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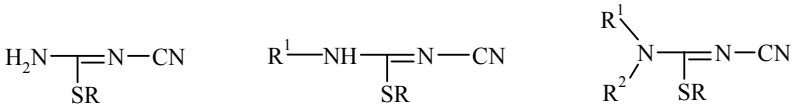
SYNTHESIS OF AZOLES AND AZINES AND THEIR CONDENSED DERIVATIVES BASED ON N-CYANO-S-ALKYLTHIOUREAS (REVIEW)

D. D. Nekrasov

Methods for the production of N-cyano-S-alkylisothioureas and their use in the synthesis of azaheterocyclic compounds are reviewed.

Keywords: azines, azoles, N-cyanoisothioureas, biological activity.

N-Cyanoisothiourea **1** and its N'-monosubstituted derivatives (**2**) and N',N'-disubstituted derivatives **3** have found widespread use in heterocyclic synthesis. This is due to the presence of cyano, imino, amino, and mercapto groups, which are capable of entering into cyclization with various electrophilic, nucleophilic, and dienophilic reagents, in the molecules of these compounds.



1 **2** **3**

On account of the presence of the =N–CN fragment in compounds **1-3** they resemble N-cyanoimines in their chemical properties [1]. However, the additional presence of the amino group and the readily leaving alkylthiolate fragment significantly extends their synthetic potential. The isothioureas **1-3** often act as intermediate compounds in synthesis, and authors therefore do not always postulate their formation.

The use of cyanoisothioureas **1-3** for the production of heterocyclic compounds in generalized form has not previously been discussed.

1. SYNTHESIS OF N-CYANO-S-ALKYLISOTHIOUREAS

The first N-cyanoisothioureas were described in 1904. They were produced by the reaction of the sodium salts of N-cyanoisothioureas **4** with alkyl iodides [2]. The salts **4** were synthesized by the reaction of isothiocyanates with cyanamide in the presence of sodium ethoxide [3].

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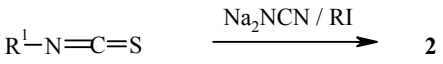
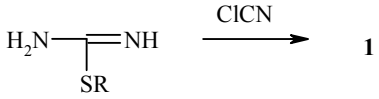
Sometimes cyanoisothioureas **2** are produced directly during the reaction of isothiocyanate, sodium cyanamide, and alkyl iodide in anhydrous alcohol [4]. The stage involving production of the isothiourea salt is not present in this modification of the method. The yields of the final products are nevertheless lower.



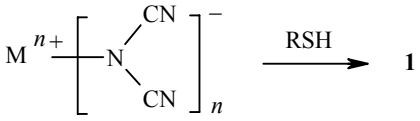
R = Me, Et, Pr, $PhCH_2$; R^1 = Me, Et, All, Ph

Cyanoisothioureas **1** are formed with preparative yields when the hydrochlorides of S-alkylisothioureas are treated with cyanogen chloride in the presence of triethylamine [5].



R = Me, Et, Pr

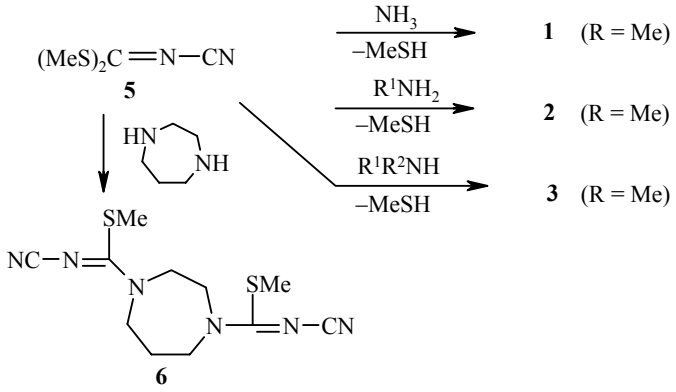
Analogous N-cyanoisothioureas **1** can be obtained by reaction of the metal derivatives of dicyanamide with thiols 50-70°C in an autoclave for 15 h [6].



R = Me, Et, Pr; M = Na, Zn; *n* = 1, 2

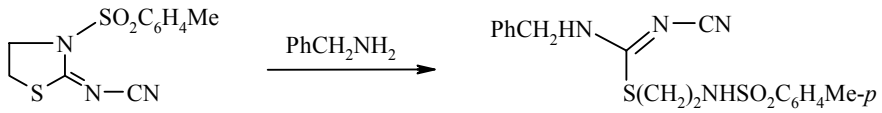
The method for the production of N-cyanoisothiourea **1** based on the reaction of S,S′-dimethyl N-cyanoimidodithioate (**5**) with ammonia has found the widest use [7].

By using various mono- or dialkylamines in this reaction it is possible to obtain good yields of the corresponding isothioureas **2** and **3** [8-10]. The reaction with aliphatic amines takes place at room temperature, while the reaction with aromatic amines takes place on heating in alcohol. With compound **5** 1,4-diazacycloheptane forms the corresponding diisothiourea **6** [9].



R^1 = Alk, Ar, Het; $R^1 + R^2 = –(CH_2)_2O–(CH_2)_2–$, $–(CH_2)_2–NH–(CH_2)_2–$

A method for the production of N-cyanoisothiourea **7** based on opening of 2-cyano-3-tosyl-iminothiazolidine with benzylamine has been patented. The process takes place when the reagents are boiled for 5 h. The product yield amounts to 86% [11].

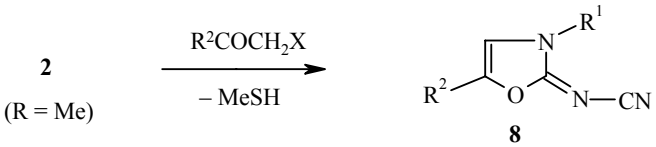


7

Derivatives of 2-cyanoiminothiazolidine can be regarded as cyclic analogs of N-cyano-S-alkylisothioureas. A separate review has been devoted to their synthesis and application [12], and we will not therefore dwell on them in detail.

2. SYNTHESIS OF AZOLES

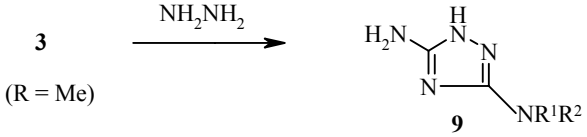
N-Cyano-S-methylisothioureas **2** react with ω-bromoacetophenone or chloroacetone to form derivatives of 2-cyanoimino-3H-oxazole **8** with yields of 15-58% [13].



8

R^1 = Ph , CH_2=CH–CH_2; R^2 = Ph, Me; X = Cl, Br

With hydrazine N-cyanoisothioureas **3** form 3-amino-substituted 5-amino-1,2,4-triazoles **9** [14].

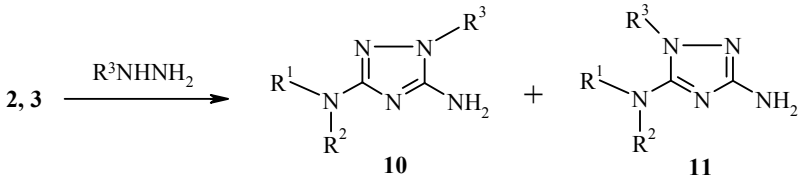


9

$R^1 = R^2$ = Et, Oct, R^1+R^2 = –$(CH_2)_2$–O–$(CH_2)_2$–

N-Cyanoisothioureas **2** [R = $EtCO_2CH_2$ and R^1 = (5-chloropyrimidin-2-yl)hydroxyethyl] react similarly with the formation of the respective triazoles **9** [14, 15].

With alkylhydrazines the cyanoisothioureas **2** and **3** form the isomeric triazoles **10** and **11** [16-18].

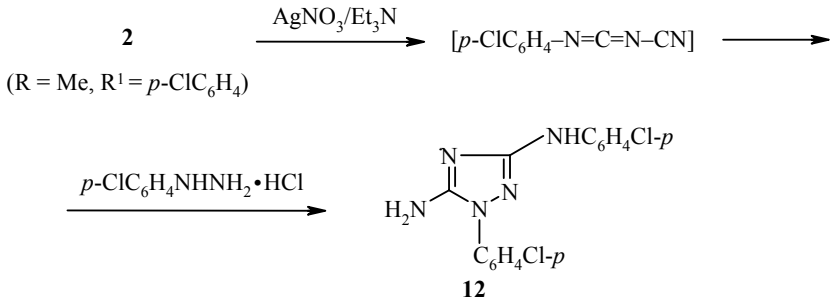


10 **11**

R^1 = Alk, Ar; R^2 = H, Alk, Ar; R^3 = Me, Bz

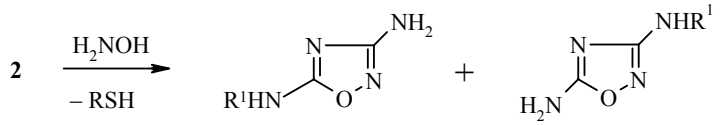
The formation of the triazole **10** and **11** depends on the substituents both in the isothioureas **2** and **3** and in the hydrazines. It is possible to change the direction of the reaction toward one or the other triazole by varying the substituents in the reagents.

The reaction of isothiourea **2** with silver nitrate in the presence of triethylamine in DMF for 2 h gives *p*-chlorophenyl diazocyanide, which is heated without isolation with *p*-chlorophenylhydrazine hydrochloride to form the triazole **12** [19].



12

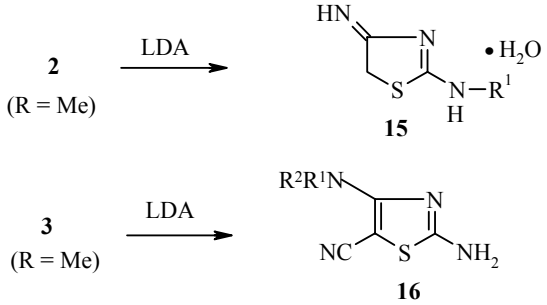
The reaction of N-cyano-S-alkylisothioureas (**2**) with hydroxylamine leads to a mixture of isomeric 3,5-diamino-1,2,4-oxadiazoles **13** and **14**. The formation of one or other isomer depends on the electronic effect of the substituents in the isothiourea [14, 20].



13 **14**

The oxadiazole **13** [R' = 3-(3-piperidinomethylphenoxy)propyl] has antiulcer activity, surpassing the medical product *cimetidine* [21].

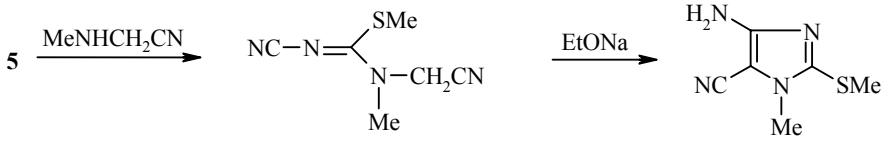
4-Imino-4,5-dihydrothiazoles **15** are formed during treatment of N-cyanoisothioureas **2** (R^1 = Ph, *c*-Hex) with lithium diisopropylamide (THF, 30°C, 20 min, argon atmosphere). 2-Amino-5-cyanothiazoles **16** were obtained similarly from compounds **3** (NR^1R^2 = morpholino, piperidino) [22].



15 **16**

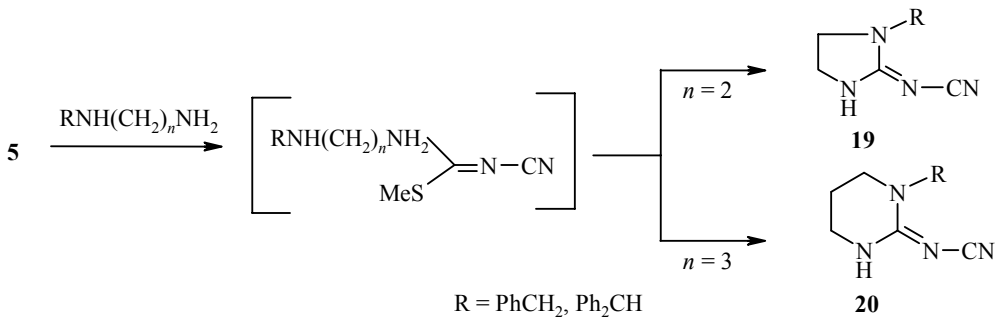
LDA – lithium diisopropylamide

With methylaminoacetonitrile the N-cyanimidodithiocarbonate **5** forms the isothiourea **17**, which undergoes cyclization to 4-amino-5-cyano-1-methyl-2-methylthioimidazole **18** under the action of sodium ethoxide [23].

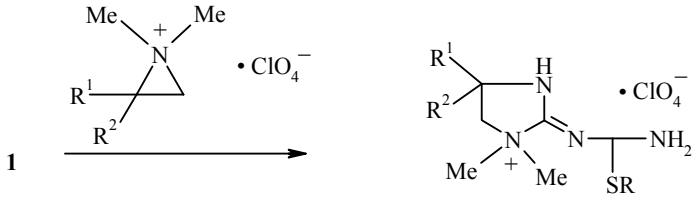


17 **18**

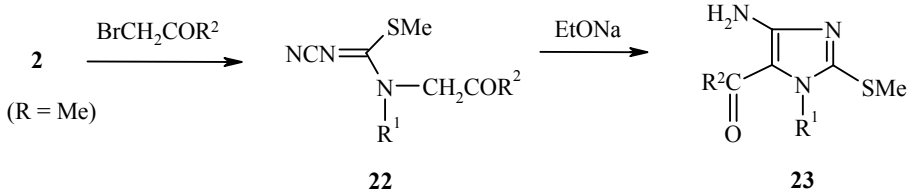
In the case of aliphatic diamines the reaction does not stop at the formation of the intermediate isothioureas, since the second amino group then undergoes aminolysis, leading to good yields of 2-cyanoiminoimidazolidine **19** or 2-cyanoimino-1,3-diazine **20** [24].



2-Isothioureido-1,1-dimethyl-5,5-pentamethyleneimidazolinium perchlorate (**21**) is obtained by boiling N-cyano-S-alkylisothioureas **1** with 1,1-dimethyl-2,2-pentamethyleneaziridinium perchlorate in dioxane for 3-5 h [25].

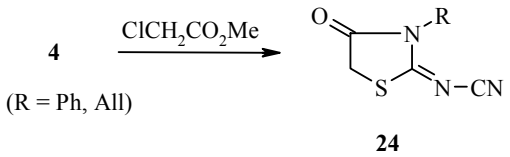


Alkylation of isothioureas **2** with bromoacetic esters and phenacyl bromide in DMF in the presence of potassium carbonate for 30-60 min at 60-80°C gave the isothioureas **22**, which underwent Thorpe cyclization to 4-aminoimidazoles **23** when treated with a solution of sodium ethoxide at 20°C for 15-20 min [26].

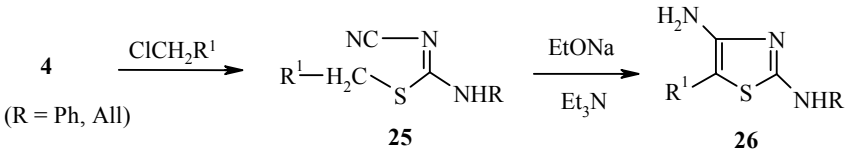


In certain cases, on account of the difficulty of isolating compounds **22**, they were submitted to cyclization with sodium ethoxide *in situ* at 60-90°C.

Treatment of the sodium salt of N-cyanoisothiourea **4** with methyl chloroacetate at 30-60°C for 1 h (R = Ph) and 24 h (R = All) gives good yields of derivatives of 2-cyanoimino-4-thiazolidinone **24** [27].



Alkylation of this salt with chloroacetone or chloroacetamide gives stable N-cyanoisothioureas **25**, which undergo cyclization to 4-aminothiazoles **26** in the presence of sodium ethoxide or triethylamine.



R = Ph, All; R^1 = Bz, Ac, H_2NCO

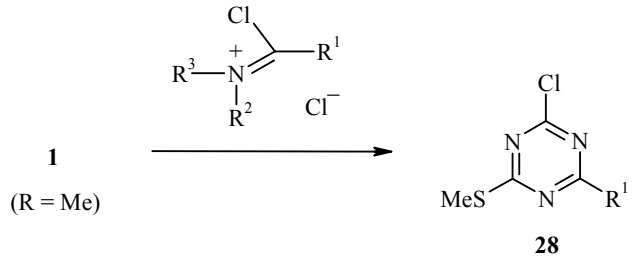
With chloroacetophenone cyclization takes place spontaneously [27].

Bromination of the sodium salt of N-cyanoisothiourea **4** in ethyl acetate (2 h, 20°C) gives preparative yields of 5-arylamino-3-bromo-1,2,4-thiadiazoles **27** [28].

R = Ph, *p*-$MeOC_6H_4$

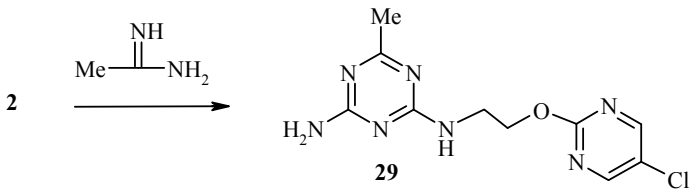
3. SYNTHESIS OF AZINES

With chloromethyleneiminium salts N-cyanoisothioureas **1** form derivatives of 1,3,5-triazine **28** [29]. The reaction is realized by boiling in acetonitrile for 1 h. The yields amount to 62-85%.



R^1 = H, Me, $ClCH_2$, Ph, 4-MeC_6H_4, 2-furyl; $R^2 = R^3$ = Me; $R^2 + R^3 = -(CH_2)_4-$

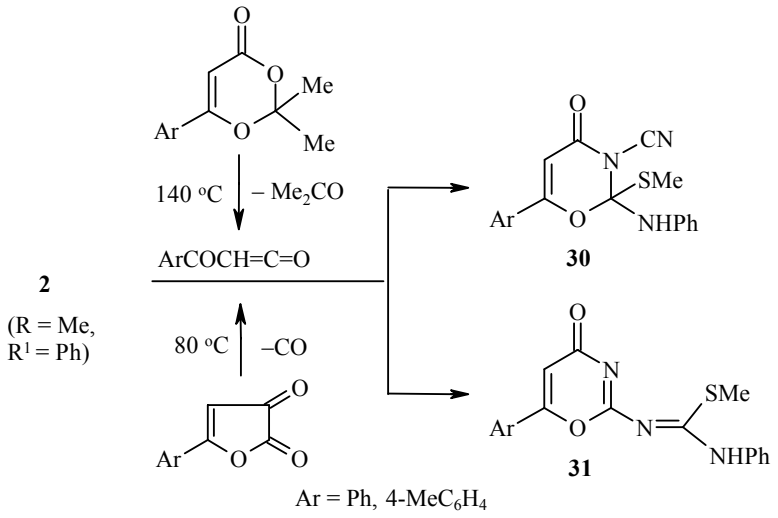
When boiled with acetamidine in alcohol N-cyano-S-methyl-N'-(5-chloropyrimidin-2-yl)]hydroxy-thylisothiourea **2** readily undergoes cyclization to the substituted triazine **29** [15].



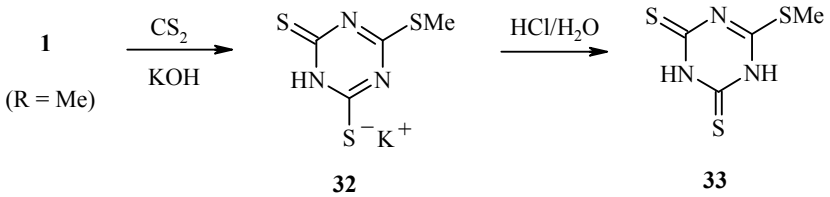
(R = Me, R^1 = –$(CH_2)_2O$–(5-chloropyrimidin-2-yl)

A similar isothiourea **2** [R = Me, R^1 = $(CH_2)_2$S-(N-methyl-2-imidazolylmethyl)] is used in the synthesis of antihistamine products [30], while the derivative with R^1 = 6-cyano-3-hydroxy-2,2-dimethyl-3,4-dihydro-2H-benzopyran-4-yl exhibits vasorelaxing activity [31].

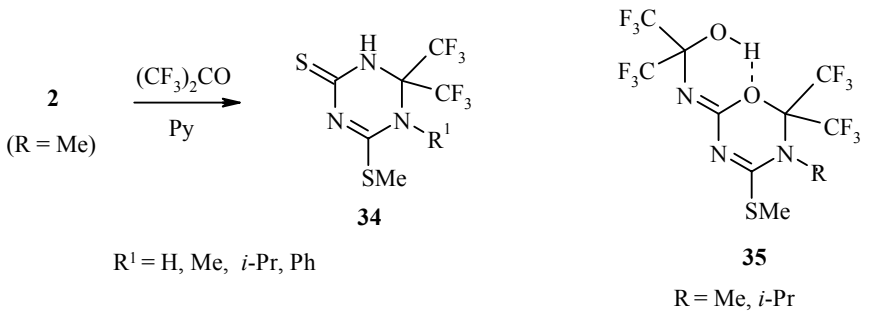
N-Cyano-N'-phenyl-S-methylisothiourea **2** acts as a dienophile in reaction with aroylketenes. With "hot" aroylketenes, generated during the thermolysis of 6-aryl-2,2-dimethyl-1,3-dioxin-3-ones, the reaction takes place at the C═N bond of the reagent, while the aroylketenes formed from 5-aryl-2,3-dihydrofuran-2,3-diones at lower temperature react through the cyano group. 2,3-Dihydro-1,3-oxazin-4-ones **30** were isolated from the reaction mixture in the first case [32], and 1,3-oxazin-4-ones **31** in the second [33]. The difference in the reactivity of the isothiourea **2** is probably due to the different temperature at which the aroylketenes are formed.



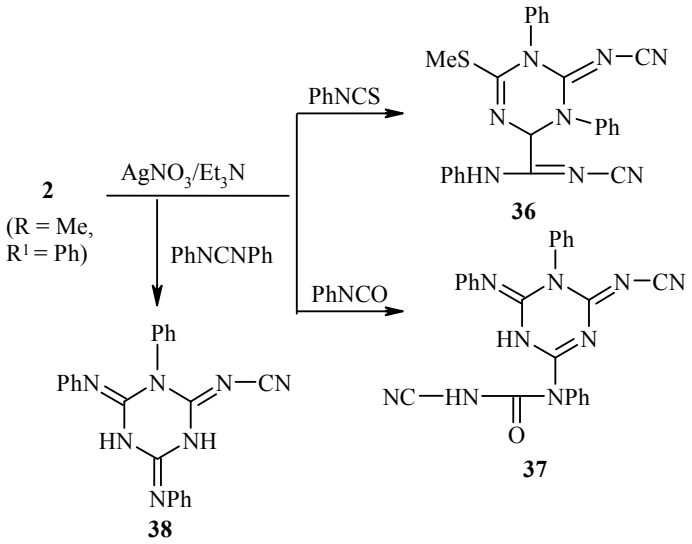
The reaction of the cyanoisothiourea **1** with carbon disulfide in alcohol in the presence of potassium hydroxide gives the salt **32**, which is converted by treatment with hydrochloric acid into 2-methylthio-3H,5H-1,3,5-triazine-4,6-dithione (**33**) [34].



The reaction of cyanoisothiourea **2** with an equivalent amount of fluoroacetones in absolute THF in the presence of pyridine gives 4-methylthio-2,2-bis(trifluoromethyl)-1H-1,3,5-triazine-6-thiones **34** [34]. With an excess of fluoroacetones this reaction gives unstable adducts **35**, which are transformed on heating at 50-70°C into compounds **34**.

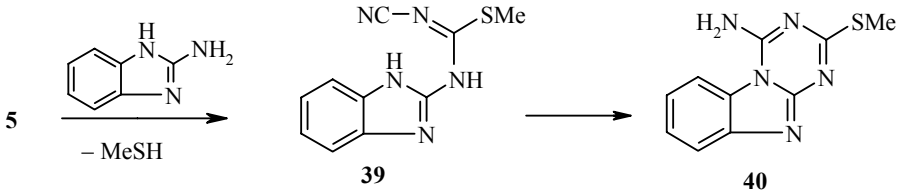


Triazines **36-38** are formed in the reaction of N-phenyl-S-methylisothiourea **2** with phenyl isothiocyanate, phenyl isocyanate, and diphenylcarbodiimide in the presence of silver nitrate and triethylamine. Their yields amount to 48-68% [35].

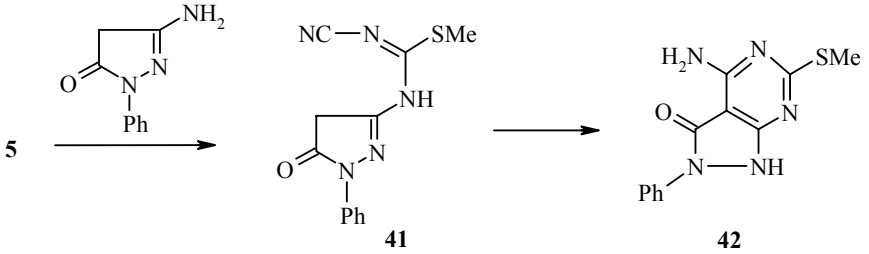


4. SYNTHESIS OF CONDENSED NITROGEN-CONTAINING SYSTEMS

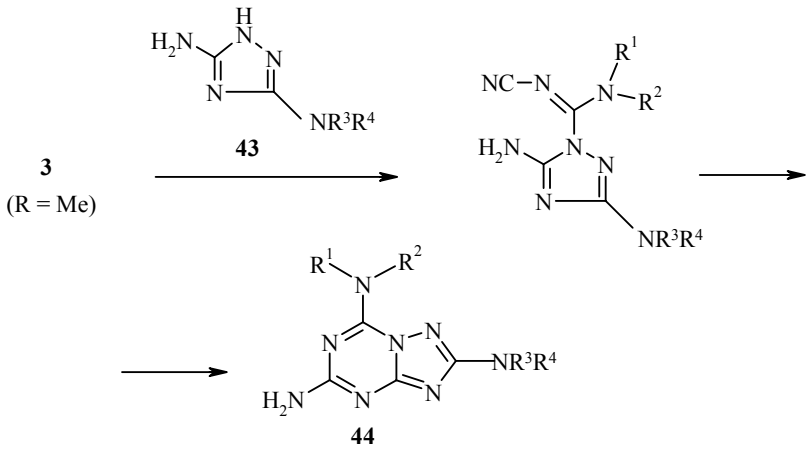
The N-Cyanimidodithiocarbonate **5** reacts with 2-aminobenzimidazole with the intermediate formation of the corresponding N-cyanoisothiourea **39**, which eliminates methylthiol under the reaction conditions and undergoes cyclization with a good yield to pyrimidobenzimidazole **40** [9].



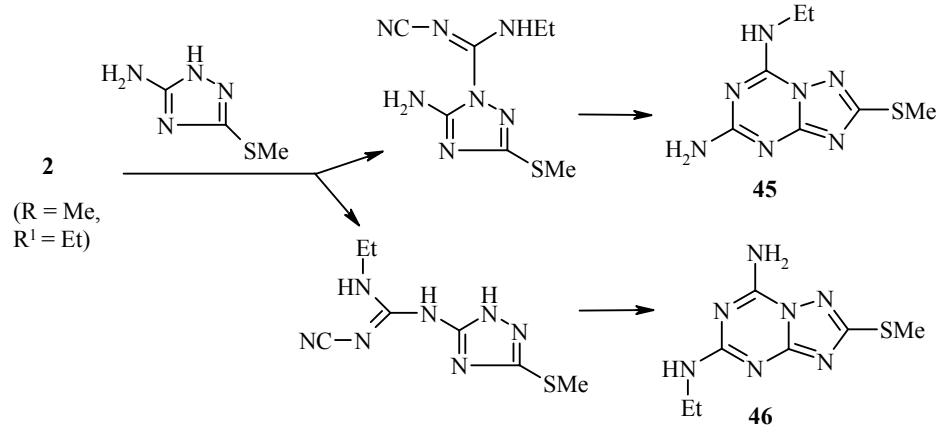
The reaction of compound **5** with 3-amino-1-phenyl-5-pyrazolone takes place similarly through the intermediate N-cyanoisothiourea **41**. In this case the reaction product is the pyrimidopyrazolone **42** [9].



In reaction with 5-aminotriazole **43** N-cyanoisothiourea **3** reacts initially at the nitrogen atom at position 1 of the heterocycle. Subsequent cyclization in the intermediate with the participation of the amino group and the cyano group leads to the formation of 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines **44** with yields of 4% [10].

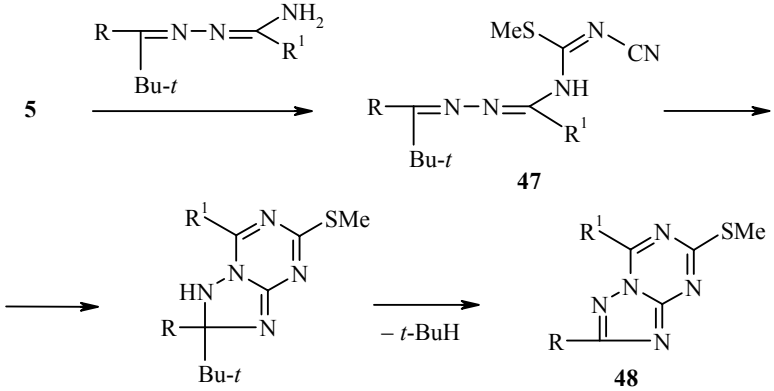


With N-cyanoisothiourea **2** (R = Me, R^1 = Et) this reaction takes place in two directions with the formation of regioisomeric 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines **45** and **46** [10].



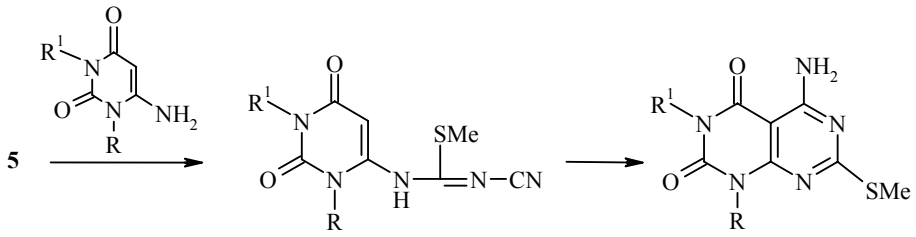
Compounds **44**-**46**, produced on the basis of the isothioureas **3**, are potential cardiovascular agents [10].

The reaction of compound **5** with diaminomethylenehydrazones (acetonitrile, 65-70°C, 1 h) leads to the intermediate N-cyanoisothioureas **47**, which eliminate a molecule of *t*-butane under the reaction conditions and form triazolotriazines **48** with yields of 52-75% [36].



R^1 = NH_2, NHMe, NMe_2; R = Me

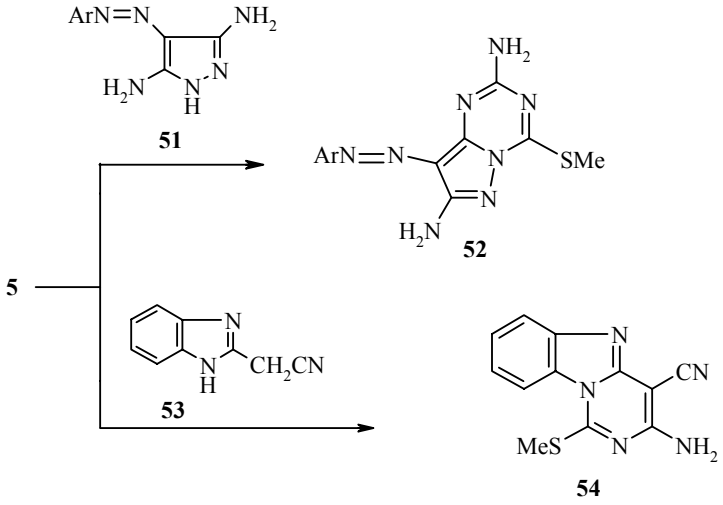
Dimethyl N-cyanimidodithiocarbonate **5** reacts with derivatives of aminouracil with the formation of intermediate N-cyanoisothioureas **49**, which undergo cyclization under the reaction conditions with the formation of pyrimido[4,5-*d*]pyrimidines **50** [37].



49 **50**

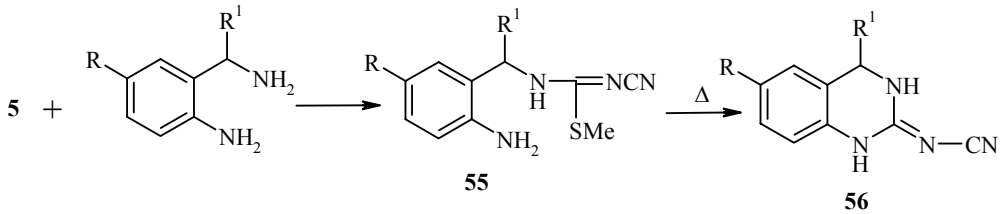
R = Me, Ph; R^1 = Me, H

In the reaction of compounds **5** with pyrazole derivatives **51** the reaction takes place in the presence of piperidine by a similar mechanism. In this case 2,7-diamino-8-(arylazo)-4-methylthiopyrazolo[1,5-*a*]-1,3,5-triazines **52** are formed with yields of 79-89%. With 2-cyanomethylbenzimidazole **53** this reaction takes place in dioxane in the presence of potassium hydroxide with the formation of 2-amino-1-cyano-4-methylthio-pyrimidino[1,6-*a*]benzimidazole **54**, the yield of which amounts to 87% [38].



51 **52** **53** **54**

2-Aminobenzylamines react with the dithioimidocarbonate **5** to form cyanoisothioureas **55**. Prolonged heating of the latter in dioxane (48 h) in the presence of a catalytic amount of sodium hydroxide leads to 2-cyanoimino-1,2,3,4-tetrahydroquinazolines **56** [39-41]. In most cases the N-cyanoisothioureas **55** undergo cyclization without being isolated from the reaction mixture. As a result of this, however, the yields of the tetrahydroquinazolines **56** are somewhat lower.

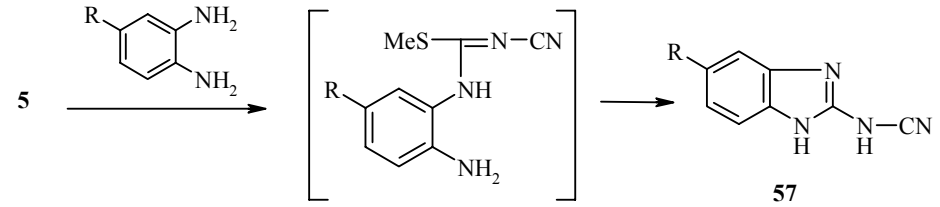


55 **56**

R = H, Me, Et, Hal; R^1 = H, Me, Ph

2-Amino-1,2,3,4-tetrahydroquinazolines **56** acted as inhibitors of the aggregation of blood platelets [36].

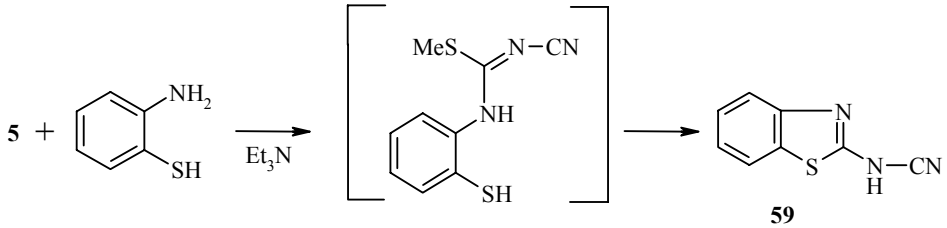
In reaction with compound **5** *o*-phenylenediamine forms 2-benzimidazolylcyanamide **57** [34]. Cyclization of the intermediate isothioureas probably takes place according to an analogous scheme.



57

R = H, Me, Et, Hal

The reaction of compound **5** with *o*-aminothiophenol was conducted in the presence of triethylamine with prolonged heating in a stream of nitrogen. The isothiourea **58** is probably formed at the first stage and then undergoes cyclization to 2-benzothiazolylcyanamide **59** [34].



58 **59**

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