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OXIMES OF FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH THREE AND FOUR HETEROATOMS 2.*SYNTHESIS OF DERIVATIVES, REACTIONS, AND BIOLOGICAL ACTIVITY (REVIEW)

E. Abele, R. Abele, and E. Lukevics

Data on the reactions of triazole, tetrazole, dioxazole, oxadiazole, and thiadiazole aldoximes, ketoximes, and amidoximes, their synthesis, and the reactions of their derivatives are reviewed. The synthesis of new heterocycles based on the oximes of five-membered heterocyclic compounds with three and four heteroatoms is examined separately. The principal results from investigation of the biological activity of ethers of these oximes are also presented.

Keywords: oxadiazole, oxime, tetrazole, thiadiazole, triazole, biological activity.

The oximes of five-membered heterocyclic compounds with three and four heteroatoms are widely used as intermediates in fine organic synthesis. In the review [1] we examined methods for their production and features of their structure. In the present article we discuss the reactions of triazole, tetrazole, dioxazole, oxadiazole, and thiadiazole aldoximes, ketoximes, and amidoximes and their derivatives. Methods for the synthesis of new heterocyclic systems from derivatives of these oximes are discussed in a separate section. In the last section of the review some results from investigation of the biological activity of the ethers of these oximes are presented.

1. CHEMICAL TRANSFORMATIONS OF THE OXIMES OF FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH THREE AND FOUR HETEROATOMS

1.1. Synthesis of O-Derivatives of the Oximes

1.1.1. O-Ethers of Triazole Oximes. The principal method for the production of the ethers of triazole oximes is alkylation with alkyl halides in the K_2CO_3/DMF [2], K_2CO_3/MeCN [3], NaOH/Bu_4NI/PhMe [4], and NaOH/$PhCH_2$/$Me_3N^+OH^-$/PhMe [5] systems. In addition, the O-ethers of triazole oximes have been

*For Communication 1, see [1].

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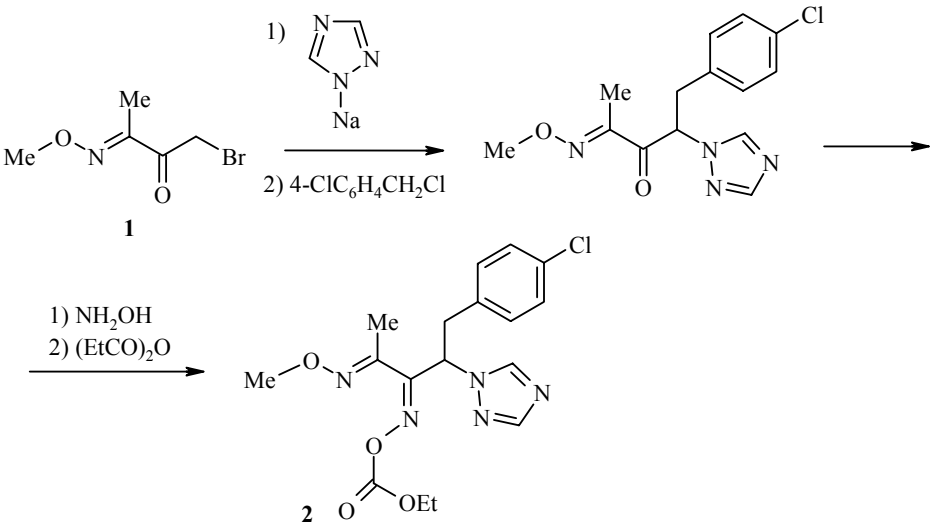
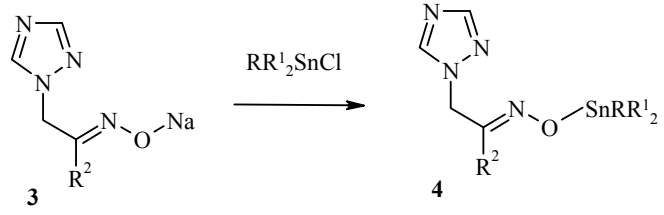
obtained from the carbonyl derivatives and O-alkyl derivatives of hydroxylamines (or their hydrochlorides) in pyridine/ethanol [6], aqueous ammonium acetate [7], or K_2CO_3/MeOH system [8].

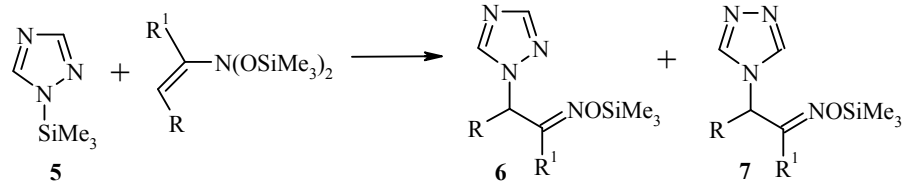
A four-stage method was developed for the synthesis of the O-ethers derivatives of triazole dioximes, used as plant growth regulators. The oxime O-ether **1** reacts with the sodium salt of triazole with subsequent alkylation of the ketone group at the α position. Reaction of the intermediate with hydroxylamine and acylation with propionic anhydride gives the O-ether **2** as the only product [9].



The sodium salts of triazole oximes **3** react readily with $RR^1{}_2SnCl$, forming the fungicidal O-trialkylstannyl oximes **4** [10]. At room temperature without a solvent N-trimethylsilyltriazole (**5**) and N,N-bis-(silyloxy)enamines, which are formal β-carbon electrophiles, form a mixture of two isomeric O-trimethylsilyl oximes **6** and **7** with a total yield of up to 100% [11].



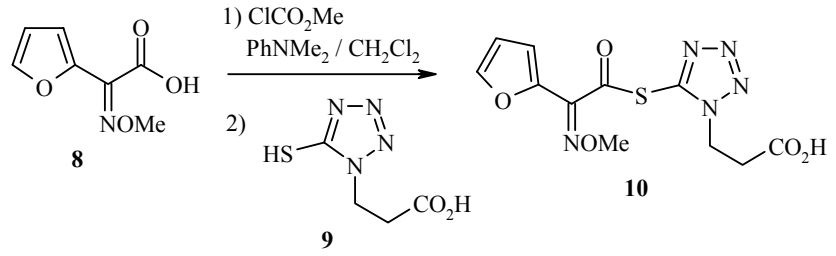
R, R^1 = Alk, Ph; R^2 = CMe_3, Ph



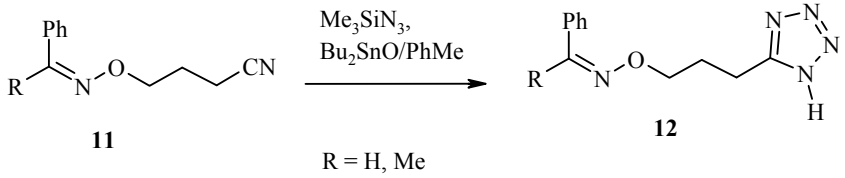
R, R^1 = H, Me

1.1.2. O-Ethers of Tetrazole Oximes. The O-ethers of tetrazole oximes are produced in the reactions of the respective oximes with alkyl halides in the NaH/DMF system [12].

Subsequent reaction of the oxime O-ether **8** with $ClCO_2Et$, dimethylaniline in CH_2Cl_2, and the tetrazole derivative **9** leads to the formation of the tetrazole oxime O-methyl ether **10** with a yield of 78% [13].

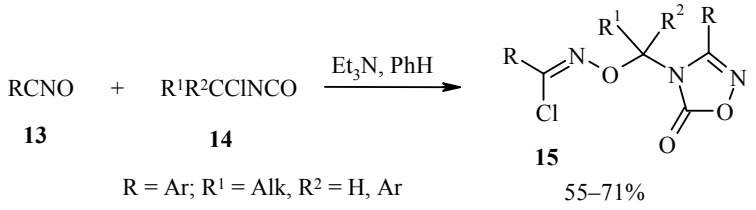


Several papers have been devoted to synthesis of the ethers of tetrazole oximes with the tetrazole fragment in the O-alkyl chain [14-16]. Thus, the reaction of the O-(3-cyanopropyl) oximes **11** in the Me_3SiN_3/Bu_2SnO/toluene system at 100°C leads to the O-[3-(5-tetrazolyl)propyl] oximes **12** with yields of 39-43% [16].

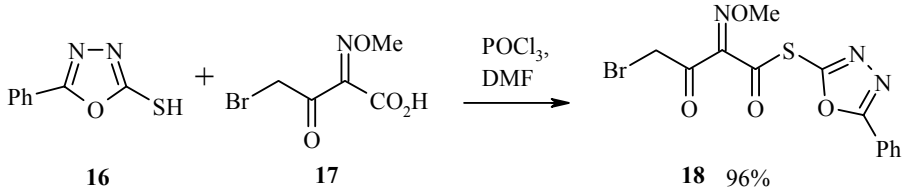


1.1.2. O-Ethers of Oxadiazole and Thiadiazole Oximes. O-Acylated 1,2,4-oxadiazoles were obtained in the reaction of the corresponding oximes in a system with an acylating agent such as $ClP(=S)(OR_2)/NaHCO_3/Bu_3N$ [17] or 1,4-diazabicyclo[2.2.2]octane/CH_2Cl_2 [18].

The oxime O-ethers **15** with a 1,2,4-oxadiazole fragment in the O-alkyl chain were obtained by the reaction of two molecules of the nitrile oxides **13** with 1-chloroalkyl isocyanates **14** in the presence of triethylamine [19]. The product **15** is formed through a [3+2] cycloaddition stage.

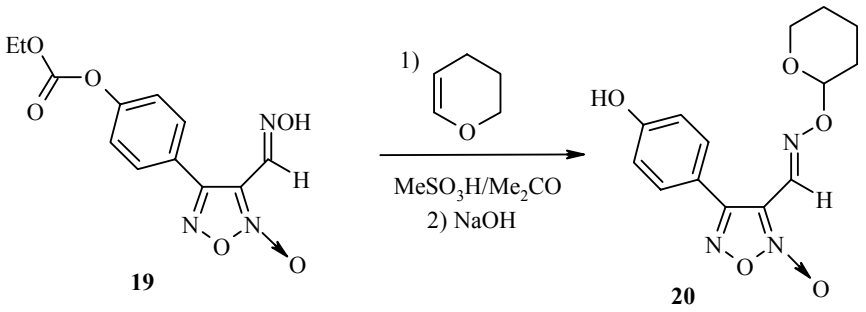


1,3,4-Oxadiazole O-alkyl oxime fragments are present in cephalosporin antibiotics. The reaction of 2-mercapto-5-phenyl-1,3,4-oxadiazole **16** with the oxime ether **17** in the presence of $POCl_3$ gives the O-ether **18**, which is an intermediate in the synthesis of antibiotics [20].

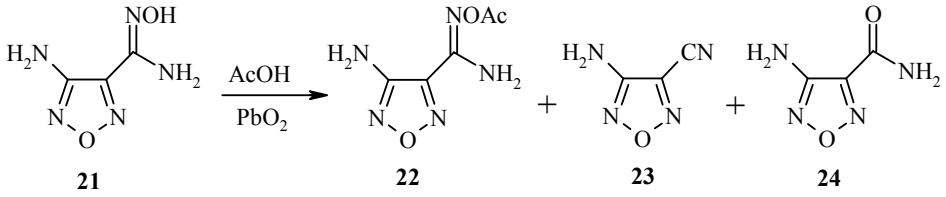


The O-ethers of furazan oximes are usually obtained by alkylation of the corresponding oximes with alkyl halides in the presence of alkali. Thus, during the alkylation of 4-aminofurazan-3-carboxamide oxime with methyl iodide in the presence of alkali the corresponding O-methyl ether is formed as the only product [21].

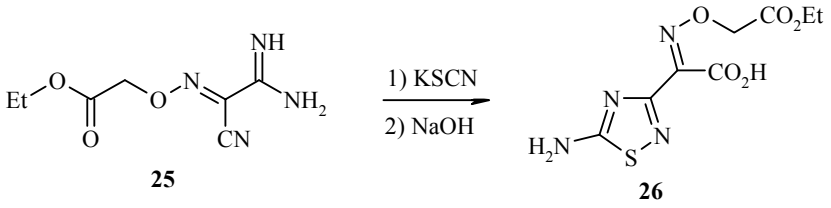
3,4-Dihydro-2H-pyran can also be used for alkylation. Its addition to the hydroxyl group of the oxime **19** in an acidic medium (methanesulfonic acid) followed by alkaline hydrolysis of the ester group gives the O-(tetrahydro-2H-pyran-2-yl) oxime **20** with a yield of 49% [22].



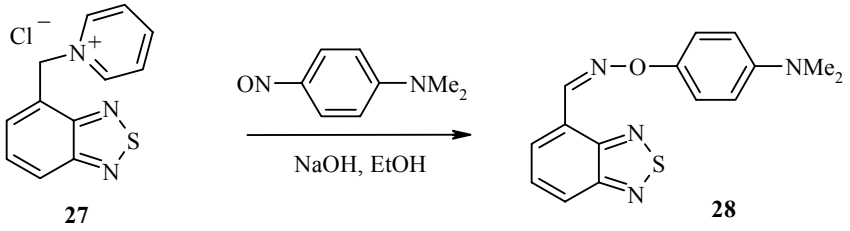
The reaction of the amidoxime of 4-aminofurazan-3-carboxylic acid (**21**) with lead dioxide leads to the formation of a mixture of three products **22**-**24**, one of which is the O-acetyl derivative **22** [23].



The O-ethers of thiadiazole oximes are widely used as intermediates in the synthesis of cephalosporin antibiotics [24-30]. The reaction of the ether **25** with potassium thiocyanate followed by hydrolysis gives the 1,2,4-thiadiazole O-alkyl oxime **26** [25].

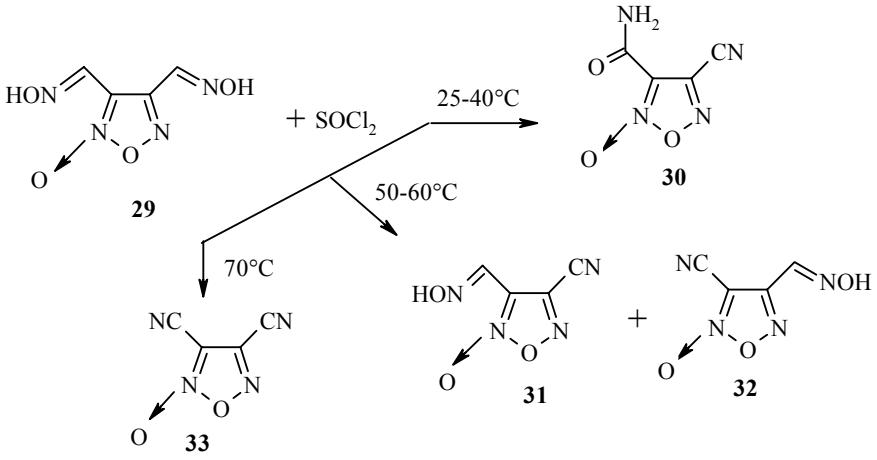


In a basic medium the pyridinium salt **27** reacts readily with nitrosodimethylaniline, forming the oxime ether **28** [31].

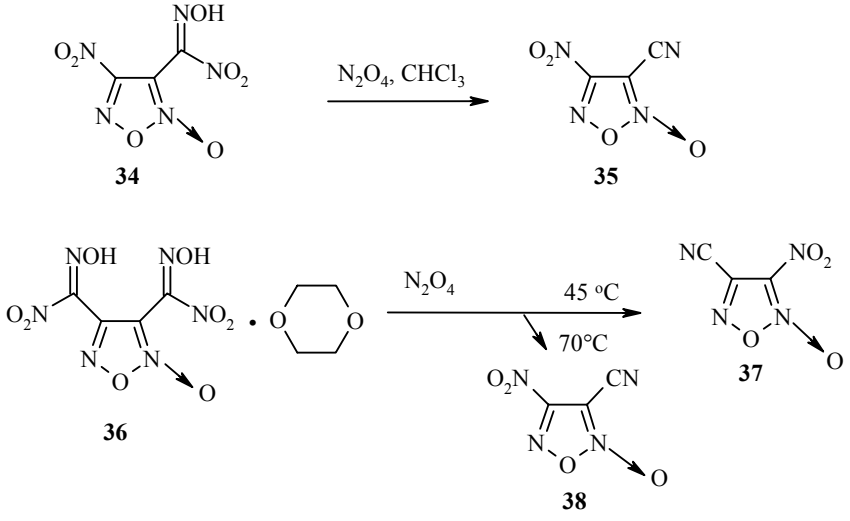


1.2. Transformations of the Oxime Group

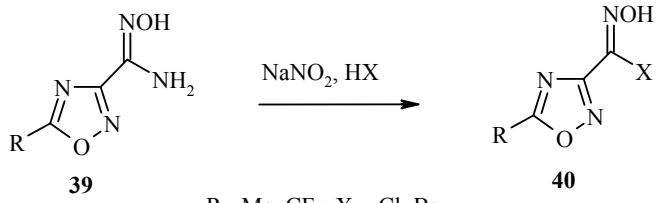
In the presence of Ac_2O [32, 33] or $SOCl_2$/DMF [22] 1,2,5-thia- and 1,2,5-oxadiazole aldoximes are converted into nitriles. The degree of dehydration of diformylfuroxan dioxime **29** depends substantially on the conditions under which it is performed [34]. In the presence of an excess of SO_2Cl at 25-40°C compound **29** is converted into 4-cyanofuroxan-3-carboxamide **30**. At increased temperature (50-60°C) and with a shorter reaction time (5 min) the formation of a mixture of isomeric mononitriles **31** and **32** is observed. In boiling thionyl chloride the dinitrile **33** is formed.



Reaction of the nitrolic acid **34** with N_2O_4 in chloroform at 60°C also leads to a nitrile **35**. At 45°C the furoxandinitrolic acid **36**, produced from furoxan dialdoxime and N_2O_4 in the N_2O_4/dioxane system, forms 4-cyano-3-nitrofuroxan **37**. At higher temperature (70°C) the more stable isomer **38** is formed [35-37].

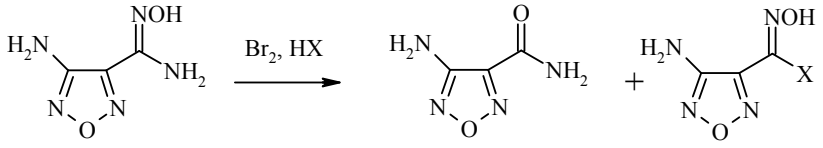


The reaction of 1,2,4-oxadiazole amidooximes**39** with sodium nitrite in hydrochloric and hydrobromic acids gives the corresponding halogen derivatives **40** with yields of 61-68% [38]. However, direct bromination of the amidoxime **41** in a solution of sulfuric or hydrobromic acid leads to a mixture of two compounds – the amide **42** and the bromide **43**. If this reaction is carried out in hydrochloric acid the chloro oxime **43** (X = Cl) is obtained [21].



39 **40**

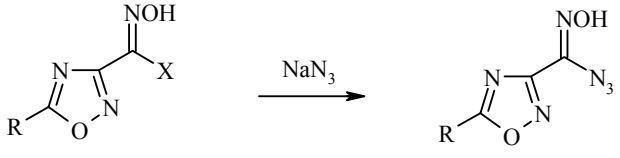
R= Me, CF_3; X = Cl, Br



41 **42** **43**

X = Cl, Br

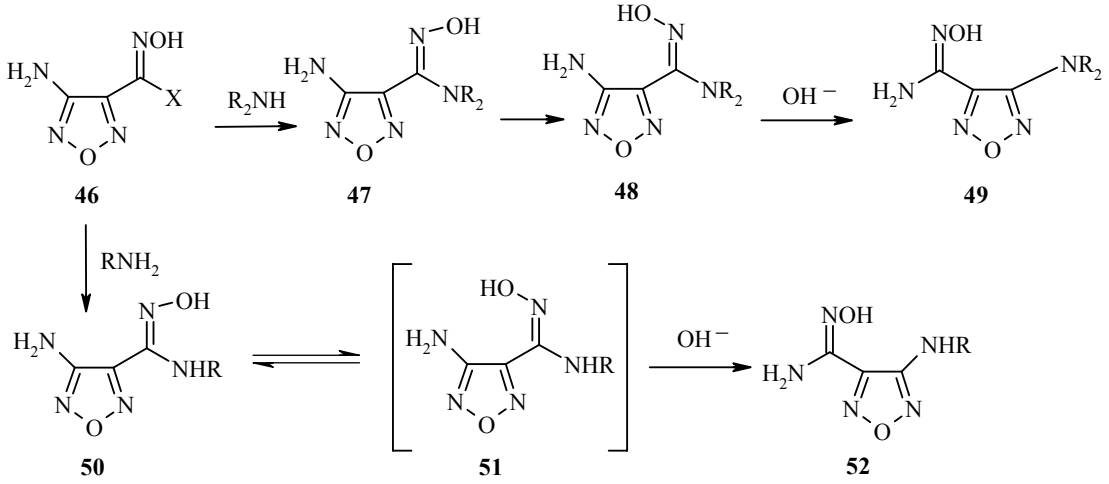
The reactions of oxadiazole halo oximes with various nucleophilic reagents have been widely investigated. Thus, in reaction with sodium azide the halogen derivatives of 1,2,4-oxadiazole-3-carbohydroxamic acids **44** give the corresponding azide derivatives **45** [39]. 1,2,5-Oxadiazole chloro oximes react in a similar way [40].



44 **45**

R = H, CF_3; X = Cl, Br

In the reaction of 4-aminofurazan-3-carbohydroxamoyl halides **46** with amines the corresponding *Z*-isomers of amidoximes are formed. N,N-Disubstituted *Z*-amidoximes **47** are unstable and readily isomerize to the *E*-amidoximes **48**. When heated in the presence of alkali these products rearrange with opening of one furazan ring and closure of the other and form the N-substituted aminofurazans **49**. For N-monosubstituted amidoximes **50** under the conditions of the rearrangement the equilibrium is displaced toward the *Z*-isomer of **50**. The reaction products **49** and **52** were isolated with yields of 65-92% [41]. Similar rearrangements of furazan amidoximes in an alkaline medium were examined in detail in the review [42] and in a series of publications (e.g., [43, 44]).

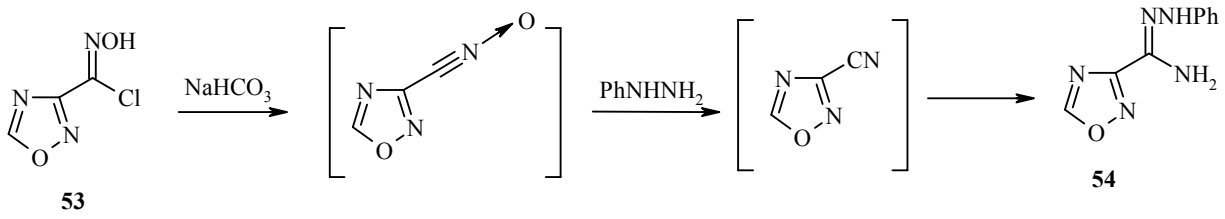


46 **47** **48** **49**

50 **51** **52**

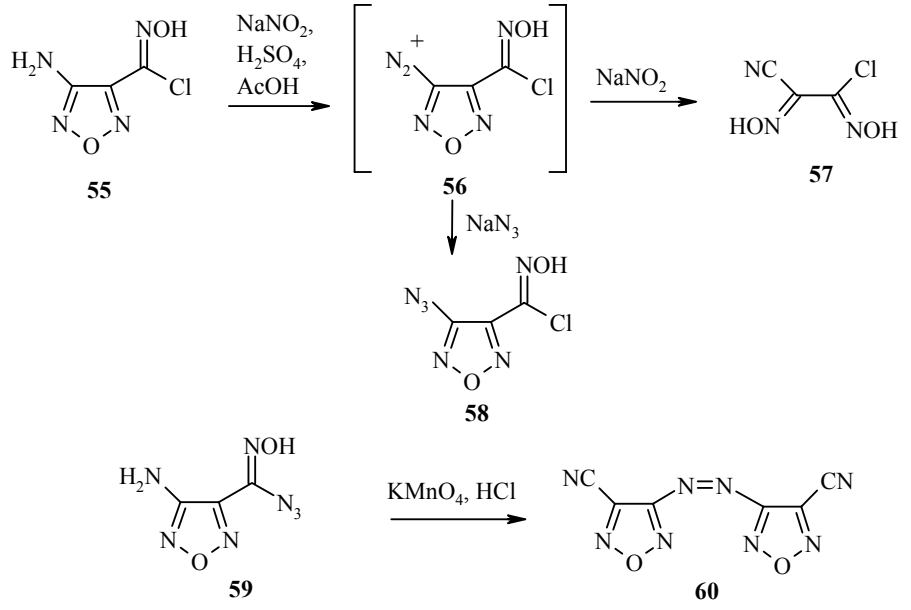
X = Cl, Br; R = Alk, Ar

Reaction of the chloro oxime **53** with phenylhydrazine in the $NaHCO_3/H_2O/Et_2O$ system gives the amidrazone **54** (yield 50%) instead of the expected hydrazine oxime [45, 46].



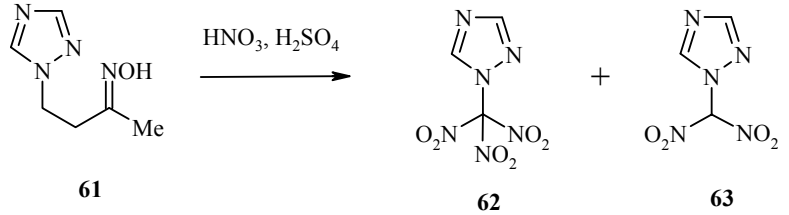
53 **54**

The synthesis and reactivity of the amino derivatives of 1,2,5-oxadiazole oximes were studied in detail by the authors of [40]. Thus, under diazotization conditions the chloro oxime **55** gives the diazonium salt **56**, which is then transformed into the dioxime **57**. It is interesting that treatment of the intermediate **56** with an aqueous solution of sodium azide leads to the oxadiazole **58** with a yield of 87%. Substitution of the chlorine by azide hardly occurs at all on account of the small equilibrium concentration of azide ion in the acidic medium. The azido oxime **59** is oxidized by potassium permanganate in 20% aqueous hydrochloric acid, forming the dicyanoazofurazan **60** with a yield of 39%.



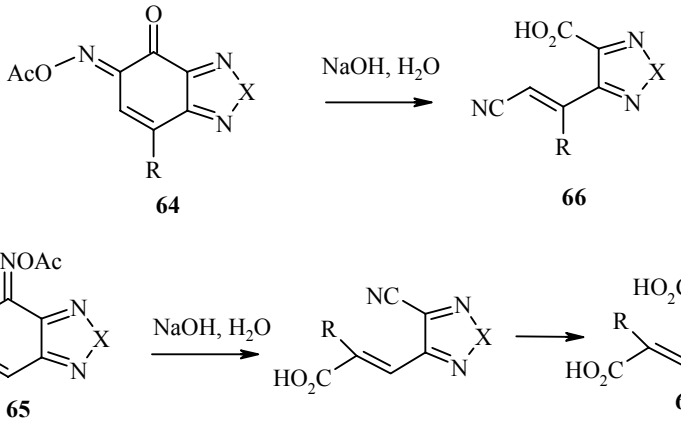
55 **56** **57** **58** **59** **60**

Nitration of the triazole oxime **61** in the HNO_3/H_2SO_4 system leads to the formation of two nitro products **62** and **63** [47].



61 **62** **63**

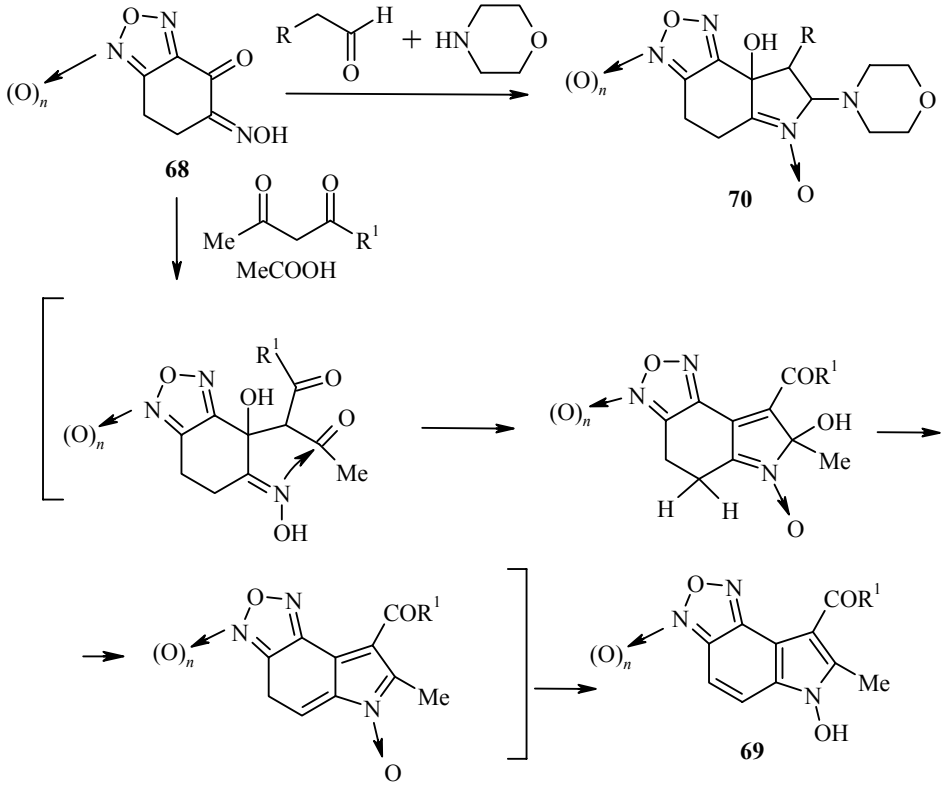
In an aqueous solution of sodium hydroxide the mono-O-acetyloximes of benz[1,2,5]oxadiazole- and benzo[1,2,5]thiadiazole-4,5-diones **64** and **65** form the oxa- and thiadiazoles **66** and **67** respectively as a result of hydrolysis and a Beckmann rearrangement [48].



X = O, S; R = H, Me, Cl

1.3. Synthesis of New Heterocyclic Systems from Five-Membered Heterocyclic Compounds with Three and Four Heteroatoms

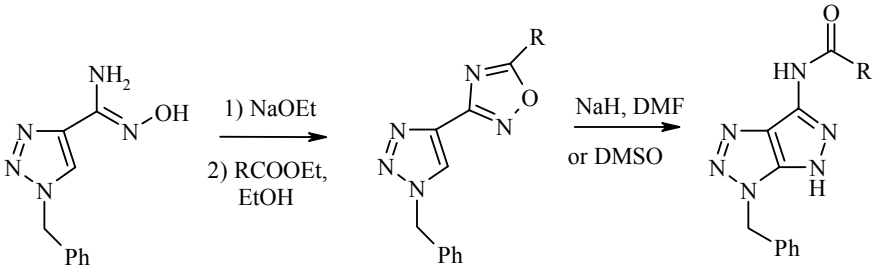
Recent advances in the synthesis of heterocyclic systems from oximes were reviewed in [49]. In this section specific reactions involving cyclization of the oximes of five-membered heterocyclic compounds with three and four heteroatoms will be set out in greater detail.



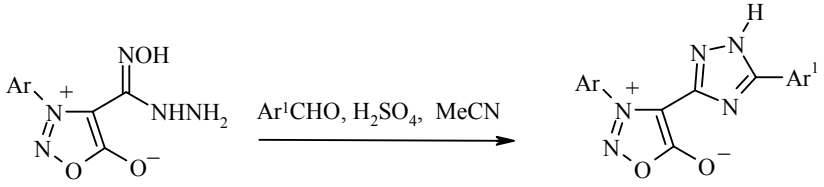
R = H, Me; R^1 = Me, OEt; *n* = 0, 1

The reaction of 5-hydroxyimino-4-oxo-4,5,6,7-tetrahydrobenzofurazan or furoxan **68** with ethyl acetate or acetoacetic ester leads to the formation of indoles **69** with yields of 46-69% [50]. The reaction of compounds **68** with aldehydes (acetaldehyde and propionaldehyde) and morpholine gives tetrahydroindoles **70** with yields of 70-82% [51, 52].

The reaction of the triazole amidoxime **71** with sodium ethoxide followed by treatment of the reaction mixture with an alcohol solution of an ester gives 1,2,4-oxadiazoles, which then rearrange in the presence of sodium hydride to the pyrazoles **72** [53].

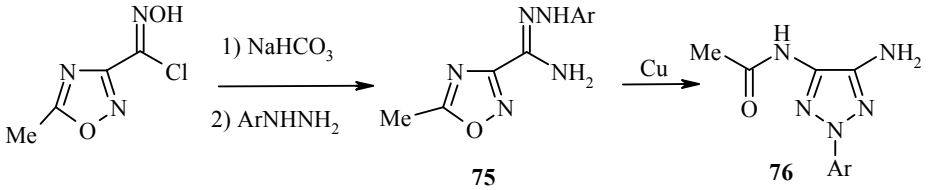


The hydrazine derivatives of oxadiazole oximes **73** and aldehydes in an acidic medium undergo cyclization with the formation of triazoles **74** [54].

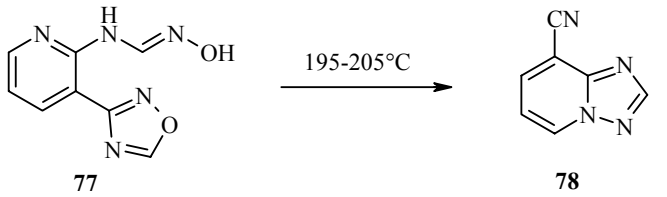


Ar = Ph, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$; Ar^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, Het

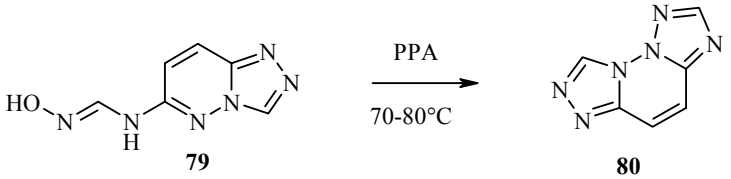
Triazoles are also produced during the rearrangement of oxadiazole oximes. Thus, the rearrangement of the amidrazone **75** in the presence of copper powder at the melting point of the substance without a solvent leads to the formation of the triazole **76** with a yield of 50% [45, 46]. The thermal reaction of the oxime **77** in a sealed tube at 195-205°C gives 8-cyanotriazolo[1,5-*a*]pyridine **78** with a yield of 37% [55]. The triazole oxime **79** in PPA at 70-80°C gives the tricyclic compound **80** with a yield of 21% [56].



Ar = 4-$NO_2C_6H_4$

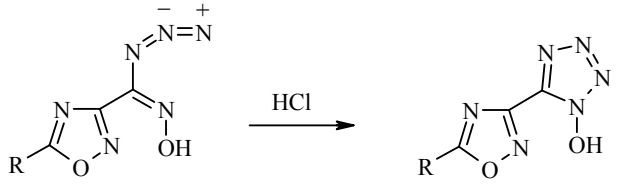


77 **78**



79 **80**

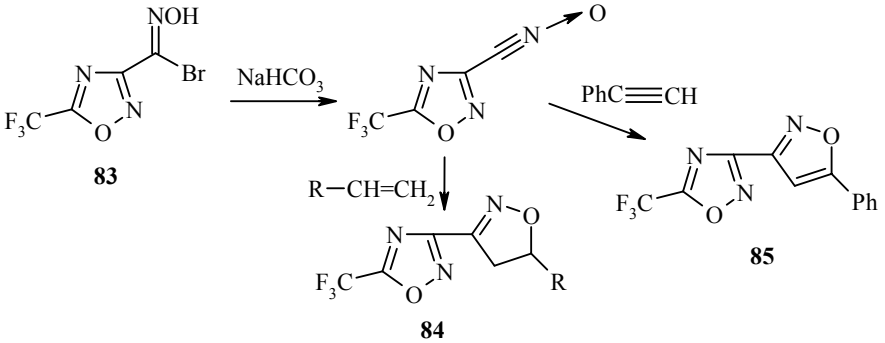
In an acidic medium oxadiazole azidoximes undergo cyclization to tetrazole derivatives [39, 40, 57]. Thus, *Z–E*-isomerization of the azidoximes **81**, which takes place readily during the action of hydrogen chloride in ether, leads to closure of the tetrazole ring **82** [39].



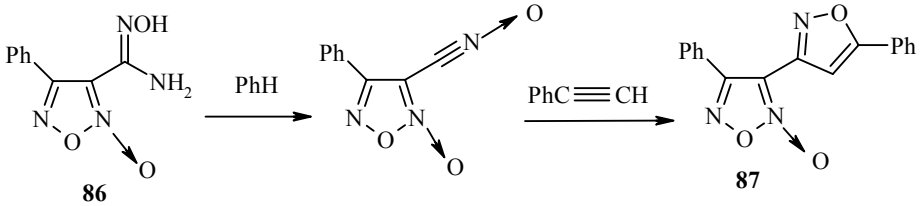
81 **82**

R = H, CF_3

A series of methods have been described for the synthesis of isoxazole derivatives from oxadiazole halo oximes and alkenes or alkynes [58, 59]. In the presence of a base ($NaHCO_3$) the bromo oxime **83** gives a nitrile oxide, which enters readily into cycloaddition with alkenes or alkynes and forms dihydroisoxazole **84** or isoxazole **85** respectively [58]. A furoxan nitrile oxide was successfully generated by the thermal reaction of the nitrolic acid **86** in boiling benzene. Its reaction with phenylacetylene gives the isoxazole **87** with a yield of 60% [60].

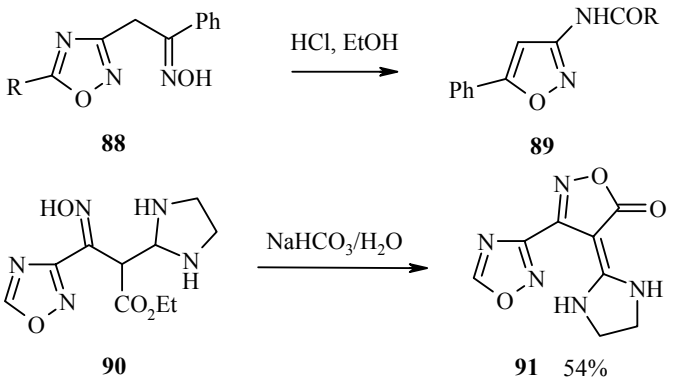


83 **84** **85**



86 **87**

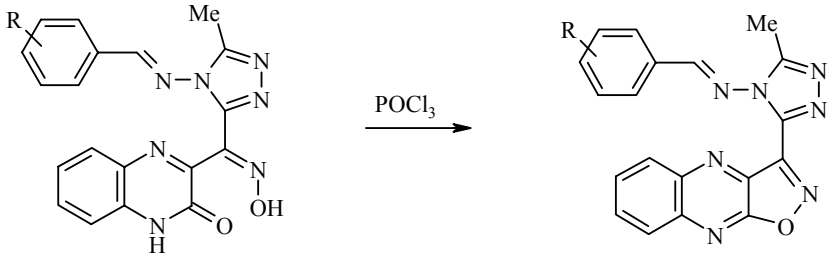
In an acidic medium the 1,2,4-oxadiazole oximes **88** rearrange and form isoxazole amides **89** [61]. In the presence of a base the oxime **90** undergoes cyclization to the isoxazolone **91** [62].



88 **89**

90 **91** 54%

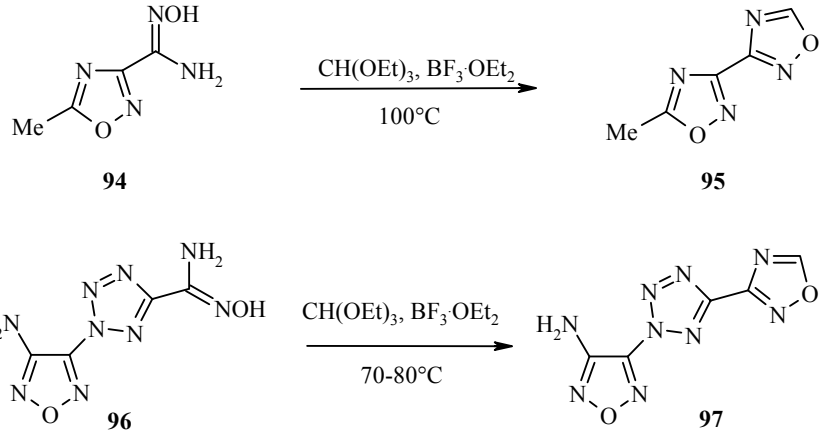
The cyclization of triazole oximes **92** takes place in boiling phosphorus oxychloride with the formation of isoxazolo[4,5-*b*]quinoxalines **93** with yields of 76-91% [63, 64].



92 **93**

R = Me, $CH_2CH{=}CH_2$

The reaction of 1,2,4-oxadiazole oxime **94** with triethyl orthoformate in the presence of boron trifluoride etherate at 100°C leads to the formation of the 1,2,4-oxadiazolyl-1,2,4-oxadiazole derivative **95** with a yield of 86% [38]. Similar closure in the case of the tetrazole oxime **96** leads to a 1,2,4-oxadiazole ring **97** [65].

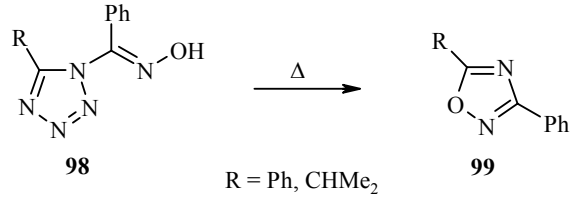


94 **95**

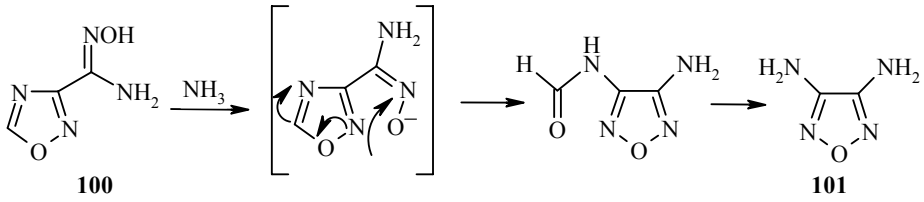
96 **97**

In the presence of an aldehyde, an acidic catalyst, and trifluoroacetic or trichloroacetic anhydride respectively 1,2,3- [66], 1,2,4- [67, 68], and 1,2,5-oxadiazole [69] amidoximes also form a new 1,2,4-oxadiazole ring.

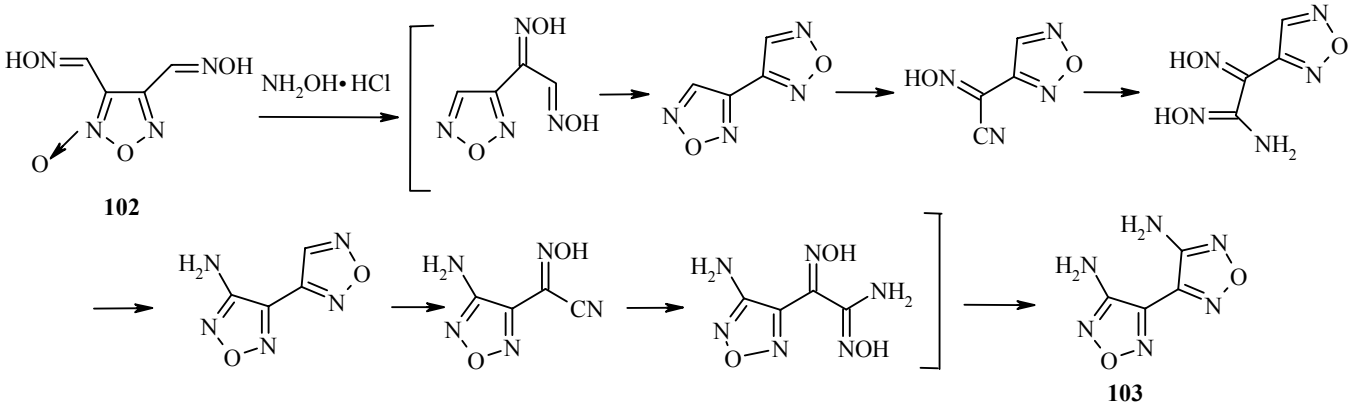
Thermolysis of 1,2,4-oxadiazole amidoximes **98** in *para*-xylene gives quantitative yields of 1,2,4-oxadiazoles **99** [70, 71].

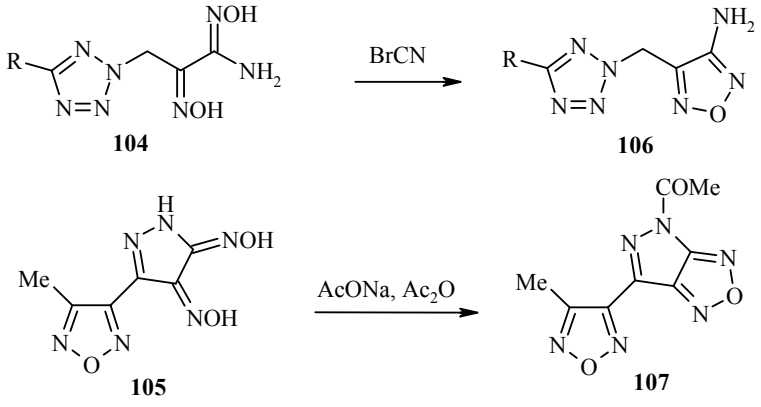


The rearrangement of 1,2,4-oxadiazole amidoximes, leading to the amino derivatives of furazans, was described in detail in the review [42] and in numerous articles such as [46, 72, 73]. Thus, in aqueous ammonia the amidoxime **100** gives the furazan **101** with a yield of 40% [72].

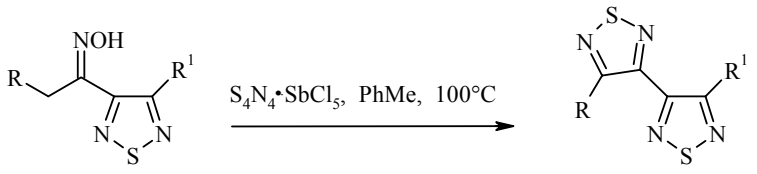


The reaction of 3,4-di(hydroxyiminomethyl)furoxan **102** with hydroxylamine hydrochloride gives 4,4′-diamino-3,3′-bifurazan **103** [74]. Cyclization of the tetrazole **104** [75] or furazan **105** [76] dioximes during the action of cyanogen bromide or in the presence of $AcONa/Ac_2O$ also leads to the formation of furazan derivatives **106** and **107** respectively.



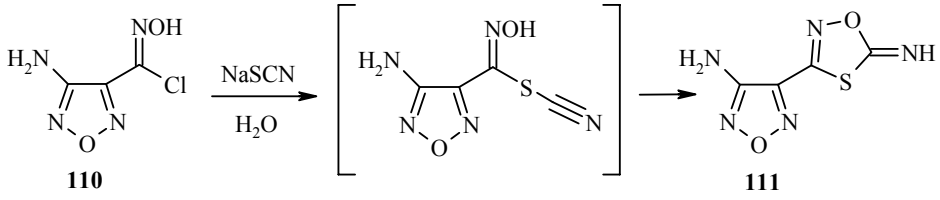


The bi-1,2,5-thidiazoles **109** were obtained by the cyclization of 1,2,5-thiadiazole ketoximes **108** in reaction with $S_4N_4 \cdot SbF_5$ in boiling toluene [77]. 3,3′:4′3″-Ter-1,2,5-thiadiazole was obtained in a similar way from thiadiazole dioxime [78].



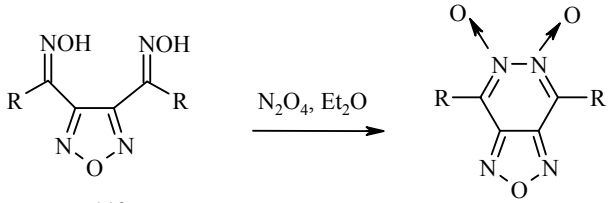
108 **109** 28-80%

The reaction of the chloro oxime **110** with sodium thiocyanate leads to the formation of a derivative of 4,1,2-thiaoxazole **111** with a yield of 59% [79].



110 **111**

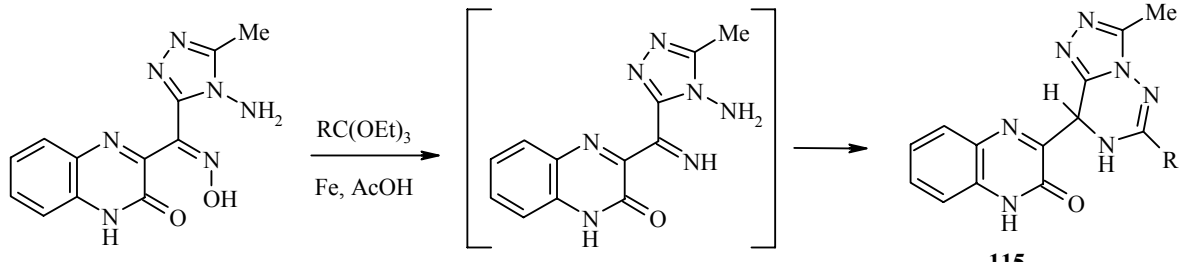
Triazole and oxadiazole oximes were also used for the synthesis of six-membered heterocyclic compounds. Thus, with liquid N_2O_4 in ether the furazan dioximes **112** undergo cyclization with the formation of a furazano[3,4-*d*]pyridazine ring **113** [80].



112 **113**

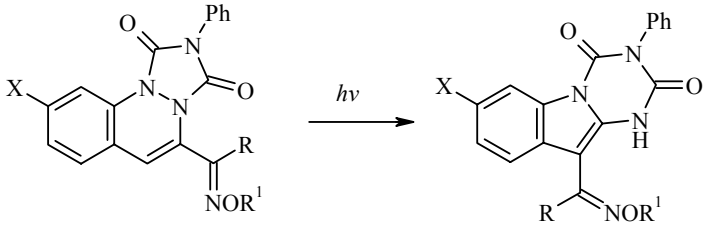
R = Alk

Cyclization of the triazole oxime **114** in the orthoether/Fe/AcOH system gives 1,2,4-triazolo[3,4-*f*]-triazines **115** with yields of 47-56% [64]. Photoirradiation of the triazole oximes **116** leads to cleavage of the N–N bond and rearrangement to the triazine oximes **117** [81].



114 **115**

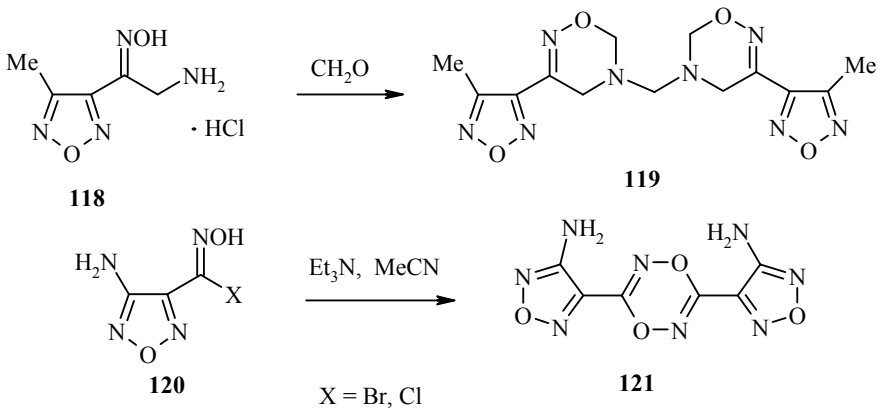
R = H, Me



116 **117**

X = H, Cl, OMe; R, R^1 = Alk

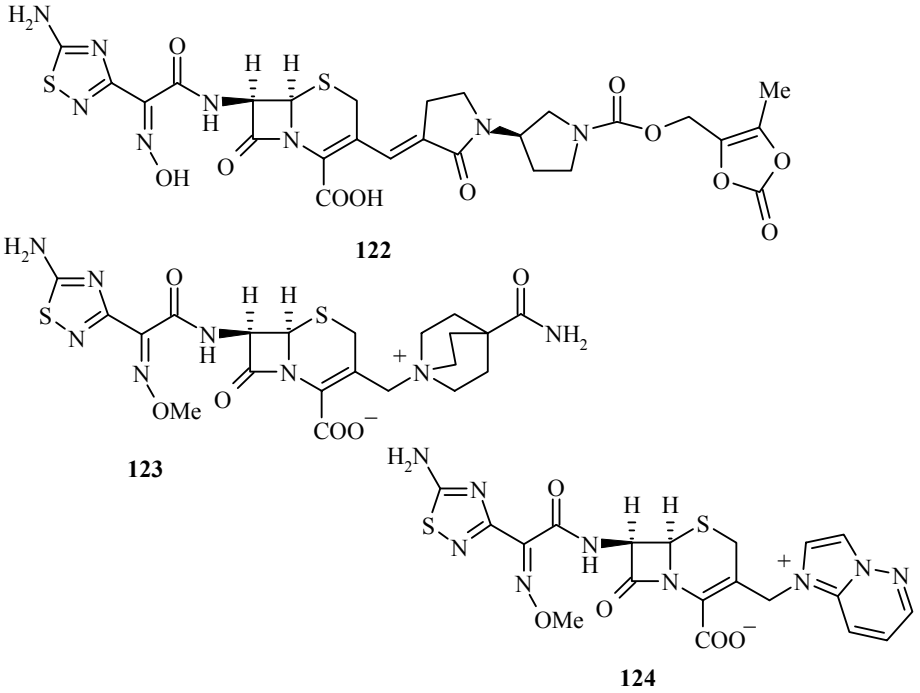
The reaction of the aminomethyl oxime hydrochloride **118** with formaldehyde leads to the oxadiazines **119** [82]. Under the influence of triethylamine the halo oximes **120** form the nitrile oxides, which dimerize to 1,4,2,5-dioxadiazine **121** [79, 83].

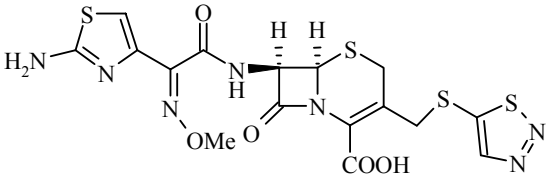


2. BIOLOGICAL ACTIVITY OF THE OXIME ETHERS OF FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH THREE AND FOUR HETEROATOMS

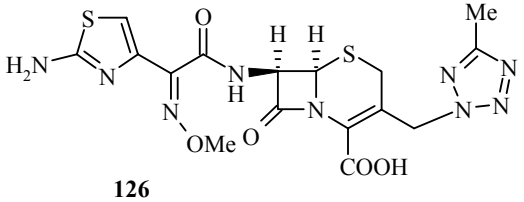
2.1. Bactericidal and Cytotoxic Activities

Antibacterical agents based on thiadiazole and tetrazole oximes *Ceftobiprole Medocaril* **122**, *Cefclidin* **123**, *Cefozopran* **124**, *Cefuzonam* **125**, *Cefteram* **126**, and *Cefmenoxime* **127** have found widespread applications [84-86]. In addition to these widely used products, it is necessary to mention the very wide range of patents and publications devoted to cephalosporin antibiotics containing hydroxyimino fragments, 1,2,4-thia-diazole [87-147] and tetrazole [148-156] fragments, and also triazole [157, 158], 1,2,4-oxadiazole [159, 160], 1,3,4-oxadiazole [161, 162], 1,2,3-thiadiazole [163, 164], and 1,3,4-thiadiazole [165-167] fragments.

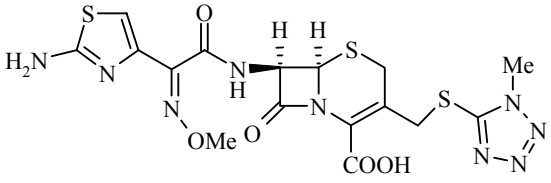




125



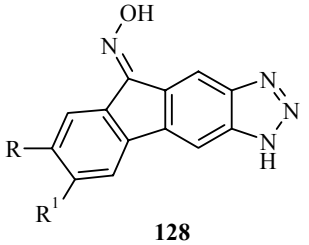
126



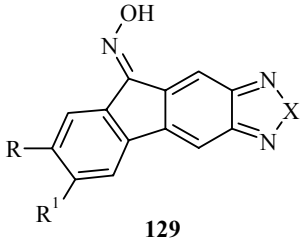
127

1,2,5-Oxadiazole amidoximes exhibited high activity against *Chlamydia pneumoniae* [168].

Fluoreno[2,3-*d*]-1,2,3-triazoles **128** and **129** inhibit various kinases. These compounds were tested as antitumor agents [169].



128



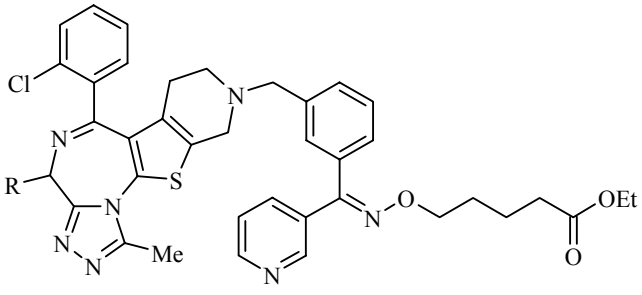
129

X = O, S; R, R^1 = H, Alk, Cl, Br

The oximes **12**, which have a tetrazole fragment in the O-alkyl chain, were investigated as cytotoxic agents on tumor cells [15].

2.2. Action on the Cardiovascular System

The oximes **130** were studied as antagonists of the thrombocytes activating factor and inhibitors of thromboxane synthetase [170-173]. These compounds can be proposed for the treatment of ischemic heart disease and other diseases associated with circulation of the blood.



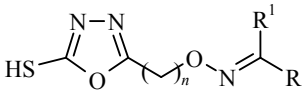
130

R = H, Me

1,2,5-Thiadiazole oximes have exhibited β-adrenergic blocking activity [174].

2.3. Anti-inflammatory Activity

The oximes **131**, which have an oxadiazole fragment in the O-alkyl chain, exhibited anti-inflammatory activity [175].

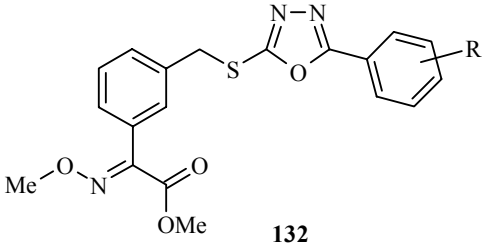


131

R, R^1 = Alk, Ph; *n* = 1, 2

2.4. Oximes of Five-Membered Heterocyclic Compounds with Three and Four Heteroatoms as Fungicides, Pesticides, Herbicides, and Insecticides

The oxime derivatives of triazole [2, 4, 176-195], tetrazole [196, 197], oxadiazole [198-202], and thiadiazole [203-205] have high fungicidal activity. Of these compounds it is necessary to mention specially the oxime ethers **132**, which have high fungicidal activity against *Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Physalospora piricola,* and *Bipolaris mayelis* [201].



132

R = H, Cl, Br, I, NO_2, Alk, OMe

Pesticidal activity was exhibited by derivatives of triazole [206-212], tetrazole [213], oxadiazole [214, 215], and thiadiazole [216] oximes.

The literature contains data on the herbicidal activity of triazole [217-219] and tetrazole [220] oximes. Triazole oximes have exhibited high insecticidal activity [221-227].

In addition, thiadiazole oximes have been used as agricultural microbicides [228], and the O-ethers of triazole oximes as plant growth regulators [9, 229, 230].

2.6. Other Activities

Triazole [231], oxadiazole [232], and thiadiazole [233] oximes have been investigated as antidotes for poisoning by organophosphorus compounds.

Triazole oximes are used as markers for cancerous diseases [234].

The oximes of dibenzo[*a*,*e*]triazolo[4,5-*c*]cycloheptanes were used for diseases associated with a growth hormone deficiency [235].

Derivatives of oxadiazole oximes are inhibitors of elastase hydroxylase [236] and antagonists of oxytocin receptors [237]. 1,2,5-Oxadiazole amidoximes have been proposed as modulators of indoleamine-2,3-dioxygenase [238].

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