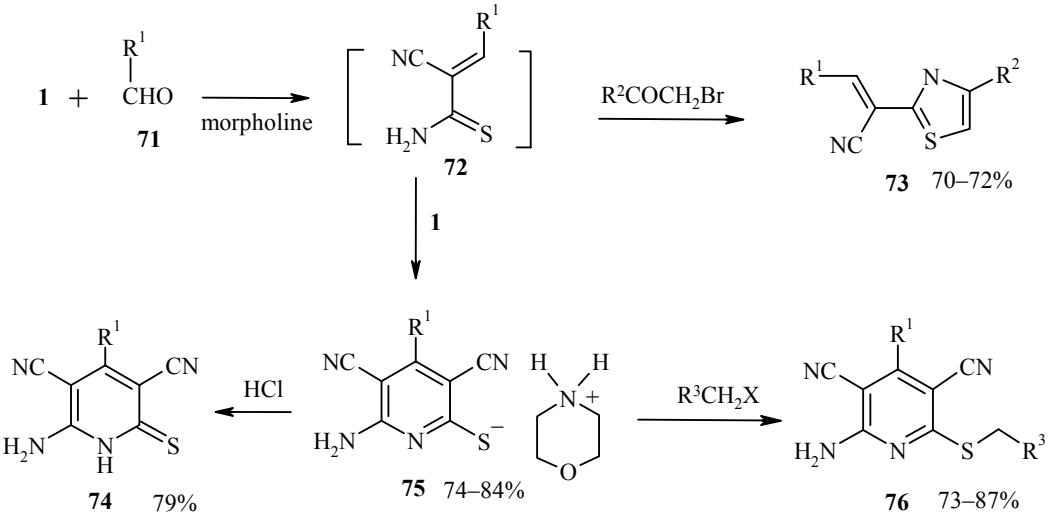
R = 2-furyl, 4-ClC_6H_4, 4-HOC_6H_4, 4-$BuOC_6H_4$; Y = Me, EtO, CH_2=$CHCH_2O$

The reaction of the thioamide **1** with 2-chlorobenzaldehyde **67** and substituted pyrazole **68** is characterized by the absence of stereoselectivity [51]. In DMSO-d_6 the obtained stereoisomers **69** and **70** undergo rapid epimerization at the C-5 atom.



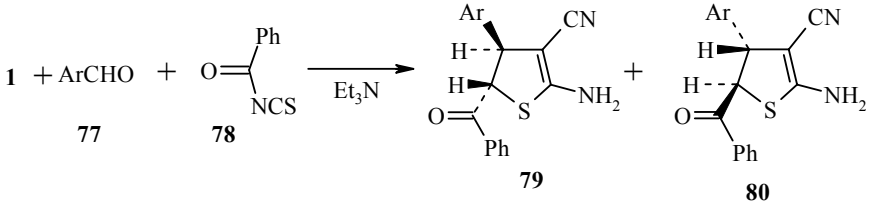
Ar = 2-ClC_6H_4

By cyclization of the cyclohexanecarbaldehyde **71** with twice the amount of the thioamide **1** it is possible to synthesize the pyridine derivative **75**, whereas the substituted thiazoles **73** are formed during the condensation of compound **1** with the aldehyde **71** and the α-halo ketones [52].



$R^1 = C_6H_{11}$; R^2 = 4-BrC_6H_4, 6,8-dibromo-2-oxochromen-3-yl;
R^3 = CN, $CONH_2$, 4-$MeOC_6H_4CO$; X = Cl, Br

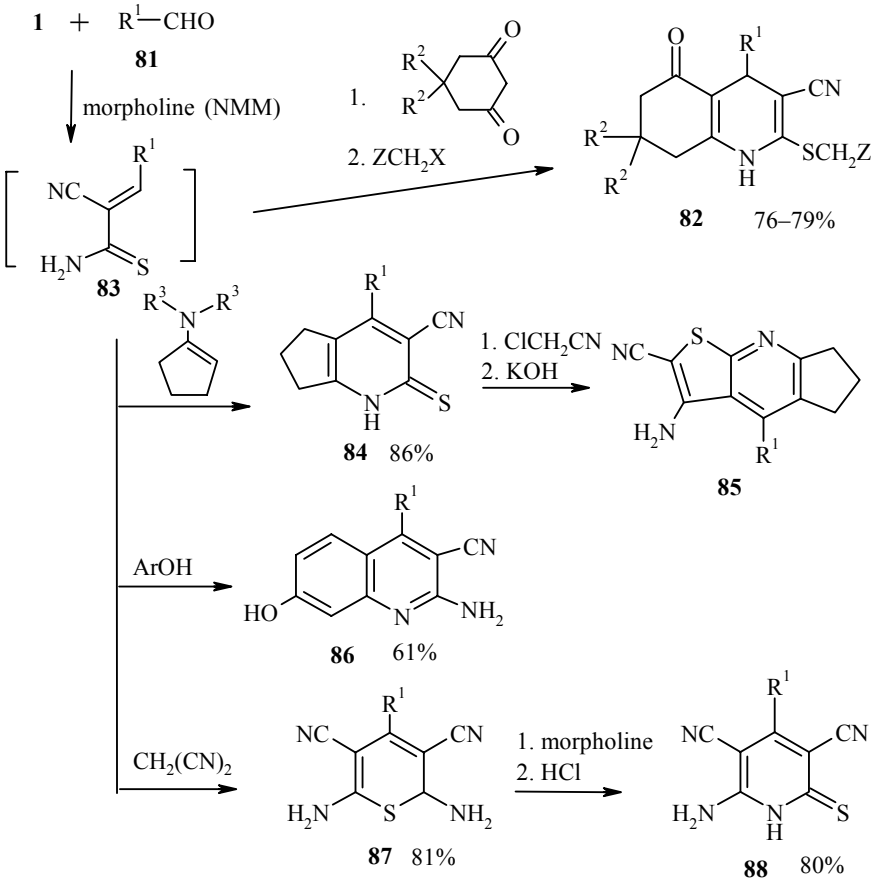
An example of a multicomponent reaction is the reaction of the cyanothioacetamide **1** with arenecarbaldehydes **77** and phenacyl isothiocyanate **78**, which leads to the production of 2-amino-4-aryl-5-benzoyl-4,5-dihydrothiophene-3-carbonitriles **79** and **80** with yields of 37-54% [53]. The data from X-ray crystallographic analysis of (4*R*,5*S*/4*S*,5*R*)-2-amino-5-benzoyl-4-(2-chlorophenyl)-4,5-dihydrothiophene-3-carbonitrile indicate that the crystal contains two types of symmetrically independent molecules **79** and **80** with extremely close geometric parameters. Thus, the reaction is stereoselective but not stereospecific.



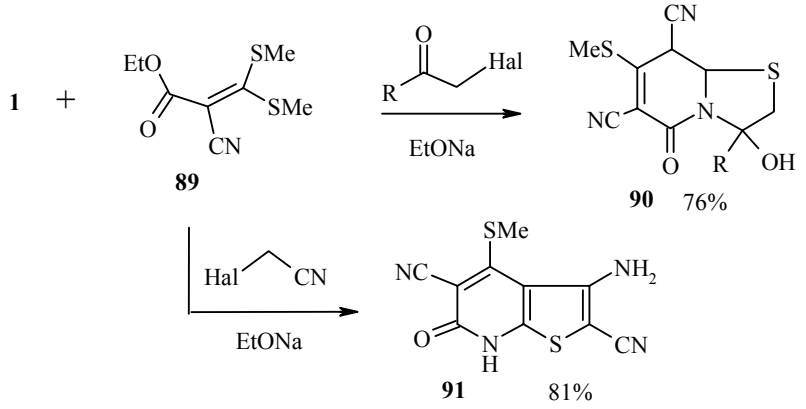
Ar = Ph, 2-ClC_6H_4, 2-furyl

It is worth mentioning the condensation of the thioamide **1** with the aldehydes **81** and with compounds containing an active methylene group (cyclohexane-1,3-dione and dimedone), enamines, and aminophenols, by means of which it is possible to synthesize derivatives of quinoline **82** and **86**, 2H-thiopyran **87**, and 3-cyanopyridine-2-thione **84** and **85** [54, 55]. It should be noted that in the presence of morpholine the 2,6-diamino-3,5-dicyano-6-(cyclohex-1-en-4-yl)-2H-thiopyran **87** undergoes recyclization to 6-amino-3,5-dicyano-1,2-dihydropyridine-2-thione **88** [54].

An original version of the three-component reaction of the thioamide **1** with ethyl 2-cyano-3,3-di(methylthio)acrylate **89** and 1,2-dielectrophilic reagents (3-coumarinyl bromomethyl ketone and chloroacetonitrile) was proposed by the authors of [56]. As a result the substituted 2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyridin-5-ones **90** and 6,7-dihydrothieno[2,3-*b*]pyridin-6-ones **91** were obtained.

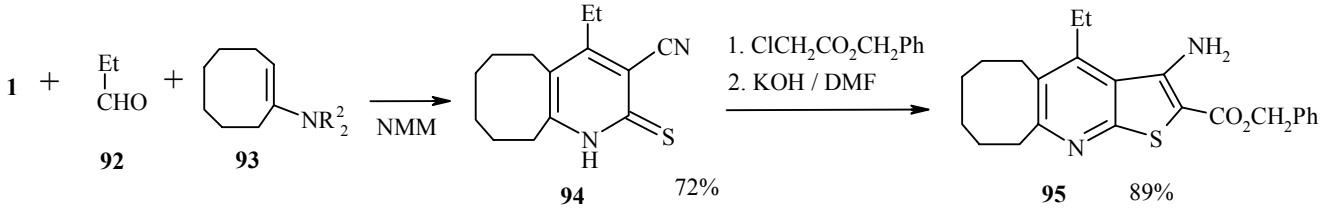


R^1 = cyclohexen-4-yl, $PhCH_2$, Me_2CHCH_2; R^2 = H, Me; $R^3 + R^3 = (CH_2)_2O(CH_2)_2$;
Z = H, CN, $CONH_2$, 4-BrC_6H_4NHCO; Ar = 3-$H_2NC_6H_4$; X = Cl, I



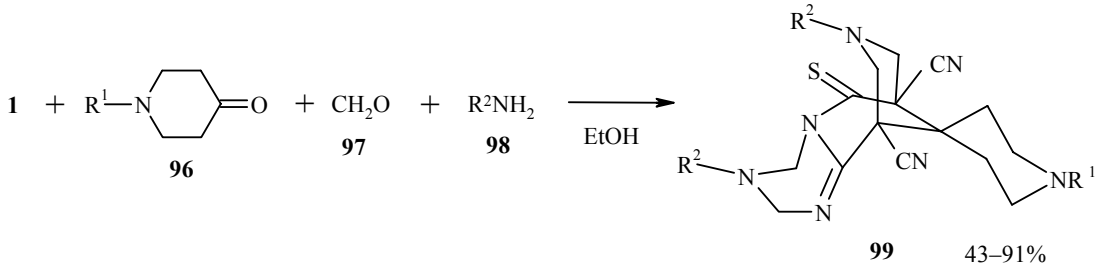
R = 3-coumarinyl; Hal = Br, Cl

The reaction of the cyanothioacetamide **1**, propanal **92**, and N-(cycloocten-1-yl)morpholine **93** provides a method for the synthesis of 3-cyano-4-ethyl-1,2,5,6,7,8,9,10-octahydrocycloocta[*b*]pyridine **94**, which is converted during annelation into the derivative of 5,6,7,8,9,10-hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridine **95** [57].



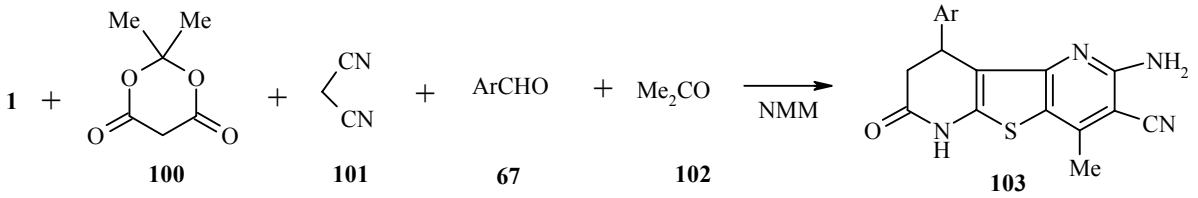
$R^2 + R^2 = (CH_2)_2O(CH_2)_2$

The aminomethylation of 6-amino-3,5-dicyano-1,4-dihydropyridine-2-thiolates with amines and formaldehyde is a successful variant of the synthesis of the derivatives of 3,5,7,11-tetraazatricyclo-[7.3.1.$0^{2,7}$]tridec-2-ene **99**, the structure of which was confirmed by X-ray crystallographic analysis [58]. These compounds, which are representatives of a previously undescribed heterosystem, were also obtained by the reaction of the thioacetamide **1**, piperidone **96**, formaldehyde **97**, and the amine **98**.



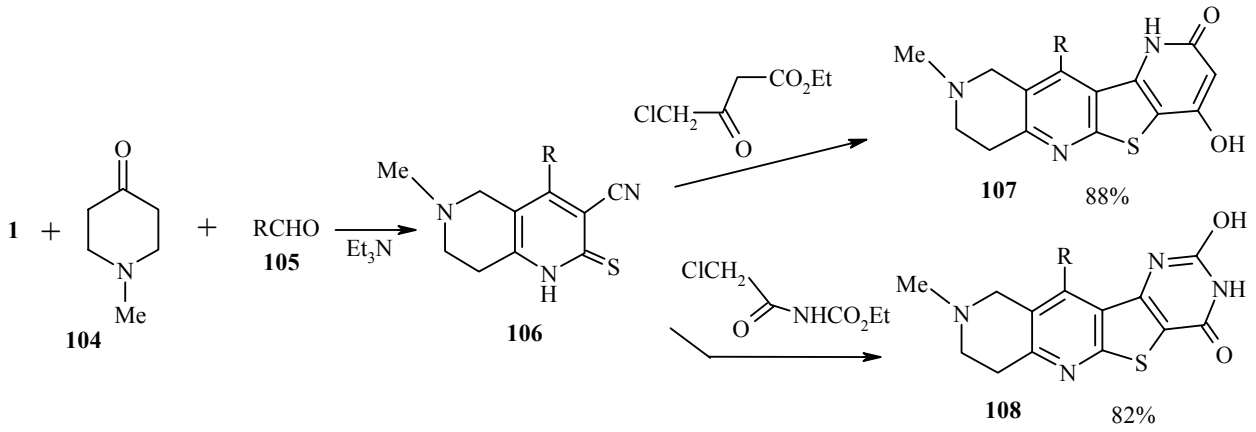
R^1 = Me, Et; R^2 = Me, $PhCH_2$

By the multicomponent reaction of the thioamide **1** with Meldrum's acid **100**, malononitrile **101**, the aldehyde **67**, and acetone **102** it was possible to synthesize the tricyclic heterosystem 6,7,8,9-tetrahydro-pyrido[2',3':4,5]thieno[2,3-*b*]pyridin-7-one **103** [59]. It should be noted that the yield of compound **103** after boiling the reaction mixture for seven days was only 7%, i.e., the method has no preparative significance. The best yield (33%) of the product **103** is observed during the condensation of 1,2,3,4-tetrahydropyridine-6-thiolate with 1,1-dicyano-2,2-dimethylethene and acetone in the presence of N-methylmorpholine. The same substance was obtained in [60] during the reaction of cyanothioacetamide, benzoyl acetate, malononitrile, arenecarb-aldehyde, and acetone.



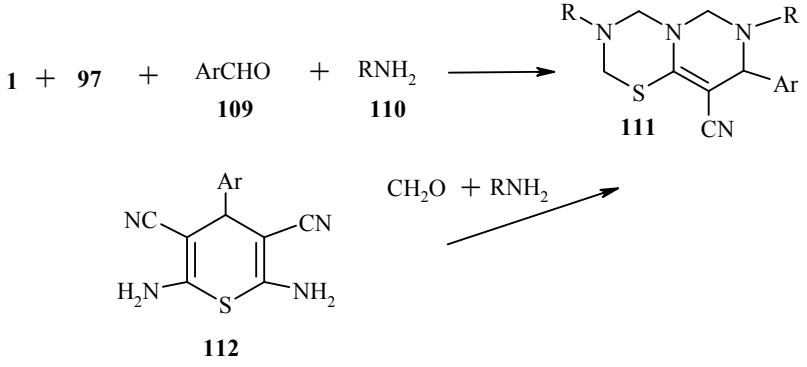
Ar = 2-ClC_6H_4

The products from the condensation of the thioacetamide **1** with N-methylpiperidin-4-one **104** and 2(3)-thiophenecarbaldehyde **105** in the presence of triethylamine and sodium thiosulfate are 3-cyano-4-R-5,6,7,8-tetrahydro[1,6]naphthiridine-2(1H)-thiones **106**, which are used as synthesis units for transformation into polyannelated naphthiridines **107** and 7,8,9,10-tetrahydropyrimido[4',5':4,5]thieno[2,3-*b*][1,6]naphthiridin-4(3H)-ones **108** [61].



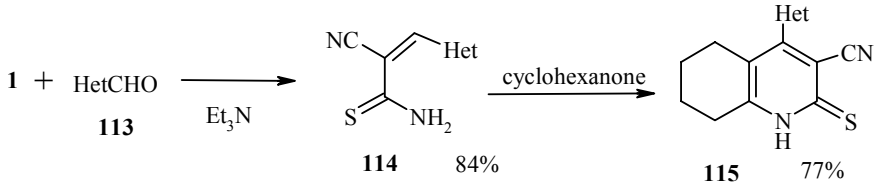
R = 2-thienyl, 3-thienyl

In [62] accessible methods were developed for the synthesis of pyrimido[4,3-*b*][1,3,5]thiadiazine derivatives **111** by the multicomponent reaction of cyanothioacetamide **1** with such acyclic reagents as formalin **97**, arenecarbaldehydes **109**, and amines **110** or by the recyclization of 4H-thiopyrans **112**. The yields of compounds **111** amount to 37-52% in the first case and 33-40% in the second.



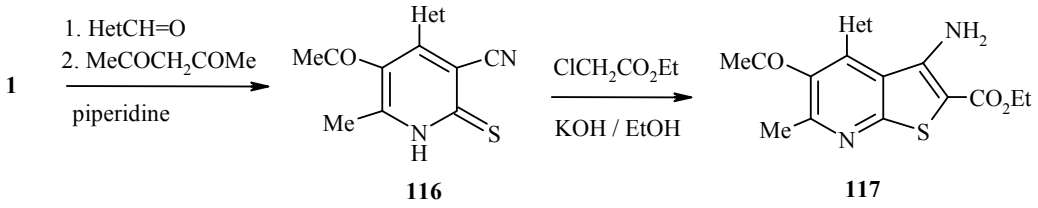
Ar = Ph, 4-MeC_6H_4, 2-ClC_6H_4

2.1.7. Multistage Methods for the Production of Heterocycles from Cyanothioacetamide and Acyclic Reagents. Currently multistage methods for the production of derivatives of 3-cyanopyridine-2-thione, accompanied by the release of intermediate acyclic compounds, are used quite rarely [63-65], since in many cases such cyclizations can be realized by a one-pot method. Nevertheless, the synthesis of 3-cyano-4-(2'-thienyl)-1,2,5,6,7,8-hexahydroquinoline-2-thione **115** by the reaction of the thioacetamide **1** with thiophene-2-carbaldehyde **113** followed by cyclization of the obtained 2-cyano-2-(2'-thienyl)methylenethioacetamide **114** with cyclohexanone was reported in [63].



Het = 2-thienyl

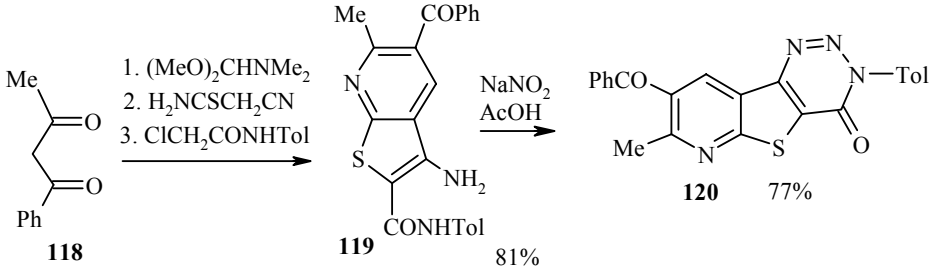
5-Acetyl-3-cyano-6-methyl-4-(3-pyridyl)pyridine-2(1H)-thione **116** was synthesized by two-stage consecutive condensation of cyanothioacetamide with 3-pyridinecarbaldehyde and acetylacetone and was used for transformation into 5-acetyl-3-amino-2-ethoxycarbonyl-6-methyl-4-(3'-pyridyl)thieno[2,3-*b*]pyridine **117** [64].



116 **117**

Het =3-pyridyl

3-Cyanopyridine-2(1H)-thiones, obtained by the two-stage reaction of benzoylacetone **118** with DMF diacetal and cyanothioacetamide, were transformed into condensed polycyclic heterosystems **119-121** [65].

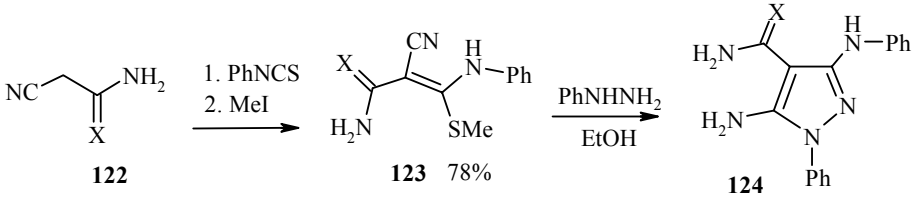


118 **119** 81% **120** 77%

Tol = 4-MeC_6H_4

121 82%

In [66] cyano(thio)acetamides **122** were used in a three-stage synthesis of pyrazoles **124**, involving successive thiocarbamoylation and alkylation of **122** with phenyl isothiocyanate and methyl iodide respectively and cyclocondensation of the isolated 3-(methylthio)-3-(phenylamino)-2-propenoyl(thio)amide **123** with phenylhydrazine.



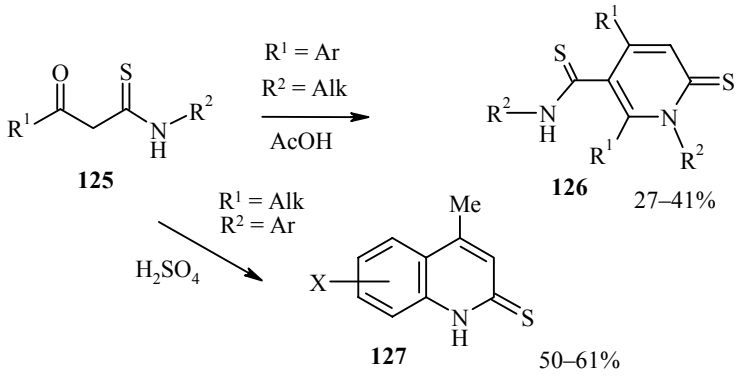
122 **123** 78% **124** 62–69%

X = S, O

2.2. Heterocyclization of 3-Oxo-3-R-propanethioamides (R = Alk, Ar)

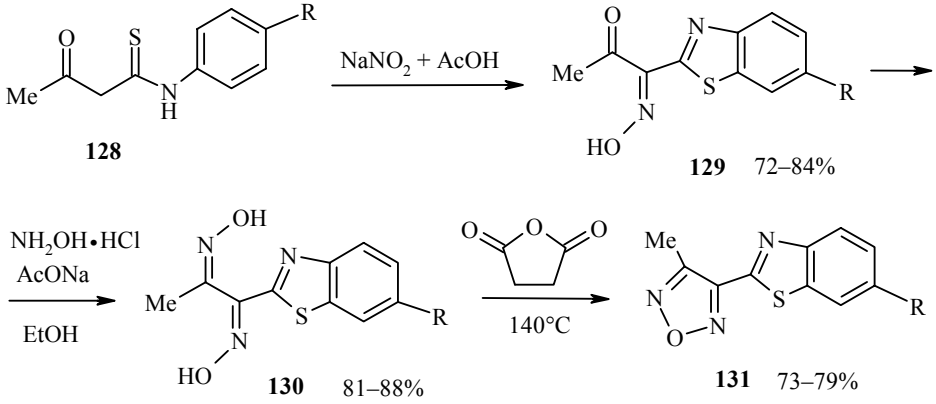
The presence of a carbonyl group in the structure of the thioacetamides not only increases their acidity in comparison with other thioacetamides [12] but also makes it possible to realize transformations involving it [3]. We note that the appearance of new methods [67] and the improvement of existing methods [3, 68-70] for the synthesis of 3-oxopropanethioamides have prompted further study of the heterocyclization of these thioamides.

2.2.1. Self-Condensation and Intramolecular Cyclization of 3-Oxopropanethioamides. During study of the cyclization of N-alkyl-3-aryl-3-oxopropanethioamides **125** with 2-amino-5-R-pyridines in acetic acid their self-condensation, accompanied by the formation of 1-alkyl-5-(N-alkylaminothiocarbonyl)-4,6-diaryl-1,2-dihydropyridine-2-thiones **126** [71, 72], was discovered. On the other hand the intramolecular cyclization of the isomeric N-aryl-3-oxobutanethioamides **125**, which takes place in concentrated sulfuric acid [72], leads to 4-methyl-6(7)-X-1,2-dihydroquinoline-2-thiones **127**.



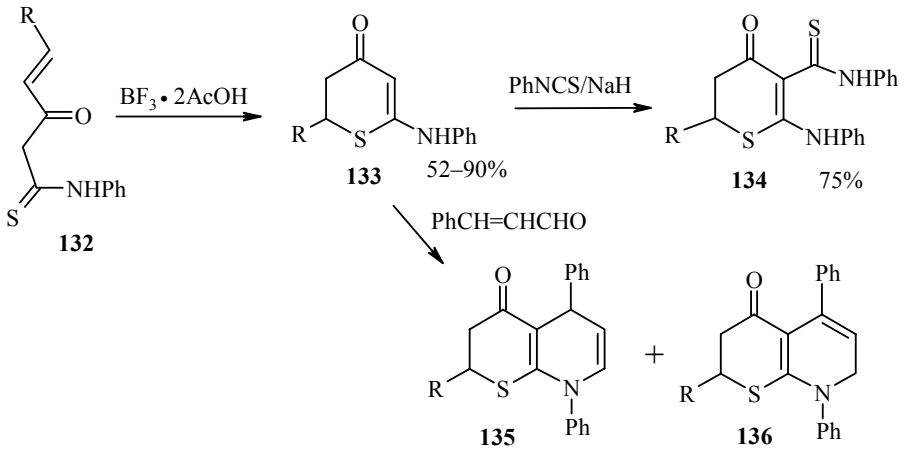
R^1 = Me, Ph, 4-ClC_6H_4; R^2 = Ph, 3-ClC_6H_4, 4-$MeOC_6H_4$, Me, Et; X = 6-H, 7-Cl, 6-MeO

An example of the dedicated use of oxidative intramolecular cyclization of N-aryl-3-oxobutanethioamides **128** to develop a new method for the production of 3-(6-R-benzothiazol-2-yl)-4-methyl-1,2,5-oxadiazoles **131** was given in [73]. It was shown that the products from nitrosation of the thioamides **128** are 1-(6-R-benzothiazol-2-yl)-1-hydroxyimino-2-propanones **129**, which are converted into 1-(6-R-benzo-thiazol-2-yl)-1,2-(dihydroxyimino)propanes **130** during oxim ation with hydroxylamine. The latter are dehydrated by the action of succinic anhydride with the formation of 1,2,5-oxadiazoles **131**.



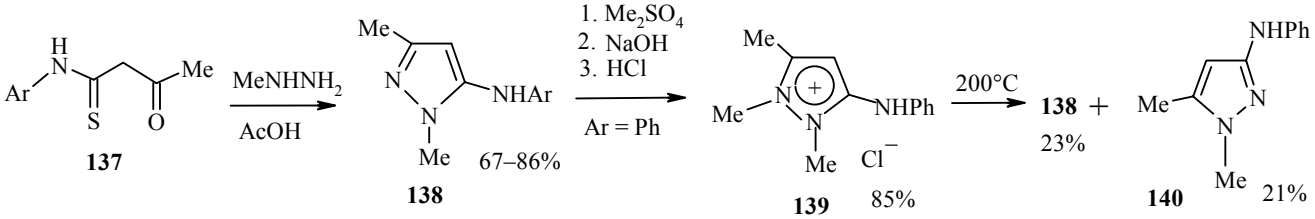
R = H, Me, OEt

Another case of successful intramolecular cyclization of 3-oxopropanethioamides was described in [68, 69]. In the presence of boron trifluoride acetate 3-alkenyl-3-oxopropanethioamides **132** are converted into 2,3-dihydro-4H-thiopyran-4-ones **133** [69], which condense nonselectively with cinnamaldehyde with the formation of a mixture of thiopyrano[3,2-*b*]pyridines (total yield 35%, **135**:**136** ratio 3:2). At the same time the C-thiocarbamoylation of thiopyran-4-ones **133** with phenyl isothiocyanate takes place selectively.



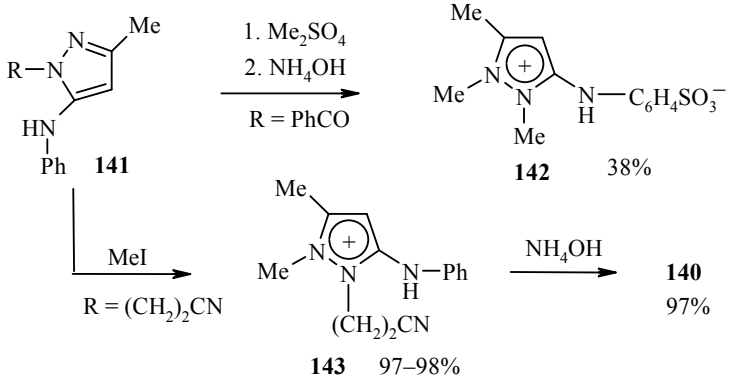
R = Ph, 2,6,6-trimethylcyclohex-2-enyl, CH_2=C(Me)$(CH_2)_3$C(Me)=CH

2.2.2. [3+2] Cyclization of 3-Oxopropanethioamides with 1,2-Dinucleophiles. The selectivity of the reaction of N-aryl-3-oxobutanethioamides **137** with an unsymmetrical 1,2-dinucleophile (methylhydrazine) was investigated in [74]. The only products of this reaction are 5-arylamino-1,3-dimethylpyrazoles **138**, from which 3-phenylamino-1,2,5-trimethyl-1H-pyrazolium chlorides **139** were synthesized. During pyrolysis of the latter 1,3-dimethyl-5-phenylaminopyrazole **138** and 1,5-dimethyl-3-phenylaminopyrazole **140** are formed in a approximately equal ratio.



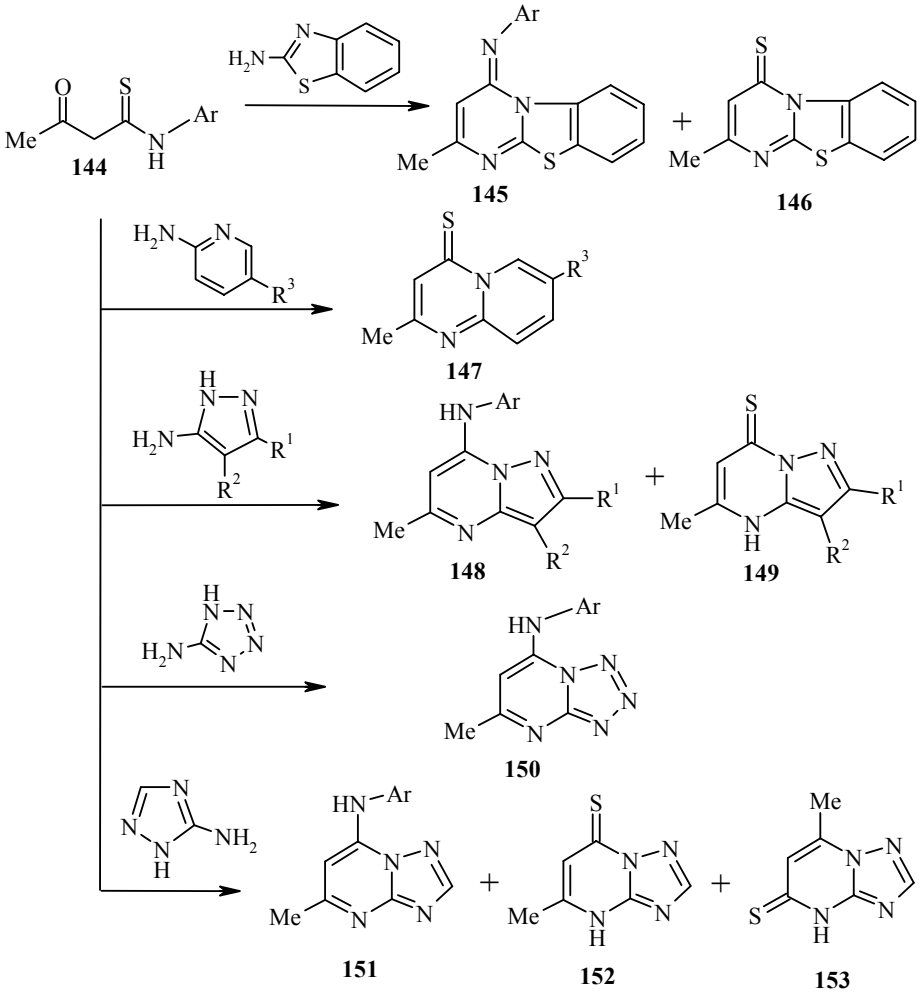
Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4

At the same time the betaine 4-(1,2,5-trimethylpyrazol-3-ylamino)benzenesulfonate **142** was unexpectedly obtained during the methylation of 1-benzoylpyrazole **141** with dimethyl sulfate [75]. In the end by improving the method of decomposition of the pyrazolium salts **143** it was possible to develop a chemoselective method for the synthesis of previously unknown 3-arylamino-1,5-dimethylpyrazoles **140** [75].



2.2.3. [3+3] Cyclocondensation of 3-Oxopropanethioamides with 1,3-Dinucleophiles. Whilst the reactions of 3-oxopropanethioamides with 1,2-dinucleophiles and 1,2- and 1,3-dielectrophilic reagents were investigated earlier, recently it was shown that they can also react with nitrogen-containing 1,3-dinucleophiles of heterocyclic [71, 76-79] and acyclic [80] structures.

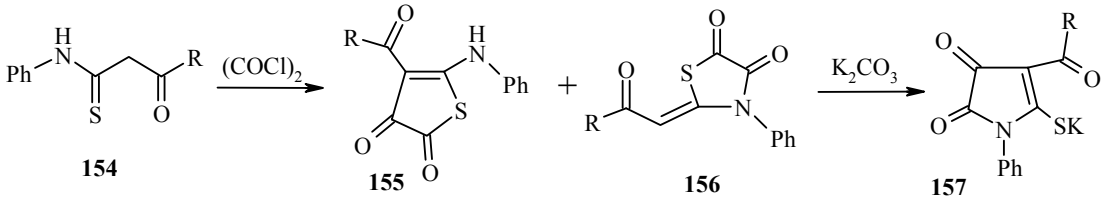
It was established that N-aryl-3-oxobutanethioamides **144** undergo cyclization with 2-amino-5-R-pyridines [71], 3-amino-5-R-1,2,4-triazoles [76], 2-amino-4-R-5-R-thiazoles [77], 5-amino-3-R^1-4-R^2-pyrazoles [78], and 5-aminotetrazole [79] to form derivatives of 4-arylaminopyrimidine **145**, **148**, **150**, and **151** and 4-pyrimidinethione **146**, **147**, **149**, **152**, and **153** [71, 76-79]. The reactions take place both in acetic acid [71, 76-79] and without a solvent [78-80]. It was found [79] that the ratio of the derivatives of 4-arylaminopyrimidine and 4-pyrimidinethione depends on three factors, i.e., the basicity of the heterocycle in the initial 2-aminoazoles(azines), the nature of the substituent in the phenyl ring of the thioamides, and the protonating ability of the solvent. Possible reasons for the chemoselectivity of the processes were considered in [79].



Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-ClC_6H_4, 3-$CF_3C_6H_4$, 4-$O_2NC_6H_4$;
R^1= H, Me; R^2 = H, CN; $R^1 + R^2$ = N=CH–CH=CH; R^3 = H, Me, Br

2.2.4. [3+3] Cyclization of 3-Oxopropanethioamides with 1,2-Dielectrophiles. During the oxalylation of N-phenyl-3-oxo-3-R-propanethioamides **154** 4-acyl-5-phenylamino-2,3-dihydrothiophene-2,3-diones **155** and 2-(2-oxo-2-R-ethylidene)-3-phenyl-1,3-thiazolidine-4,5-diones **156** are formed. In the presence of potassium

carbonate they undergo recyclization to the potassium salts of 4-acyl-5-mercapto-1-phenyl-2,3-dihydro-1H-pyrrole-2,3-dione **157** [81]. In all probability the reason for the recyclization is the lability of the S–C=O bond.

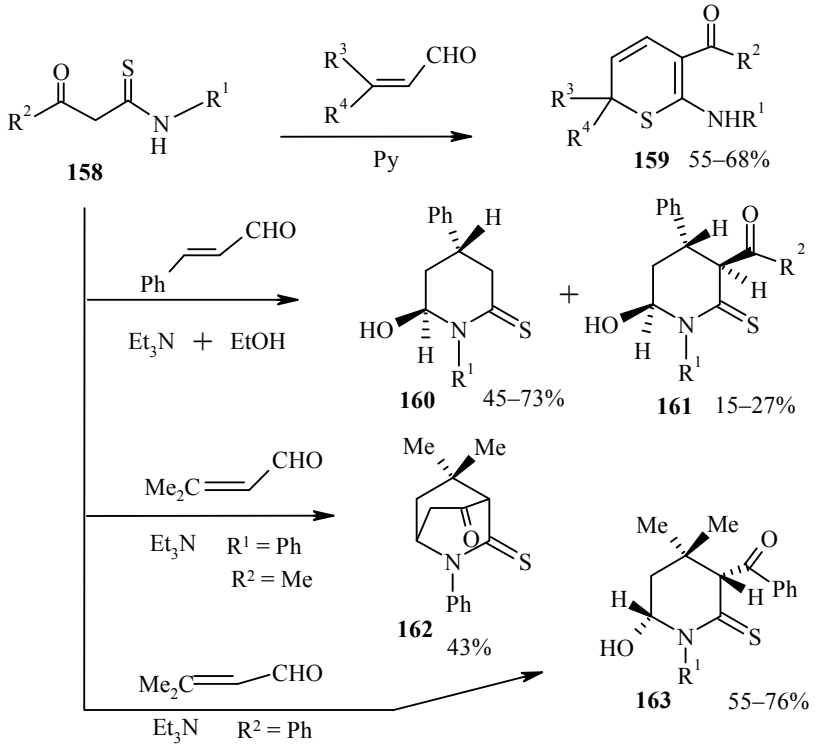


R = Me, Ph

The reaction of 3-alkenyl-3-oxopropanethioamides with ethyl chloroacetate takes place according to the Hantsch process and is accompanied by the formation of derivatives of thiazolidin-4-one [69].

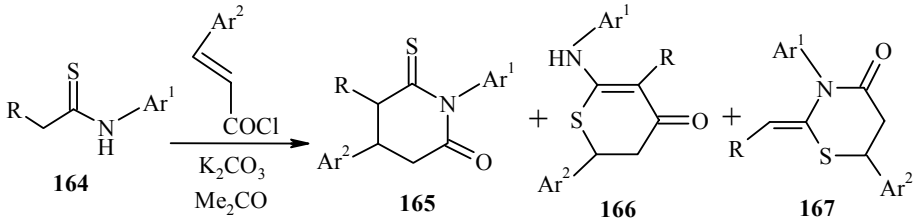
2.2.5. [3+3] Cyclization of 3-Oxopropanethioamides with 1,3-Dielectrophiles. The cyclocondensation of 3-oxopropanethioamides with derivatives of α-unsaturated aldehydes [82] and acids [83-86] usually takes place according to a [3+3] cyclization scheme with the participation of the C(2) and N(S) atoms of the thioamides. In many cases [82-84, 86] the reactions take place nonselectively, and this is explained both by the ambident characteristics of the intermediately formed anions and by some instability in the final compounds [82]. The strength of the base and the structure of the initial thioamides play no small role in the selectivity of the reaction [82-84].

During cyclization of the thioamides **158** with 3-phenylpropenal and 3,3-dimethylpropenal in the presence of triethylamine the products from the Michael reaction are formed – derivatives of piperidine-2-thione **160**, **161**, and **163** and 3-thioxo-2-azabicyclo[2.2.2]octan-5-one **162** – whereas the products from the Knoevenagel reaction 2H-thiopyrans **159** are isolated in the case of pyridine [82]. The structure of compounds **159-163** is confirmed by the data from 1D and 2D NMR spectroscopy.



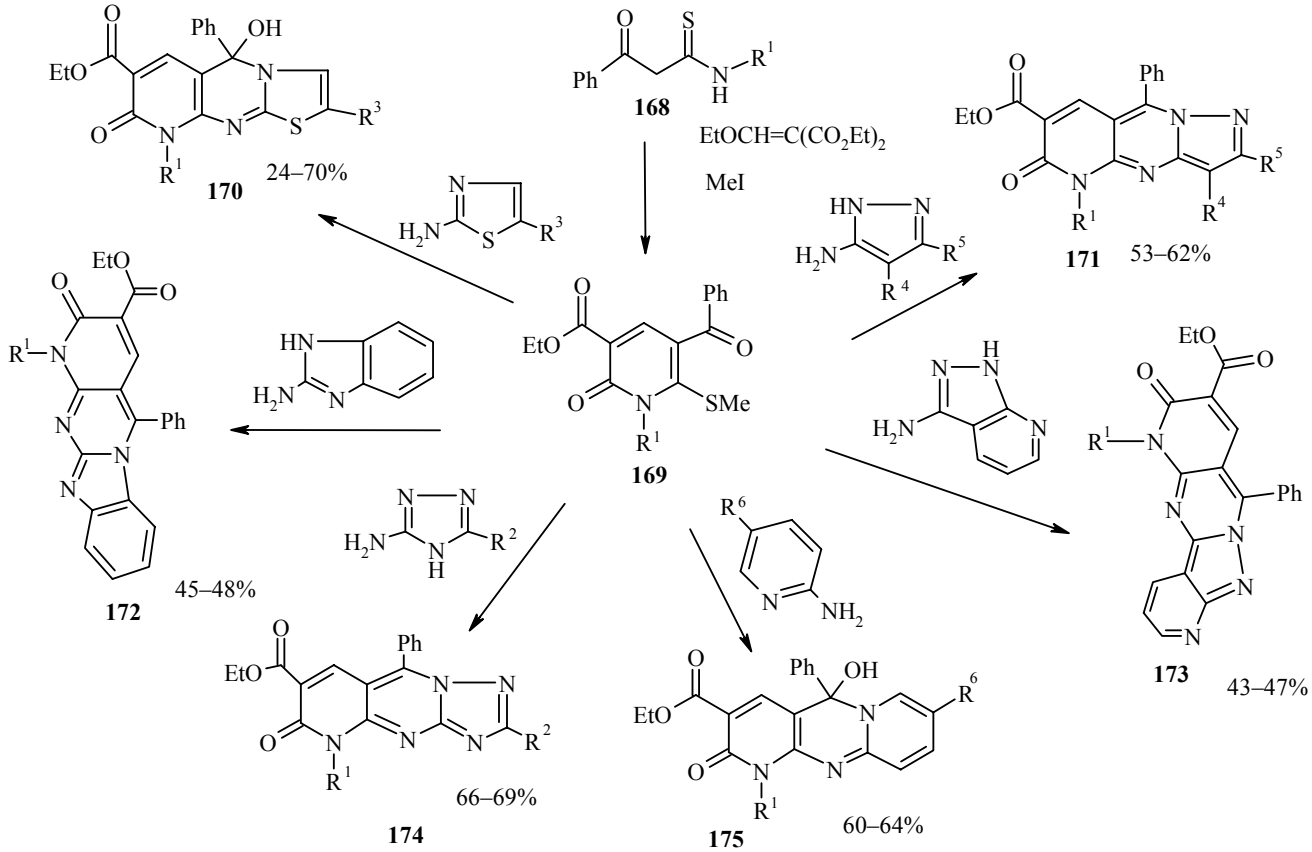
R^1 = Me, Et, Pr, Ph; R^2 = Me, Ph; R^3 = Me, Ph; R^4 = H, Me

In [83-86] the possibility of using 3-aryl-2-propenoyl chlorides for the cycloacylation of thioamides with an active methylene group **164** was demonstrated for the first time. The reaction is carried out in the presence of potassium carbonate in acetone, and in most cases it takes place nonselectively [83, 84, 86] with the formation of three groups of products **165-167**. It was established [86] that the acidity (pK_a) of the thioamides and the reactivity of the 3-aryl-2-propenoyl chlorides (the latter can be determined indirectly from the pK_a value of the corresponding 3-aryl-2-propenoic acid) are the main factors affecting the regioselectivity of this cyclization.



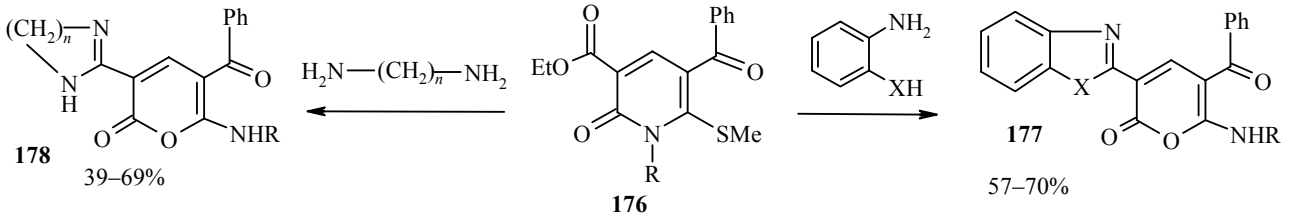
Ar^1 = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$; Ar^2 = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-ClC_6H_4, 2-thienyl; R = PhCO, MeCO, CN, $PhSO_2$

The reaction of 3-oxopropanethioamides **168** with diethyl ethoxymethylenemalonate (DEEM), the ethoxy group of which is a good nucleofuge (as follows from the reviews [17, 89]), was investigated in [87, 88]. As a result conditions were found for the preparative one-pot synthesis of 5-benzoyl-3-ethoxycarbonyl-6-methylthio-1-R-1,2-dihydropyridin-2-ones **169**, and the possibility of using them for the selective production of condensed polycyclic heterosystems, including previously undescribed pyrido[2,3-*d*]pyrimidine derivatives **170**, **171**, **173**, and **174**, was demonstrated [87, 88].



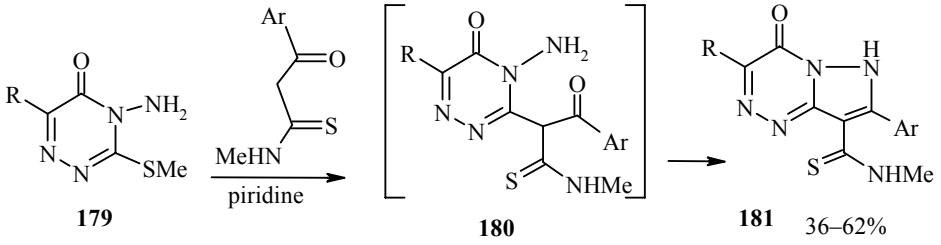
R^1 = Me, Et; R^2 = H, SMe; R^3 = H, Me; R^4 = H, CN; R^5 = H, Me; R^6 = H, Me

During an attempt to realize similar cyclizations for 1-R-1,2-dihydropyridin-2-ones **176** with 1,4- and 1,5-dinucleophiles (1,2-diaminobenzene, 1-amino-2-mercaptobenzene, 1,2-diaminoethane, 1,3-diaminopropane) it was not possible to obtain the expected 1,4-diazepines (thiazepines) – the products were derivatives of 6-(R-amino)-5-benzoyl-2H-2-pyranone **177** and **178** [90, 91]. A special feature of this recyclization is its general character and the possibility of obtaining previously unknown substituted 2H-2-pyranones.



R = Me, Et; X = S, NH; *n* = 2, 3

2.2.6. Other Cyclocondensations of 3-Oxo-3-R-propanethioamides. A quite rare case of the use of 3-oxopropanethioamides as 1,2-dipolar reagents was presented in [92]. As found, the products from [3+2] condensation of N-methyl-3-aryl-3-oxopropanethioamides with 4-amino-3-methylthio-6-R-4,5-dihydro-1,2,4-triazin- 5-ones **179** are 7-aryl-8-(methylthiocarbamoyl)-3-R-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazin-4-ones **181**. The reaction probably takes place through the intermediate **180**.

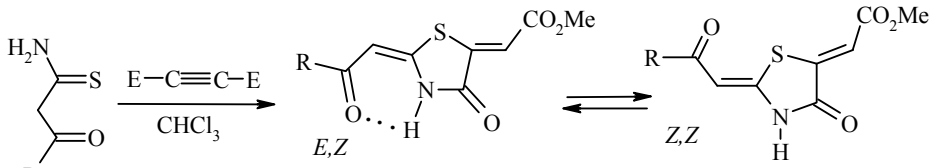


R = Me, Bu, Ph; Ar = Ph, 4-ClC_6H_4

2.3. Heterocyclization of Malono(di)thioamides

Notwithstanding the significant number of publications on the chemistry of malono(di)thioamides the literature does not contain any reviews that reveal their synthetic possibilities. To some degree the prevailing trends in the use of such thioamides are reflected in the reviews [5-8]. It should be noted that in comparison with the above-mentioned thioacetamides a special feature of the malono(di)thioamides is their ability to react as N–C–C–C–N, S–C–C–C–S, and N–C–C–C–S components.

2.3.1. [3+2] Cyclocondensation of Malono(di)thioamides with 1,2-Dielectrophiles. The cyclization of thioamides **182** with acetylenedicarboxylic ester and investigation of the *E*,*Z*-isomerism in the reaction products **183** were described in [93, 94]. New derivatives of thiazolidin-4-one were obtained, and it was shown that they exist as *E*,*Z*- (**183A)** and *Z*,*Z*- (1**83B)** isomers [93]. It was found that the *E*,*Z*-isomers are formed first and are then transformed into the *Z*,*Z*-compounds. Isomerization occurs as a result of rotation of part of the molecule about the exocyclic double bond C=C(2), which is explained by the presence of the enamine fragment in the structures of **183**. All compounds **183A** undergo isomerization, but as a result of the low inversion barrier it is not always possible to separate the thiazolidin-4-ones **183A** and **183B**.

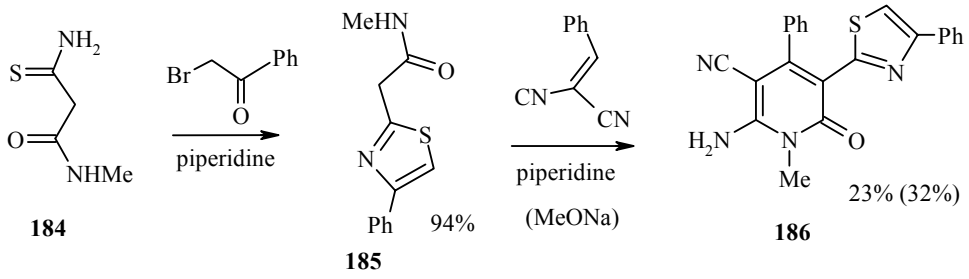


182 **183A** 46–83% **183B**

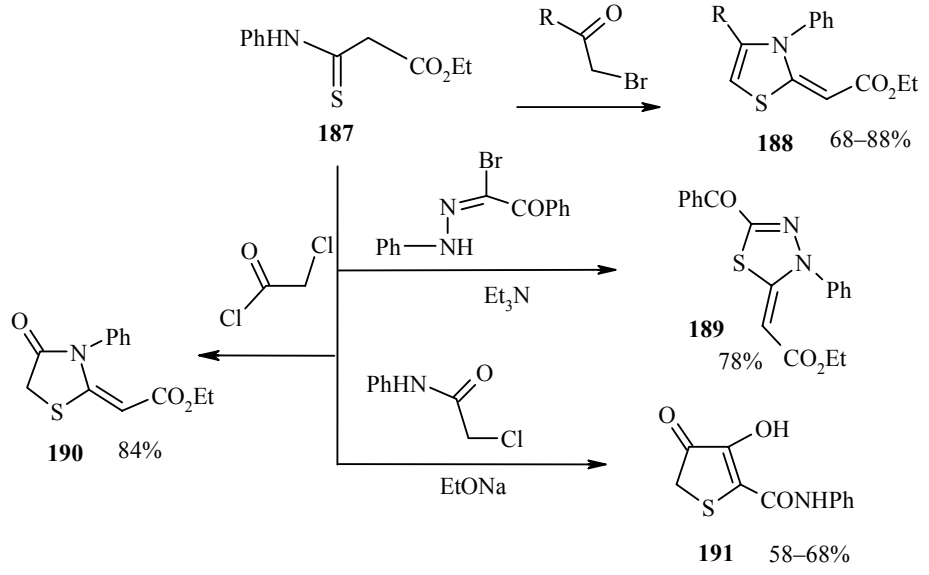
E = CO_2Me; R = OEt, MeNH, NMe_2, PhNH, $PhCH_2NH$, 2,6-$Cl_2C_6H_3NH$, 2,4,6-$Cl_3C_6H_2NH$, 2-MeC_6H_4NH, $O(CH_2)_4N$, 2-$MeOC_6H_4NH$, 3-$MeOC_6H_4NH$, 4-$MeOC_6H_4NH$, $C_6H_{11}NH$, 2-FC_6H_4NH, 4-FC_6H_4NH

It was established that electron-donating substituents in the aryl ring stabilize the *E,Z*-form while electron-withdrawing substituents stabilize the *Z,Z*-form [94]. The ratio of the *Z,Z*/*E,Z*-configurations is also affected by steric factors; in the case of R = 2,6-$Cl_2C_6H_3NH$, 2,4,6-$Cl_3C_6H_2NH$, and $C_6H_{11}NH$ the equilibrium is displaced almost completely toward the *Z,Z*-isomer. The nature of the solvent also affects the ratio of the *Z,Z*- and *E,Z*-forms; the percentage of the *E,Z*-form is increased in chloroform, and the percentage of the *Z,Z*-form in DMSO. This fact indicates cleavage of the intramolecular hydrogen bond NH···C=O in **183A** and, probably, the formation of intermolecular hydrogen bonds between the polar solvent (DMSO) and the thiazolidin-4-one **183B**.

Malonothiodiamides have found use in Hantsch syntheses [95, 96]. Thus, the reaction of N-methylmalonothiodiamide **184** with α-bromoacetophenone leads to the formation of 2-(N-methylaminocarbonyl)methyl-4-phenylthiazole **185** [95]. The latter enters into reaction with benzylidenemalononitrile, resulting in the isolation of 2-amino-3-cyano-1-methyl-6-oxo-4-phenyl-5-(4-phenyl-1,3-thiazol-2-yl)-1,6-dihydropyridine **186**.



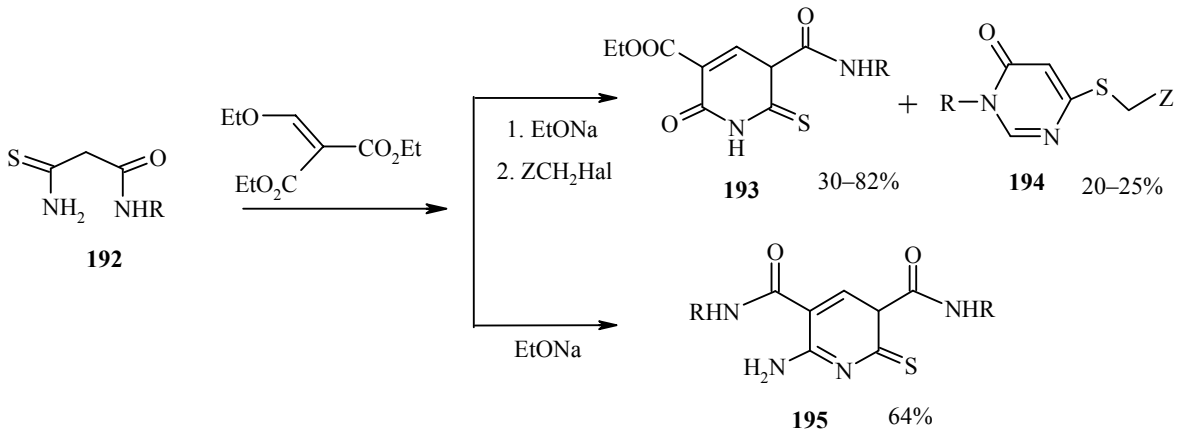
184 **185** 94% 23% (32%) **186**



187 **188** 68–88% **189** 78% **190** 84% **191** 58–68%

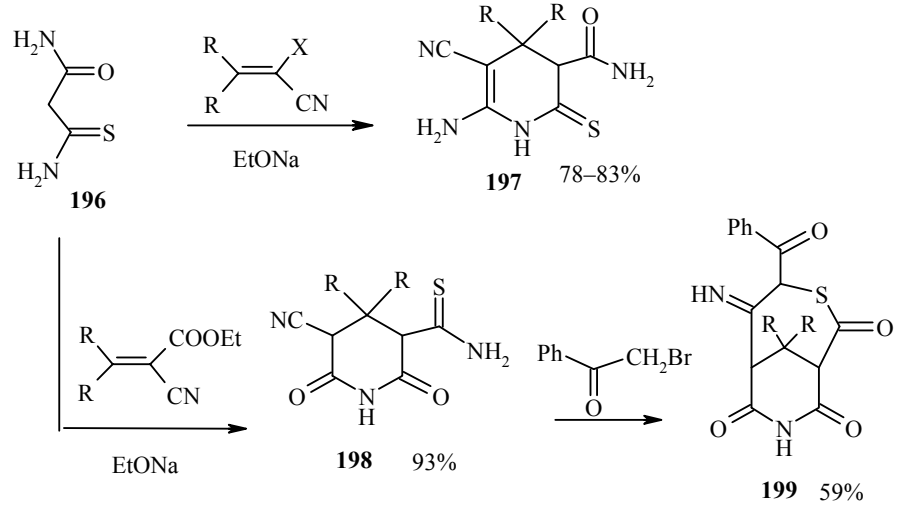
The products from the condensation of O-ethyl-N-arylmalonothioamide **187** [96] with α-halo ketones, (phenylhydrazono)bromomethyl phenyl ketone, N-aryl-2-chloroacetamide, and chloroacetyl chloride are derivatives of thiazoline **188**, 1,3,4-thiadiazoline **189**, thiazolidin-4-one **190**, and thiophen-4-one **191** respectively.

2.3.2. Cyclocondensation of Malono(di)thioamides with 1,3-Dielectrophilic Reagents. The reaction of the malonothioamides **192** with DEEM takes place in three directions [97]. In the case of an equimolar ratio of the initial reagents condensation occurs according to [3+3] and [5+1] cyclization schemes with the formation of 1,2,5,6-tetrahydro-6-thioxopyridin-2-ones **193** (the predominant products) and 1-R-5,6-dihydro-pyrimidin-6-ones **194** respectively. With a twofold excess of the malonothioamides the DEEM reacts by "transfer" of the methine fragment, as a result of which the 6-amino-2,3-dihydropyridine-2-thiones **195** are obtained selectively by a [3+2+1] cyclization scheme.



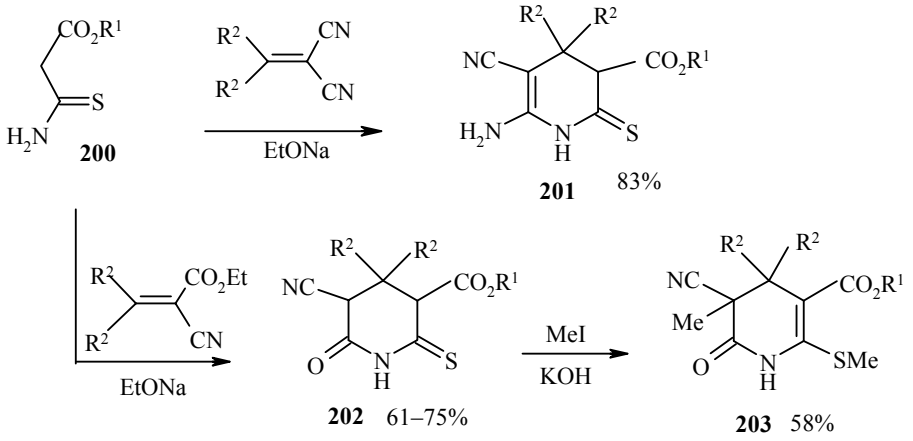
R = H, Ph, 2-$MeOC_6H_4$, 2-MeC_6H_4, 3-MeC_6H_4; Z = Me, $(CH_2)_3Me$, $CH{=}CH_2$; Hal = Br

The reaction of malonothiodiamide **196** with 2-cyano-2-(cyclohexylidene)thioacetamide (cyclohexylidenemalononitrile) and cyanocyclohexylideneacetic ester in the presence of sodium ethoxide leads to 6-amino-3-carbamoyl-5-cyano-4-spirocyclohexane-3,4-dihydropyridine-2-thione **197** and 5-cyano-4-spirocyclohexane-3-thiocarbamoylpiperidine-2,6-dione **198** respectively [98]. In reaction with α-bromoacetophenone the last compound is converted into a hetero framework compound – 4-benzoyl-5-imino-10-spirocyclohexane-8-aza-3-thiabicyclo[1,3,4]decane-2,7,9-trione **199**.



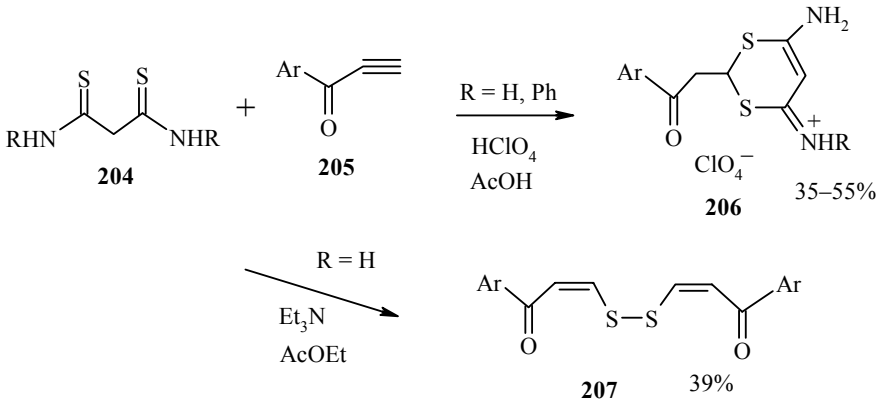
R + R = $(CH_2)_5$; X = CN, $C(S)NH_2$

The same authors investigated the condensation of (alkoxycarbonyl)thioacetamides **200** with 2-cyclohexylidenemalononitrile and methyl 2-cyano-2-cyclohexylideneacetate [99]. In both cases cyclization takes place with the participation of the N and C(2) atoms of the substrates **200** and the formation of derivatives of 2H-pyridine-2-thiones **201** and **202**. Compounds **202** are alkylated in an alkaline medium to 3,4-dihydropyridin-2-ones **203**, indicating high acidity for the methine group C(5) of compounds **202**.



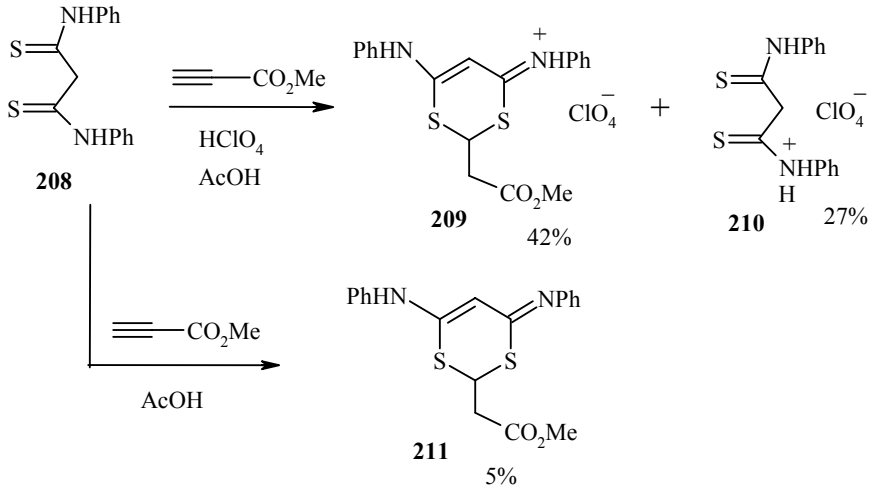
R^1 = Me, Et; $R^2 + R^2 = (CH_2)_5$

2.3.3. [5+1] Cyclocondensation of Malonodithioamides with Acetylene Derivatives. A cycle of investigations of malonothioamides with acetylene derivatives was undertaken in [100-105]. It was shown [100-103] that the products from the reaction of malonodithioamides **204** with aroylacetylenes **205** in the presence of an equimolar amount of $HClO_4$ are 2-acylmethyl-4-amino-1,3-dithiin-6-R-iminium perchlorates **206**. With the presence of triethylamine in the reaction solution cyclization of the acetylenes with malonodithioamides was not observed [104], and the only product was *cis*-(benzoylvinyl) disulfide **207**.



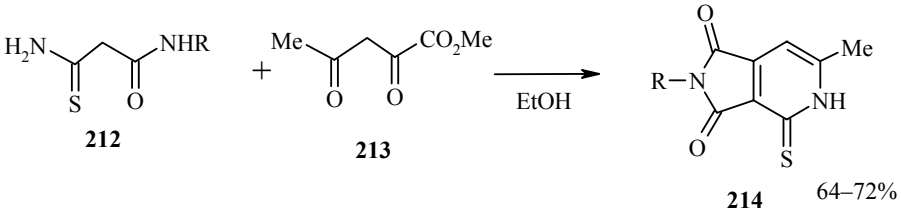
R = H, Ph; Ar = Ph, 2-thienyl

Malonodithioanilide **208** reacts with methyl propiolate in the presence of an excess of $HClO_4$ to form 4-phenylamino-2-methoxycarbonylmethyl-1,3-dithiin-6-phenyliminium **209** and malonodithiodianilide **210** perchlorates [105]. It was noticed that the yield of the 1,3-dithiin **211** during the reaction without the perchloric acid amounted to only 5%.



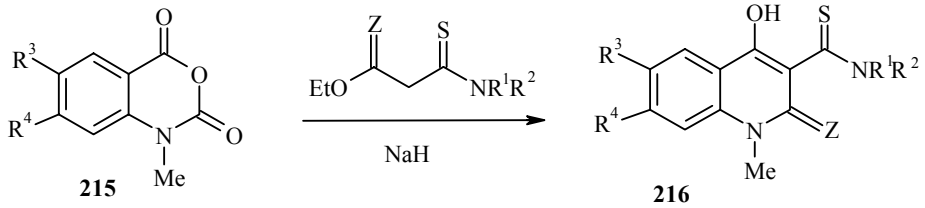
On the whole it can be concluded that [5+1] cyclization of malonodithioamides in an acidic medium is realized with the participation of the S,S atoms (on account probably of the protonation of the N,N atoms) [100-103, 105], whereas in a basic medium it takes place at the C, N and N,N atoms [97].

2.3.4. Cyclization of Malonodithioamides with 1,2,4-Trielectrophiles. An example of a nontrivial approach to the synthesis of heterocycles from malonothioamides is found in [106]. The authors used the presence of three nucleophilic centers in the malonothioamides **212** and three electrophilic centers in methyl acetylpyruvate **213** for the single-stage production of 4-thioxopyrrolo[3,4-*c*]pyridines **214**.



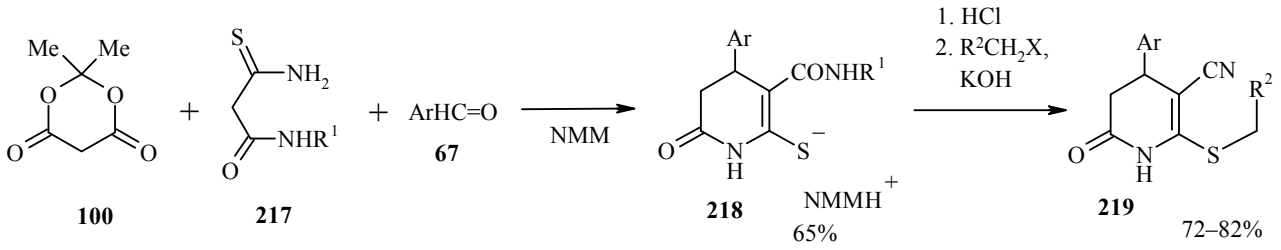
R = H, Me, Bu, 4-$MeOC_6H_4$, 2,4-$Me_2C_6H_3$

2.3.5. Recyclizations with the Participation of Malono(di)thioamides. Unlike heterocyclizations little attention has been paid to recyclizations [107, 108]. It was found that 1-methyl-1,4-dihydro-2H-3,1-benzoxazine-2,4-diones **215** are transformed by the action of ethoxy(thio)carbonylthioacetamides into 3-thiocarbamoylquinolines **216** [107].



Z = S, O; R^1= Ph; R^2 = Me; R^3 = H, Me, MeS, MeO, Cl, Br; R^4 = H, Cl

It is also possible to assign the condensations of Meldrum's acid **100** with N-(4-bromophenyl)-1-amino-1-thiomalonamide **217** and 2-chlorobenzaldehyde **67** to recyclizations [108]. Its products 1,2,3,4-tetrahydropyridines **218** are converted regioselectively into the S-alkyl derivatives **219** in an alkaline medium.

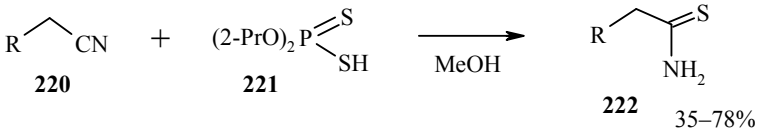


Ar = 2-ClC_6H_4; R^1 = 4-BrC_6H_4; R^2 = H, $CH_2CONHCH_2Ph$; X = Cl, I

2.4. Heterocyclizations of Phosphonylthioacetamides

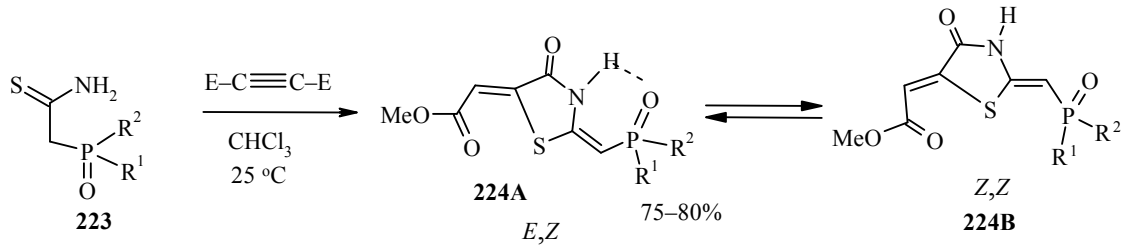
Unlike the thioamides with an active methylene group examined above, 2-phosphonylthioacetamides are less accessible, and their transformations have been studied little. At the same time, however, the phosphorus-containing compounds exhibit certain types of biological activity [109-111]. The recently developed new preparative method for the synthesis of 2-phosphonylthioacetamides [112] has therefore prompted development of the chemistry of these compounds [113, 114].

The new method for the production of 2-phosphonylthioacetamides **222** is based on the reaction of nitriles **220** with O,O-diisopropyl dithiophosphate **221**, and this made it possible to sulfohydrogenate the nitriles **220** readily and effectively to the thioamides **222** [112].



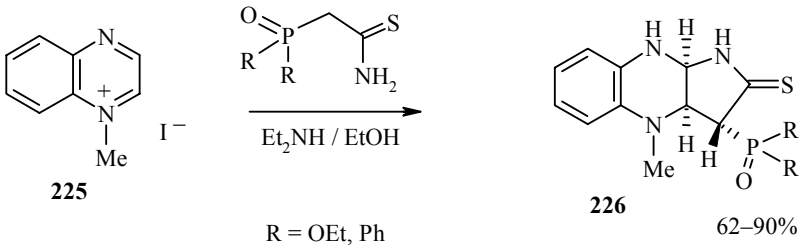
R = $(EtO)_2PO$, Me(2-Pr)PO, Ph(EtO)PO, Ph_2PO, $Ph_3P^+Cl^-$, $(EtO)_2P(S)S$–

The cyclization of phosphonyl-containing compounds **223** with acetylenedicarboxylic ester [113] proved to be a convenient regiospecific method for the synthesis of phosphorylated thiazolidin-4-ones **224A**, the structure of which was confirmed by X-ray crystallographic analysis. In solution the latter undergo polymerization to *Z,Z*-thiazolidin-4-ones **224B** probably through the imine configuration. The position of the equilibrium depends on the polarity of the solvent – in the transition from CCl_4 to DMSO-d_6 (i.e., with increase of polarity) the content of the *Z,Z*-form **224B** increases, due probably to cleavage of the NH···O=P hydrogen bonds on account of solvation of the thiazolidin-4-ones **224A** by the solvent. According to quantum-chemical calculations using the B3Pw91/6-31G* basis set, the *E,Z*-structure is somewhat more favorable than *Z,Z* for N(3)-unsubstituted thiazolidin-4-ones.



R^1, R^2 = OEt, Ph; E = CO_2Me

To this day the paper [114] remains the only example of the use of 2-phosphonylthioacetamides as N,C,C components. Thus, their heterocyclization with methylquinoxalinium iodide **225** takes place stereoselectively with the formation of thiolactams – *cis*-1,3,3a,4,9,9a-hexahydro-2H-pyrrolo[2,3-*b*]quinoxaline-2-thiones **226**.



225 **226**

2.5. Heterocyclization of 2-Alkyl(aryl)sulfonylthioacetamides

2-Alkyl(aryl)sulfonylthioacetamides are characterized by high strength for the SO_2–CH_2 bond, a multistage character of their production process [115], the chemical inertness of the sulfonyl group, and low acidity [12]. The described thioamides have therefore only been used as N,C,S components in the synthesis of thiazoles by the Hantsch method [116, 117]. The latter were used in the creation of combinatorial libraries of compounds – inhibitors of the enzymes CDK5 [116] and PARP-1 [117].

* *
*

We have, thus, analyzed and classified published data on the heterocyclization of thioamides containing an active methylene group. The presented information indicates that such thioamides are valuable starting reagents for the selective synthesis of five- and six-membered mono- and polycyclic heterosystems with various structures. Particularly promising compounds for experimental investigations are the 2-cyanothioacetamides, 3-oxopropanethioamides, and malono(di)thioamides, and this is due to their availability and to the high reactivity of their methylene group.

The data that we have analyzed make it possible to conclude that dynamic developments in the chemistry of these thioamides will continue in the short term on the basis both of new approaches and of new reactions (e.g., one-pot and "green" syntheses, the production of new heterosystems, recyclization transformations).

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