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N-CYANOIMINES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS. (REVIEW)

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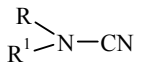
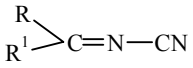
Methods for the synthesis of N-cyanoimines in the period between 1959 and 2003 and their chemical properties are examined.

Keywords: N-cyanoimines, preparation, cyclization.

In previous reviews we considered the synthesis and chemical properties of alkyl- and hetarylcyanamides [1-3]. They can formally be grouped together with the N-cyanoamines. In this review methods for the synthesis of N-cyanoimines, which are structurally similar to cyanamides, and their chemical properties are analyzed. The presence of the C=N bond conjugated with the cyano group in N-cyanoimines affects their physicochemical properties to a considerable degree [4] and widens the possibilities of their use as synthons.



cyanamides
N-cyanoamides



N-cyanoimines

During examination of the chemical properties of compounds containing a cyanoimino group particular attention has been paid to intramolecular cyclization reactions, which lead to various azaheterocycles. Information on N-cyanoimines has not been reviewed before. The synthesis and chemical transformations of N-cyanoimidates, N-cyanimidodithiocarbonic esters, N-cyanoamidines, N-cyanoisoureas, N-cyanoguanidines, and other compounds containing an N-cyanoimine fragment remain outside the scope of the present review, since it is proposed to examine their properties in forthcoming papers.

1. METHODS OF PREPARATION

There are three main methods for the preparation of N-cyanoimines: 1) Reaction of carbonyl compounds with cyanamide or bis(trimethylsilyl)carbodiimide; 2) dehydration of monosubstituted cyanamides; 3) reactions of olefins with cyanogen azide.

N-Cyanoimines **1** were obtained by the first method from acetone, methyl ethyl ketone, and cyclohexanone (reagent ratios 2:1, 60°C, 6 h) according to the following scheme [5]:

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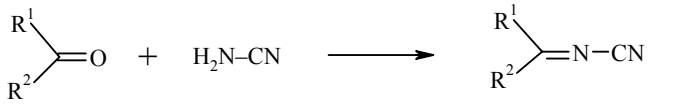
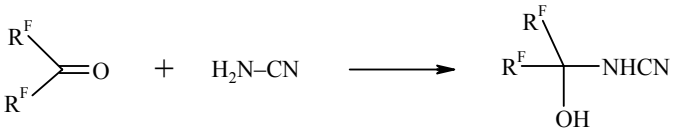


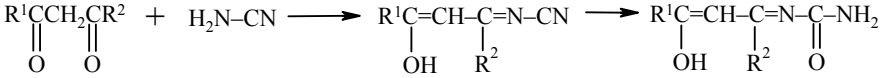
1 (15–60%)

Unlike acetone, at 0-10°C hexafluoroacetone and dichlorotetrafluoroacetone form hydroxyalkylcyanamides **2** and not N-cyanoimines [6].



2

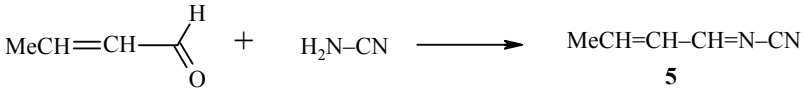
1,3-Diketones react with an aqueous solution of cyanamide at room temperature with the formation of unstable N-cyanoimines **3**, which are hydrolyzed under the reaction conditions to the corresponding hydroxyureas **4**.



3 **4**

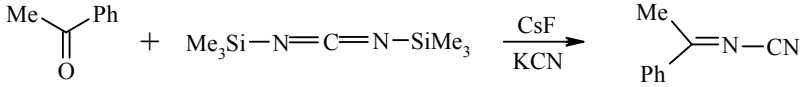
The brief action of 2 N hydrochloric acid on the ureas **4** leads to the cyanoimines **3** with yields of 29% [7].

The N-cyanoimine **5** was obtained with a quantitative yield from 2-butenal and cyanamide (in ethyl acetate solution, at 60°C, 5 h) [8].



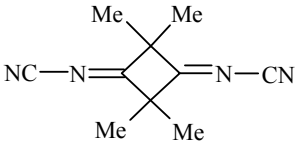
5

With acetophenone bis(trimethylsilyl)carbodiimide forms the N-cyanoimine **6** [9]. Potassium cyanide or cesium fluoride is used as catalyst, and the process is carried out in acetonitrile or 18-crown-6 ether and takes 22 h.



6 (23%)

From 2,2,3,3-tetramethyl-1,4-cyclobutanedione, *p*-quinone, and anthraquinone in an analogous reaction the corresponding N,N'-dicyanodiimines **7-9** were obtained. In this case titanium(IV) chloride was used as catalyst. The yields of compounds **7-9** amounted to 34-75%.



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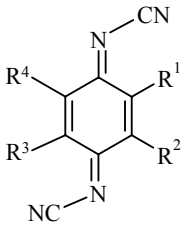

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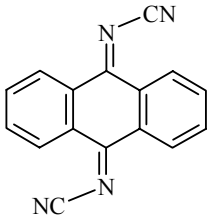
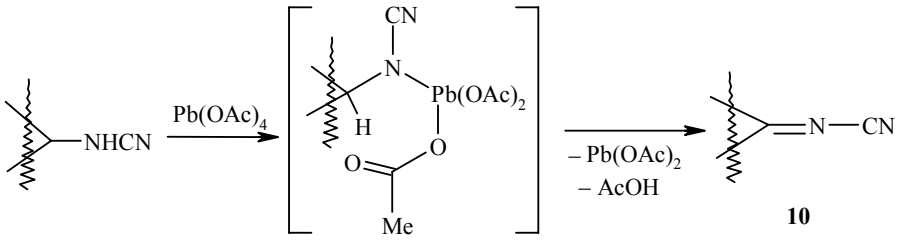


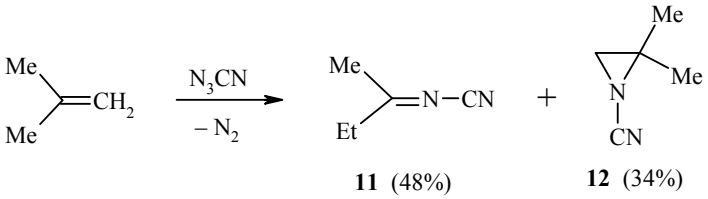
9

The second group of methods for the production of cyanoimines has been less widely used. Thus, for example, in [10] it was reported that cyanamides containing a steroid or terpene substituent are easily dehydrogenated with lead tetraacetate in a mixture of cyclohexane and dichloromethane (1 h) with the formation of the corresponding N-cyanoimines **10**.



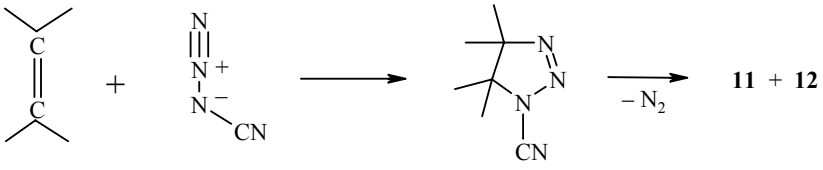
10

The third method for the preparation of N-cyanoimines is represented by the next two reactions. The action of cyanogen azide on isobutylene led to the formation of the N-cyanoimine **11**. N-Cyano-2,2-dimethylaziridine **12** was isolated as side product [11, 12].

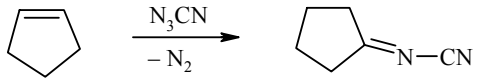


11 (48%) **12** (34%)

The mechanism of this reaction involves addition of the azide group to the double bond of the alkene with the formation of 1-cyanotriazoline, which decomposes under the reaction conditions with the release of nitrogen (the group migrates in the cationic intermediate), leading to a mixture of compounds **11** and **12**.

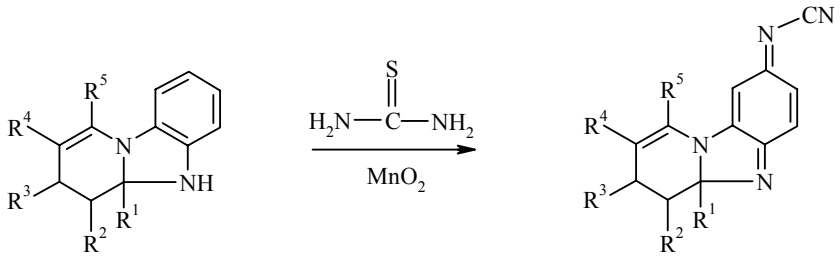


Cyclopentene in this reaction gave the corresponding alicyclic N-cyanoimine **13**. In both cases the process is carried out below 0°C, since cyanogen azide has brisant characteristics.



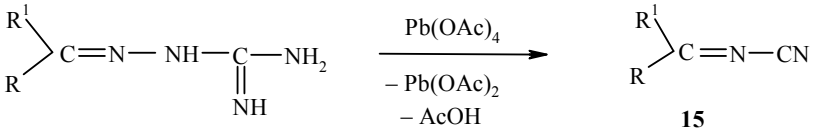
13 (94%)

The production of the tricyclic N-cyanoimines **14** is unusual. The method is based on the joint oxidation of 4a,9-diaza-1,2,4a,9a-tetrahydro-9H-fluorene derivatives and thiourea with manganese dioxide at room temperature [13, 14].



14 (42–95%)

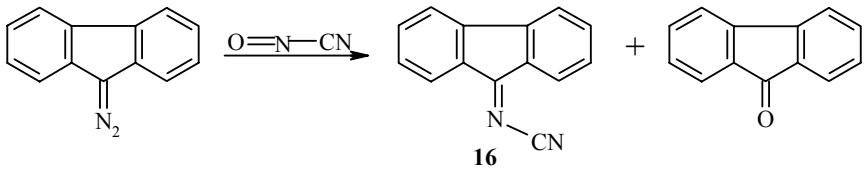
The oxidation of acetophenone guanidinehydrazones, 1- or 2-naphthyl methyl ketone, and benzophenone with lead tetraacetate in mixture with dichloromethaneacetic acid leads to the corresponding N-cyanoimines **15** [15].



15

R = Ph, R^1 = Me; R = α-Np, R^1 = Me; R = β-Np, R^1 = H; R = R^1 = Ph

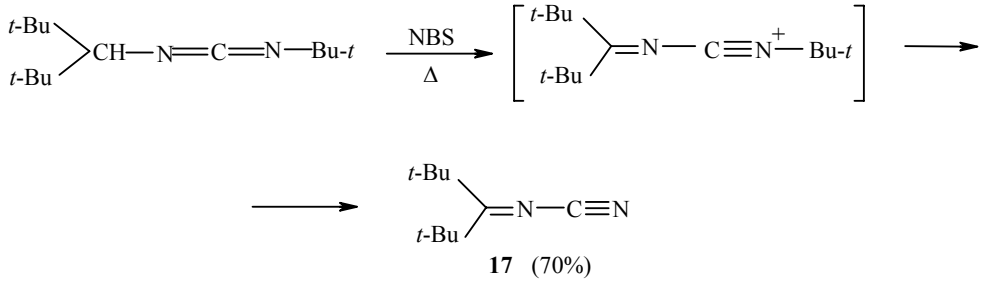
Nitrosyl cyanide converts diazofluorene into 9-cyanoiminofluorene **16** and fluorenone [16].



16

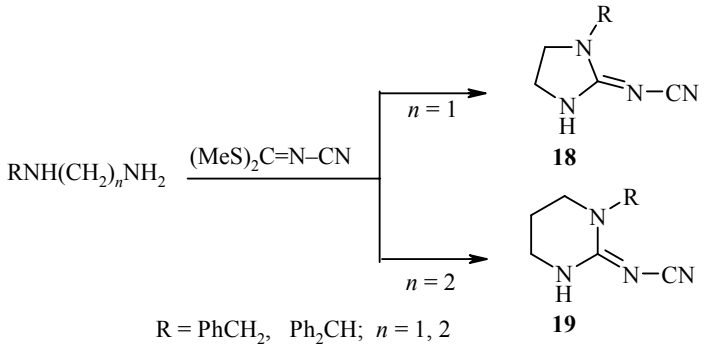
The corresponding cyanoimine **15** (R = R^1 = Ph) and benzophenone are formed similarly from Ph_2CN_2.

When 1-*tert*-butyl-3-(1-*tert*-butyl-2,2-dimethylpropyl)carbodiimide was boiled for 3.5 h with N-bromosuccinimide and then kept at 5°C for 24 h the N-cyanoimine **17** was obtained [17].

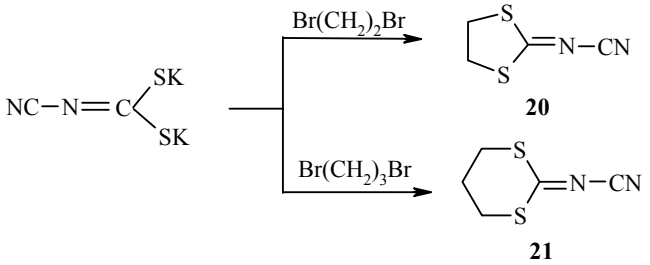


17 (70%)

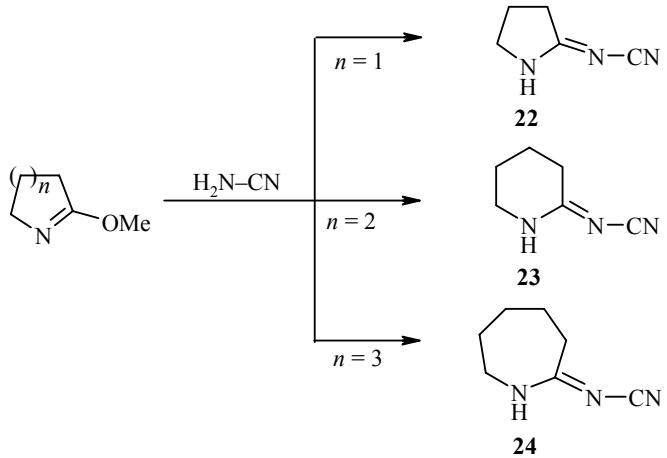
Azaheterocycles and thiaheterocycles containing an N-cyanoimino group were obtained from the alkyl esters of N-cyanodithiocarbonimidic acids or their potassium salts. Thus, for example, 2-cyanoiminoimidazolidines **18** (n = 1) and 2-cyanoimino-1,3-diazines **19** (n = 2) were obtained with good yields by heating dimethyl N-cyanodithiocarbonimidates with diamines (100-200°C, 15 min) [18].



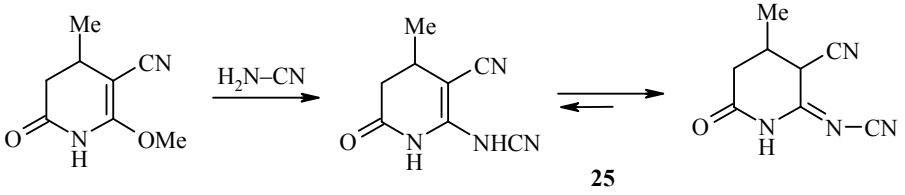
A solution of dipotassium N-cyanodithiocarbonimidate in aqueous acetone reacts with 1,2-dibromoethane and 1,3-dibromopropane at room temperature to form the corresponding 2-cyanoiminodithiolane **20** and 2-cyanoimino-1,3-dithiane **21** [19].



2-Cyanoiminopyrrolidine (**22**), 2-cyanoiminopiperidine (**23**), and 2-cyanoiminohexahydroazepine (**24**) were obtained by the reaction of lactim ethers with cyanamide. The reaction goes smoothly under mild conditions and gives high yields [20].

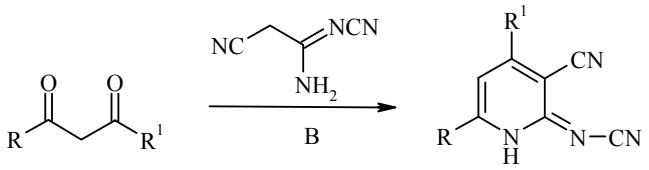


When 5-cyano-6-methoxy-4-methyl-3,4-dihydro-2-pyridone is boiled with cyanamide in dioxane in the presence of sodium and the product is treated with the stoichiometric amount of hydrochloric acid in absolute ethanol or methanol, 5-cyano-6-cyanoimino-4-methyl-3,4-dihydro-2-pyridone (**25**) is obtained. According to the PMR spectra, it exists in equilibrium with the 6-cyanoimino form [21].



25

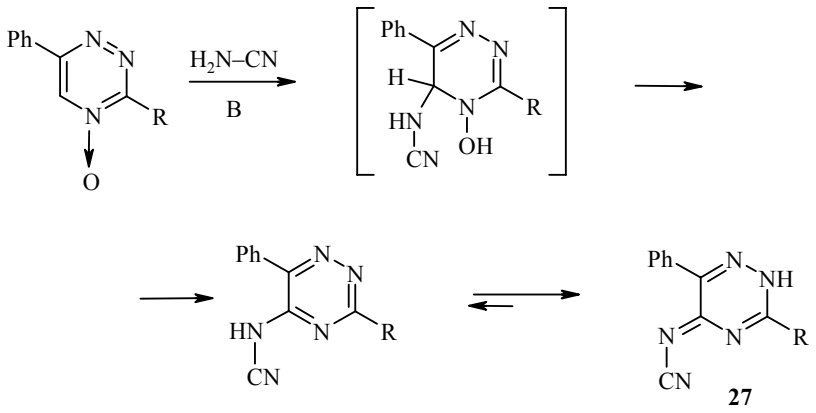
3-Cyano-2-cyanoiminopyridines **26** were obtained from (N-cyano)cyanoacetamidine [22].



26 (42–93%)

R = R^1 = Me; R = Ph, R^1 = Me; R = Ph, R^1 = CF_3

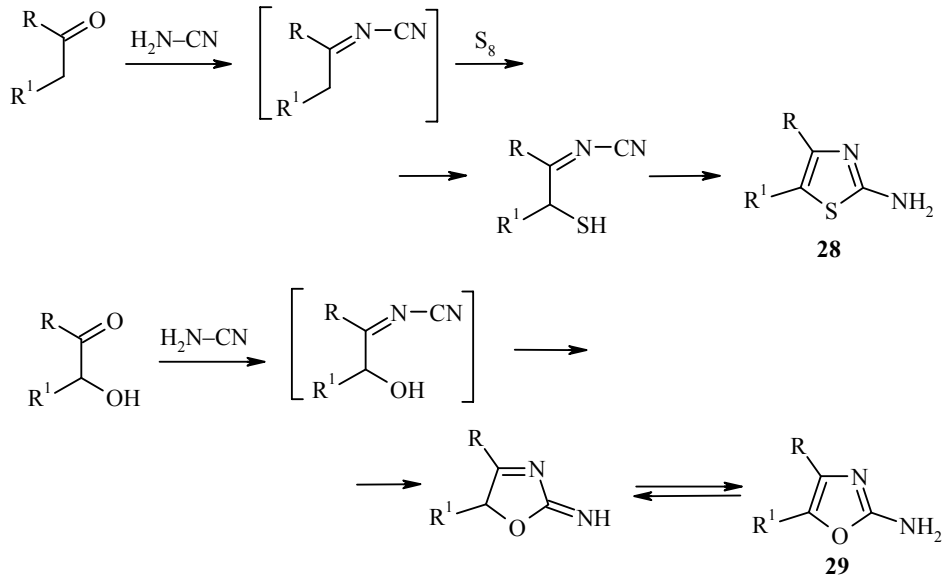
The reaction of the N-oxides of substituted 1,2,4-triazines with cyanamide in the presence of bases gives the corresponding triazinylcyanamide, which exists predominantly in the cyanoimino form **27** [23].



27

2. CHEMICAL PROPERTIES

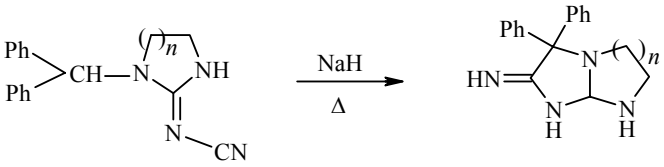
Some examples of intramolecular cyclizations involving an N-cyanoimine fragment, formed as intermediate, and neighboring nucleophilic groups are described in the monographs [24, 25]. Thus, for example, N-cyanoimine fragments are hypothetical intermediate products in the synthesis of 2-aminothiazoles **28** [26] and 2-aminooxazoles **29** [27, 28].



28

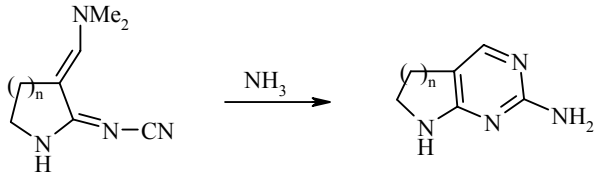
29

The cyclization of substituted 2-cyanoimino-1,3-diazacycloalkanes **18** and **19** to 2-iminoimidazo[1,2-*a*]pyrimidines (*n* = 1) **30** and 2-iminoimidazo[1,2-*a*]pyrimidines (*n* = 2) **31** by heating with sodium hydride has been described [29].



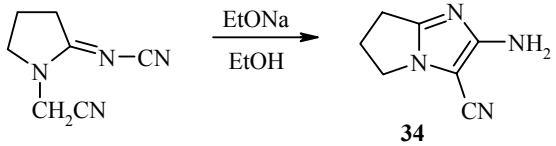
18, **19** **30**, **31**

The condensed pyrrolidines **32** and **33** were obtained by heating 3-dimethylaminomethylene-2-cyanoiminopiperidine and hexahydroazepine with ammonia [20].



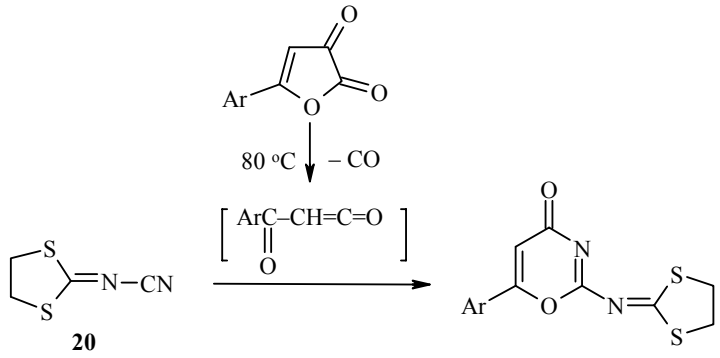
n = 2, 3 **32**, **33**

Brief heating of 1-cyanomethyl-2-cyanoiminopyrrolidine in an alcohol solution of sodium ethoxide (70°C, 5 min) leads to Thorpe–Ziegler cyclization and the formation of 2-amino-3-cyano-5,6-dihydro-7H-pyrrolo[1,2-*a*]imidazole (**34**) [30].

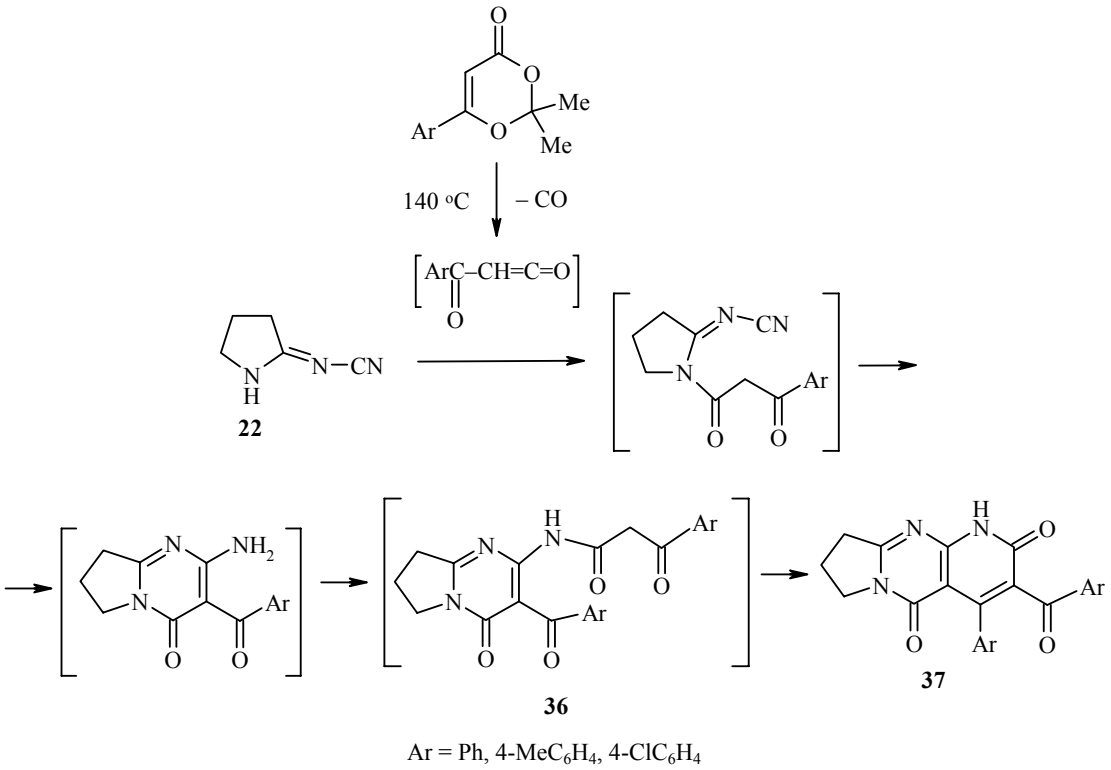


34

2-Cyanoiminodithiolane reacts with aroylketenes, generated from 5-aryl-2,3-dihydrofuran-2,3-diones, with the formation of 2-substituted 6-aryl-1,3-oxazin-4-ones **35** [31]. The reaction takes place by a mechanism of the [4+2]-cycloaddition type, where the aroylketene acts as diene and the cyano group as dienophile. The aroylketene dimers were isolated from the reaction mixture in addition to the oxazinones **35**, indicating that the C≡N bond in cyanoimines has lower reactivity than in cyanamides [32].

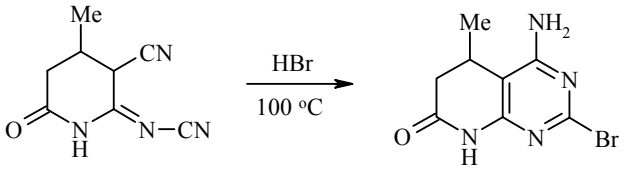


The aroylketenes generated from furandiones do not react with cyanoiminopyrrolidine **22**. However, the aroylketenes obtained from 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones acylate compound **22** at the amino group, and this is followed by intramolecular cyclization of the cyano and methylene groups. The amino group formed in the course of cyclization reacts with a second molecule of the aroylketene. The intermediate compound **36** again undergoes cyclization, giving the condensed pyridopyrimidines **37** [33].



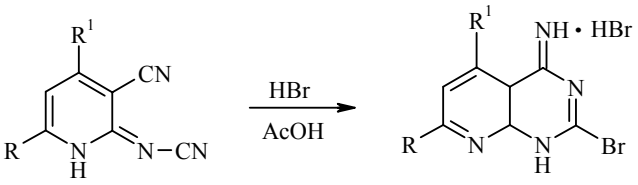
Diketene reacts similarly with the N-cyanoimines **22-24**.

When heated with hydrobromic acid, the N-cyanoimine **25** undergoes cyclization to 5-amino-7-bromo-4-methyl-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1H)-one **38** [21].



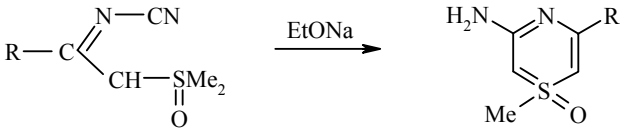
25 **38**

Unlike the N-cyanoimines **25**, the N-cyanoimines **26** undergo cyclization under the action of hydrobromic acid to the hydrobromides of 4-imino-2-bromopyrido[2,3-*d*]pyrimidines **39** [22].



26 **39**

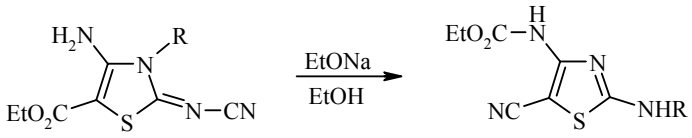
When boiled in ethanol in the presence of sodium ethoxide the N-cyanoimines **40** undergo cyclization to the thiazine 1-oxides **41** [34].



40 **41** (48–82%)

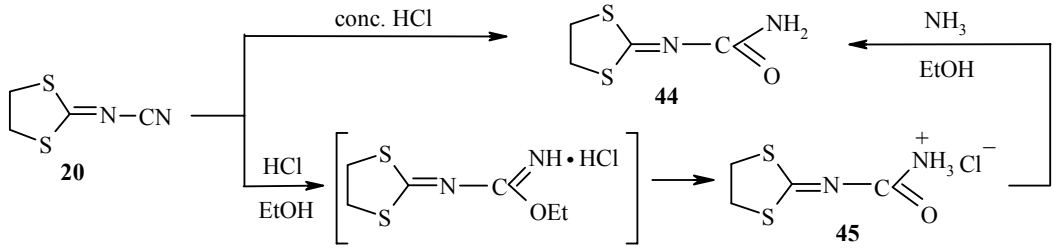
R = Ar, 2-thiophenyl; R^1 = Me, Et

Under the influence of sodium ethoxide the derivatives of 2-cyanoiminothiazoles **42** rearrange to the corresponding thiazole derivatives **43** [35].



42 **43**

An example of the hydrolysis of the cyano group in cyanoimines **20** is the formation of the corresponding ureas **44** and **45** [20].



Compounds **18** and **19** are hydrolyzed similarly [18].

The useful characteristics of cyanoimines may find practical applications in medicine. Thus, for example, the cyanoimines **18** exhibited hypoglycemic activity [18]. The cyanoimines **14** have good electron-accepting characteristics [11]. The cyanoimine **20**, which is a cyclic analog of dimethyl dithiocarbonimidate, has found use as a synthon [19].

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