ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 11, pp. 1565–1579. © Pleiades Publishing, Ltd., 2008.
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REVIEW

Chemical Properties of Cyanoacetanilides and Synthesis of Biologically Active Compounds Around Them

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Received October 3, 2007

Abstract—The review compiles and systematizes the published data on the application of cyanoacetanilides in the organic synthesis, and the biological activity of compounds obtained on the basis of cyanoacetanilides is described.

DOI: 10.1134/S1070428008110018

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Field of scientific interests: organic chemistry, chemistry of biologically active heterocycles, multicomponent condensation.

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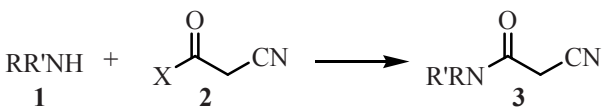
Field of scientific interests: alkenes chemistry.

Anilides of cyanoacetic acid are reagents widely used both in the synthesis of polysubstituted heterocycles and of open-chain systems exhibiting versatile biological activity. A large number of the cyanoacetanilide derivatives and of compounds obtained therefrom are used in medicine. Therefore the number of studies on these problems is constantly growing, and the published material requires systematization and generalization. We report here on the analysis of publications of the last decade on the preparation and properties of cyanoacetanilides.

1. PREPARATION OF ANILIDES OF CYANOACETIC ACID

The main commonly used preparation method for cyanoacetanilides is the acylation of aromatic amines **1** with the cyanoacetic acid or its derivatives (esters or acid halides) **2.** Recently the transacetylation effected by 1-cyanoacetyl-3,5-dimethylpyrazole found extensive application.



R = Ar, Ht; R' = H, Alk; X = OH, OAlk, Cl, 3,5-dimethylpyrazole-1-yl.

The acylation of aromatic amines with the cyanoacetic acid is performed as a rule in DMF [1–4] or acetic

anhydride [5]. The acylation with the acid chloride is carried out in pyridine [6] or in a two-phase system water solution of Na_2CO_3–CH_2Cl_2 [7]. Transcyanoacetylation with 3,5-dimethyl-1-cyanoacetylpyrazole is a new preparative procedure for the sysnthesis of difficultly available cyanoacetanilides [8].

Among the obtained anilides **3** were found antagonists of bradykinin B_1 receptors, therapeutical agents for treating chronic pains and inflammations [1–3], new specific inhibitors of acyltransferase-*b* of the lysophosphatic acid (LPAAT-*b*) [6].

As particular procedures of cyanoacetanilides syntheses the following reactions may be cited: the condensation of aryl isothiocyanates **4** and cyanoacetohydrazide **5** in the presence of triethylamine to give anilides **6** [9], and the ammonolysis of benzoxazepine **7** in the presence of excess sodium cyanide to form anilide **8** [10].

Further hydrolysis of compound **8** in the presence of a base followed by the treatment with 2-chloroacetyl chloride provided pyrimidoquinazoline-4,6-dione **9** capable of linking DNA to topoisomerase **II**. The double inhibition of protein kinase and topoisomerase **II** with these pyrimidoquinazolines underlies their anticancer activity [10].

Hence the synthesized anilides are endowed with the biological activity and are capable to serve building blocks in designing various pharmaceuticals.

2. CHEMICAL PROPERTIES OF CYANOACETANILIDES

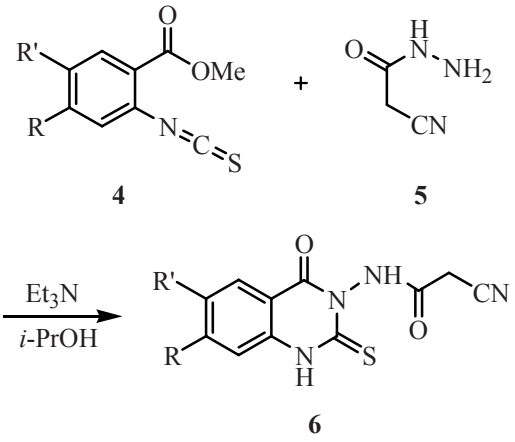
2.1. Reactions at CH_2 *Group*

The presence of two electron-withdrawing groups results in the high activity of cyanoacetanilides as CH-acids. Consequently the reactions involving the methylene group often are carried out in the presence of bases. This reaction as a rule is the first stage of the subsequent heterocyclization involving the anilide or the carbonitrile group.

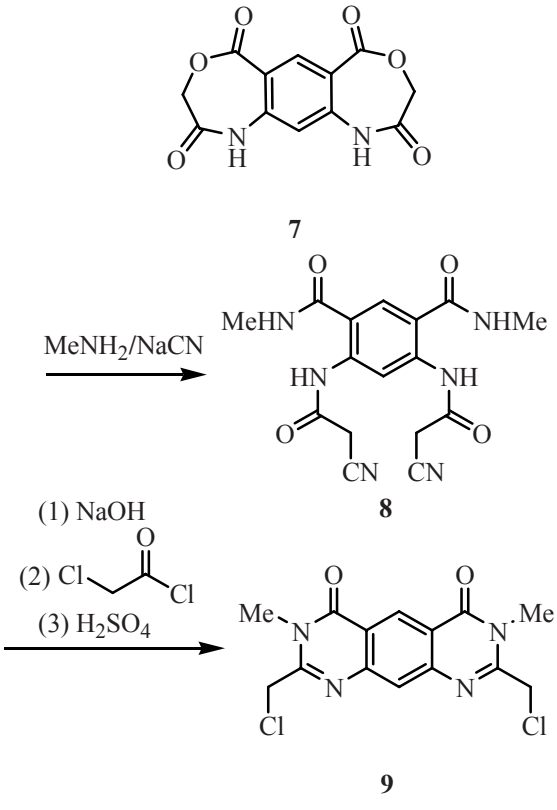
At heating in the alkaline environment cyanoacetanilides **3** are capable of dimerization like the malonodinitrile [11]. However in contrast to the latter the reaction did not stop at the formation of linear structure **10** but it gave rise to pyridin-2-ones **11** resulting from the intramolecular heterocyclization [12].

Cyanoacetanilides **3** reacted with carbonyl compounds **12** and sulfur (Gewald reaction) under the action of the

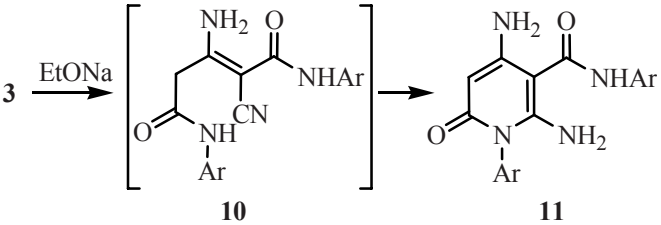
Scheme 1.



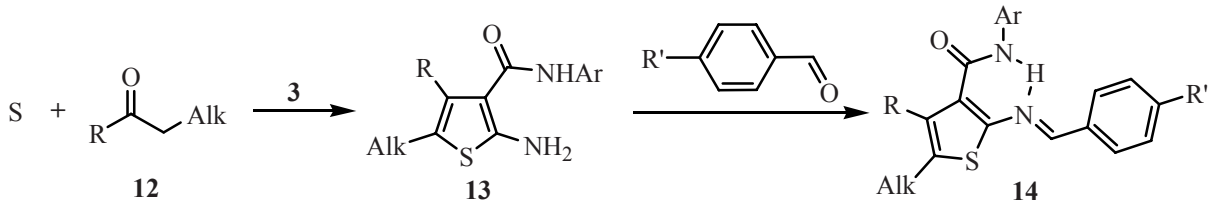
Scheme 2.



Scheme 3.



Scheme 4.



R = H, Alk; R' = Alk, OAlk.

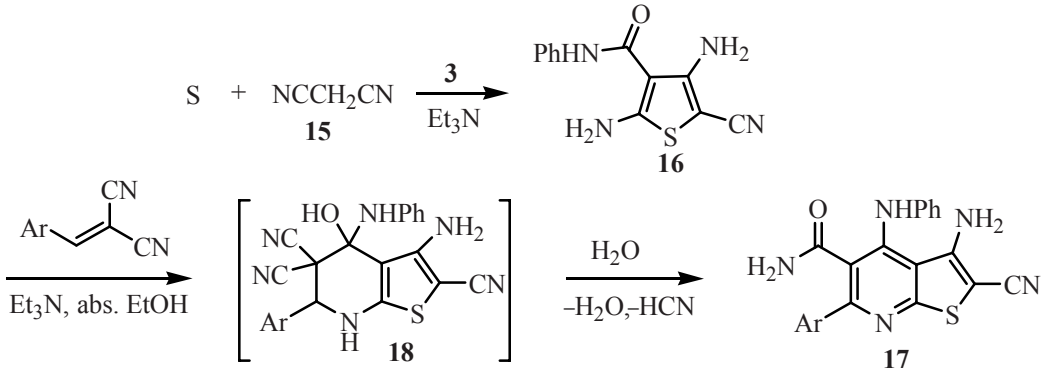
microwave radiation without solvent or in the presence of a little morpholine or Al_2O_3 as solid base [13], or in polar solvent in the presence of organic base [14–17]. The obtained 2-aminothiophene derivatives **13** are promising as antiviral agents [14], are allosteric enhancers affecting the human receptors of adenosine A_1 [16]. In obtained from thiophenes **13** compounds **14** the toluidine ring is coplanar with the thiophene cycle since the intramolecular hydrogen bond N–H···N eliminates the conformational lability. Otero et al. ascribed the fungicidal and bactericidal activity of compound **14** to the above mentioned structural feature [17] (Scheme 4).

The introduction of sulfur into the reaction with CH-acids **3** and **15** led to the formation of substituted thiophene **16** underlying the preparation of thieno-[2,3-*b*]pyridine derivative **17** possessing the fungicidal and bactericidal activity, especially with respect to gram-positive bacteria [18]. The suggested by Mohareb et al. reaction mechanism involves the β-addition of amino group located in the position *2* of thiophene **16** to the activated double bond of dinitrile and as believed the authors followed by the intramolecular cyclization into compound **18**. The latter suffers the dehydration with the subsequent hydrolysis at the cyano group and through HCN elimination forms aromatic system **17** [18] (Scheme 5). However the suggested by Mohareb et al. hydrolysis of the cyano group is rather doubtful under the reaction conditions, and the formation of an amido group is more likely to arise through a chain of successive reactions of formation and recyclization of oxacycles [19].

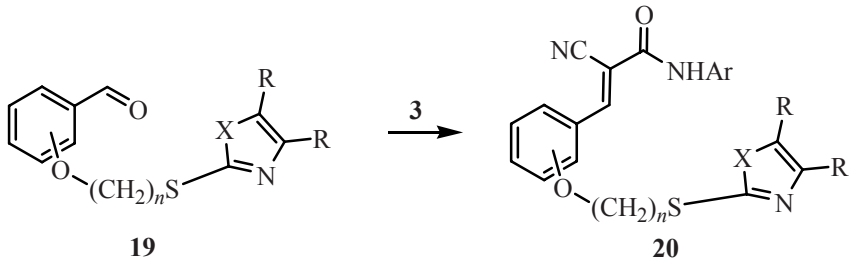
The cyanoacetanilides play the role of the active methylene component in the Knoevenagel reaction both with aliphatic and aromatic aldehydes providing compounds of practical importance.

For instance, proceeding from compounds **3** and **19** a synthesis was performed of a new class potential anticancer drugs **20,** nonpeptide inhibitors of farnesyltransferase lacking the sulfhydryl group [20] (Scheme 6).

Scheme 5.

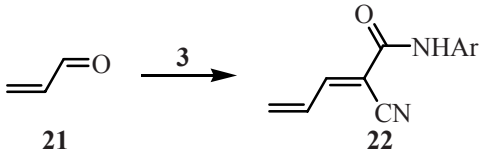


Scheme 6.



X = S, NH; R = H, R, R = $(CH)_4$; n = 2–5.

The condensation of CH-acids **3** with acrolein **21** in a mixture dioxane–DMSO in the presence of $Zn(OAc)_2 \cdot 2H_2O$ yielded amides of 2-cyanopenta-2*E*,4-dienic acid **22** interesting as cross-linking comonomers at the preparation of heat-resistant polymeric items [21].



21 **22**

Ar = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4.

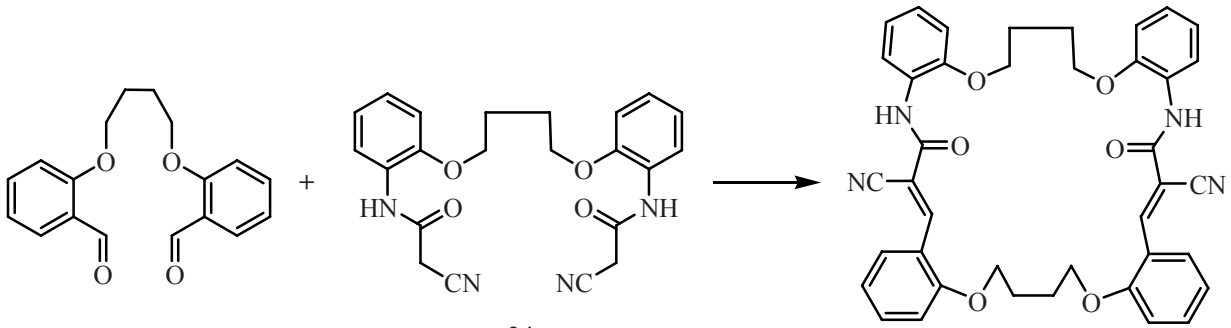
A convenient synthetic approach based on the Knoevenagel condensation of benzaldehydes **23** with cyanoacetanilides **24** was developed for the preparation of polymember benzofuzed macrocyclic diamines **25** [22] (Scheme 7).

The products of Knoevenagel reaction can be subjected in situ to further heterocyclization involving the cyano group or the anilide fragment. For instance, the reaction of aromatic *O*-hydroxyaldehydes **26** with anilides **3** resulted in 2*H*-chromen-2-imines **27** [8, 23–26]. The reaction was carried out in anhydrous alcohol using a double excess of piperidine, or under the conditions of microwave radiation. The heating of products **27** in acid medium led to the formation of coumarin derivatives **28** endowed with the antiphlogistic activity [25] and possessing a high potential of exhibiting the activity of tyrosine kinase inhibitor [24]. A group of structures **28** was isolated for designing on their basis of a focus data-base for screening with respect to inhibition of abl-kinase, an important biotarget involved into the process of leukemia development [24]. The treatment with anhydrides of compounds **27** results in their acylation at the imino group. The obtained 2-acyliminocoumarin-3-carboxamides **29** possess antimicrobial activity [23].

2-Aminopyridine-3-carbaldehyde reacted with anilides **3** to furnish naphthyridines **30**. Compounds **31** prepared therefrom might simultaneously behave like donors and acceptors of electrons in the formation of a hydrogen bond to give complexes **32**. Such duplexes may function as predictable and programmed molecular recognition units for the control of the intermolecular interactions [27].

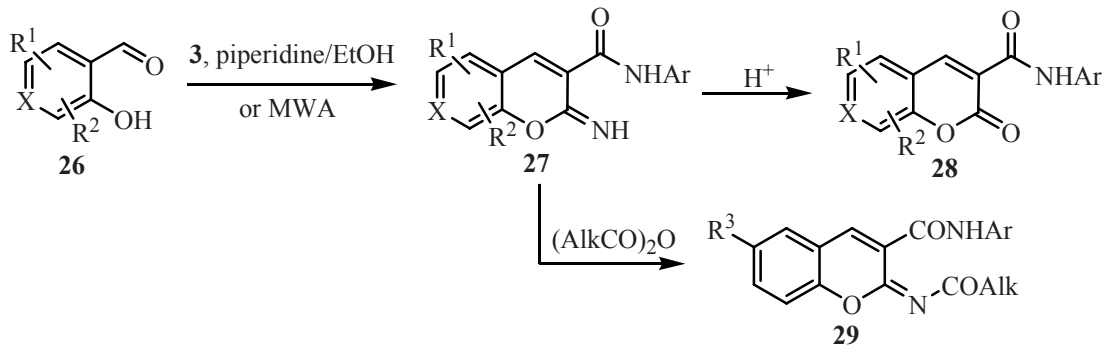
The product of isopentanal reaction with CH-acid **33,** olefin **34**, dimerized in situ giving heterocyclic system **35**. We suggest a reaction mechanism involving successively occurring Knoevenagel and Michael reactions followed by intramolecular heterocyclization [28].

Scheme 7.



23 **24** **25**

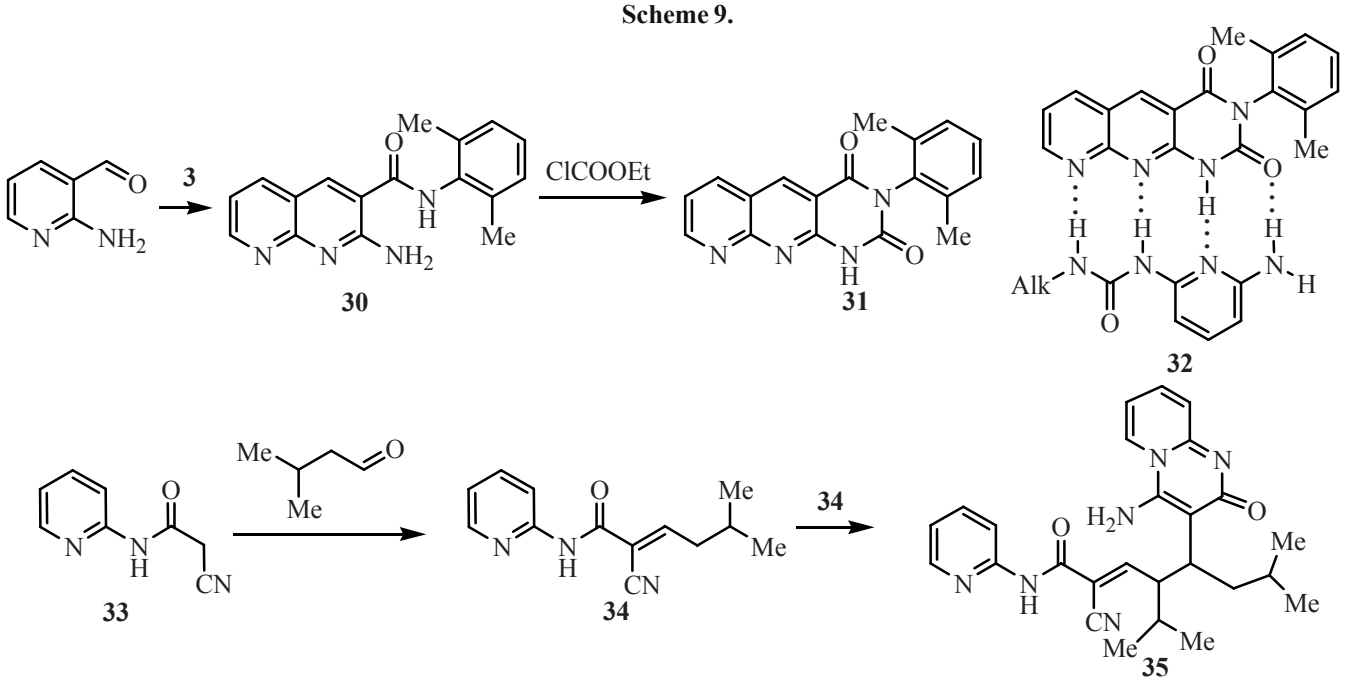
Scheme 8.



26 **27** **28** **29**

X = CH, N; R^1, R^2, R^3 = H, NO_2, Alk.

Scheme 9.



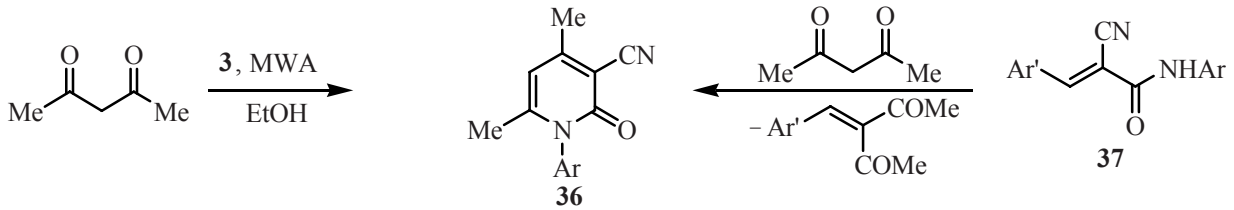
Reactions of 1,3-diketones with cyanoacetanilides **3** occurred as Knoevenagel condensation with the subsequent hetrocyclization involving the anilide moiety. The pyridin-2-ones **36** were obtained under various conditions, including the phase-transfer catalysis, enzymatic reactions, microwave irradiation [29, 30]. The application of arylmethylidene derivative of cyanoacetanilide **37** involved an exchange of methylene components [12].

The reaction of hydroxyimines with cyanoacetanilides **3** led to the formation of *N*-aryl-5-nitroso-2-oxopyridines **38,** intermediate compounds in the synthesis of antimetabolites [31].

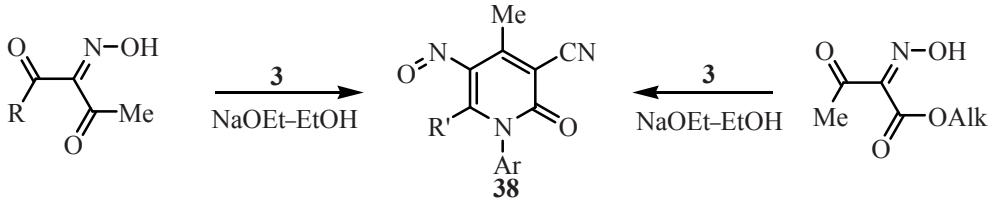
When pyran derivatives **39** and **40** were involved the reaction proceeded with the recyclization of the products of Knoevenagel condensation **41** and **42** into the corresponding acyclo-C-nucleosides **43** [32, 33] and pyridones **44** [34] (Schemes 12, 13).

A three-component condensation of aromatic aldehydes and two CH-acid occurred through a succession of reactions of Knoevenagel, Michael, and intramolecular heterocyclization. Likewise at the use of amides **45** pyridones **46** were obtained in a high yield [12, 35]. The application of thioamide **47** depending on the reac-tion conditions provided either linear mercaptothio-amines

Scheme 10.

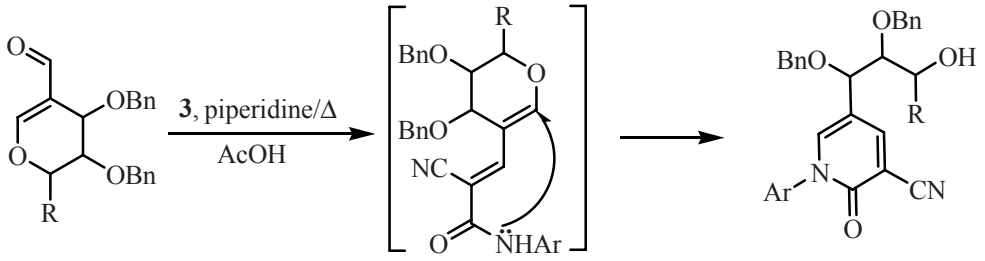


Scheme 11.



R = Me, Ph; R' = OH, Me, Ph.

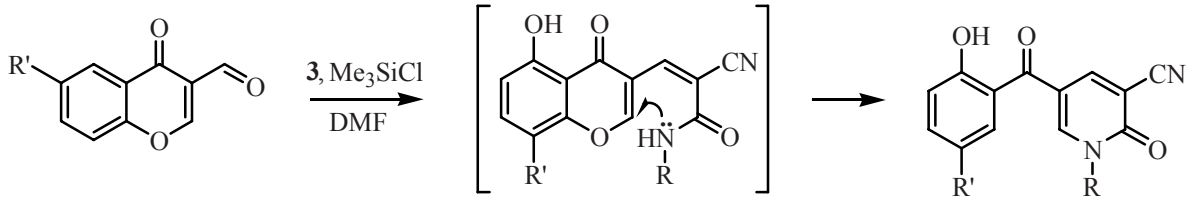
Scheme 12.



39 **41** **43**

R = H, OBn.

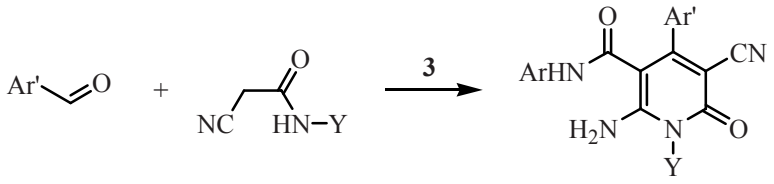
Scheme 13.



40 **42** **44**

R = Ar, Ht; R' = H, Me, Cl, OMe.

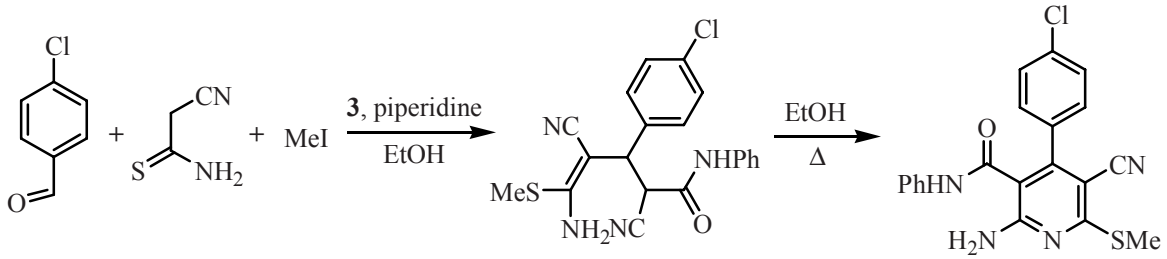
Scheme 14.



45 **46**

Y = H, NH_2, Ar.

Scheme 15.



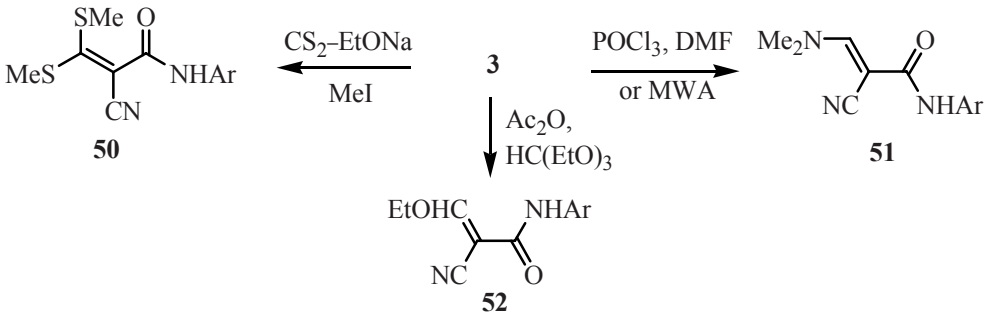
47 **48** **49**

48 or the products of their cyclization and oxidation **49** [36].

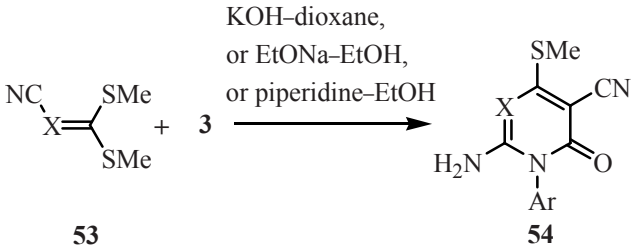
Among the series of cyanoacetanilides derivatives fairly popular became the reaction of the formation of activated olefins **50–52** containing a nucleofugal group: alkylmercapto [29, 37–40], dimethylamino [8, 41, 42], or ethoxy group [43]. The products of nucleophilic vinyl substitution (S_NVin) of olefins **50** [29, 37–40, 44], **51** [8, 41], and **52** [45] as a rule suffer in situ further heterocyclization to provide compounds with a versatile biological activity.

Cyanoacetanilides **3** are capable to enter into the nucleophilic vinyl substitution in the role of a CH-acid component as C-nucleophiles in reactions with

Scheme 16.



dithioacetals, dialkylamino- and ethoxymethylidene derivatives. Thus the reaction with ketenes dithioacetals and azaketenes **53** resulted in the formation of 2-pyridones [46] and pyrimidinones **54** [47].



The reaction with enamines **55** led to the formation of a new series on indole derivatives **56** that were purposeful prepared for examination of pharmacophore models of glycine-bonding area associated with NMDA receptor [48] (Scheme 17).

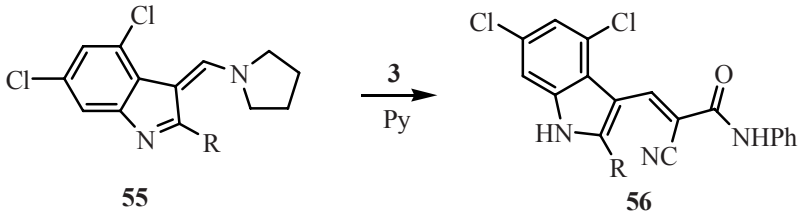
The reaction of ethoxymethylenemalonic ester with anilides **3** in a basic environment results in the formation of products of nucleophilic vinyl substitution **57** undergoing *in situ* the intramolecular heterocyclization into pyridones **58** [49] (Scheme 18).

One-component reaction of CH-acids **3** and **59** with DMF dimethylacetal results in different products depending on the reaction conditions. In the presence of catalytic quantity of piperidine under microwave irradiation the cyclization occurred at the cyano group giving amides **60** [8]. At a double excess of the piperidine the cyclization proceeded at the nitrogen atom of the anilide group providing carbonitriles **61** [50] (Scheme 19).

When acetophenone derivative **62** is involved into the reaction the process occurred with an exchange of the methylene components **63** and **64** [8] (Scheme 20).

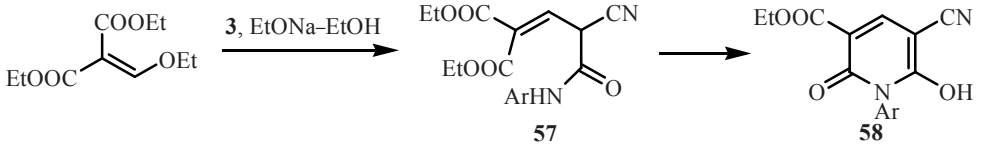
By an intramolecular Claisen condensation of *N*-acylated esters of *o*-aminobenzoic acid **65** quinolin-2(1*H*)-one **66** was obtained. The reaction was performed in two ways: by heating in methanol in the presence of a base [51], or by treating with the OH-form of the resin *Amberlyst A-26* at room temperature. The latter procedure gave the target product in high yield and of a high purity [7]. 4-Hydroxyquinolin-2(l*H*)-ones **66** are promising as antibacterial, antiphlogistic, and anticancer agents, local anesthetics, antagonists of the hormones of the thyroid gland (*N*-methyl-*D*-aspartate and serotonin).

Scheme 17.

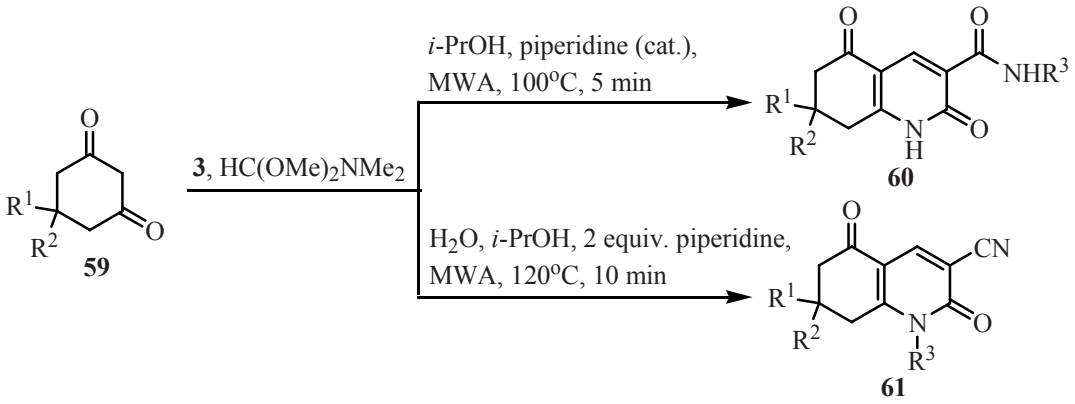


R = COOEt, $COOCH_2CH{=}CH_2$.

Scheme 18.

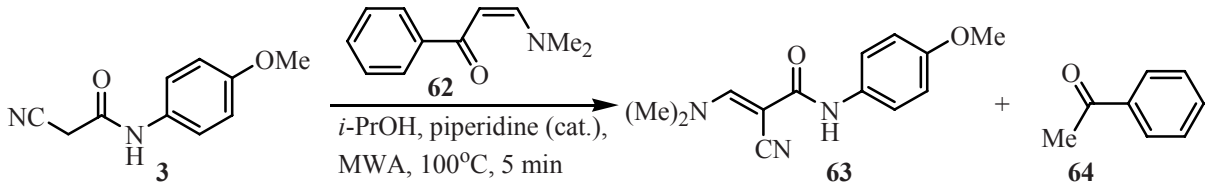


Scheme 19.

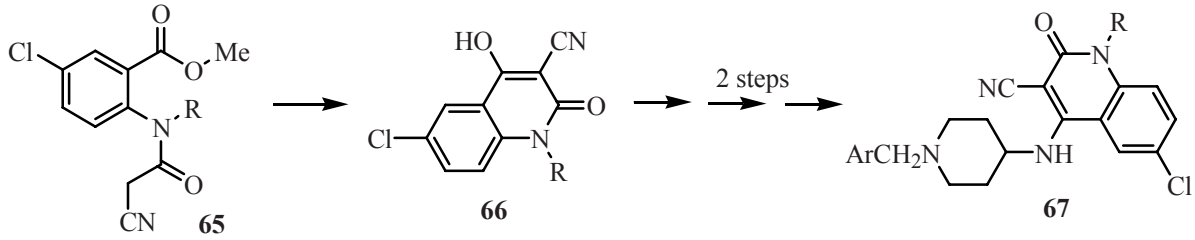


R^1 = H, Me; R^2 = H, Me, Ar, Fu; R^3 = Ar, Ht.

Scheme 20.



Scheme 21.



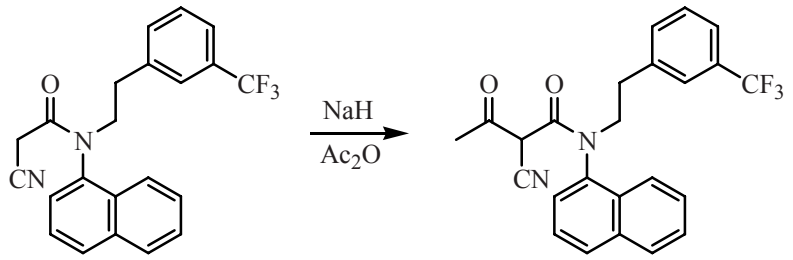
The successive treatment of compound **66** with $POCl_3$ and a substituted 4-aminopiperidine resulted in quinolone **67** (Scheme 21). The obtained 4-aminoquinolones are inhibitors of potassium channels hERG in the heart tissues and antagonists of the melanin-concentrating hormone MCHr1. On the basis of pharmacological studies the peroral administration of quinolones **67** was suggested as a new trend in obesity treatment [51].

The acylation of cyanoacetanilides at the carbon atom results both in anhydrides and in acid chlorides in strongly basic media. CH-acid **68** is acylated with the formation of strong antibacterial agents **69** active against *Staphylococcus aureus* [52] (Scheme 22).

The acylation with acid chlorides gives active metabolites of leflunomide, compound **70** [4, 53–56] that are powerful inhibitors of tyrosine kinase [54] and dehydrogenase dihydoorotate [4]. The X-ray diffraction study of the structure of compound **70** revealed that the molecule existed in a materially planar conformation originating from the intramolecular hydrogen bonds between the hydroxy and the amide groups. An intermolecular hydrogen bond was found between the CN group and the amide group of the symmetrically bound dimer **71** (Scheme 23). The conformation of these compounds corresponds to the energy minimum of the molecular position formulated at the docking with the tyrosine kinase [53].

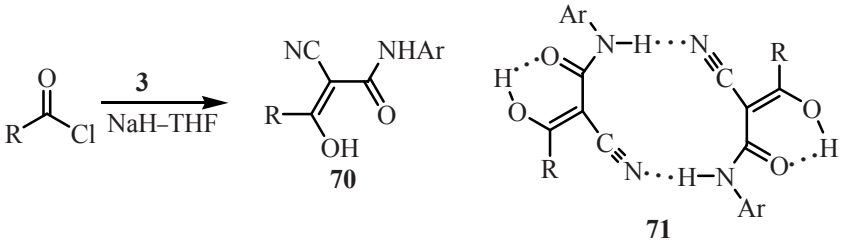
The acylation with bromine-containing acid chlorides led to the formation of cyclic enol ethers **72** with predominantly (90%) (*Z*)-configuration (Scheme 24). They

Scheme 22.



68 **69**

Scheme 23.



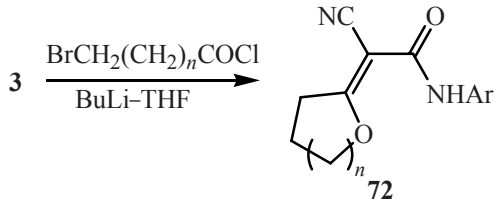
can be converted into (*E*)-isomers by keeping for 48 h in DMSO. The structures obtained were used in the study of the dependence structure–biological action on leflunomide derivatives [57, 58].

Cyanoacetanilides **3** enter into Michael reaction as CH-acid component followed by the intramolecular heterocyclization of the arising adducts. It is possible in the reaction with α,β-unsaturated ketones **73** to isolate Michael adducts **74** [59]. At heating the reaction mixture they undergo the intramolecular heterocyclization to pyrans **75** and turn into pyridones **76** via subsequent Dimroth rearrangement [12] (Scheme 25).

The reaction of cyanoacetanilides **3** with malonodinitrile derivatives **77** led to pyridones **78**. The reaction with the malonodinitrile dimer proceeded through intermediate **79** [12]. Obtained pyridone **78** is of interest for the synthesis of a wide range of new fused heterocycles **80–83** [12] (Scheme 26).

Aromatic isocyanates and isothiocyanates in reactions with cyanoacetanilides **3** in a basic medium formed a new C–C bond giving linear compounds **84** [60] and **85** respectively [61] (Scheme 17). The product of the reaction with isothiocyanate **85** is prone to be alkylated at the sulfur giving sulfide **86** [61] (Scheme 28).

Scheme 24.

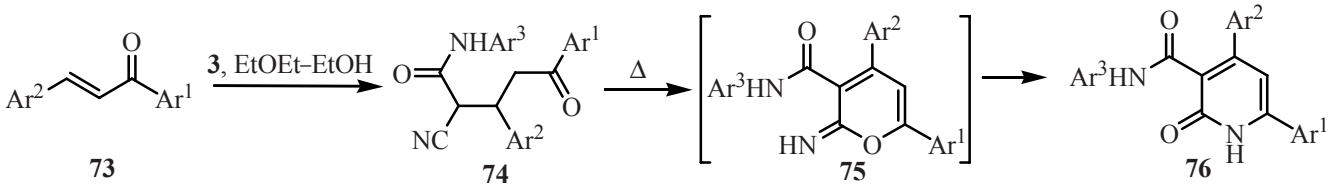


The addition of sulfur into the reaction of anilide **6** with isothiocyanate **87** led to the formation of the C–S bond and resulted in the system **88** originating from a tandem reaction [9] (Scheme 29).

The active methylene group of cyanoacetanilides **3** is capable of C=N bond formation in reactions with compounds containing nitro and nitroso groups, with esters of the nitrous acid, diazo compounds, and azides.

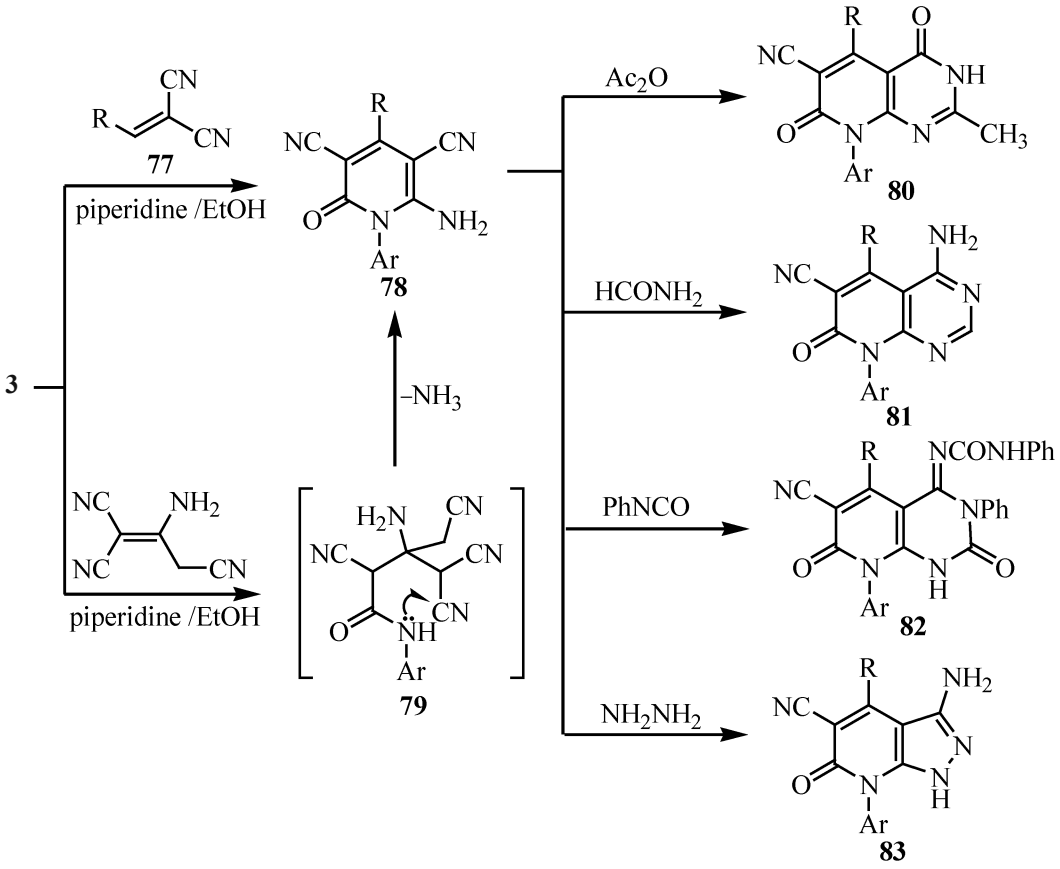
On adding a solution of ethyl nitrite to anilide **3** in the presence of an equimolar amount of sodium ethylate a fast formation a high yield of sodium salts of oximes

Scheme 25.

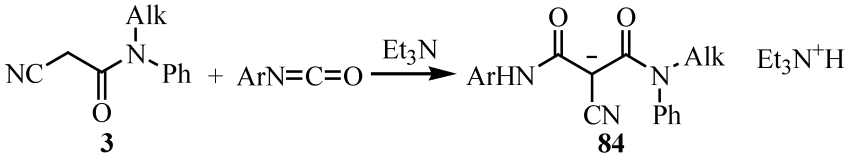


73 **74** **75** **76**

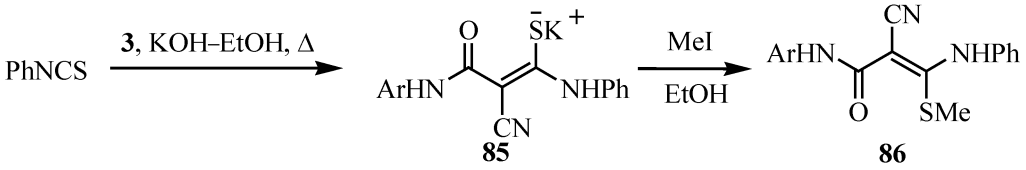
Scheme 26.



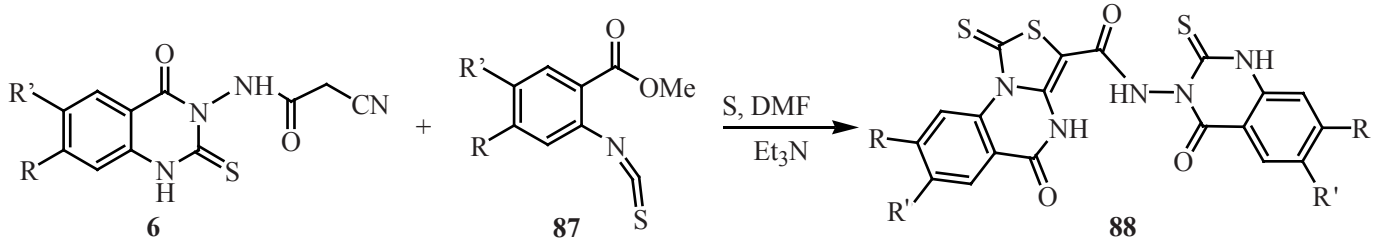
Scheme 27.



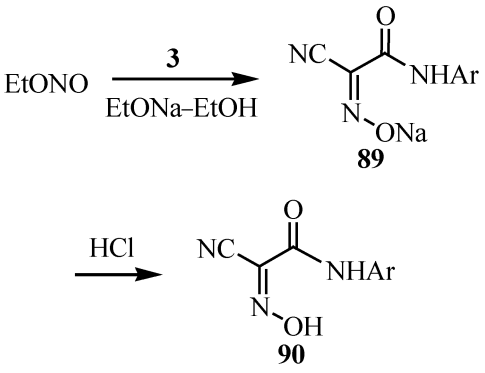
Scheme 28.



Scheme 29.

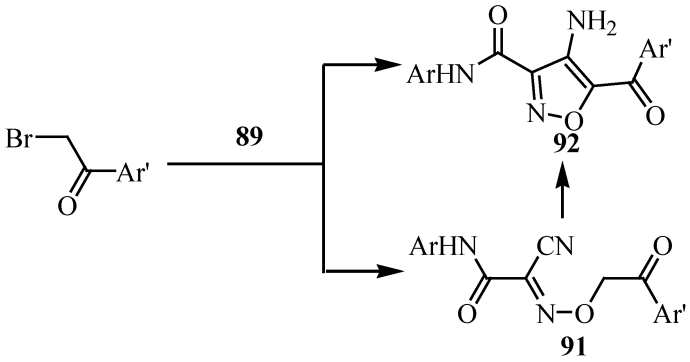


R, R' = H, OAlk, –OCH_2O–.



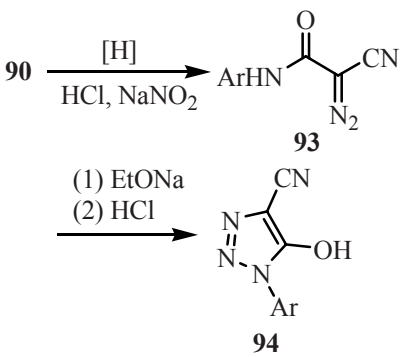
89 was observed. The acidification results in the formation of oximes **90** proper [62, 63].

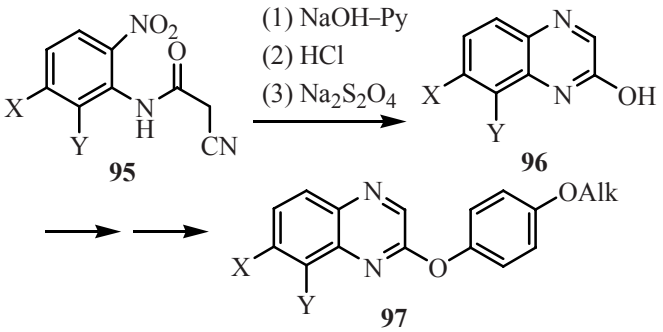
The reaction of sodium salts of oximes **89** with α,4-dibromoacetophenone resulted in the O-alkylation to yield oximes **91** that on treatment with lithium or potassium hydroxide in water or in aqueous alcohol were converted into aminoisoxazoles **92** [62].



Ar = Ph, 2-$MeOC_6H_4$; Ar' = 4-BrC_6H_4.

Diazocompounds **93** obtained from oximes **90** are convenient reagents for preparation of versatile 1,2,3-triazole derivatives [63]. The successive treatment of compounds **93** with sodium ethylate solution and hydrochloric acid gave triazoles **94** that were also obtained by the recrystallization of diazocompounds **93** from water. Based on theoretical and kinetic



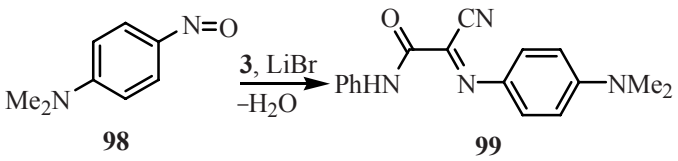


X, Y = Cl, OMe.

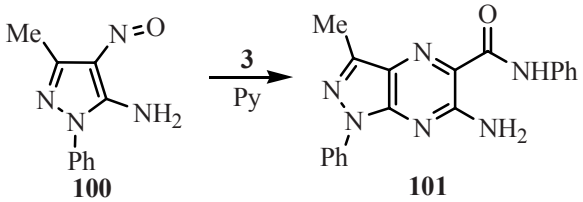
investigations of this reaction a conclusion was made on the mechanism of the process including a stage of 2-diazoacetimidates heterocyclization [63].

Hazeldine et al. [64] proceeding from anilide **95** in several stages performed a synthesis of quinoxalines **96** and **97**. It was presumed that compound **97** was capable of reacting with topoisomerase-**IIβ** and therefore was endowed with antileukemic activity and activity against B16 melanoma alongside weak cytotoxic properties.

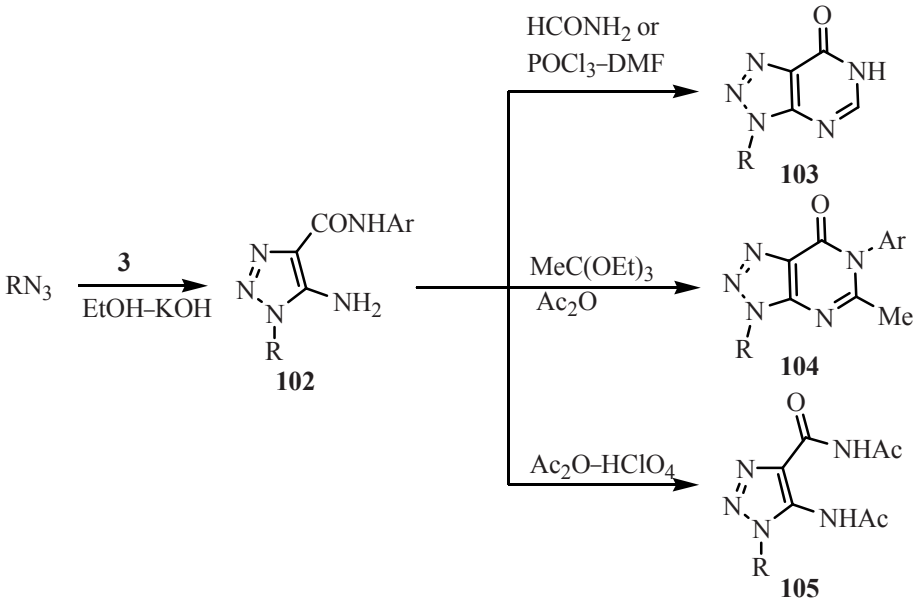
The reaction of anilides with arylnitrosocompounds **98** in the presence of lithium bromide without solvent (Ehrlich–Sachs reaction) gave imines **99**. Commonly the yields in Ehrlich–Sachs reaction are relatively small, but under the microwave radiation the yield grows to 85% [65].



On the condensation in pyridine of cyanoacetanilide **3** and 4-nitroso-5-aminopyrazole **100** new pyrazolo-[3,4-*b*]pyrazines **101** were obtained exhibiting fungicidal and antiparasitic properties [66].



The reaction of anilides **3** with aliphatic and aromatic azides in basic medium resulted in triazoles **102** [67, 68] formation which served for preparation of 8-azapurines **103** and **104**. At boiling in acetic anhydride in the presence of $HClO_4$ unexpectedly instead of the planned



R = Ar, Alk.

8-azapurines compounds **105** were isolated resulting from the dearylation of the amide group and its subsequent acylation [67].

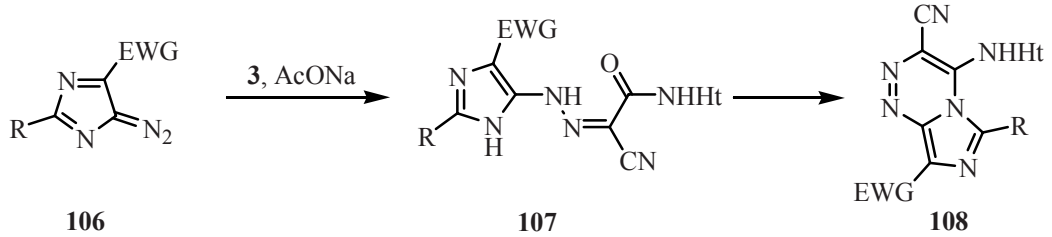
The azocoupling of imidazole **106** with methylene-active compounds **3** followed by cyclization of hydrazones **107** gave rise to imidazo[5,1-*C*][1,2,4]triazines **108** [69] (Scheme 30).

2.2. Reactions at the Cyano and Anilide Groups

The most popular reaction of cyanoacetanilides **3** involving the cyano group is the reaction with hydrogen sulfide and its derivatives [70]. The hydrogen sulfide addition occurs in the presence of catalytic quantities of a base, and it leads to the formation of thioamides **109** used as CH-acid component in syntheses of various heterocycles [44].

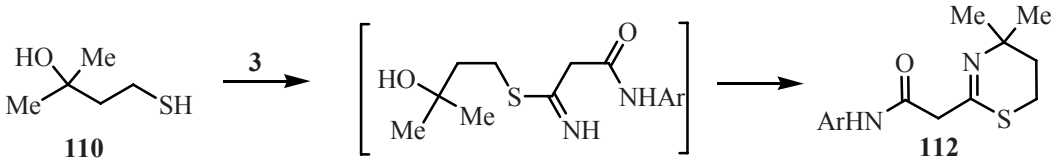
The reaction of cyanoacetanilides **3** with thiols **110** and **111** ended as an intramolecular regioselective heterocyclization involving the electron-deficient carbon atom and the nitrogen atom of the newly formed imino group. The reaction gave in quantitative yields dihydrothiazines **112** [71] (Scheme 31) and 2-alkylidene-4-oxothiazolidine

Scheme 30.

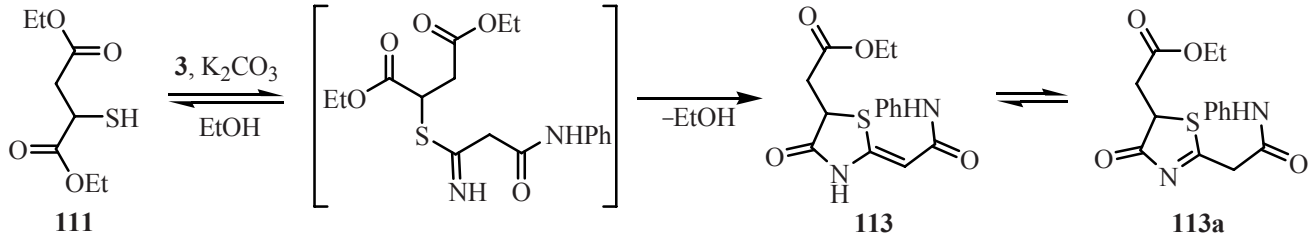


R = H, SH, SMe, CH_2COOH.

Scheme 31.



Scheme 32.



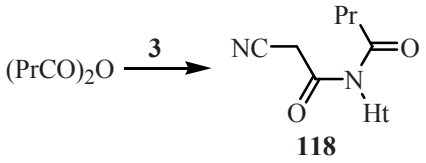
111 **113** **113a**

113 capable of a prototropic tautomerism leading to compound **113a** [72–75] (Scheme 32).

Caddick et al. [76] developed an improved procedure for the cyano group reduction tolerant to the other functional groups consisting in the treatment with nickel chloride, sodium hydroborate, and boc_2O under a nitrogen atmosphere. The process provided amines **114** (Scheme 33).

The treatment of acetanilides **3** with triethyloxonium tetrafluoroborate led to the O-alkylation and to the formation of imidoethers **115**. The subsequent Claisen condensation and the reaction with substituted anilines afforded 3-amino-2-cyanoimidacrylates **116** [77]. Zinc complexes **117** obtained from β-diimines **116** exhibited a high activity as homogeneous catalysts of the copolymerization of cyclohexene oxide with CO_2 (Scheme 34).

The reaction of amides **3** with butyric aldehyde in the absence of a base occurred as a regiospecific acylation at the nitrogen of the amide group forming N acylanilide **118** [28].



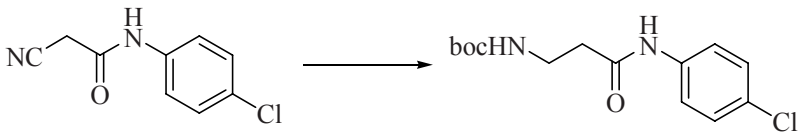
118

CONCLUSION

In the last decade a large experimental material was accumulated with respect to modification methods of cyanoacetanilides and their derivatives. The presence in the cyanoacetanilides of three reactive group (methylene, carbonitrile, and anilide groups) makes it possible to apply them as promising reagents in the synthesis of versatile functionalized open-chain and heterocyclic compounds.

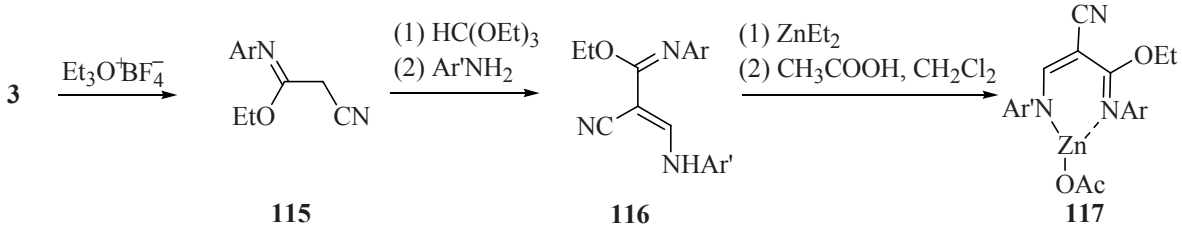
The main trend in the chemistry of cyanoacetanilides **3** is the purposeful synthesis of biologically active compounds of a wide range of action.

Scheme 33.



3 **114**

Scheme 34.



115 **116** **117**

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