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# OXIMES OF FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH THREE AND FOUR HETEROATOMS 1. SYNTHESIS AND STRUCTURE (REVIEW)

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

*Data on the production methods and structure of triazole, tetrazole, dioxazole, oxadiazole, and thiadiazole aldoximes and ketoximes and their derivatives are reviewed.*

**Keywords:** dioxazole, oxadiazole, oxime, tetrazole, thiadiazole, triazole.

The oximes of five-membered heterocyclic compounds are widely used as intermediates in fine organic synthesis. In this review the principal methods for the production of triazole, dioxazole, oxadiazole, and thiadiazole aldoximes, ketoximes, and amidoximes and their derivatives are summarized. The principal methods for the investigation of the structure of the oximes of five-membered heterocyclic compounds with three and four heteroatoms are examined briefly with due regard to isomerism. The reactions and the biological activity of the oximes of five-membered heterocyclic compounds with two heteroatoms will be examined in the second part of the review.

## 1. SYNTHESIS

### 1.1. Synthesis of Triazole Aldoximes, Ketoximes, and Amidoximes

The classical method for the synthesis of triazole ketoximes is based on the reaction of a ketone with hydroxylamine in pyridine [2] or an aqueous solution of $K_2CO_3$ [3].

Triazole oximes were obtained as a result of nitrosation of the alkyl chain in the corresponding alkyl derivatives. The nitrosating agents included $NaNO_2$/HCl [4, 5], $NaNO_2/H_2O$/AcOH [6, 7], $NaNO_2/H_2O/H_2SO_4$ [8], and *i*-BuONO/NaOEt/EtOH [9]. Sometimes different products are formed depending on the amount of the nitrosating agent. Thus, the reaction of the triazole **1** with 1.25 equiv of the nitrosating agent ($HNO_2$) leads to the N-amino derivative **2** with a yield of 79%. If the same reaction is conducted in the presence of 2.5 equiv of $HNO_2$ the triazole oxime **3** is formed as the only product [10].

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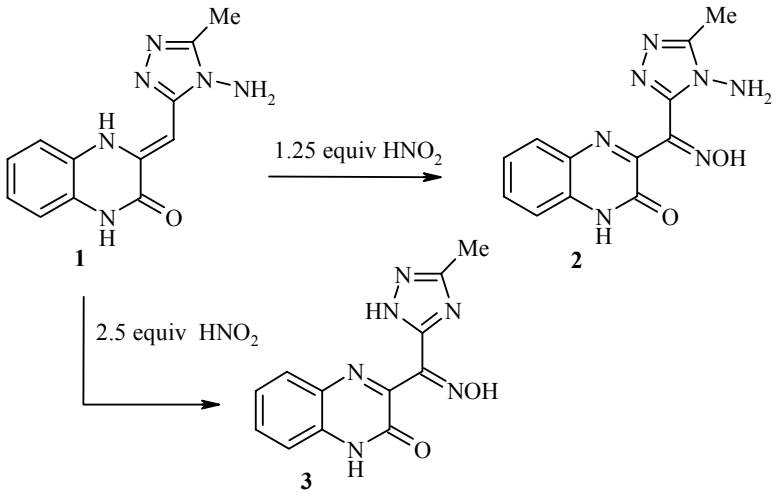
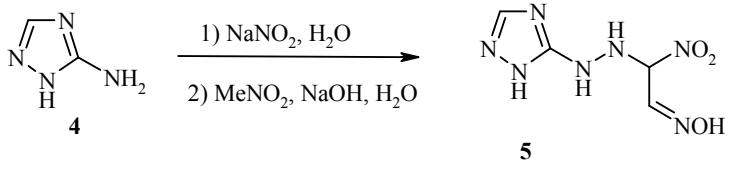
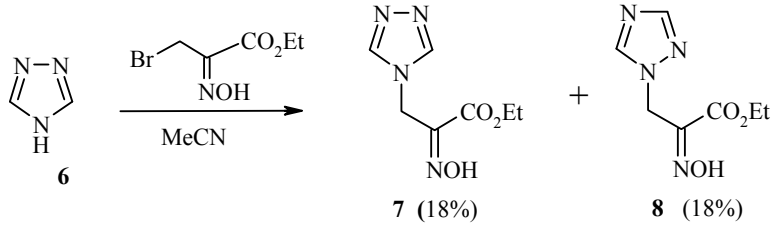
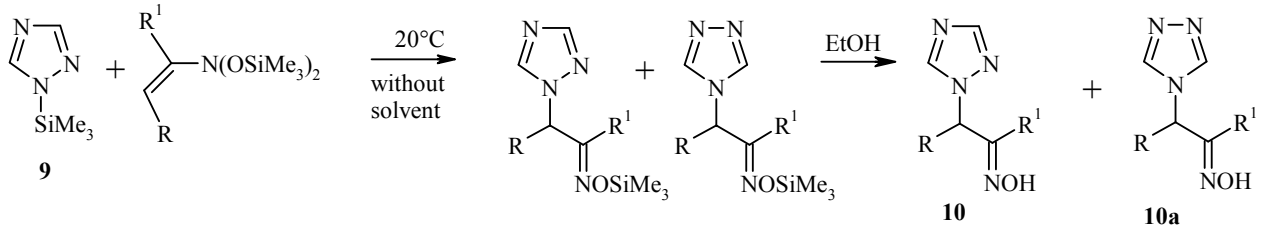



The diazotization of 3-amino-1,2,4-triazole (**4**) with sodium nitrite followed by treatment of the reaction mixture with an alkaline solution of nitromethane gives the oxime **5** with a yield of 42% [11]. The product **5** is formed through a diazotization stage followed by reaction with the sodium salt of nitromethane.



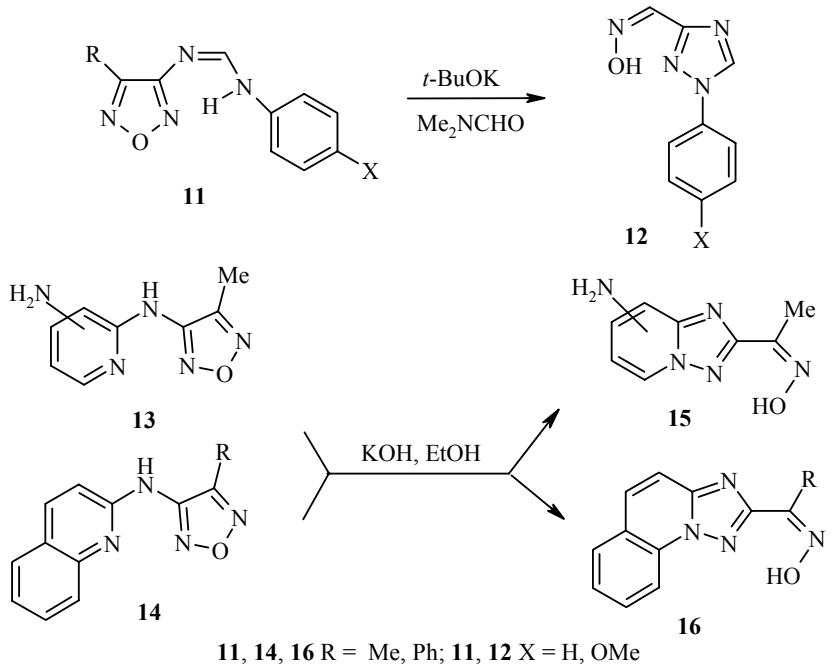

There are published data on the synthesis of N-triazolylalkanone oximes. The alkylation of 1,2,4-triazole (**6**) with ethyl 3-bromo-2-hydroxyiminopropionate in acetonitrile gives a mixture of two isomeric oximes **7** and **8** [12]. The addition of N-trimethylsilyltriazole (**9**) to N,N-bis(silyloxy)enamines, which are formal analogs of β-carbon electrophiles, followed by desilylation with ethanol gives the isomeric triazole oximes **10** and **10a** with yields of up to 100% [13].




R, R$^1$ = H, Me

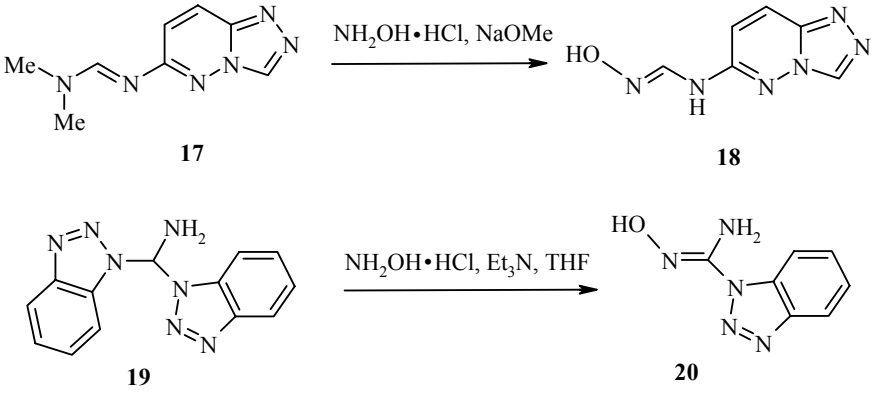
Opening of the oxadiazole ring in the imino derivatives of 1,2,5-oxadiazoles (**11**) by the action of potassium *tert*-butoxide gives the triazole aldoximes **12** with yields of 60-80% [14, 15]. In an alcohol solution of alkali the pyridyl- and quinolylaminooxadiazoles **13** and **14** also open the oxadiazole ring and then undergo cyclization to triazoles with inclusion of the pyridine nitrogen in the ring. Here the oximes of triazolo-[1,5-*a*]pyridines **15** or triazolo[1,5-*a*]quinolines **16** are formed with yields of up to 70% [16].



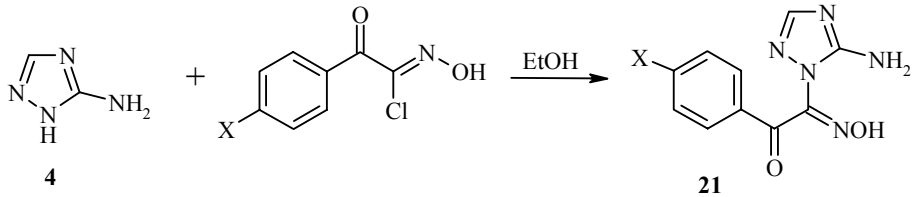

**11**, **12** X = H, OMe

**13**, **14**, **15**, **16** R = Me, Ph

Triazole amidoximes are usually obtained from the corresponding nitriles and hydroxylamine in ethanol [17], but imines can also be used for this purpose. Thus, 6-hydroxyiminomethyleneiminotriazolo-[4,3-*b*]pyridazine (**18**) was obtained from the imine **17** in the $NH_2OH{\cdot}HCl/NaOMe$ system [18]. A good leaving group in this reaction is benzotriazole. For example, [di(1H-1,2,3-benzotriazol-1-yl)methyl]amine (**19**) in the $NH_2OH{\cdot}HCl/Et_3N/THF$ system gives the amidoximes (**20**) with a yield of 89% [19].

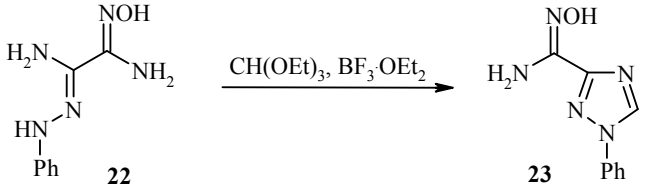



3-Amino-1,2,4-triazole **4** and α-chlorooximes of the $XC_6H_4COC(Cl){=}NOH$ type in ethanol are easily transformed into the corresponding amidoximes **21**, isolated with yields of 60-75% [20].

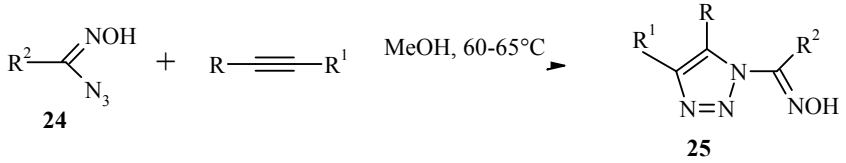


X = H, $NO_2$

The cyclization of the oxime **22** with orthoformic ester in the presence of $BF_3 \cdot OEt_2$ gives the amidoximes of 1-phenyl-1,2,4-triazole-3-carboxylic acid (**23**) with a yield of 38% [21].

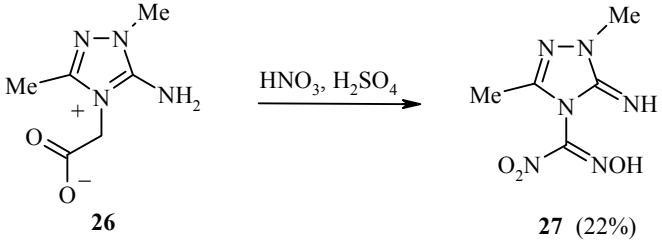


1,3-Dipolar cycloaddition of the azidoximes **24** to alkynes in methanol leads to the formation of triazole oximes **25** with yields of 15-79% [22, 23].



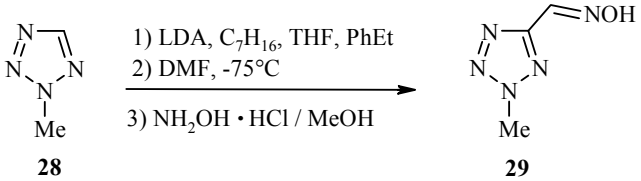
R = H, COOMe; $R^1$ = COOMe, $CH_2OH$, Ph; $R^2$ = Alk, Ar

Reaction of the triazolium salt **26** with a nitrating mixture ($HNO_3/H_2SO_4$) gives the oxime **27** [24].

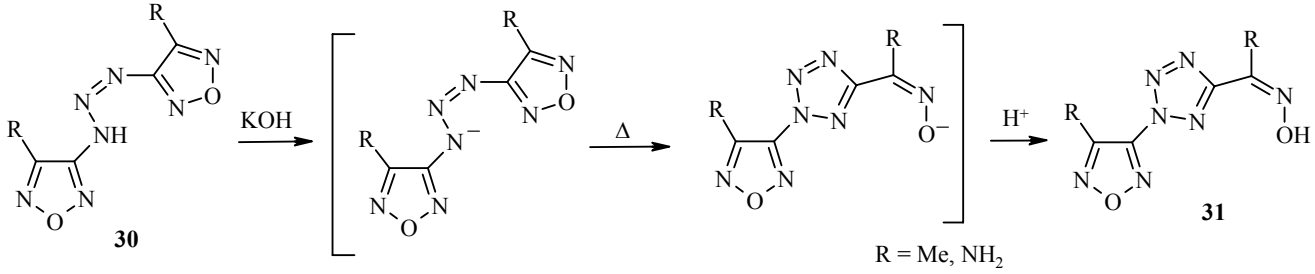


## 1.2. Synthesis of Tetrazole Aldoximes, Ketoximes, and Amidoximes

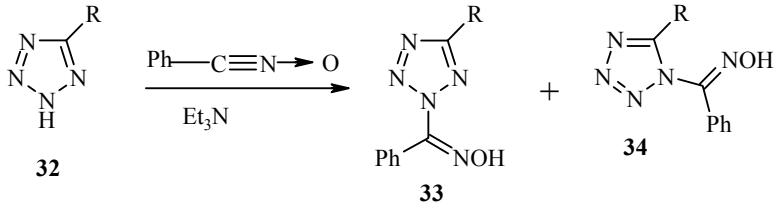
Tetrazole aldoximes and ketoximes are usually obtained from the corresponding carbonyl compounds and hydroxylamine hydrochloride in the presence of pyridine in ethanol [25] or sodium acetate in methanol [26]. A new method was recently developed for the synthesis of the tetrazole aldoxime **29** from N-methyl-tetrazole (**28**) in the lithium diisopropyl amide (LDA)/THF/heptane/ethylbenzene system followed by treatment of the reaction mixture with DMFA and hydroxylamine hydrochloride [27].



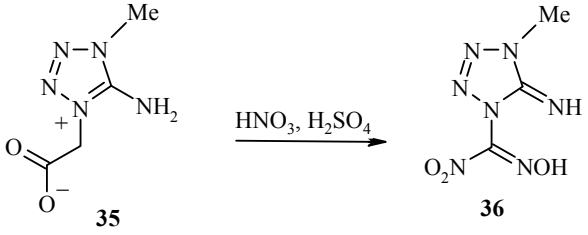
Under the conditions of base catalysis (KOH in water) the difurazanyltriazenes **30** form the oxime derivatives of 2-furazanyltetrazoles **31** with yields of 74-86% as a result of rearrangement of one of the heterocycles [28].




The reaction of tetrazoles **32** with benzonitrile N-oxide and triethylamine in dioxane gives a mixture of two tetrazole oximes **33** and **34** [29].

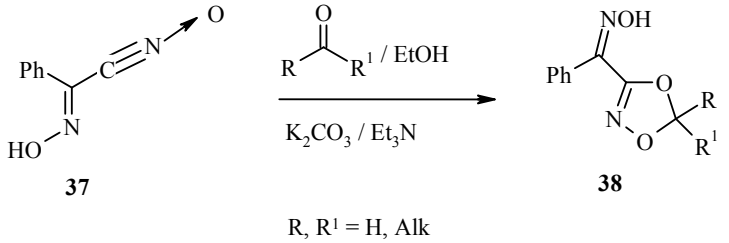



With a nitrating mixture ($HNO_3/H_2SO_4$) the betaine **35** gives the oxime **36** with a yield of 10% [24].



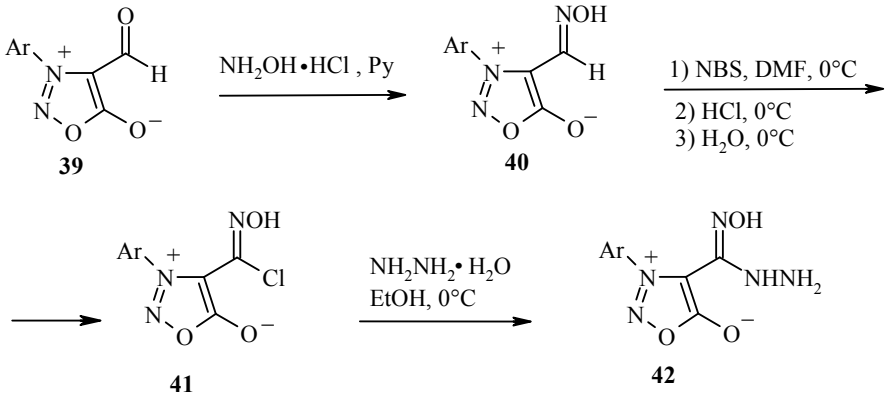

### 1.3. Synthesis of 1,4,2-Dioxazole Ketoximes

α-Hydroxyiminonitrile oxide **37** reacts readily with aldehydes and ketones, forming 1,4,2-dioxazole ketoximes **38** [30].

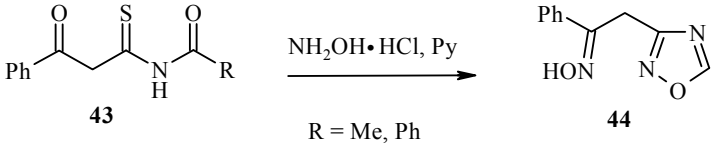


### 1.4. Synthesis of 1,2,3- and 1,2,4-Oxadiazole Aldoximes, Ketoximes, and Amidoximes

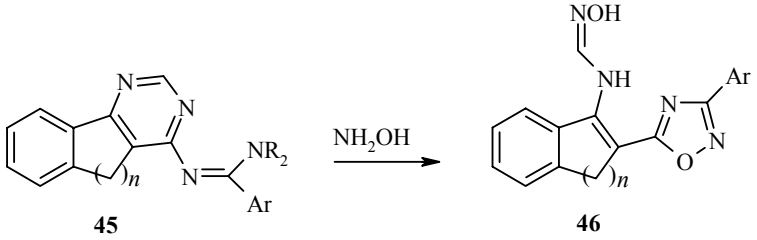
The synthesis of oxime derivatives of 1,2,3-oxadiazoles was described in detail in [31]. The aldehydes **39** and hydroxylamine hydrochloride in pyridine give the aldoximes **40**. The latter are readily halogenated in NBS/DMF and then with HCl, forming the corresponding chlorides **41**. The reaction of compound **41** and hydrazine in ethanol gives the hydrazine derivatives **42** with yields of 83-95%.

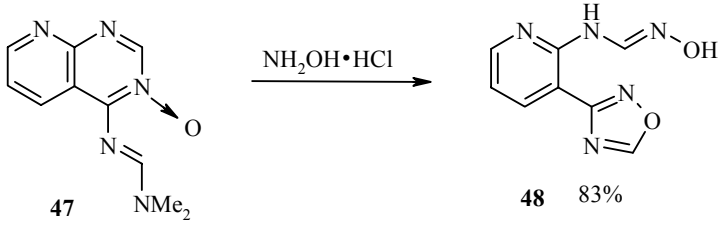



The acylated benzoylthioacetamides **43** and hydroxylamine hydrochloride in pyridine form the oximes of 1,2,4-oxadiazoles **44** [32].

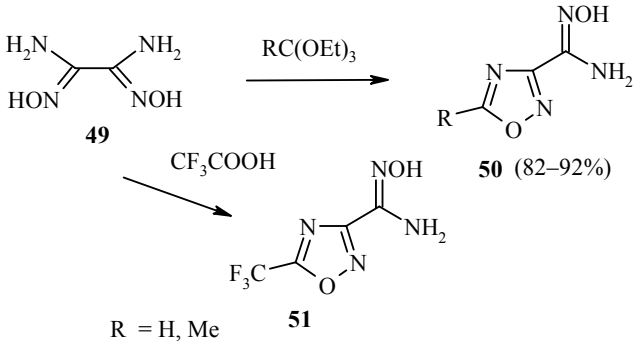



The amidoximes of 1,2,4-oxadiazoles are obtained from the corresponding nitriles and hydroxylamine hydrochloride in the presence of sodium methoxide in methanol [33]. They can also be obtained from amidines containing a pyrimidine ring. The action of an excess of hydroxylamine on them leads to cyclization of the amidine group to 1,2,4-oxadiazole, while the pyrimidine ring is split with the formation of amidoximes. 1,2,4-Oxadiazole amidoximes **46** were successfully synthesized in this way from the amidines **45** [34]. The oxime **48** is formed in a similar way from the N,N-dimethylaminomethyleneamino derivative **47** and hydroxylamine hydrochloride in methanol [35].



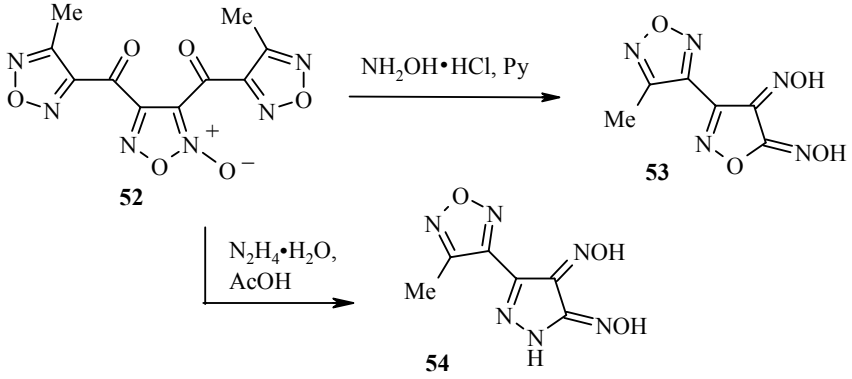
The reaction of diaminoglyoxime (**49**) with ethyl orthoformate and orthoacetate (a twofold excess in relation to the substrate) in the presence of boron trifluoride etherate leads to the amidoximes of 1,2,4-oxadiazole-3-carboxylic acid **50**. If the reaction time is increased and larger amounts of the orthoester are used both oxime groups enter into the reaction, and bisoxadiazoles are formed. If the cyclization of the substrate **49** is carried out in trifluoroacetic acid 5-trifluoromethyl-1,2,4-oxadiazole-3-carboxamide (**51**) is isolated as the main product with a yield of 30% [36, 37].



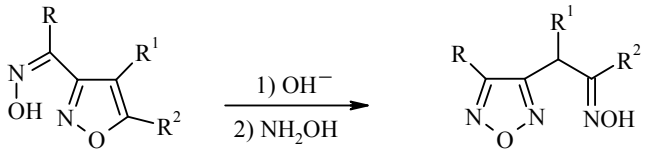

## 1.5. Synthesis of 1,2,5-Oxadiazole Aldoximes, Ketoximes, and Amidoximes

The synthesis of furazan (1,2,5-oxadiazole) derivatives, including oxime derivatives, by rearrangement of the oximes of 3-acyl-1-oxa-2-azoles was described in detail in the review [38], and we therefore examined this question briefly in this article.

A series of papers have been devoted to the synthesis of furazan ketoximes. The classical method for the synthesis of these compounds is based on the reaction of the respective ketones with $NH_2OH \cdot HCl$ in water [39, 40]. In these cases only the carbonyl groups react with the hydroxylamine. However, the oximation is usually accompanied by further transformations. Thus, the reaction of 3,4-bis(4-methyl-3-furazanoyl)furoxan **52** with hydroxylamine gives the furazan dioxime **53** with a yield of 32% [39]. The similar reaction of the substrate **52** with hydrazine hydrate in acetic acid leads to the dioxime **54** [41].



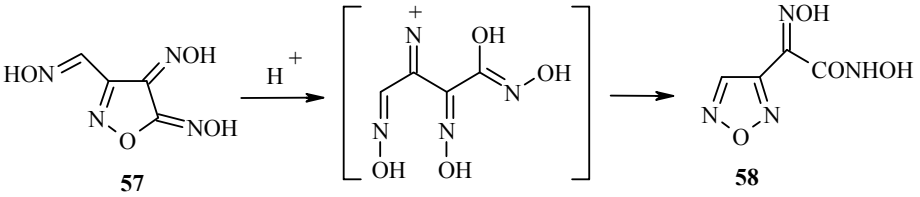

Under the influence of alkali the isoxazole *E*-oximes **55** rearrange to ketofurazans. If the reaction is carried out in the presence of hydroxylamine, the furazan oximes **56** are isolated as products. However, the rearrangement of *Z*-oximes is more difficult because *Z-E* isomerization must occur at the first stage of the reaction [38].




**55** **56**

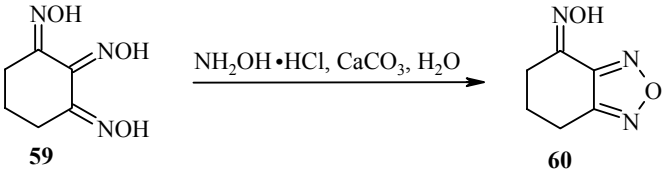
R = Alk, Ar, Het; $R^1$ = H, Ph, COPh; $R^2$ = H, Me, Ph

In the presence of acids the trioximes **57** are transformed into the furoxan oximes **58**. The products **58** are formed through the stage of acyclic products [42].

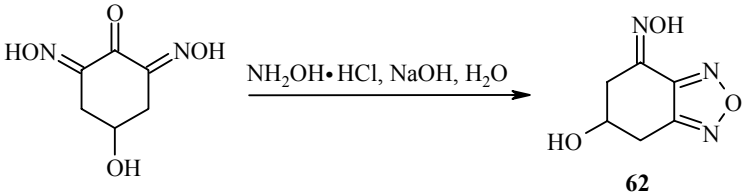



**57** **58**

1,2,3-Cyclohexanetrione trioxime (**59**) in the $NH_2OH{\cdot}HCl/CaCO_3/H_2O$ system gives 4-hydroxyamino-4,5,6,7-tetrahydrobenzofurazan (**60**) with a yield of 39% [43]. In the presence of free hydroxylamine 4-hydroxy-2,6-di(hydroxyimino)cyclohexanone (**61**) is transformed into the furazan **62** (yield 50%), which represents a mixture of isomers separated by chromatography in a *Z*/*E* ratio of ~4:1 [44].

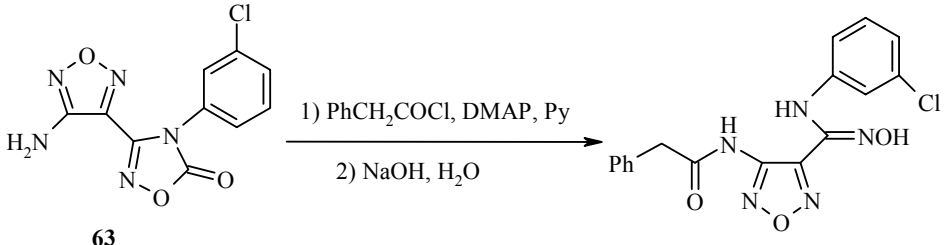



**59** **60**



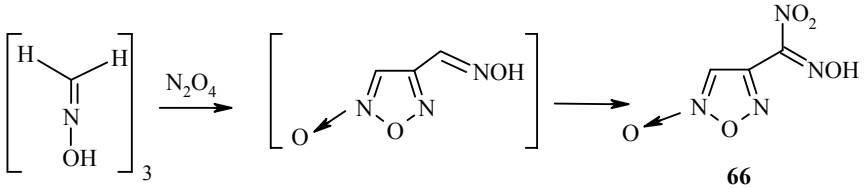

**61** **62**

The amidoximes of 1,2,5-oxadiazoles were obtained from the corresponding nitriles and hydroxylamine in aqueous alcohol [45]. 1,2,5-Oxadiazoles form amidoximes during alkaline hydrolysis. Thus, in the $PhCH_2COCl$/4-dimethylaminopyridine (DMAP)/pyridine system after alkaline hydrolysis 3-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1,2,4-oxadiazol-5(4H)-one (**63**) gives the 1,2,5-oxadiazole oxime **64** with a yield of 45% [46].




**63** **64**

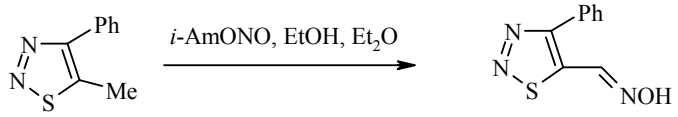
The cyclization of trihydroxyiminopropane (**65**) with $N_2O_4$ in diethyl ether or methylene chloride gives furoxan-4-nitrolic acid (**66**), which is produced through furoxan 4-aldoxime [47].



**65** **66**

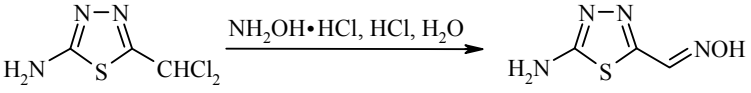
### 1.6. Synthesis of 1,2,3-, 1,3,4-, and 1,3,5-Thiadiazole Aldoximes and Ketoximes

4-Phenyl-1,2,3-thiadiazole aldoxime **68** was obtained successfully from the methyl-substituted thiadiazole **67** in the isoamyl nitrite/ethanol/ether system [48].



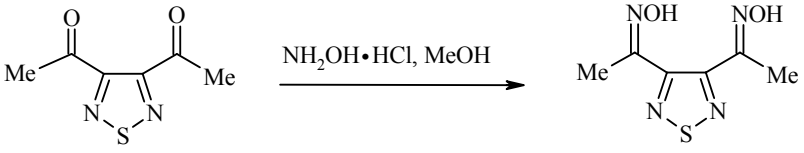
**67** **68** (49%)

The classical method for the synthesis of 1,3,4-thiadiazole ketoximes is based on the reaction of the ketone with hydroxylamine hydrochloride in pyridine [49]. It is interesting that the dichloromethyl derivative of 1,3,4-thiadiazole **69** forms 2-amino-1,3,4-thiadiazole-5-carbaldehyde oxime **70** in the presence of hydroxylamine hydrochloride and conc. hydrochloric acid [50, 51].



**69** **70**

1,3,5-Thiadiazole aldoximes and ketoximes were obtained by the reaction of the aldehyde or ketone with hydroxylamine hydrochloride in aqueous sodium hydroxide [52] or methanol [53]. The 1,3,5-thiadiazole dioxime (**72**) was obtained from the diketone **71** and $NH_2OH{\cdot}HCl$ in methanol [54].

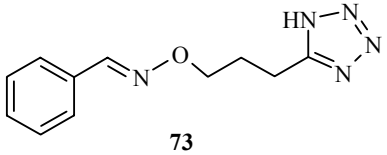


**71** **72** (86%)

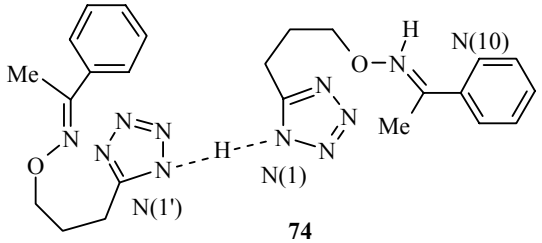
## 2. STRUCTURE

One of the most reliable methods for determining the structure of the isomeric oximes of five-membered heterocyclic compounds with three and four heteroatoms is NMR spectroscopy. The $^1H$ NMR and $^{13}C$ NMR spectra of the oximes of triazole [9, 14, 23, 55-57], tetrazole [28, 58-60], 1,2,4-oxadiazole [32, 36], 1,2,5-oxadiazole [45, 61], and 1,2,3-, 1,2,4- [62] and 1,2,5-thiadiazole [61, 63] have been investigated in greatest detail.

The structure of benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime (**73**) and acetophenone O-[3-(5-tetrazolyl)propyl]oxime (**74**) was confirmed by the data from X-ray crystallographic analysis [62]. Unusual protonation is observed in the crystals of compound **74**. In the crystal of the compound **74** molecule two molecules crystallize in the form of associates. Here proton transfer from the tetrazole atom N(1) to the oxime atom N(10) occurs during crystallization. The proton of the tetrazole ring has bridging characteristics, linking the N(1) atom of the tetrazole and the N(1') atom of the tetrazole fragment of the neighboring molecule. The lengths of the N(1)–H and N(1′)–H bonds are 1.394 and 1.402 Å respectively. In contrast to compound **74** such proton transfer does not occur in the structure of benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime (**73**).

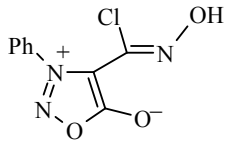


**73**

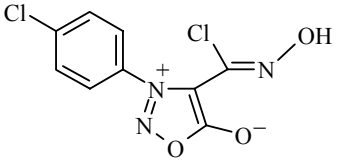


**74**

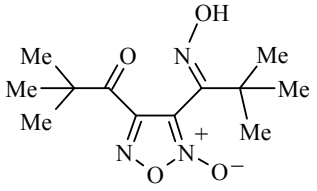
The structures of the sodium salt of acetylpyridine O-[3-(5-tetrazolyl)propyl]oxime [59], 3-arylsydnone-4-carbohydroxamoyl chlorides **75** and **76** [31], and 1-[4-(2,2-dimethylpropionyl)-5-hydroxyfurazan-3-yl]-2,2-dimethylpropan-1-one oxime (**77**) [39] were also confirmed by X-ray crystallographic analysis.



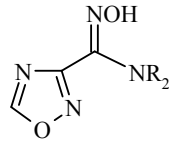
**75**



**76**



**77**



**78**

IR spectroscopy has also been used to study the structure of triazole [20, 21], oxadiazole [65, 66], and thiadiazole [53] oximes. In addition, the ionization constants of 1,2,5-thiadiazoles in water were investigated [64].

The transition from the *Z*-isomers to the *E*-isomers of the amidoximes of 1,2,4-oxadiazole-3-carboxylic acid **78** was examined in detail in [36].

It was shown that substituents at the nitrogen atom of the amidoximes group have a significant effect both on the relative stability of the *Z*- and *E*-isomers and on the size of the barrier to *E*–*Z* isomerization. The unsubstituted amidoximes are only known in the form of the thermodynamically more stable *Z*-isomers. The

*Z*-isomer is also more favorable for the N-alkyl-substituted compounds. In the case of the N,N-dialkyl-substituted amidoximes **78**, however, the *E*-isomer is more favorable. The *Z–E* isomerization can usually be accelerated by the use of an acidic catalyst.

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