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Advances in the synthesis of non-annelated polynuclear heterocyclic systems comprising the 1,2,5-oxadiazole ring

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This review is concerned with recently developed synthetic methods for non-annelated polynuclear heterocyclic systems that incorporate, along with a furazan and(or) furoxan ring, polynitrogen and nitrogen – oxygen heterocycles (1,2,4- and 1,3,4-oxadiazole, 1,2,3- and 1,2,4-triazole, tetrazole, pyrazole, *sym*-triazine, 1,2,4,5-tetrazine and so on) linked *via* C – C or C – N bonds or heteroatomic [N, O, S, N=N, N(O)=N] bridges. Methods for preparing assemblies in which a furazan ring and(or) a furoxan ring are linked to one another by C – C bonds or heteroatoms (N, O, S) are surveyed. Potential applications of the synthesized structures as pharmacologically active and high-energy compounds are discussed.
The bibliography includes 266 references.

Contents

I. Introduction 1097
II. Formation of the 1,2,5-oxadiazole ring from precursors containing heterocyclic moieties 1098
III. Heterocyclization of functional groups in functionalized 1,2,5-oxadiazoles 1105
IV. Synthesis of 1,2,5-oxadiazoles linked by heteroatomic bridges to other heterocycles 1133
V. Pharmacological activity of polynuclear heterocyclic structures based on 1,2,5-oxadiazoles 1139
VI. Conclusion 1139

I. Introduction

One of major trends in modern organic chemistry is the design of non-annelated polynuclear heterocyclic systems of various degrees of complexity in which each moiety possesses some practically useful properties.[1–4] For preparing these structures, optimal methods based on one-pot processes and available precursors are being developed.[5–9] These compounds are primarily used for the design of new pharmaceutical drugs with improved pharmacological profiles due to the combination, in one molecule, of pharmacophoric, primarily heterocyclic, moieties with known biological activity.[10–13]

1,2,5-Oxadiazoles (furazans) and their 2-oxides (furoxans) occupy an important position among the numerous heterocycles. The first furazan and furoxan derivatives were prepared as long ago as in the 19th century, but their structure was not unambiguously determined at that time. Since then, the synthesis and properties of these heterocyclic systems have been extensively studied, and several relevant reviews were published. The chemistry of furoxans was comprehensively systematized in a two-volume monograph of Khmel'nitsky *et al.*[14,15] The syntheses and reactions of monocyclic furazan and furoxan derivatives were covered in a review.[16] Methods for preparation and some aspects of reactivity of furazans, furoxans and their annelated derivatives are considered in a number of reviews.[17–23]

The great interest in the chemistry of 1,2,5-oxadiazoles arises from their potential application as pharmaceuticals and components of high-energy formulations. Among 1,2,5-oxadiazole derivatives, there are compounds with antiparasitic activity,[24,25] cytotoxic, antitumour and anticancer activities,[26–31] inhibitors of several human α-carbonic anhydrase isoforms and efficient agents for treating several glaucoma animal models.[32] Hydroxyfurazans are non-classical carboxyl group bioisosteres.[33] Furoxans containing a phthalimide moiety can be used in the therapy of sickle cell anaemia.[34] Some furoxan derivatives are regarded as potential drugs for the treatment of diabetic neuropathy[35] and Alzheimer's disease.[36] The wide spectrum of pharmacological activity of furoxans is primarily due to their ability to function as exogenic donors of nitric oxide (NO),[37–44] a versatile regulator of cell metabolism that has the key effect

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on various physiological and pathophysiological processes in the body.[45 – 49]

A large series of structures combining pharmacologically active moieties, primarily heterocyclic ones, with a furoxan ring [25, 34, 38, 40, 50 – 55] and with a furazan ring [56, 57] in one molecule have now been synthesized.

The applicability of both furazans and furoxans as components of high-energy formulations is due to their high positive enthalpies of formation and the presence of active oxygen atoms in their molecules. Syntheses of high-energy compounds incorporating 1,2,5-oxadiazoles are extensively conducted in laboratories over the world.[58 – 66] Therefore, the systematic consideration of the data concerning methods for the preparation of non-annelated polynuclear heterocyclic structures that contain some pharmacophore or high-energy heterocyclic moieties, in addition to a furazan (furoxan) ring, can appear useful to researchers engaged in the design of dual-use materials.

In recent years, the number of publications on the 1,2,5-oxadiazole chemistry has been increasing. However, whereas data on the synthesis of fused structures were adequately systematized in recent reviews,[18, 19, 67 – 70] information on the preparation of non-annelated derivatives of these heterocycles, especially linked to other heterocycles, has not been properly covered. Therefore, in this review, we summarize the published data of the last 10 – 15 years concerning the syntheses of non-annelated polynuclear heterocyclic structures based on furazans and furoxans with various pharmacophore and(or) high-enthalpy heterocyclic substituents. The data considered earlier are partially included in the present review whenever necessary.

The published data covered in the review on the preparation of non-annelated polynuclear heterocyclic systems based on furazans and furoxans may be roughly classified into two main groups: closure of the 1,2,5-oxadiazole ring in precursors that already contain heterocyclic moieties and formation of heterocyclic substituents by the cyclization of functional groups linked to the furazan and furoxan rings. Synthetic routes to heterocyclic assemblies the structural elements of which are 1,2,5-oxadiazole rings linked to one another or to other heterocycles *via* heteroatomic bridges will also be considered.

II. Formation of the 1,2,5-oxadiazole ring from precursors containing heterocyclic moieties

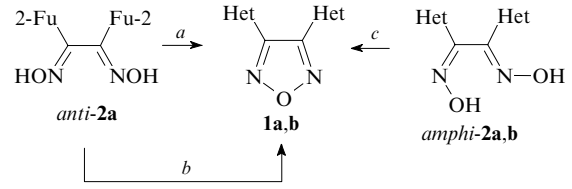
This Section will be started with reactions involving glyoximes with heterocyclic substituents which can be dehydrated to give furazans and be oxidized to yield furoxans. Further, reactions that yield only hetaryl-substituted furoxans will be discussed, and finally the Section will be ended with reactions that yield hetaryl-substituted furazans.

II.1. Preparation of furazans and furoxans with heterocyclic substituents *via* the dehydration or oxidation of mono- and dihetarylglyoximes

The most extensive series of mono- and disubstituted 1,2,5-oxadiazoles was prepared from vicinal dioxime (glyoxime) precursors. Glyoximes are cyclized to furazans on treatment with dehydrating reagents, whereas their oxidation leads to furoxans. In general, both a furazan and a furoxan can be obtained from the same glyoxime. For this reason, we do not separate the reactions considered below which yield furazans or furoxans into individual subsections.

The configuration of a glyoxime can have a certain effect on its dehydration or oxidation. For example, bis(2-furyl)furazan (**1a**) was formed in 58% yield when glyoxime *anti*-**2a** was heated with an aqueous urea solution. However, the *amphi*-isomer reacts under more drastic conditions (in a sealed tube) and gives a lower yield (21%) of the final product **1a** (Scheme 1).[71] Bis(2-pyridyl)glyoxime (**2b**) is also dehydrated at high temperature to produce furazan **1b** in a moderate yield (44%).[72] The yield of compound **1b** appreciably increases when KOH is used as the dehydrating agent.[73] Difurylfurazan **1a** can be prepared in a relatively low yield (8%) *via* the Trofimov reaction by passing acetylene through a solution of *anti*-difurylglyoxime **2a** in DMSO in the presence of alkali (see Scheme 1).[74] In the absence of acetylene, this cyclization does not occur.

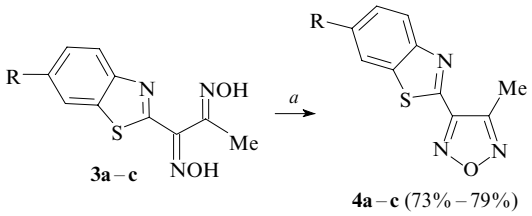
Scheme 1



Het = 2-Fu (**a**), 2-Py (**b**); (*a*) $(H_2N)_2CO$, H_2O, 80 °C; (*b*) HC≡CH (14 atm), KOH, DMSO, 80 °C; (*c*) 165 – 185 °C; Fu is furyl, Py is pyridyl

Dicarboxylic acid anhydrides can be used to dehydrate hetarylglyoximes to final furazans. In particular, heating of benzothiazolylglyoximes **3a – c** with succinic anhydride in the absence of solvent produces furazans **4a – c** in good yields (Scheme 2).[75]

Scheme 2



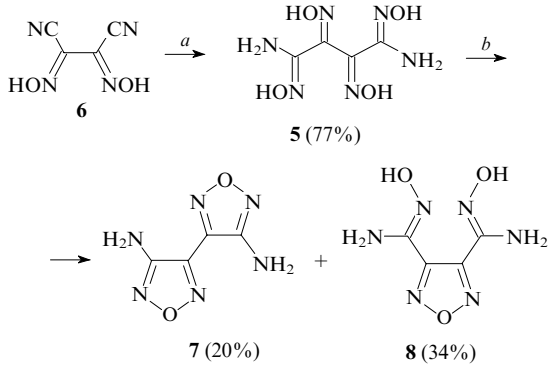
R = H (**a**), Me (**b**), OEt (**c**); (*a*) succinic anhydride, 140 °C

When tetraoxime **5**, which is prepared by the reaction of dicyanoglyoxime **6** with hydroxylamine, is heated in the presence of alkali, two 1,2,5-oxadiazole rings are simultaneously formed to yield 4,4′-diamino-3,3′-bifurazan **7**. The major product of this reaction is, however, bis(amidoxime) **8**. Apparently, the dehydration of the central glyoxime moiety is thermodynamically a little more favourable than a similar cyclization of two pairs of aminoglyoxime groups (Scheme 3).[76]

In some cases, hetarylglyoximes can be generated *in situ*. Refluxing cyanoximes **9a – c** with hydroxylamine in alkaline medium induces a tandem process comprising the formation of aminoglyoximes **10a – c** followed by their cyclodehydration to furazans **11a – c** (Scheme 4).[77 – 79]

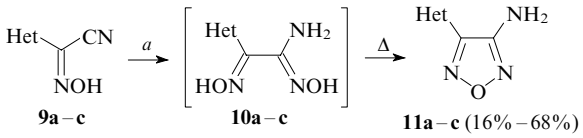
A similar two-step one-pot procedure for preparing aminofurazan **11d** from cyanoxime **9d** using phosphorus pentachloride as the dehydrating agent in the second step afforded the target product in a moderate yield (Scheme 5).[80]

Scheme 3



(*a*) NH_2OH, H_2O, 60 °C; (*b*) NaOH, 135 °C

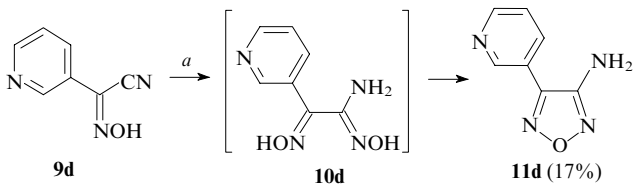
Scheme 4



Het = 2-Th (**a**, 68% yield), quinolin-2-yl (**b**, 16%), benzimidazol-2-yl (**c**, 66%); (*a*) NH_2OH, NaOH or KOH, H_2O, Δ;
Th is thienyl

In some cases, cyanoximes themselves can be generated *in situ* and then converted to aminofurazans. Scheme 6 exemplifies the implementation of this approach. The nitrosation of the reactive methylene group in functionalized azabenzimidazole derivatives **12a – f** gives geminal cyanoximes **13a – f**, which are then converted to desired aminofurazans **14a – f** on treatment with hydroxylamine in a basic medium *via* the cyclodehydration of the *in situ* formed aminoglyoximes **15a – f**.[81 – 85]

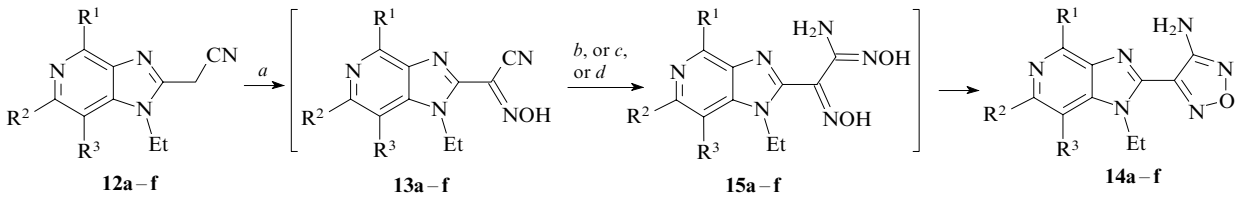
Scheme 5



(*a*) 1) $NH_2OH \cdot HCl$, NaOAc, EtOH, Δ; 2) PCl_5

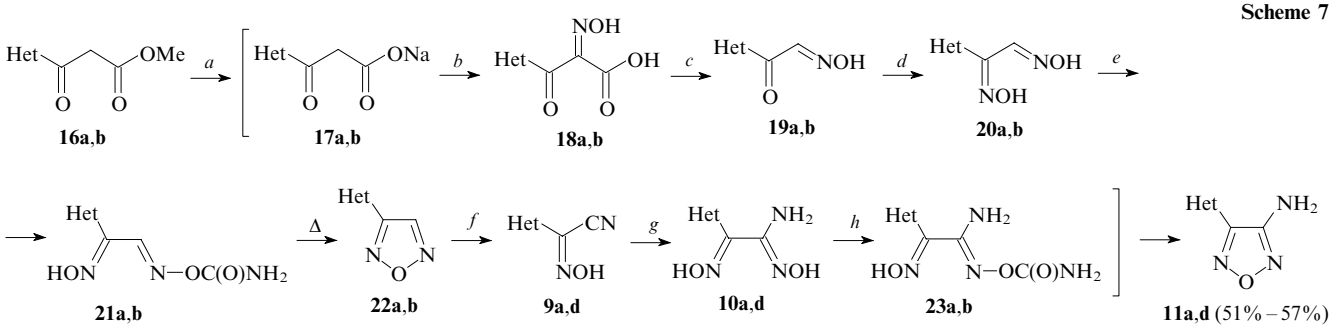
In 2005, Sheremetev[86] proposed a convenient and original method for preparing 3-amino-4-hetarylfurazans **11a**,**d**, based on a cascade of conversions of hetaroyl acetic esters **16a**,**b** (Scheme 7). 1,3-Dicarbonyl compounds **16a**,**b** are hydrolyzed in alkaline medium to give sodium salts **17a**,**b**, which are then nitrosated at the reactive methylene group on treatment with sodium nitrite and perchloric acid, and intermediate oximes **18a**,**b** are decarboxylated *in situ*. Next, intermediates **19a**,**b** react with hydroxylamine to yield hetarylglyoximes **20a**,**b**, which are then treated with urea to give carbamoyl derivatives **21a**,**b**, and the latter cyclize to monosubstituted hetarylfurazans **22a**,**b** under reflux. However, the reaction does not stop at this step, as the monosubstituted furazan ring is opened at high temperatures in alkaline medium to yield cyanoximes **9a**,**d**, which then react with excessive hydroxylamine giving aminoglyoxime intermediates **10a**,**d**. Treatment with urea converts compounds **10a**,**d** to intermediates **23a**,**b**; their cyclization furnishes the final 3-amino-4-hetarylfurazans **11a**,**d**.[86] The overall process shown in Scheme 7 can be classified as a domino reaction of

Scheme 6



$R^1 = R^2 = H$: $R^3 = H$ (**a**, 43% yield), Br (**b**, 45%); $R^1 = R^3 = H$: R^2 = OMe (**c**, 25%), OC_6H_4NHTs-3 (**d**, 37%); R^1 = Cl: R^2 = Br, $R^3 = H$ (**e**, 43%); $R^2 = H$, R^3 = Br (**f**, 43%); (*a*) $NaNO_2$, HCl, MeOH, rt; (*b*) NH_2OH, NaOH, H_2O, 90 °C; (*c*) 1) NH_2OH, Et_3N, THF, Δ; 2) Et_3N, THF, Δ; (*d*) 1) NH_2OH, Et_3N, THF – H_2O, 90 °C; 2) Et_3N, dioxane, 150 °C, sealed tube; Ts is *p*-toluenesulfonyl

Scheme 7



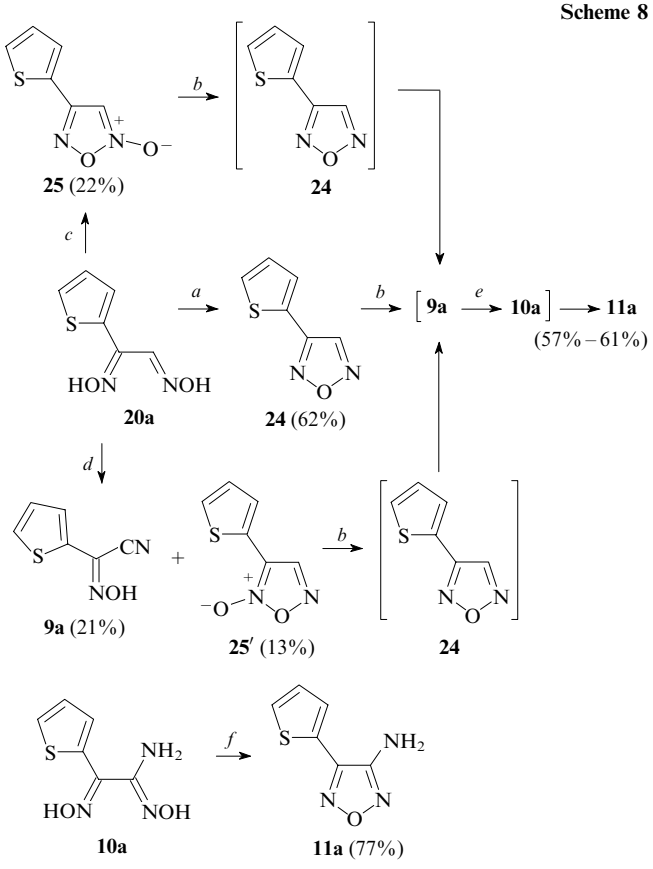
9 – 11: Het = 2-Th (**a**), 3-Py (**d**); **16 – 23**: Het = 2-Th (**a**), 3-Py (**b**); (*a*) 2.2 M NaOH; (*b*) $NaNO_2$, 20% $HClO_4$; (*c*) H^+; (*d*) $NH_2OH \cdot HCl$, 11 M NaOH; (*e*) $(H_2N)_2CO$, 95 °C; (*f*) NaOH; (*g*) NH_2OH; (*h*) $(H_2N)_2CO$

hetaroyl acetic esters. Recently, an environmentally friendly method was developed for the electrochemical oxidation of aminofurazans, specifically those containing heterocyclic substituents in the furazan ring, to azo derivatives.[87]

Heating of thienylglyoxime **20a** with succinic anhydride promotes its intramolecular dehydration to thienylfurazan **24** (Scheme 8). A similar reaction with thienylaminoglyoxime **10a** yields aminofurazan **11a**. Compound **11a** is also formed when furazan **24** reacts with hydroxylamine. Under the reaction conditions, the furazan ring in substrate **24** is opened to yield a cyanoxime moiety. The resulting intermediate **9a** then adds a hydroxylamine molecule to form aminoglyoxime intermediate **10a**, which cyclizes to aminofurazan **11a** in alkaline medium.

The oxidation reactivity of the initial thienylglyoxime **20a** was also studied. It was shown that treatment of compound **20a** with nitrogen(IV) oxide produces 4-thienylfuroxan **25**. When potassium hexacyanoferrate(III) serves as the oxidant, the cyclization yields 3-thienylfuroxan **25′** in which the N-oxide group is located on the other side of the ring. In the latter case, however, the major reaction product is cyanoxime **9a**, which results from elimination of a water molecule. Both isomeric furoxans **25** and **25′** are converted to aminofurazan **11a** in moderate yields (57% – 61%) when treated with hydroxylamine in alkaline medium. The authors suggest that hydroxylamine reduces the N-oxide in the initial furoxans **25** and **25′** to furazan **24**, which is then converted to aminofurazan **11a** through intermediates **9a** and **10a** (see Scheme 8).[77]

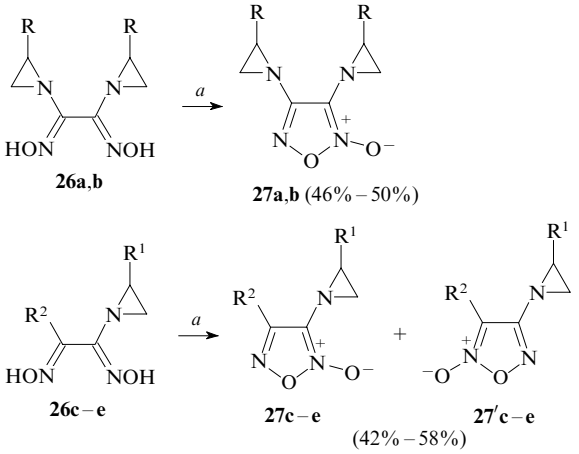
Scheme 8



(*a*) Succinic anhydride, 120 °C; (*b*) $NH_2OH \cdot HCl$, KOH, H_2O, Δ; (*c*) N_2O_4, Et_2O; (*d*) $K_3[Fe(CN)_6]$, NH_3, H_2O; (*e*) NH_2OH; (*f*) NaOH, $(CH_2OH)_2$, 150 °C

The oxidation of aziridinyl-substituted glyoximes **26a**,**b** to furoxans **27a**,**b** proceeds smoothly under the action of potassium hexacyanoferrate(III) in aqueous ammonia. Reactions of asymmetrically substituted glyoximes **26c – e** yield mixtures of isomeric furoxans **27c – e** and **27′c – e** (Scheme 9).[14]

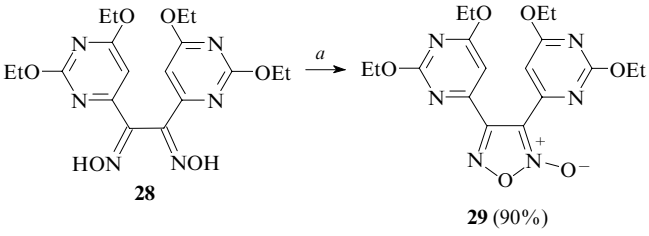
Scheme 9



R = H (**a**), Me (**b**); R^1 = H: R^2 = Me (**c**), Ph (**d**); R^1 = R^2 = Me (**e**); (*a*) $K_3[Fe(CN)_6]$, NH_3, H_2O, 15 °C

A similar oxidation of glyoxime **28** with nitrogen(IV) oxide resulted in the synthesis of 3,4-bis(2,6-diethoxypyrimidin-4-yl)furoxan (**29**) (Scheme 10).[14]

Scheme 10

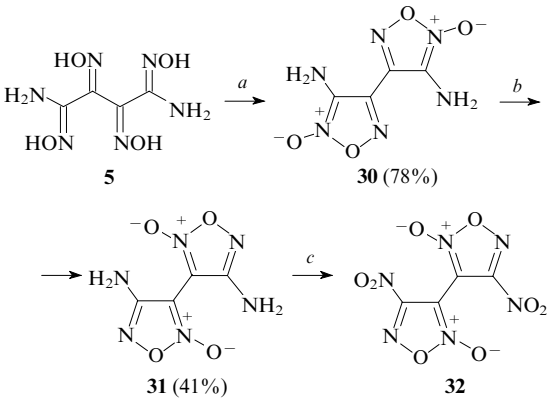


(*a*) N_2O_4, $CHCl_3$, 20 °C

Bromine successfully oxidizes tetraoxime **5** simultaneously at two glyoxime groups to regioselectively yield 3,3′-diamino-4,4′-bifuroxan (**30**). On refluxing in dioxane, both 3-aminofuroxanyl moieties isomerize to 4-aminofuroxanyl groups, which are thermodynamically more stable, to yield 4,4′-diamino-3,3′-bifuroxan (**31**). The oxidation of amino groups in compound **31** was successful only using ammonium persulfate in 50% H_2O_2 and concentrated sulfuric acid (Scheme 11). However, even under these conditions, only few of the isolated crystals of 4,4′-dinitro-3,3′-bifuroxan (**32**) were suitable for X-ray crystallography.[88]

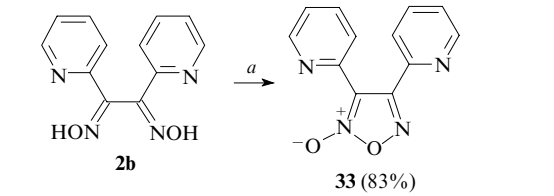
An original two-step sequence was proposed for preparing bis(2-pyridyl)furoxan, which started with complexing initial glyoxime **2b** with Cu^{II} ions and was accompanied by intramolecular electron transfer from the oxime group to the Cu^{II} ion. Thus, copper(II) perchlorate in this process serves as an oxidant, which is reduced during the reaction to yield the complex $Cu(MeCN)_4ClO_4$. The subsequent treatment of the reaction mixture with aqueous ammonia in order to remove residual copper ions makes it possible to isolate furoxan **33** in a good yield (Scheme 12).[89,90]

Scheme 11



(*a*) Br_2, 1 M HCl; (*b*) dioxane, Δ; (*c*) $(NH_4)_2S_2O_8$, 50% H_2O_2, conc. H_2SO_4, 50 °C

Scheme 12



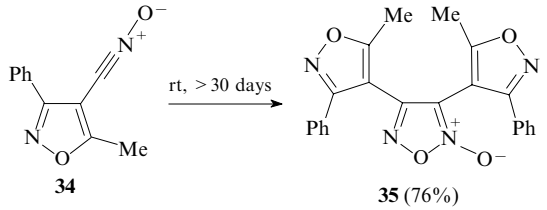
(*a*) 1) $Cu(ClO_4)_2 \cdot 6H_2O$, MeCN, rt; 2) 25% NH_3, H_2O

II.2. Preparation of 3,4-bis(hetaryl)furoxans by cyclodimerization of hetarylcarbonitrile oxides

The major and widely used method for the preparation of 3,4-bis(hetaryl)furoxans is cyclodimerization of hetarylcarbonitrile oxides. Usually, nitrile oxides are generated as intermediate products from various precursors; however, there are several examples of storage-stable nitrile oxides with heterocyclic substituents.

(5-Methyl-3-phenylisoxazol-4-yl)carbonitrile oxide (**34**) has been known for a long time as the only stable nitrile oxide of this type; upon long-term storage at room temperature (for more than 30 days), it dimerized to furoxan **35** (Scheme 13).[14]

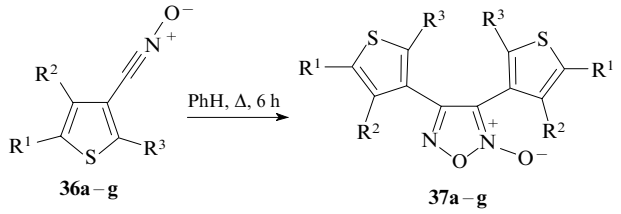
Scheme 13



Later, a series of stable thienylcarbonitrile oxide derivatives **36a**–**g** were prepared, which could be converted to furoxans **37a**–**g** only by prolonged refluxing in benzene (Scheme 14).[14] 3,4-Bis(2-oxo-2*H*-[1]benzopyran-4-yl)furoxan was synthesized in the same manner.[91]

Most frequently, however, nitrile oxides are generated *in situ* from various precursors to be subjected to further cyclodimerization to furoxans. Examples of nitrile oxide precursors are hydroxamoyl chlorides, specifically, hetaryl

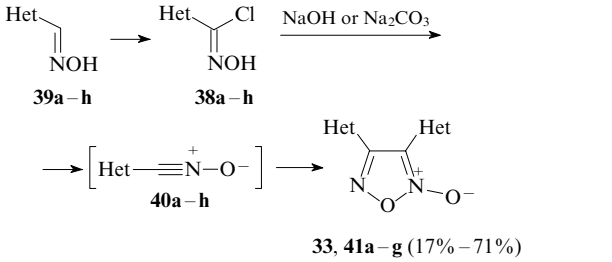
Scheme 14



$R^3 = SO_2Me$: R^1 = Me, R^2 = H (**a**, 85% yield); R^1 = OMe, R^2 = H (**b**, 82%); R^1 = Me, R^2 = Br (**d**, 95%); $R^1 = R^2$ = H: $R^3 = SO_2Bu^t$ (**c**, 58%) SO_2Et (**e**, 85%); $R^1 = R^2 = SO_2Me$, R^3 = H (**f**, 90%); R^1 = Me, R^2 = Br R^3 = SMe (**g**, 80%)

hydroxamoyl chlorides **38a**–**h**, which are prepared by chlorinaton of the appropriate hetaryl aldoximes **39a**–**h** with chlorine,[92] Bu^tOCl,[93] *N*-*tert*-butyl-*N*-chlorocyanamide[94] or *N*-chlorosuccinimide (NCS).[95,96] On treatment with aqueous alkali or sodium carbonate, acid chlorides **38a**–**h** eliminate hydrogen chloride to yield nitrile oxides **40a**–**h**, which then dimerize to 3,4-bis(hetaryl)furoxans **33**, **41a**–**g** (Scheme 15).[14,92,97]

Scheme 15

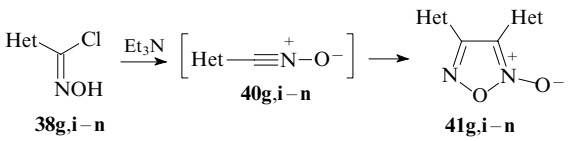


33, **41a**–**g** (17% – 71%)

38–**41**: Het = 2-Fu (**a**, 53% yield), isoxazol-3-yl (**b**, 54%), isoxazol-5-yl (**c**, 40%), 1,2,4-triazol-3-yl (**d**, 71%), 6-formaldoximinopyridin-2-yl (**e**, 46%), 3-Py (**f**, 25%), 4-Py (**g**, 17%); **33**, **38h**–**40h**: Het = 2-Py (27%)

This method was later improved by replacement of inorganic base with triethylamine. This change resulted in a 2.5-times higher yield of 3,4-bis(4-pyridyl)furoxan (**41g**), while furoxans **41i**–**n** (including those comprising carbohydrate residues) were formed in nearly quantitative yields (Scheme 16).[14,98,99]

Scheme 16

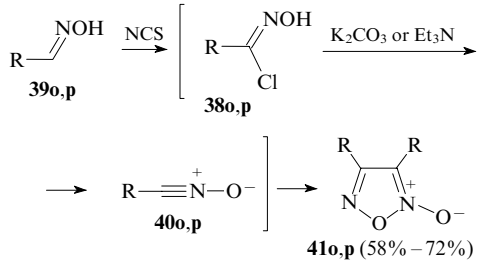


Het = 4-Py (**g**, 43% yield), 2-Th (**i**, 97%), 5-chlorothien-2-yl (**j**, 99%), D-glucopyranosyl (**k**, 96%), D-mannopyranosyl (**l**, 95%), tetra-*O*-acetyl-D-glucopyranosyl (**m**, 96%), tetra-*O*-acetyl-D-mannopyranosyl (**n**, 95%)

The synthesis of bis(hetaryl)furoxans based on the dehydrochlorination of hydroxamoyl chlorides was, in some cases, performed as a one-pot process using aldoximes as the initial compounds. *N*-Chlorosuccinimide was used to chlorinate substrates **39o**,**p**, and then a base was added to the resulting chloroximes **38o**,**p** to generate *in situ* nitrile

oxides **40o**,**p**, which were then dimerized to desired furoxans **41o**,**p** (Scheme 17).[100, 101]

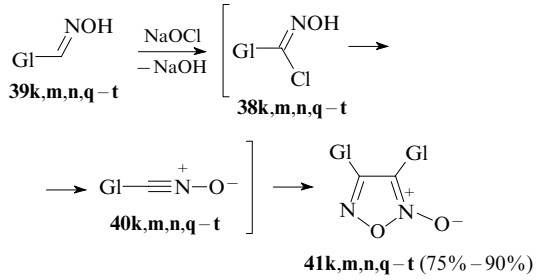
Scheme 17



R is imidazol-2-yl (**o**), 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl (**p**)

To prepare furoxans **41** that contain carbohydrate residues in one synthetic step, another method was employed. This method consisted of treating aldoximes with sodium hypochlorite. In this case, NaOCl played a dual role of the chlorinating agent and the base (Scheme 18).[98, 99]

Scheme 18

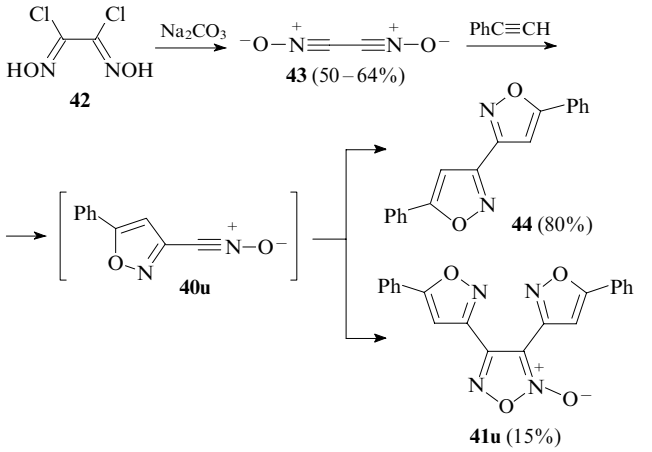


Gl is D-glucopyranosyl (**k**, 88%), tetra-*O*-acetyl-D-glucopyranosyl (**m**, 88%), tetra-*O*-acetyl-D-mannopyranosyl (**n**, 75%), D-galactopyranosyl (**q**, 90%), D-xylyl (**r**, 89%), tetra-*O*-acetyl-D-galactopyranosyl (**s**, 90%), tri-*O*-acetyl-D-xylyl (**t**, 88%)

In several studies,[98, 102–107] bis(hetaryl)furoxans were also formed as side products of the 1,3-dipolar cycloaddition of dipolarophiles to nitrile oxides, which were generated *in situ* from hydroxamoyl chlorides.

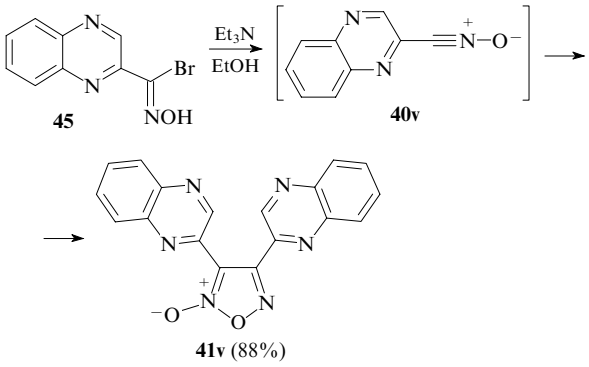
Dichloroglyoxime (**42**) served as the intermediate in the preparation of cyanogen di-N-oxide (**43**), the simplest bisnitrile oxide, as a solution in CH_2Cl_2. Compound **43** undergoes 1,3-dipolar cycloaddition on treatment with 2 moles of phenylacetylene. Most of di-N-oxide **43** reacts with the dipolarophile at both nitrile oxide groups to give bisisoxazole **44**, but some part of intermediate **40u** dimerizes to furoxan compound **41u** through the free nitrile oxide group (Scheme 19).[108]

Scheme 19



Hydroxamic acid bromides are used much less frequently to prepare 3,4-bis(hetaryl)furoxans. The only known example is dehydrobromination of quinoxazoline derivative **45** by triethylamine, followed by one-pot cyclodimerization of the resulting nitrile oxide **40v** to furoxan **41v** (Scheme 20).[109]

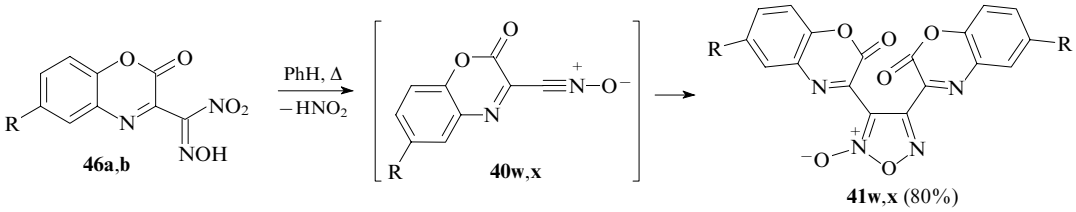
Scheme 20



Apart from hetarylhydroxamic acid halides, nitrolic acids, which eliminate nitrous acid at elevated temperatures, can also serve as the source of nitrile oxide moiety. In particular, thermolysis of nitrolic acids **46a**,**b**, which contain the 1,4-benzoxazin-2-one moiety, yields furoxans **41w**,**x** in good yields (Scheme 21).[14]

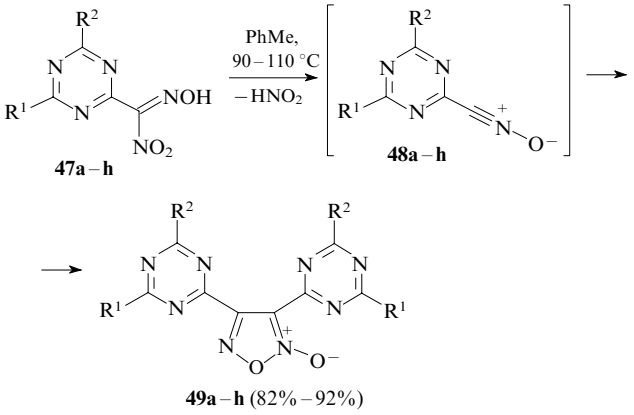
In the same way, heating of nitrolic acids **47a**–**h** with 1,3,5-triazine substituents induces the elimination of nitrous acid to generate nitrile oxides **48a**–**h**, which dimerize *in situ* to 3,4-bis(1,3,5-triazin-2-yl)furoxans **49a**–**h** (Scheme 22).[110]

Scheme 21



R = H (**40w**, **41w**, **46a**), Me (**40x**, **41x**, **46b**)

Scheme 22



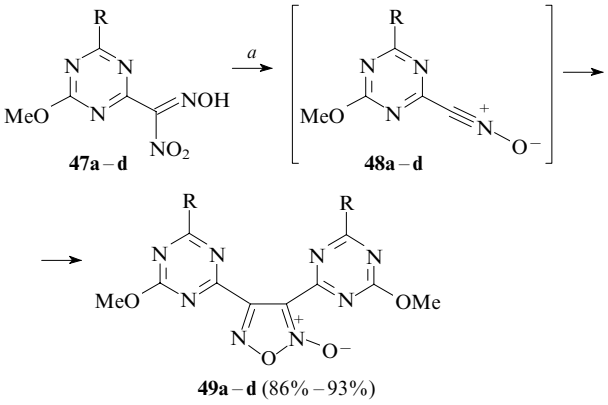
47a – h **48a – h** **49a – h** (82% – 92%)

R^1 = OMe: R^2 = NMe_2 (**a**), $N(CH_2)_4$-cyclo (**b**), $N(CH_2)_5$-cyclo (**c**), $N(CH_2CH_2)_2O$-cyclo (**d**); R^1 = R^2 = NMe_2 (**e**), OMe (**g**), OPr^n (**h**); R^1 = $OC_6H_4NO_2$-4, R^2 = NMe_2 (**f**)

Attempts to conduct thermolysis of compounds **47a – d** in aliphatic nitriles in order to trap intermediate nitrile oxides **48a – d** *via* [3 + 2]-cycloaddition reactions were unsuccessful.

In all cases, only bis(triazinyl)furoxans **49a – d** were formed in high yields (Scheme 23).[111]

Scheme 23



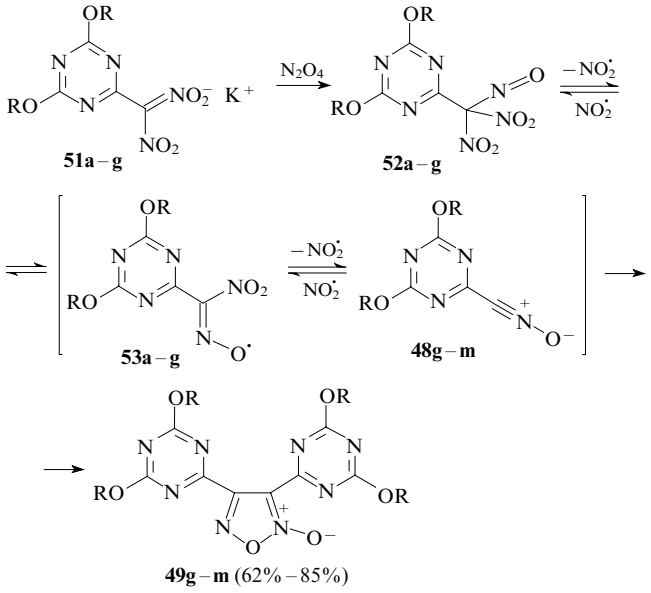
47a – d **48a – d** **49a – d** (86% – 93%)

R = NMe_2 (**a**), $N(CH_2)_4$-cyclo (**b**), $N(CH_2)_5$-cyclo (**c**), $N(CH_2CH_2)_2O$-cyclo (**d**); (*a*) MeCN, Δ or BnCN, 100 – 110 °C

However, refluxing of compounds **47a**,**d**,**g** in toluene and acrylonitrile mixtures always gives equimolar mixtures of furoxans **49a**,**d**,**g** and triazinyldihydroisoxazoles **50a**,**d**,**g** (Scheme 24).[112] When thermolysis is performed in the absence of an inert solvent, cyclodimerization of nitrile oxides **48a**,**d**,**g** is completely inhibited, and dihydroisoxazoles **50a**,**d**,**g** are formed regioselectively in good yields.

A special route to generate nitrile oxides is treating hetaryldinitromethane salts, specifically dinitromethyltriazines **51a – g**, with nitrogen(IV) oxide.[113] The mechanism of this reaction was determined by dynamic NMR spectroscopy, and now it is generally accepted (Scheme 25).[114] The mechanism includes nitrosation of dinitromethyl anions in potassium salts **51a – g** to give dinitronitroso derivatives **52a – g** followed by elimination of nitrogen dioxide to give iminoxyl radicals **53a – g**. The subsequent elimination of a second nitrogen dioxide molecule generates nitrile oxides **48g – m**, which then dimerize to furoxans **49g – m**.

Scheme 25

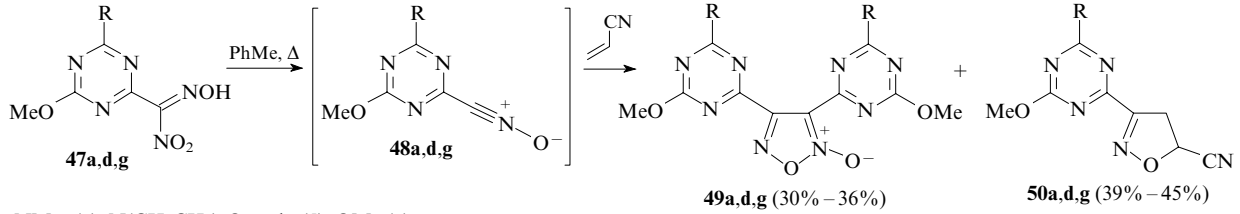


51a – g **52a – g** **53a – g** **48g – m** **49g – m** (62% – 85%)

48, **49**: R = Me (**g**), Pr^n (**h**), Pr^i (**i**), Bu^n (**j**), cyclo-C_6H_{11} (**k**), C_6H_4Br-4 (**l**), $C_6H_4CO_2Me$-4 (**m**);
51 – 53: R = Me (**a**), Pr^n (**b**), Pr^i (**c**), Bu^n (**d**), cyclo-C_6H_{11} (**e**), C_6H_4Br-4 (**f**), $C_6H_4CO_2Me$-4 (**g**)

Aliphatic nitro compounds can also serve as precursors for nitrile oxides. The dehydration of hetarylnitromethanes **54a – e** with an aryl isocyanate and triethylamine mixture yields nitrile oxides **40n**,**t** and **55a**,**d**,**e**, which dimerize to furoxans **41n**,**t** and **56a**,**d**,**e**;[99, 115] the dimerization of intermediate **55a** yields a mixture of diastereomers **56a** and **56′a** in 56 : 44 ratio.[115] In some cases, in particular for nitro compound **54f**, gentle heating is sufficient for generating nitrile oxide **55f**, which dimerizes, despite steric hindrance,

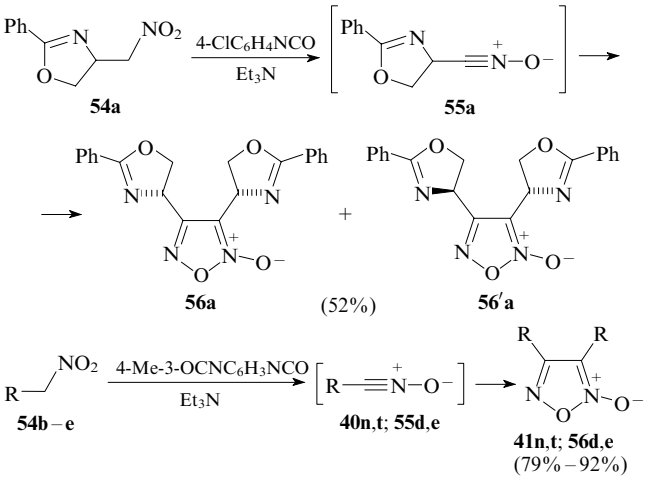
Scheme 24



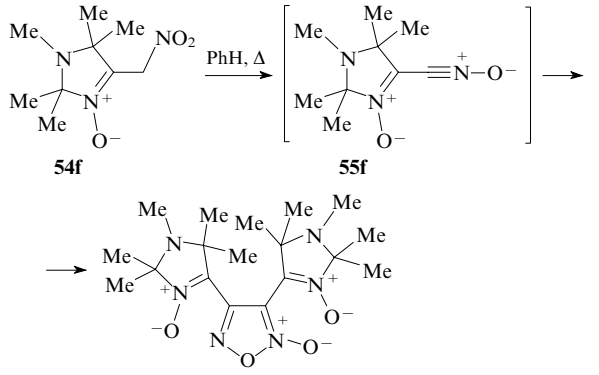
47a,**d**,**g** **48a**,**d**,**g** **49a**,**d**,**g** (30% – 36%) **50a**,**d**,**g** (39% – 45%)

R = NMe_2 (**a**), $N(CH_2CH_2)_2O$-cyclo (**d**), OMe (**g**)

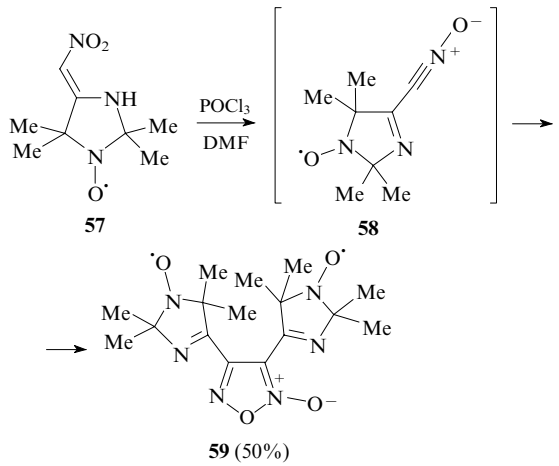
Scheme 26



R is tetra-*O*-acetyl-D-mannopyranosyl (**40n**, **41n**, **54b**), tri-*O*-acetyl-D-xylyl (**40t**, **41t**, **54c**), tri-*O*-acetyl-D-fucosyl (**54d**, **55d**, **56d**), *O*,*O*′-isopropylidene-D-mannopyranosyl (**54e**, **55e**, **56e**)



Scheme 27



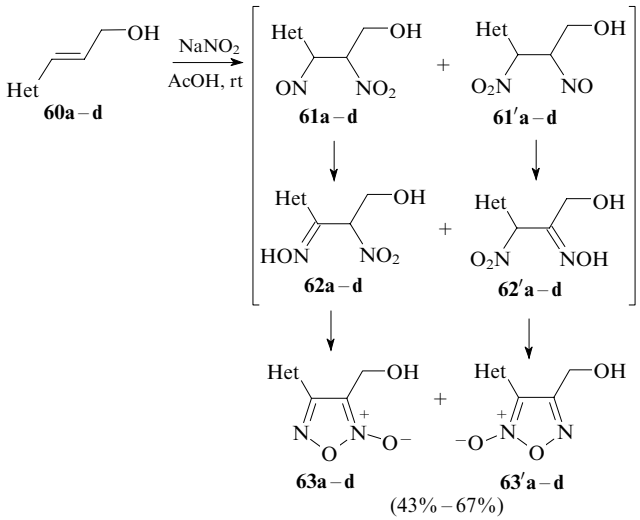
to give 3,4-bis(imidazol-4-yl)furoxan **56f** in a good yield (Scheme 26).[116]

α,β-Unsaturated nitro compounds can also be employed as nitrile oxide precursors. In particular, nitroenamine **57** generates nitrile oxide **58** in the Vilsmeier–Haack reaction, which ultimately yields furoxan **59** (Scheme 27).[117]

II.3. Dehydration of hetaryl-substituted α-nitroximes as a route to hetarylfuroxans

One more method suitable for the design of only hetarylfuroxans is based on nitrosation of heterocyclic analogues of cinnamic alcohol **60a–d**. The reaction proceeds *via* the addition of N_2O_3, formed upon the reaction of sodium nitrite with acetic acid, to the double bond of starting **60a–d** to produce isomeric pseudonitrosites **61a–d** and **61′a–d**, which isomerize *in situ* to α-nitroximes **62a–d** and **62′a–d**. The cyclodehydration of intermediates **62a–d** and **62′a–d** yields furoxans **63a–d** and **63′a–d** (Scheme 28).[24] The main disadvantage of the method is the formation of a mixture of isomeric hetarylfuroxans in all cases.

Scheme 28

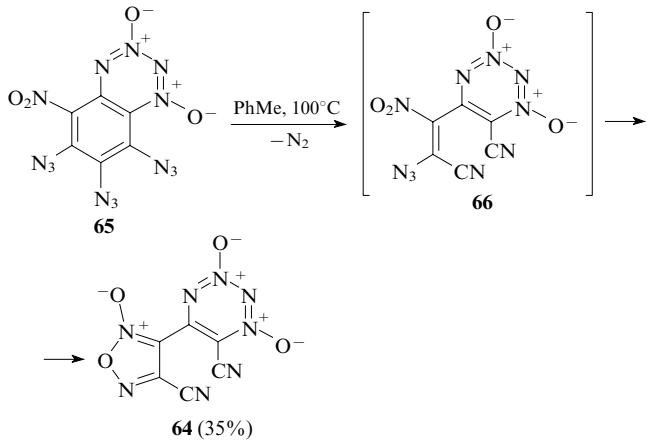


Het = 2-Fu (**a**), 5-nitro-2-furyl (**b**), 2-Th (**c**), (3-hydroxymethylfuroxan-4-yl)thien-2-yl (**d**)

II.4. Other synthetic routes to hetarylfuroxans from hetaryl-containing precursors

In 2006, an original route to high-energy polynitrogen heterocyclic structure **64**, in which the furoxan ring is linked to the 1,2,3,4-tetrazine 1,3-dioxide moiety, *via* the thermolysis of triazidobenzotetrazine dioxide **65** was proposed.[118] The reaction includes the initial cleavage of the benzene ring with nitrogen elimination and the subsequent cyclization of the azidonitroethylene moiety in intermediate **66** to give a

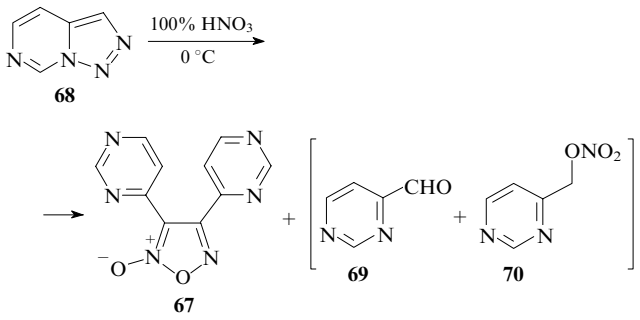
Scheme 29



furoxan ring (Scheme 29). However, the authors cannot exclude the reverse order of these two steps: the furoxan ring formation upon the thermolysis of *o*-nitrophenyl azide followed by a benzene ring bond cleavage with nitrogen evolution.

This Section should also cover the nontrivial method for preparing 3,4-bis(pyrimidin-4-yl)furoxan **67** by treatment of 1,2,3-triazolo[1,5-*c*]pyrimidine (**68**) with fuming nitric acid (Scheme 30).[119] The presence of aldehyde **69** and nitro ester **70** in the reaction mixture along with desired product **67** was detected by IR and NMR spectroscopy and mass spectrometry. However, only furoxan **67** was isolated by chromatography, although its yield was not reported. This synthetic route to furoxan **67** is more of theoretical interest, as other authors[119] failed to reproduce the preparation of the indicated heterocyclic structure, and one of their experiments was accompanied by explosion.

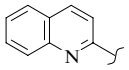
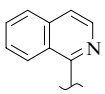
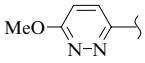
Scheme 30



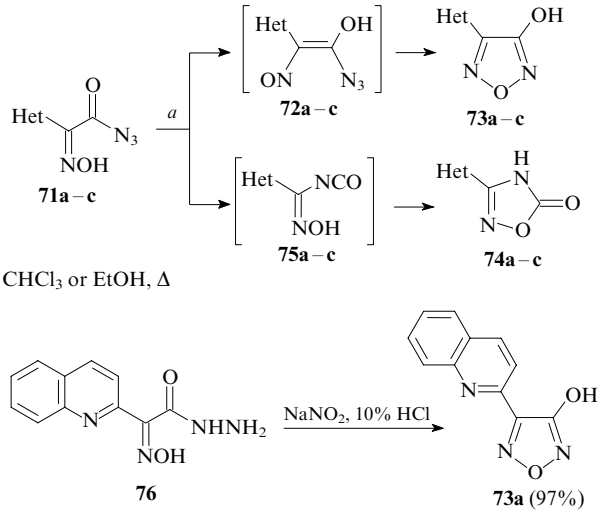
II.5. Preparation of hetarylhydroxyfurazans by thermolysis of α-hydroxyimino(hetarylmethyl)carbonyl azides

Along with the dehydration of hetarylglyoximes, there is one more approach to the preparation of furazans with heterocyclic substituents, which is based on the thermolysis of α-hydroxyiminohetarylmethylcarbonyl azides **71a – c**.[78] The thermolysis of compounds **71a – c** promotes the shift of tautomeric equilibrium and generation of vicinal nitrosoazides **72a – c**, which cyclize to give hydroxyfurazans **73a – c** (Scheme 31, Table 1). However, apart from compounds **73a – c**, 1,2,4-oxadiazol-5-ones **74a – c** were isolated in all cases. Compounds **74a – c** are formed upon competing Curtius rearrangement, which also proceeds at high temperatures *via* isocyanate intermediates **75a – c**. It is noteworthy that conduction of the thermolysis of starting carbonyl azides **71a**,**b** in chloroform results in higher yields of furazans **73a**,**b**, whereas the use of a polar solvent (ethanol) promotes the formation of oxadiazolones **74a**,**b**. However, this trend is violated for substrate **71c** incorporating pyridazyl substituent: in this case, oxadiazolone **74c** is preferably formed, regardless of the reaction medium (see Table 1).[78] Attempts at preparing carbonyl azide **71a** by the nitrosation of hydrazide **76** unexpectedly resulted in hydroxyfurazan **73a** in a nearly quantitative yield.[120]

Table 1. Yields of hydroxyfurazans **73a – c** and 1,2,4-oxadiazol-5-ones **74a – c**.[78]

Compounds **71 – 75**	Het	Solvent	Yield (%)	
			73	**74**
a		$CHCl_3$	70	17
		EtOH	5	77
b		$CHCl_3$	58	28
		EtOH	Traces	92
c		$CHCl_3$	10	76
		EtOH	Traces	80

Scheme 31



III. Heterocyclization of functional groups in functionalized 1,2,5-oxadiazoles

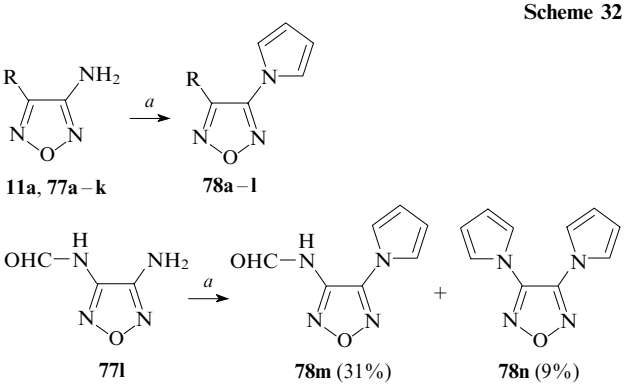
The group of methods discussed in this Section is fairly diversified, as different approaches are required to form different types of heterocycles. For this reason, the data are arranged according to the type of the forming heterocyclic substituent linked to 1,2,5-oxadiazole and in the order of increasing number of heteroatoms.

III.1. Preparation of heteronuclear heterocyclic systems based on furazans and furoxans linked to heterocycles with one heteroatom

Below the data related to synthetic routes to furazans that contain a pyrrole, thiophene, indole or indolizine ring as the heterocyclic substituent are described. Among the synthesis of furoxans that are linked to heterocycles with one heteroatom, only syntheses of pyrrolylfuroxans are available from the literature.

The Clauson – Kaas condensation of aminofurazans **11a** or **77a – k** with 2,5-dimethoxytetrahydrofuran on short refluxing with acetic acid affords pyrrolylfurazans **78a – l** (Scheme 32).[121, 122] The product yields depend considerably on the nature of the second substituent in the furazan ring. The low yields of compounds **78i**,**j**[121, 122] were attributed to the parallel oxidation processes caused by the presence of nitro and azofurazanyl groups in substrates **77i**,**j**. However, pyrrolylfurazan **78k** was prepared in 30% yield, apparently, due to decomposition of the starting 1,2,4-oxadiazolylfurazan **77k** under the reaction conditions. The reaction of *N*-monoformyl-substituted diaminofurazan **77l** with 2,5-dimethoxytetrahydrofuran follows an unusual pathway. Dipyrrolylfurazan **78n** was isolated in an insignificant yield together with expected product **78m**, obviously due to the *in situ* deformylation of starting compound **77l** to diaminofurazan (see Scheme 32).[121] Meanwhile, when diaminofur-

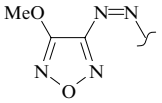
Scheme 32



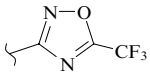
11a, **77a – k** **78a – l**

77l **78m** (31%) **78n** (9%)

77, **78**: R = Me (**a**, 67% yield), Ph (**b**, 87%), OMe (**c**, 64%), Ac (**d**, 74%), I (**e**, 32%), CO_2H (**f**, 80%), CO_2Me (**g**, 59%), CN (**h**, 51%), NO_2 (**i**, 16%)



(**j**, 13%),



(**k**, 30%);
R = 2-Th (**9a**; **78l**, 64%);

(*a*) 2,5-dimethoxytetrahydrofuran, AcOH, Δ

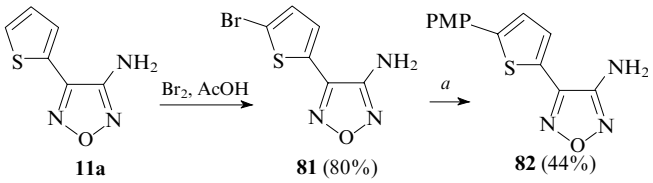
azan was introduced into the Clauson – Kaas reaction, a complex mixture of products was formed, which the authors failed to separate.

The reactivity of pyrrolylfurazans towards aromatic electrophilic substitution was studied in relation to 3-methyl-4-(pyrrol-1-yl)furazan (**78a**).[123] The reaction of compound **78a** with *N*-chlorosuccinimide favours the selective formation of dichloro derivative **78o**, whereas a similar bromination reaction with *N*-bromosuccinimide (NBS) yields tribromopyrrolylfurazan **78p**. The tetrabromo-substituted product was detected by gas chromatography/mass spectrometry (GC-MS), but was not isolated, probably, because of its hydrolytic lability. The nitration of substrate **78a** yields a mixture of mononitro-substituted pyrroles **78q** and **78r** in the 2.5 : 1 ratio. The subsequent treatment of compound **78q** by a stronger nitrating system of 100% HNO_3 – trifluoroacetic anhydride (TFAA) promotes the formation of a mixture of 2,5- (**78s**) and 2,4- (**78t**) dinitro derivatives. However, a similar nitration reaction carried out for nitropyrrole **78r** results in the formation of pyrrolylfurazan **78t** in 69% yield. The Vilsmeier – Haack formylation of compound **78a** yields (2-formylpyrrolyl)furazan **78u** (Scheme 33).

The three-component condensation of 3-amino-4-methylfurazan (**77a**) with anisaldehyde and tricarbonyl compound **79** produced 1-(4-methylfurazan-3-yl)-1,5-dihydropyrrol-2-one derivative **80** (Scheme 34).[124] Trimethylchlorosilane (TMSCl) is an efficient promoter of ultrasound-assisted cyclization, whereas refluxing in acetic acid reduces the target product yield almost to one-half.

The bromination of 3-amino-4-(2-thienyl)furazan (**11a**) yields monobromo derivative **81** as the thiophene ring is less π-excessive than the pyrrole ring. The Suzuki – Miyaura reaction of compound **81** with 4-methoxyphenylboronic

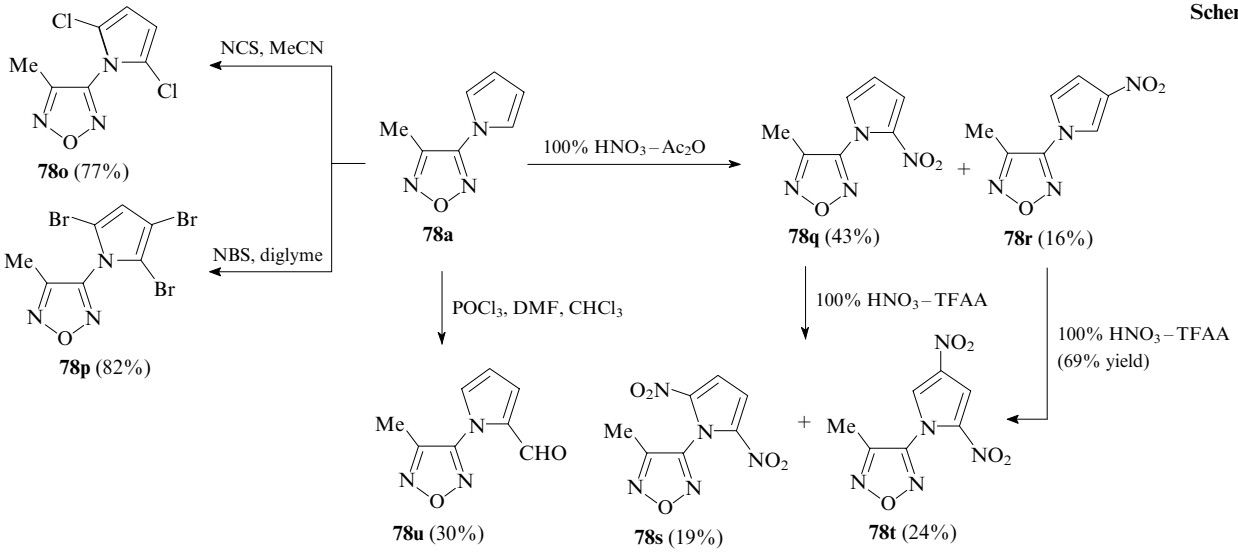
Scheme 35



11a **81** (80%) **82** (44%)

(*a*) $PMPB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, Δ

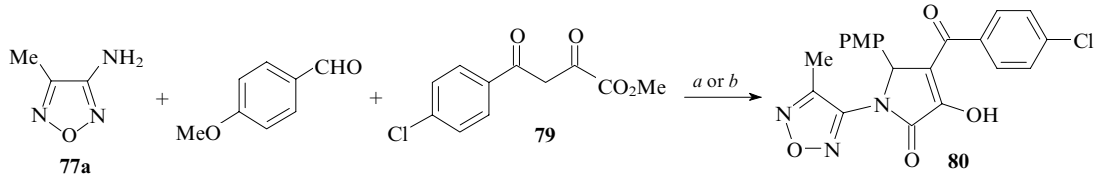
Scheme 33



78o (77%) **78a** **78q** (43%) **78r** (16%)

78p (82%) **78u** (30%) **78s** (19%) **78t** (24%)

Scheme 34



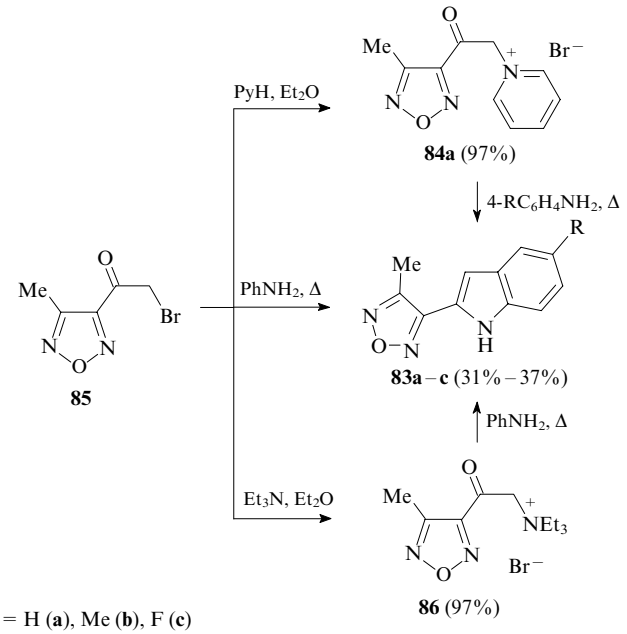
77a **79** **80**

(*a*) 1) TMSCl (5 equiv.), DMF, 100 °C, sealed tube; 2) US (73% yield); (*b*) 1) AcOH, Δ; 2) US (42% yield); PMP = 4-$MeOC_6H_4$

acid in dimethoxyethane (DME) affords cross-coupling adduct **82** in a moderate yield (Scheme 35).[125]

Indolylfurazans **83a – c** (annelated analogues of pyrrolylfurazans) were synthesized from pyridinium salt **84a**, which was prepared from 3-bromoacetyl-4-methylfurazan (**85**) (Scheme 36).[126] The use of furazan **85** or its triethylammonium salt **86** in the Bischler – Mohlau reaction with unsubstituted aniline resulted in desired indole **83a**, but in both cases, the yields were lower (11% and 19%). Attempts to introduce anilines bearing strong electron-withdrawing groups (NO_2, CF_3 or CO_2Me) in the *para*-position of the benzene ring into a similar heterocyclization reaction were not a success.

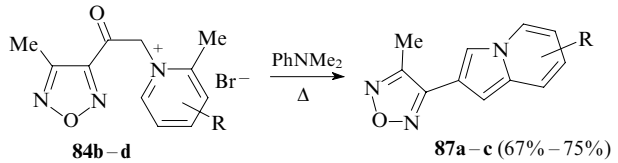
Scheme 36



R = H (**a**), Me (**b**), F (**c**)

When pyridinium salts **84b – d**, prepared from bromoacetylmethylfurazan, are refluxed in *N*,*N*-dimethylaniline, the pyridinium moiety is no longer the leaving group (unlike in the conversions depicted in Scheme 36), but rather is a structural moiety necessary for building the indolizine ring. This approach provided the route to bicyclic structures **87a – c** in good yields (Scheme 37).[127]

Scheme 37

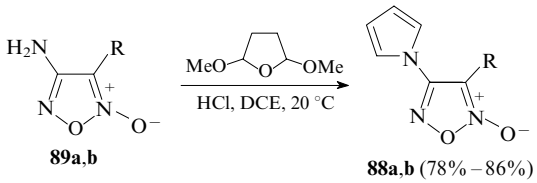


84: R = H (**b**), 3-Me (**c**), 5-Et (**d**); **87**: R = H (**a**), 8-Me (**b**), 6-Et (**c**)

As was mentioned above, pyrrolylfuroxans **88a**,**b** are the only known furoxans that are linked to heterocycles with one heteroatom.[128]

These compounds were recently prepared by the Clauson – Kaas condensation of aminofuroxans **89a**,**b** with 2,5-dimethoxytetrahydrofuran. It is noteworthy that conventional reaction conditions (refluxing in acetic acid) were unacceptable in this case, unlike with aminofurazans. For this transformation to proceed, acetic acid was replaced by hydrochloric acid, which can additionally activate protonated 2,5-dimethoxytetrahydrofuran by increasing the electrophilicity of the carbon atom in position 2; this allows the reaction to proceed with low-basicity amines such as 4-aminofuroxans. In order to prevent pyrrole polymerization in strongly acidic medium (this is the major side process in the Clauson – Kaas pyrrole synthesis), the reaction was performed in a hydrochloric acid – dichloroethane (DCE) two-phase system. Under these conditions, the formed pyrrole moved to the organic phase, and this made it possible to isolate pyrrolylfuroxans **88a**,**b** in high yields (Scheme 38).

Scheme 38



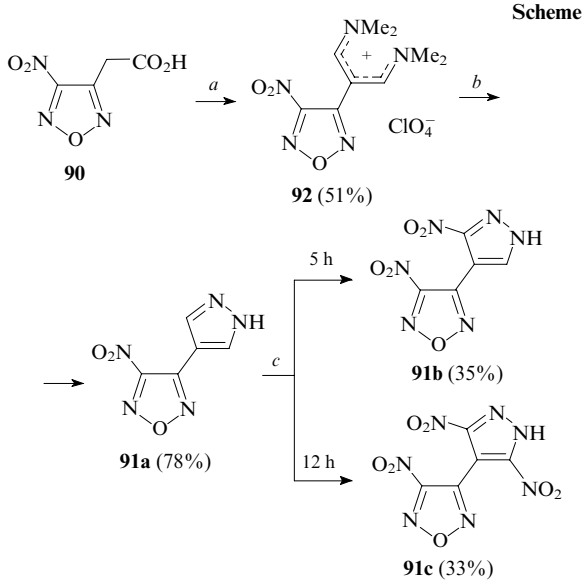
R = Ac (**a**), CO_2Me (**b**)

III.2. Preparation of hetarylfurazans and hetarylfuroxans linked to heterocycles with two heteroatoms

The preparation of this type of structure is mainly exemplified by hetarylfurazans. The known synthetic approaches to furoxans that are linked to heterocycles with two heteroatoms are considered at the end of this Section.

Nitrofurazanylacetic acid **90** serves as the initial compound in the three-step synthesis of 3-nitro-4-(1*H*-pyrazol-4-yl)furazan (**91a**).[129] The first two steps are implemented as a one-pot process: compound **90** is introduced into the Vilsmeier – Haack reaction to give tetramethylpropanediamine, which can be isolated as salt **92** upon addition of an aqueous solution of sodium perchlorate to the reaction mixture. The subsequent treatment of salt **92** with hydrazine hydrate induces cyclization to desired pyrazole **91a**. The nitration of heterocyclic system **91a** by a 100% HNO_3 – 20% oleum mixture yields either nitro pyrazolylfurazan **91b** or dinitro derivative **91c**, depending on the reaction conditions (Scheme 39).

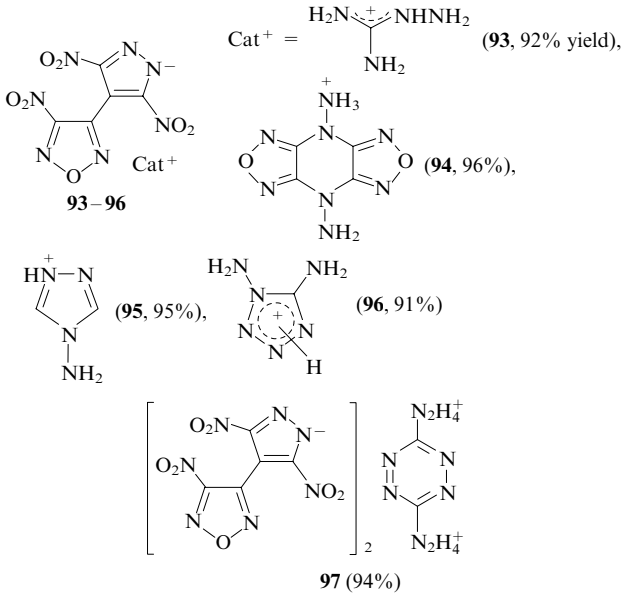
Scheme 39



(*a*) 1) $POCl_3$, DMF, 100 °C; 2) $NaClO_4$, H_2O; (*b*) $NH_2NH_2 \cdot H_2O$, NaOAc, EtOH; (*c*) 100% HNO_3 – 20% oleum

Due to the active hydrogen atom in the pyrazole ring, compound **91c** was used to prepare a set of high-energy salts **93**–**97** in high yields.[129]

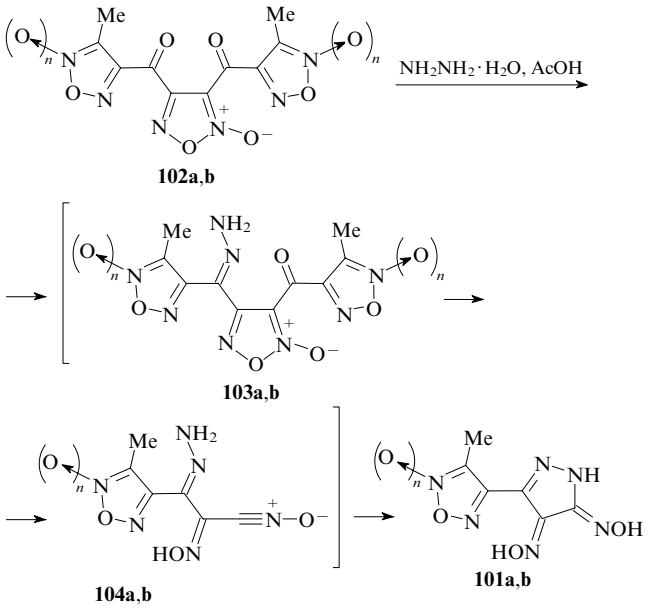
Structures 93–97



The cyclization of enaminoketone **98** with hydrazine hydrate furnishes 3-methyl-4-(1*H*-pyrazol-3-yl)furazan (**99**) in high yield, and the latter can be used to prepare diverse pyrazole derivatives that contain the furoxan ring along with the nitro group.[130] In particular, the nitration of compound **99** by concentrated nitric and sulfuric acid mixture on heating yields 4-nitropyrazole **100a**. Treatment with 100% HNO_3 mixed with acetic anhydride and trifluoroacetic acid (TFA) selectively yields *N*-nitropyrazole **100b**. The same mixture efficiently nitrates nitropyrazole **100a** to dinitro derivative **100c**. The thermal rearrangement of compound **100b** selectively yields 3-nitropyrazole **100d**, which is then nitrated to 1,3-dinitro (**100e**) or 3,4-dinitro derivative (**100f**) depending on reaction conditions (Scheme 40).

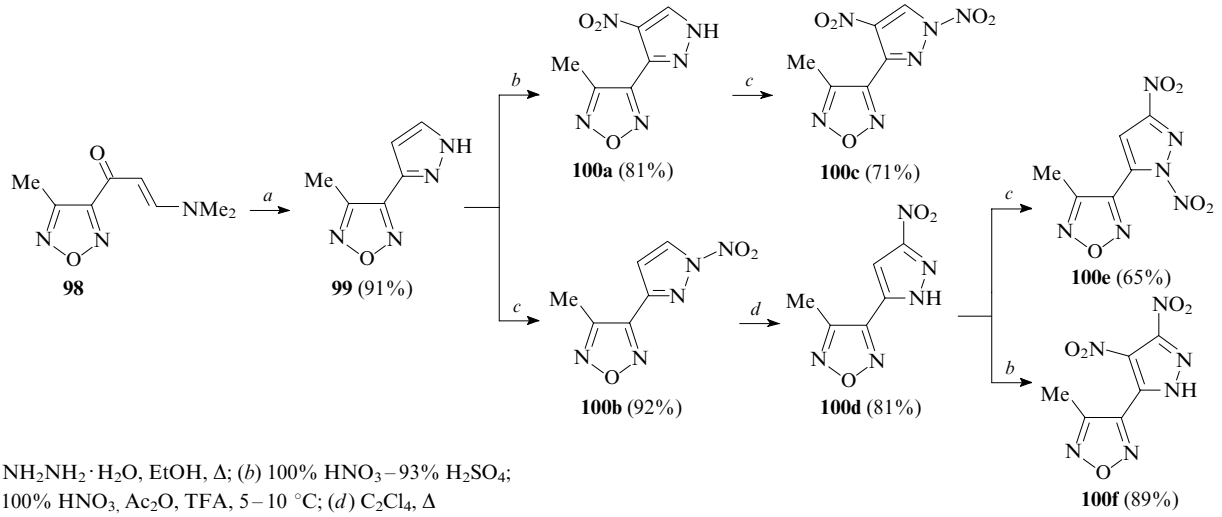
Furazanyl- and furoxanylpyrazole dioximes **101a**,**b** were prepared by the reaction of 3,4-bis(furazanoyl)- and 3,4-bis(furoxanoyl)furoxans **102a**,**b** with hydrazine hydrate.[131] The authors suppose that the first step gives hydrazones **103a**,**b**, which eliminate furazan(furoxan)carboxylic acid hydrazide under the action of a second hydrazine hydrate molecule. This transformation is accompanied by opening of the central furoxan ring to give hydroxyiminoacetonitrile oxides **104a**,**b**, which undergo ring transformation to afford final pyrazoles **101a**,**b** (Scheme 41). Unfortunately, the authors cited [131] did not report the yields of compounds **101a**,**b**.

Scheme 41



The reaction of α,β-unsaturated aminofurazanyl ketones **105a**,**b** with hydrazine hydrate resulted in the synthesis of pyrazolinylfurazan derivatives **106a**,**b** in quantitative yields. A similar reaction of compound **105a** with phenylhydrazine

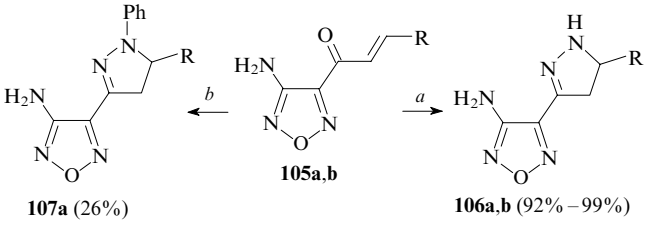
Scheme 40



(*a*) $NH_2NH_2 \cdot H_2O$, EtOH, Δ; (*b*) 100% HNO_3–93% H_2SO_4;
(*c*) 100% HNO_3, Ac_2O, TFA, 5–10 °C; (*d*) C_2Cl_4, Δ

led to heterocyclic system **107a** in a low yield (Scheme 42).[132]

Scheme 42

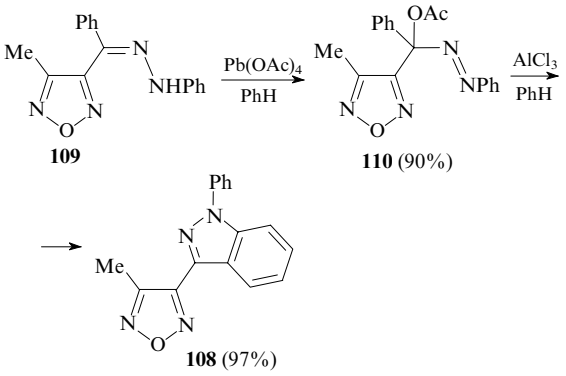


107a (26%) **105a**,**b** **106a**,**b** (92% – 99%)

R = 2-Fu (**a**), cyclo-C_3H_5 (**b**); (*a*) $NH_2NH_2 \cdot H_2O$, THF, rt; (*b*) $PhNHNH_2$, THF, EtOH, rt

The only known example of the synthesis of furazanylindazole **108** (which is a benzo-annelated analogue of furazanylpyrazole) represents a two-step transformation of hydrazone **109**.[133] The reaction of compound **109** with lead tetraacetate produces azoacetate **110**, which undergoes intramolecular cyclization in the presence of a Lewis acid ($AlCl_3$) to give indazole **108** in a nearly quantitative yield (Scheme 43).

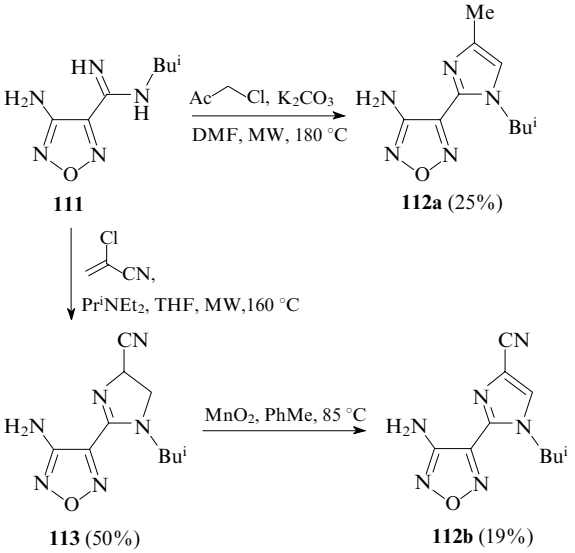
Scheme 43



109 **110** (90%) **108** (97%)

The reactions of aminofurazanylamidine derivative **111** with electrophilic agents were utilized to develop a microwave-assisted (MW) method for preparing imidazolylfurazans.[134] The cyclization of compound **111** with 1-chloropropanone yields imidazole **112a** in a low yield. Amidine **111** reacts with 2-chloroacrylonitrile to afford heterocyclic structure **113** incorporating imidazoline ring, which is oxidized to the imidazole one by manganese(IV) oxide, thus yielding compound **112b** (Scheme 44).

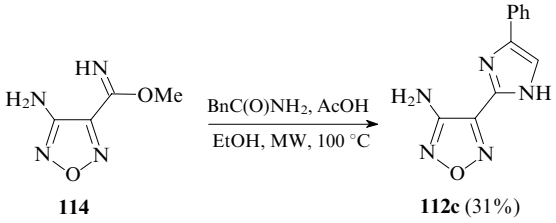
Scheme 44



111 **112a** (25%) **113** (50%) **112b** (19%)

Iminoester **114** is more reactive towards cyclization: it reacts with phenylacetamide at lower temperature to produce imidazolylfurazan **112c** in satisfactory yields (Scheme 45).[134]

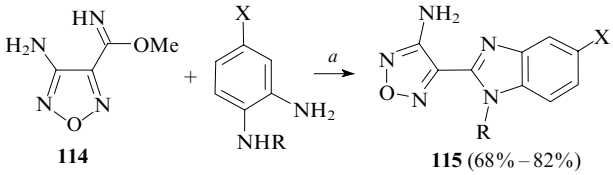
Scheme 45



114 **112c** (31%)

Iminoester **114** can also serve for efficient synthesis of benzimidazolylfurazans **115**. Twenty such derivatives were prepared by reactions of compound **114** with *o*-phenylenediamine derivatives (Scheme 46).[134, 135]

Scheme 46

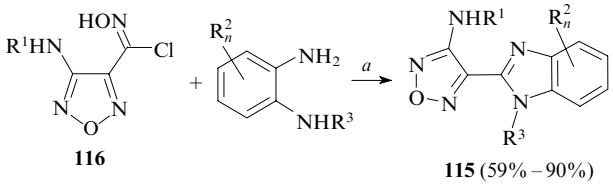


114 **115** (68% – 82%)

X = H, OH, NH_2; R = H, Alk, Ar; (*a*) EtOH or AcOH, Δ

An alternative synthetic route has recently been proposed to prepare heterocycles of type **115**, using furazan-derived chloroximes **116** as precursors. In the condensation of compounds **116** with *o*-phenylenediamines, the best product yields were achieved for chloroximes with $R^1 = H$ (see Scheme 47; the substituent positions in the initial diamine are indicated).[26]

Scheme 47

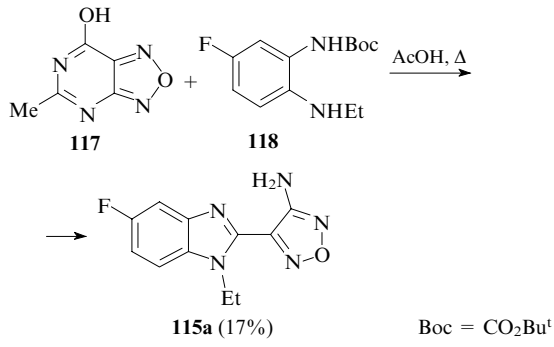


116 **115** (59% – 90%)

R^1 = H, C_6H_4OMe-4, Bn; R^2_n = H, 3-Me, 4-Me, 3,4-Me_2, 4-F, 3-Cl, 4-Cl, 4-OMe, 3,6-$(OMe)_2$, 4-CO_2H, 4-CO_2Me, 4-CN, 4-CF_3; R^3 = H, Me, Et, C_6H_4OMe-4; (*a*) EtOH, Δ

Benzimidazolylfurazan **115a** was prepared by the reaction of bicyclic furazanopyrimidine **117** with substituted *o*-phenylenediamine **118**. The yield of final compound **115a**, however, was only 17% (Scheme 48).[81]

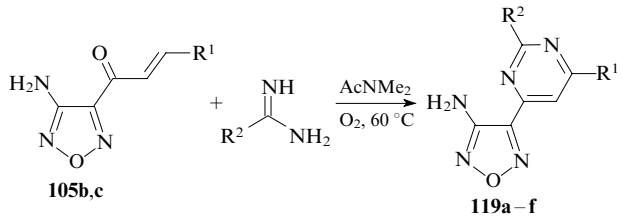
Scheme 48



115a (17%) Boc = CO_2Bu^t

The reactions of α,β-unsaturated aminofurazanyl ketones **105b**,**c** with various dinucleophiles, *e.g.*, amidines and guanidines, give rise to pyrimidinylfurazans **119a – f**, although they are formed in moderate yields (Scheme 49).[132]

Scheme 49



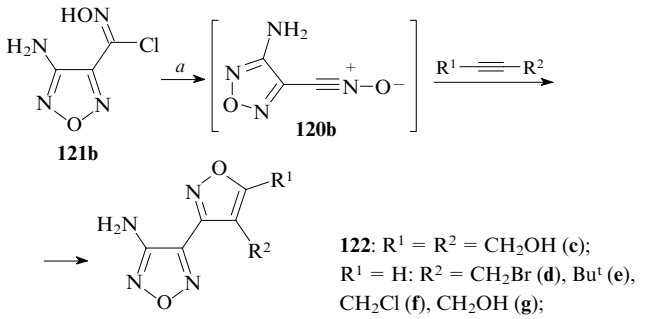
105b,**c** **119a – f**

R^1 = cyclo-C_3H_5 (**105b**, **119a – e**), C_6H_4OMe-4 (**105c**, **119f**);
119: R^2 = Me (**a**), Ph (**b**), C_6H_4OMe-4 (**c**), NHPh (**d**), NHBn (**e**) (14% – 29% yields), NHC_6H_4Me-3 (**f**, 56%)

It was shown[136] that nitrile oxide **120a**, which can be generated in the reaction of triethylamine with hydroxamoyl chloride **121a** in the presence of methyl acrylate or ethyl propiolate, undergoes [3 + 2]-cycloaddition reaction with dipolarophiles to furnish isoxazolylfurazans (**122a**,**b**) or isoxazolinylfurazan (**123**) (Scheme 50). The ratio between regioisomers **122a** and **122b** was 3 : 2, as indicated by ^{1}H NMR spectroscopy, but only isoxazole **122a** was isolated. The product of cyclodimerization of nitrile oxide **120a** [3,4-bis(furazanyl)furoxan] was not detected.

The generation of nitrile oxide **120b** from hydroxamoyl chloride **121b** on treatment with hexa-n-butyldistannane proceeds relatively slowly.[137] Addition of alkynes to the reaction mixture, induces 1,3-dipolar cycloaddition to 1,3-dipole **120b** yielding isoxazolylfurazans **122c – g** (Scheme 51). Since the concentration of alkynes is significantly higher than the concentration of intermediate **120b** and due to the presence of the strong electron-withdrawing furazan substituent in nitrile oxide **120b**, its cyclodimerization is noticeably inhibited, like in the previous case (see Scheme 50), and a furoxan product is not formed.

Scheme 51



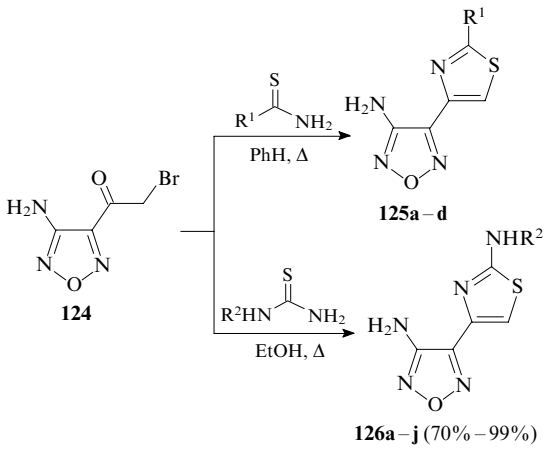
121b **120b**

122: $R^1 = R^2 = CH_2OH$ (**c**);
R^1 = H: $R^2 = CH_2Br$ (**d**), Bu^t (**e**), CH_2Cl (**f**), CH_2OH (**g**);
(*a*) $Bu^n_3SnSnBu^n_3$, *hv*

122c – g (65% – 73%)

The cyclization of bromoacetylaminofurazan **124** with thioamides was utilized[132] for developing a convenient and efficient method for the preparation of amino(thiazolyl)furazans **125a – d** and amino(aminothiazolyl)furazans **126a – j** (Scheme 52).

Scheme 52

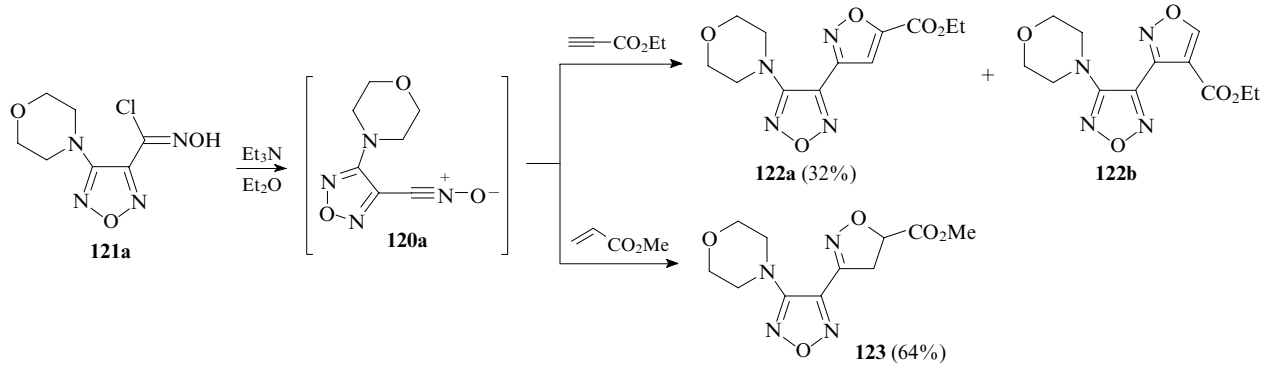


124 **125a – d**

126a – j (70% – 99%)

125: $R^1 = CH_2CN$ (**a**, 60% yield), 3-Py (**b**, 26%), Me (**c**, 34%), Ph (**d**, 93%); **126**: R^2 = H (**a**), Me (**b**), Bn (**c**), $CH_2C_6H_4Cl$-2 (**d**), $CH_2C_6H_3(CF_3)_2$-3,5 (**e**), C_6H_4Cl-2 (**f**), $C_6H_3Cl_2$-2,6 (**g**), $C_6H_3Cl_2$-2,4 (**h**), $C_6H_3(CF_3)_2$-2,4 (**i**), 3-Py (**j**)

Scheme 50

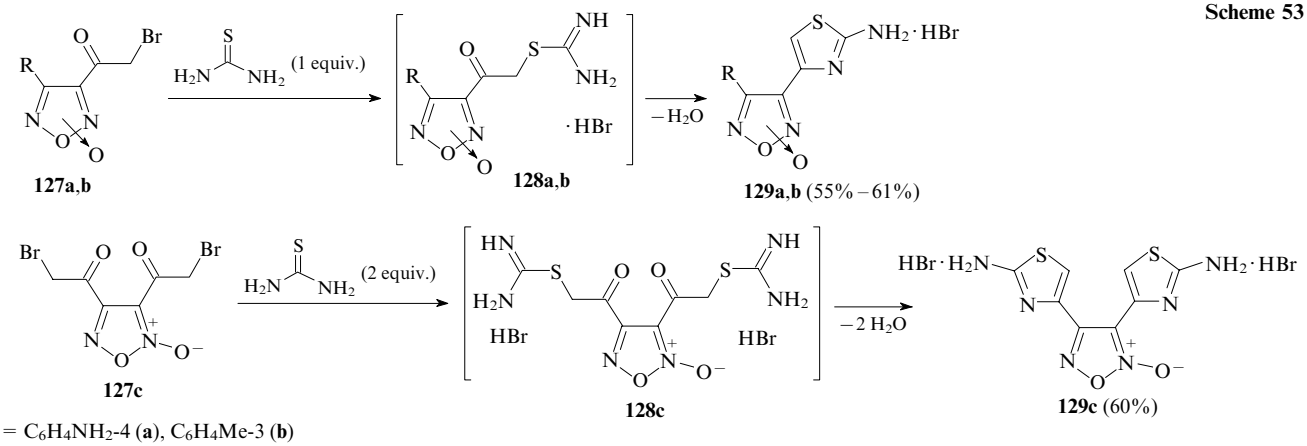


121a **120a**

122a (32%) **122b**

123 (64%)

Scheme 53

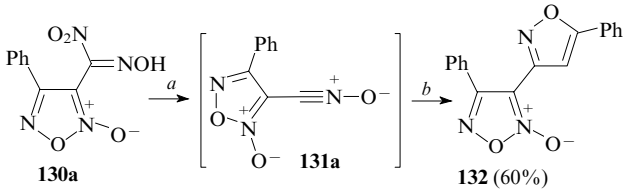


R = $C_6H_4NH_2$-4 (**a**), C_6H_4Me-3 (**b**)

In the same manner, bromoacetylfuroxan derivatives **127a – c** react with thiourea in acetone at room temperature yielding isothiouronium salts **128a – c**, which are further cyclodehydrated according to the Hantzsch reaction pathway to give 2-aminothiazole derivatives **129a – c** (Scheme 53).[138] The reaction proceeds regardless of the position of the N-oxide oxygen atom with respect to the bromoacetyl moiety in the initial furoxan.[132]

There is only a single example of the synthesis of unsymmetrically substituted furoxan with heterocyclic substituents based on the 1,3-dipolar cycloaddition of substituted furoxancarbonitrile oxides to dipolarophiles. For example, thermolysis of the pre-synthesized nitrolic acid **130a** in the presence of phenylacetylene completely suppresses the dimerization of nitrile oxide **131a** and promotes [3 + 2]-cycloaddition to yield isoxazolylfuroxan **132** (Scheme 54).[139]

Scheme 54



(*a*) PhH, Δ ($-HNO_2$); (*b*) PhC≡CH

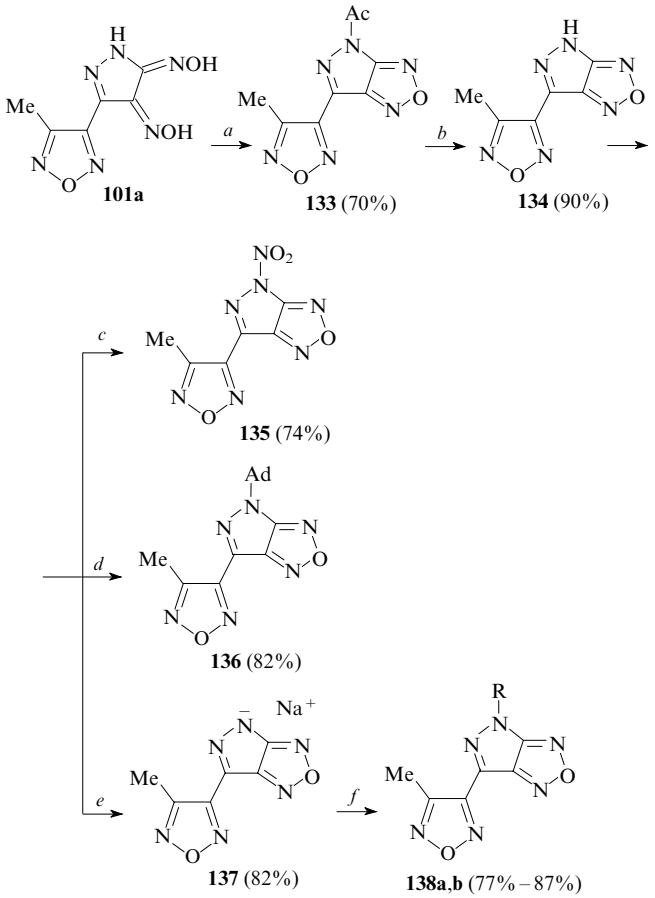
III.3. Preparation of furazans with bi- and tricyclic heterocyclic substituents

This Section covers the routes to furazans that are linked to bicyclic heterocyclic systems in which each ring contains two to four heteroatoms. There are no analogues of such structures in the furoxan series. Several examples of synthesis of furazans with tricyclic heterocyclic substituents will also be presented.

Refluxing of pyrazolylfurazan **101a** in acetic anhydride in the presence of sodium acetate induces intramolecular dehydration of the glyoxime moiety to form *N*-acetylpyrazolofurazan **133**, which is treated with aqueous alkali to remove the acetyl protecting group.[131] The resulting heterocyclic system **134**, being an NH-acid, is efficiently nitrated at the pyrazole ring nitrogen to yield nitro derivative **135** and also reacts with adamantan-1-ol (AdOH) in concentrated H_2SO_4 to give *N*-(1-adamantyl)pyrazolofurazan **136**. Treatment of compound **134** with aqueous alkali yields stable sodium salt **137**, which can react with alkyl halides to afford N-substituted bicyclic structures **138a**,**b** (Scheme 55).

The synthetic sequence shown in Scheme 56 was developed for the construction of high-energy heterocyclic systems based on furazans containing the 1,2,3-triazolo[4,5-*c*]-1,2,5-oxadiazole bicyclic substituent at the furazan ring.[140] At the first step, diaminofurazan **139** is oxidized by ammonium persulfate. The resulting diaminoazofurazan **140** is subjected to nitrosation followed by the treatment of the

Scheme 55



138: R = Me (**a**), CH_2CO_2H (**b**);
(*a*) NaOAc, Ac_2O, Δ; (*b*) NaOH, H_2O; (*c*) 100% HNO_3, 98% H_2SO_4;
(*d*) AdOH, 94% H_2SO_4; (*e*) NaOH, H_2O, 50 °C;
(*f*) RHal, KOH, EtOH or H_2O, Δ

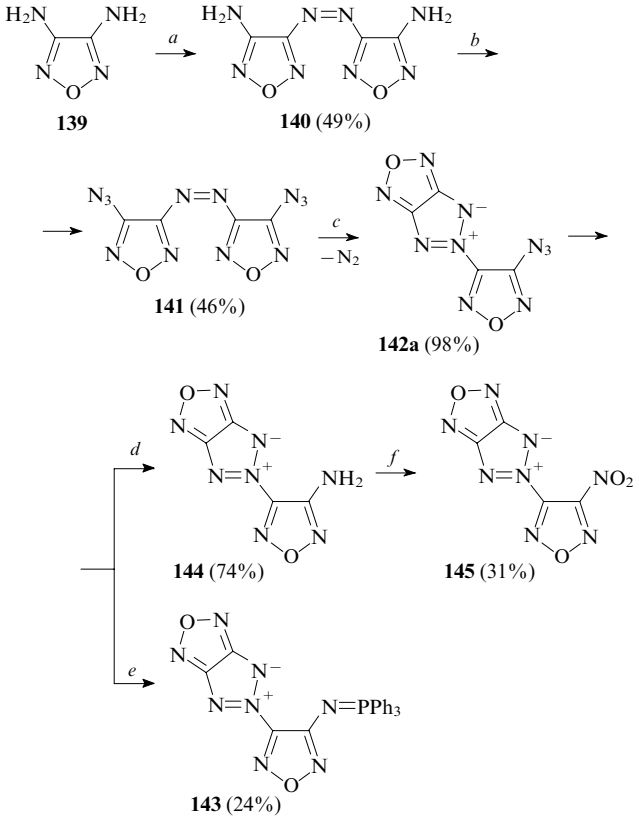
in situ formed diazonium salts with an aqueous sodium azide solution to yield highly unstable diazidoazofurazan **141**. When the latter is refluxed in acetonitrile, the triazole ring is closed with elimination of nitrogen. Azidofurazan **142a**, formed in a nearly quantitative yield, can further be modified by means of chemical conversion of the azide group: it reacts with triphenylphosphine to form iminophosphorane **143** in a low yield and can be reduced to aminofurazan **144** on treatment with tin dichloride. The subsequent oxidation of the amino group in compound **144** requires a relatively strong oxidizing system, namely, a mixture of hydrogen peroxide and concentrated sulfuric acid with addition of ammonium persulfate, as the basicity of this amino group is significantly decreased by the strong electron-withdrawing substituent. This also accounts for the rather low yield of nitrofurazan **145**.

Nonetheless, aminofurazan **144** can participate in the Mannich reaction with paraformaldehyde to give methylene-bis(amino) derivative **146**.[141] Both NH groups in dimer **146** are efficiently nitrated by a mixture of fuming nitric acid with acetic anhydride to produce compound **147** in nearly quantitative yield (Scheme 57).

Aminofurazan **144** is also capable of oxidative condensation with nitrosofurazan **148** induced by dibromoisocyanurate (DBI).[142] The treatment of azoxy derivative **149** with trifluoroacetic acid removes trifluoroacetyl protecting group from the aminofurazanyl moiety, which allows compound **150** to undergo oxidation affording polyheterocyclic structure **151** in nearly quantitative yield (Scheme 58).

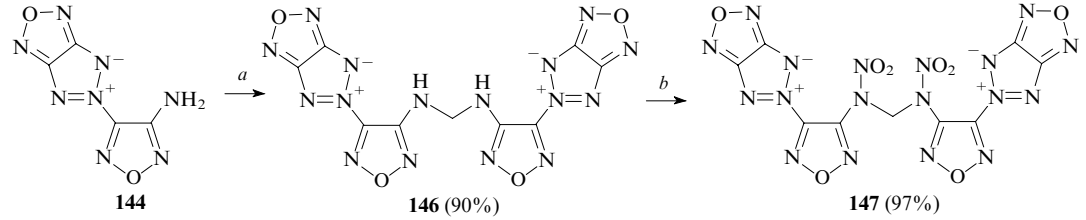
Furazan derivatives **152a**–**c**, comprising the 1,2,4-triazolo[4,3-*b*]tetrazine bicyclic moiety, were prepared by the intramolecular dehydration of furazanoylhydrazines **153a**–**d**.[143] The latter were obtained by nucleophilic displacement of one of the dimethylpyrazole moieties in *sym*-tetrazines **154a**,**b** with furazancarboxylic acid hydrazides

Scheme 56



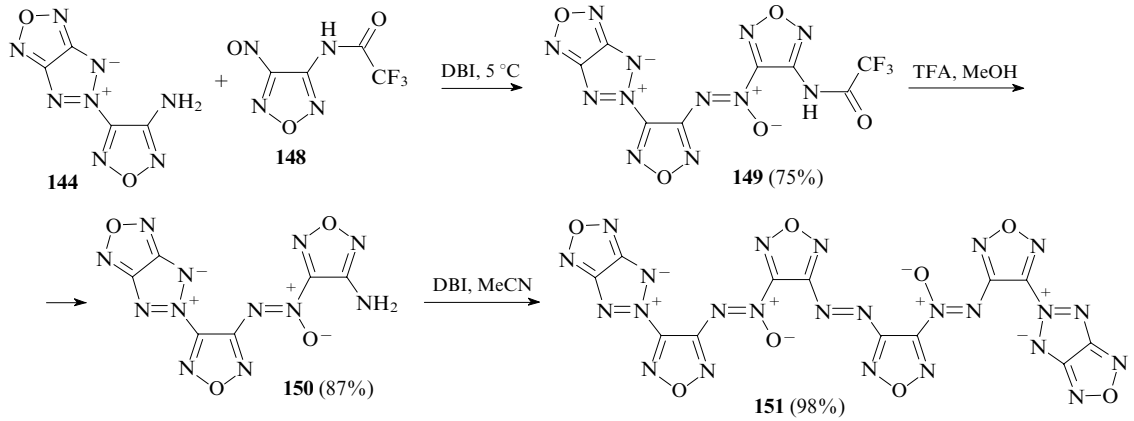
(*a*) $(NH_4)_2S_2O_8$, H_2O, 70 °C; (*b*) 1) $NaNO_2$, H_2SO_4–AcOH, 0–5 °C; 2) NaN_3, H_2O, 0–5 °C; (*c*) MeCN, Δ; (*d*) $SnCl_2$, MeOH, rt; (*e*) PPh_3, THF, H_2O; (*f*) $(NH_4)_2S_2O_8$, H_2O_2, conc. H_2SO_4

Scheme 57

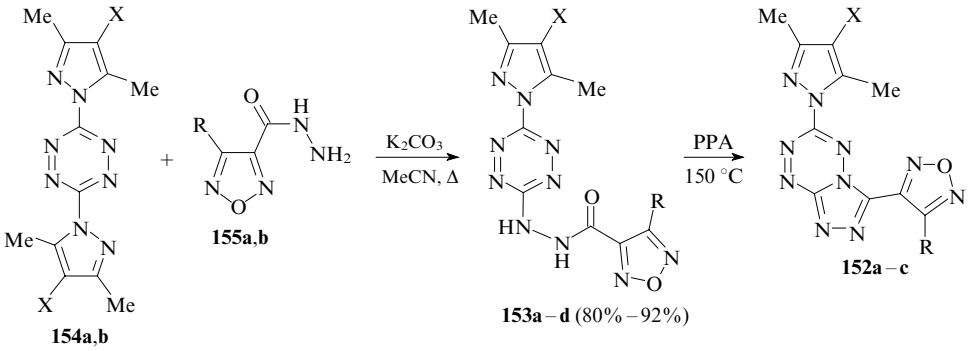


(*a*) $(CH_2O)_n$, HCl, 100 °C; (*b*) HNO_3, Ac_2O, 0 °C

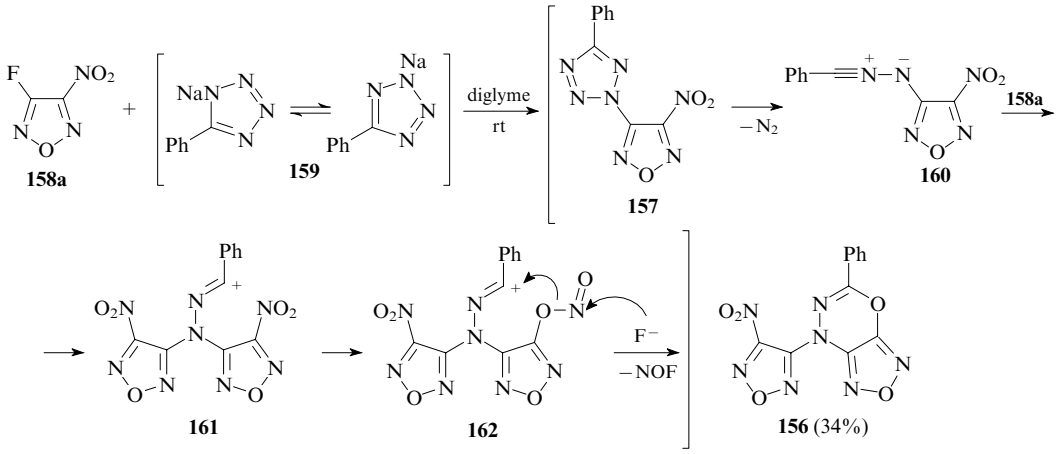
Scheme 58



Scheme 59



Scheme 60

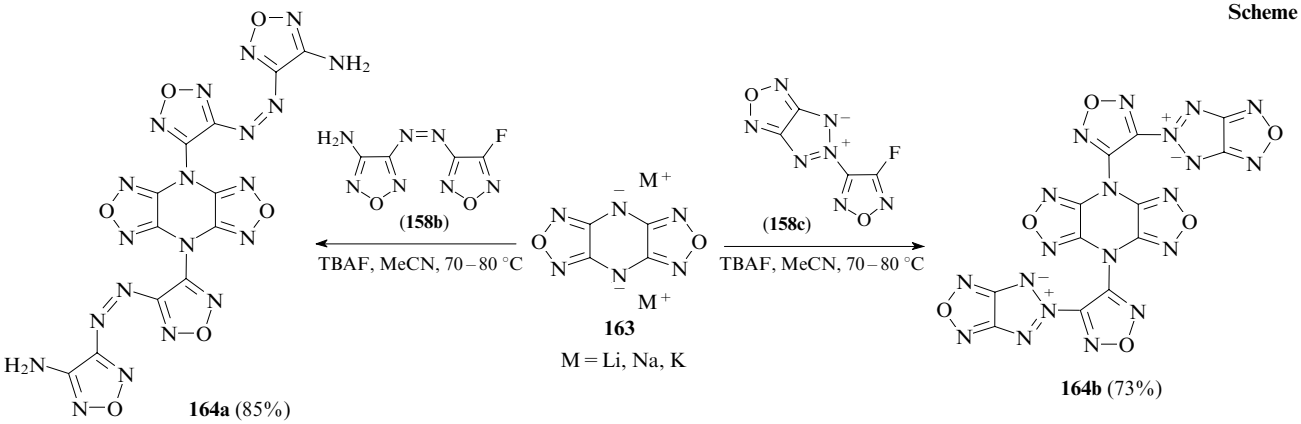


155a,**b** (Scheme 59). The cyclization proceeds in polyphosphoric acid (PPA) at temperatures above 150 °C, which is responsible for the low yield of amino derivative **152b** (2%) and total decomposition of thermally unstable compound **153d** under the reaction conditions.

Sheremetev *et al.*[144] unexpectedly isolated heterocyclic system **156** in which the nitrofurazanyl moiety was linked to the previously unknown 4*H*-furazano[3,4-*e*]-1,3,4-oxadiazine bicyclic system, which formed in the reaction. The authors intended initially to obtain tetrazolylfurazan **157** by nucleophilic displacement of the fluoride anion in nitrofluorofurazan **158a** on treatment with phenyltetrazole sodium salt **159**. It is likely that tetrazolylfurazan **157** is formed as an intermediate under these conditions and then spontaneously eliminates a nitrogen molecule to give nitrile imine **160**. Dipole **160** reacts with a second molecule of substrate **158a** to yield carbocation **161**, in which one of the nitro groups undergoes the nitro – nitrite rearrangement. At the final step, the oxadiazine ring in intermediate **162** is closed with simultaneous elimination of an NOF molecule and formation of final structure **156** (Scheme 60).

The nucleophilic displacement of fluoride anions in fluorofurazans **158b**,**c** by bisfurazano[3,4-*b*;3′,4′-*e*]pyrazine dianion **163** was used to obtain heterocyclic structures **164a**,**b** (Scheme 61).[145] The presence of tetra-n-butylammonium fluoride (TBAF) exerts the crucial effect on the selectivity: the reaction of fluorofurazan **158b** with dianion **163** produces disubstituted product **164a** in high yield, whereas in the absence of a phase transfer catalyst, the reaction furnishes a mixture of mono- and disubstituted adducts.

Scheme 61

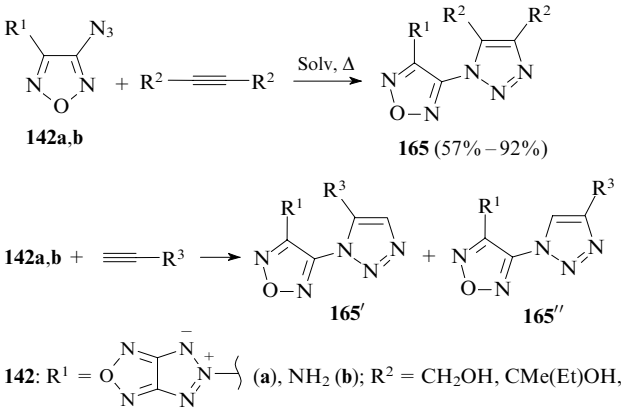


III.4. Preparation of furazans and furoxans linked to heterocycles with three nitrogen atoms in the ring

This Section focuses on the preparation and some chemical properties of 1,2,3-triazolylfurazan derivatives. Then, the known approaches to prepare 1,2,4-triazolylfurazans will be discussed and, by the end, the preparation methods of a very narrow circle of isomeric 1,2,3- and 1,2,4-triazolylfuroxans will be presented.

The most widely used method for preparing 1,2,3-triazolylfurazans is based on the 1,3-dipolar cycloaddition of various dipolarophiles to azidofurazans. The reaction of starting azides **142a**,**b** with terminal and internal alkynes yields mono- and disubstituted 1,2,3-triazolylfurazans **165**.[146] The triazolylfurazan yields are appreciably influenced by both the structure of acetylene derivatives (the triple bond position) and the nature of the substituent. In general, final product yields are higher for internal alkynes; only the yield of compound **165**, where $R^2 = CO_2H$, was 30%, obviously due to possible decarboxylation. Terminal alkynes provide mixtures of regioisomeric triazoles **165′** and **165″** in the 1 : 1 ratio in a total yield of 5% to 87%; the highest yield is achieved when $R^3 = CMe_2OH$ (87%), and the lowest yield is for $R^3 = CO_2Me$ or CO_2Et (Scheme 62).

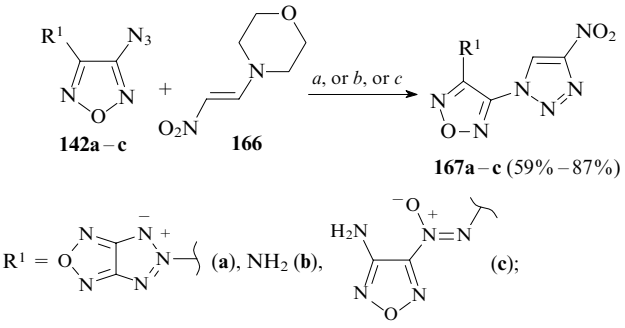
Scheme 62



The use of 1-n-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquid as a solvent in a similar reaction enhances the yield of target triazolylfurazan **165a**, increases the ratio of regioisomers **165′a** : **165″a** in favour of the former and decreases 3 – 5-fold the reaction time (Scheme 63).[147]

The [3 + 2]-cycloaddition reaction of morpholinonitroethylene **166** with azidofurazans **142a** – **c** occurs as the regioselective formation of 4-nitrotriazolylfurazans **167a** – **c** accompanied by elimination of a morpholine molecule (Scheme 64).[142, 148] Thus, dipolarophile **166** acts in this process as a synthetic equivalent of nitroacetylene. Compound **167b** was also obtained using the [bmim]PF_6 ionic liquid as the reaction medium, which made it possible to appreciably shorten the reaction time, but the product yield decreased to 35%.[147]

Scheme 64



(*a*) MeCN, Δ; (*b*) PhMe, Δ; (*c*) $HC(OEt)_3$, PhH, Δ

Owing to the free amino group, triazolylfurazan **167c** is oxidized by dibromoisocyanurate to yield polyheterocyclic system **168**. Meanwhile, aminofurazan **167b** is converted to azoxyfurazan **169** upon oxidative condensation with nitrosofurazan **148**; with subsequent removal of the trifluoroacetyl protecting group from the amino group that is linked to the furazan ring. In addition, in this case, bis(azoxy) product **170** was isolated in a trace amount (Scheme 65).[142]

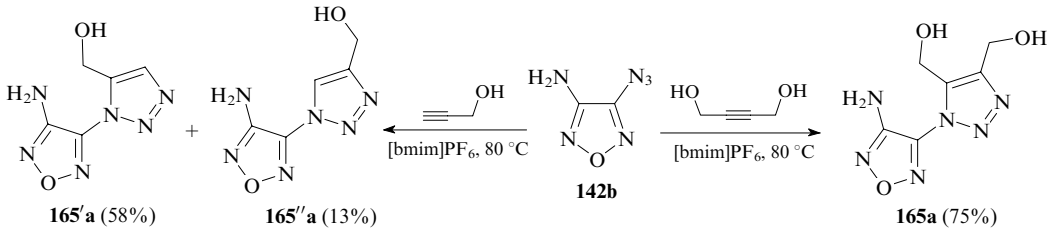
Azidofurazans **142b**,**d** – **g** undergo [3 + 2]-cycloaddition reaction with enolate anions of β-dicarbonyl compounds, which are generated *in situ* in the presence of a substoichiometric amount of an organic or inorganic base (B). This is a general approach; it was used to obtain 27 triazolylfurazans **171** with aliphatic, aromatic and heterocyclic substituents both in the furazan and triazole rings, in most cases, in high yields (Scheme 66).[149 – 155]

3-Azido-4-(pyrrol-1-yl)furazan (**142h**) prepared by Clauson – Kaas condensation reacts with acetylacetone and acetoacetic ester by the [3 + 2]-cycloaddition pathway to produce triazolylfurazans **171a**,**b** in 55% – 65% yields.[153] The same products can be prepared in higher yields (74% – 82%) from aminofurazans **171c**,**d** and 2,5-dimethoxytetrahydrofuran (Scheme 67).

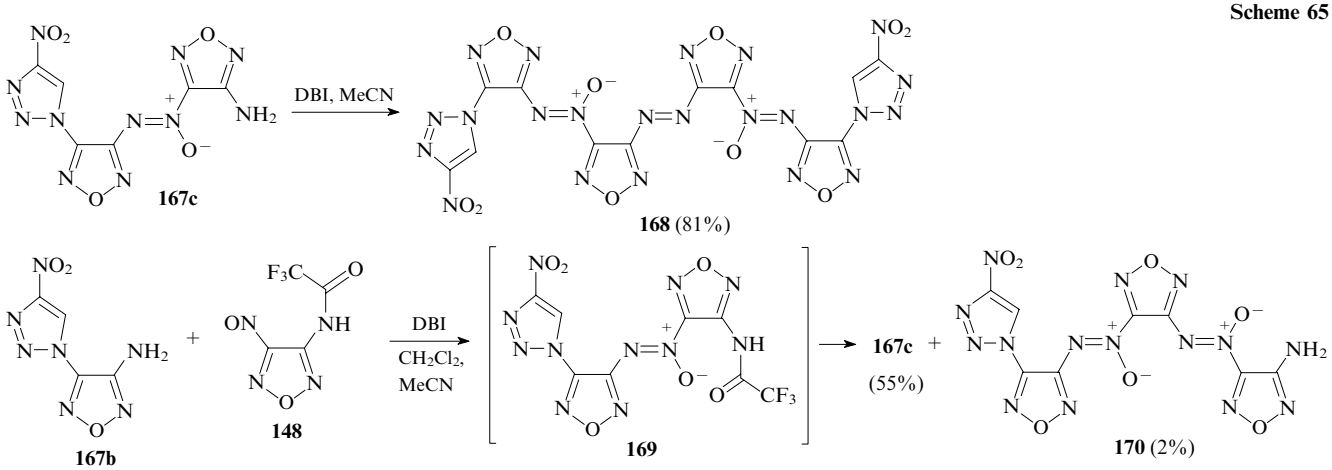
In the 1,3-dipolar cycloaddition to β-dicarbonyl compounds, *N*,*N′*-bis(4-azidofurazan-5-yl)methylenediamine (**142i**) reacts by both azide groups to yield symmetric heterocyclic assemblies **171e** – **g** (Scheme 68).[156]

The amino groups in triazolylfurazans **171h**,**i** are converted to azide groups in a two-step cascade, the mechanism of which is shown in Scheme 69.[153] The first step is nitrosation of the amino group of **171h**,**i** to generate diazonium

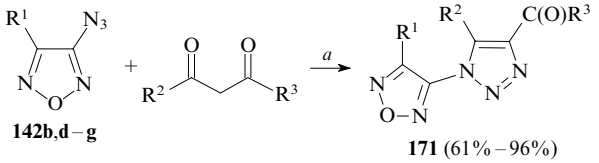
Scheme 63



Scheme 65

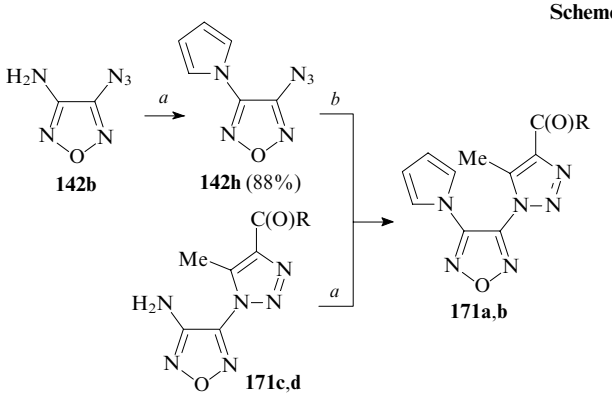


Scheme 66



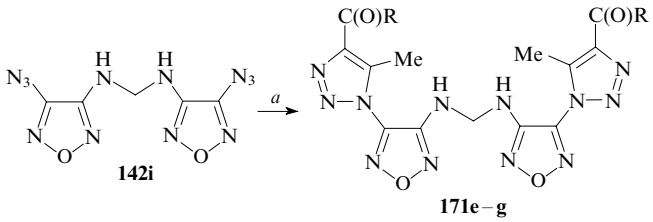
142: $R^1 = NH_2$ (**b**), Me (**d**), OMe (**e**), Ph (**f**), 5-methyl-1,2,4-oxadiazol-3-yl (**g**); R^2 = Alk, Ar, Het; R^3 = Alk, Ar, OAlk;
(*a*) B, H_2O or EtOH

Scheme 67



171: R = Me (**a**, **c**), OEt (**b**, **d**); (*a*) 2,5-dimethoxytetrahydrofuran, AcOH, Δ; *b* — $AcCH_2C(O)R$, K_2CO_3, Me_2CO, H_2O

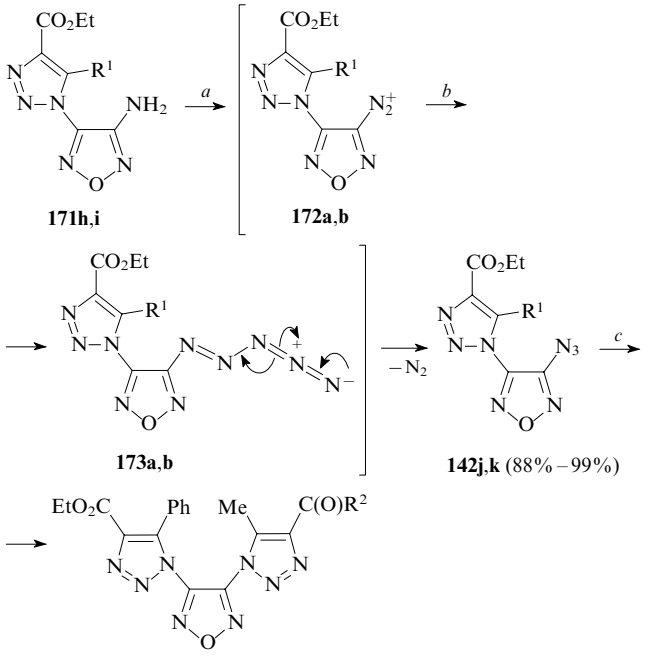
Scheme 68



171: R = Me (**e**), OEt (**f**), NEt_2 (**g**);
(*a*) $AcCH_2C(O)R$, K_2CO_3 or Et_3N, Me_2CO or EtOH, Δ

cations **172a**,**b**, which add the azide anion under the action of an aqueous solution of sodium azide with generation of pentazene intermediates **173a**,**b**. Intermediates **173a**,**b** are extremely unstable and eliminate a nitrogen molecule to yield target azidofurazans **142j**,**k**. The reaction of compound **142j** with acetylacetone and acetoacetic ester proceeds as [3 + 2]-cycloaddition to furnish bis(triazolyl)-furazans **174a**,**b** (see Scheme 69).

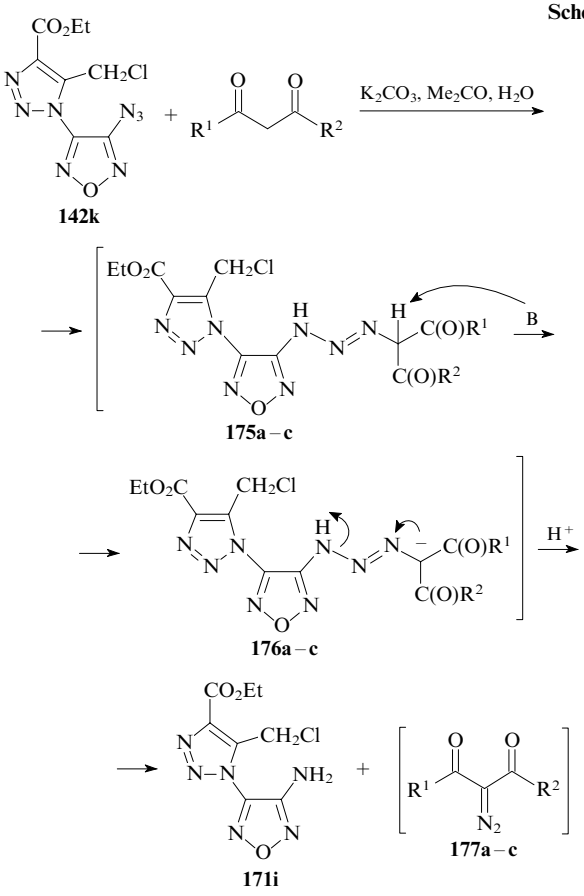
Scheme 69



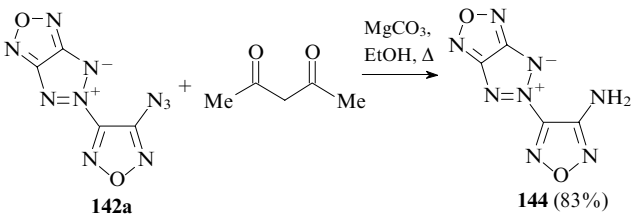
R^1 = Ph (**142j**, **171h**, **172a**, **173a**), CH_2Cl (**142k**, **171i**, **172b**, **173b**);
R^2 = Me (**174a**), OEt (**174b**); (*a*) $NaNO_2$, H_2SO_4, H_3PO_4; (*b*) NaN_3, H_2O; (*c*) for R^1 = Ph: $AcCH_2C(O)R^2$ (R^2 = Me, OEt), Et_3N, EtOH

Utilization of azidofurazan **142k**, incorporating a chloromethyl substituent in position 5 of the triazole ring, in a similar cycloaddition reaction yields only amine **171i** *via* diazo transfer.[153] The mechanism of this unusual transformation comprises the initial addition of the anion of a 1,3-dicarbonyl compound to the azide group of substrate **142k** followed by base-catalyzed proton transfer in triazenes **175a** – **c** and the generation of intermediates **176a** – **c**. The electron transfer, accompanied by N — N bond cleavage in structures **176a** – **c**, gives aminofurazan **171i** and diazo

Scheme 70



175 – 177: $R^1 = R^2 = Me$ (**a**); $R^1 = CH_2Cl$: $R^2 = Me$ (**b**), OEt (**c**)

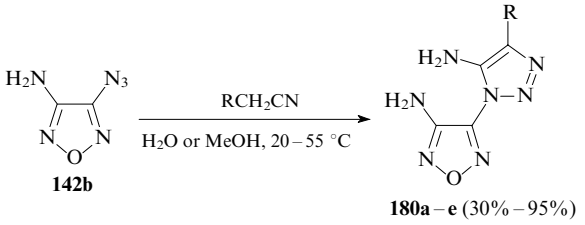


compounds **177a – c**;[157] however, the latter were not isolated (Scheme 70). A similar situation is observed in the reaction of furazanyl azide **142a** with acetylacetone: only aminofurazan **144** was isolated in this case.[149] Intermediates **175a – c** are apparently formed also in the [3 + 2]-cycloaddition, but then 1,2,3-triazole derivatives are produced *via* intramolecular attack of the negatively charged nitrogen atom on one of the carbonyl groups followed by elimination of water.

The result of the [3 + 2]-cycloaddition of azidofurazans to dicarbonyl compounds also strongly depends on the structures of dipolarophiles, which can reveal dual reactivity. In particular, cyclohexane-1,3-dione can successfully react with azidoaminofurazan **142b** to form bicyclic system **171j**. However, when indanedione (another cyclic diketone) reacted with the same substrate **142b**, only diazo compound **178** was isolated (Scheme 71).[149] Compound **178** was formed upon self-condensation of the initial diketone followed by the diazo-transfer reaction induced by azidofurazan **142b**. The formation of diaminofurazan **139** and diazoindanedione **179** was also detected by chromatography and mass spectrometry (see Scheme 71).

1,3-Dipolar cycloaddition involving azidoaminofurazan **142b** can also successfully proceed at the C – C bonds of nitriles possessing an active methylene group to yield aminotriazolylfurazans **180a – e** (Scheme 72).[158]

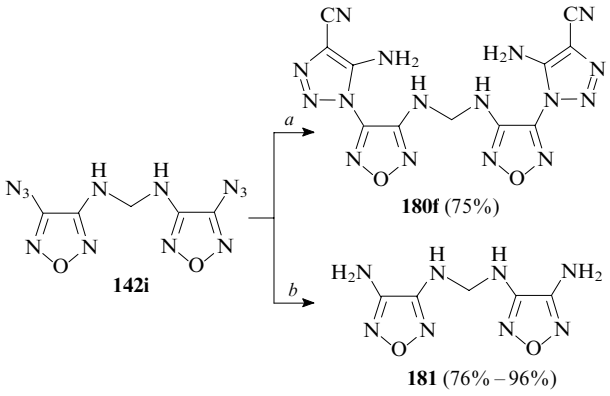
Scheme 72



180: R = CN (**a**), $C(O)NH_2$ (**b**), $C_6H_4NO_2$-4 (**c**), C_6H_4Cl-4 (**d**), $C(S)NH_2$ (**e**)

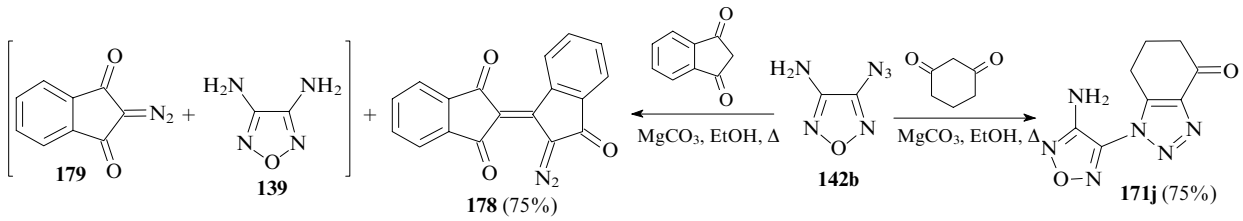
The reaction of *N*,*N*′-bis(4-azidofurazan-3-yl)methylenediamine (**142i**) with malononitrile proceeds in a similar way at both azide groups (compound **180f**), whereas the reaction of ethyl cyanoacetate or cyanoacetic acid diethylamide yields exclusively diamino derivative **181** as a result of diazo transfer (Scheme 73).[156]

Scheme 73



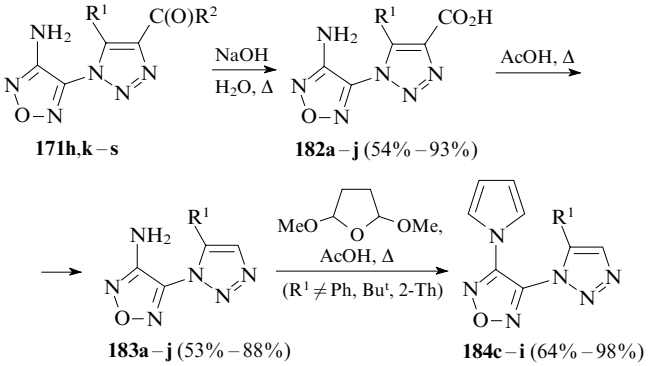
(*a*) $NCCH_2CN$, K_2CO_3, MeOH;
(*b*) $NCCH_2C(O)R$ (R = OEt, NEt_2), Et_3N, EtOH

Scheme 71



The ester group in triazolylfurazans **171h**,**k** – **s** is easily hydrolyzed in alkaline medium to give carboxylic acids **182a** – **j**, which are then decarboxylated upon refluxing in acetic acid to yield monosubstituted triazoles **183a** – **j** (Scheme 74).[151, 152] Compounds **183c** – **i** were then converted to 3-(pyrrol-1-yl)-4-(1,2,3-triazol-1-yl)furazans **184c** – **i** *via* Clauson – Kaas condensation.[152]

Scheme 74



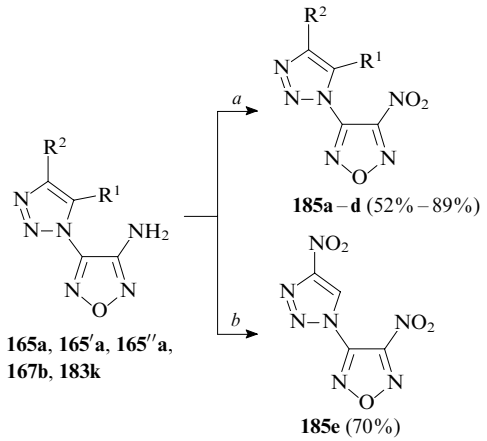
171h,**k** – **s** **182a** – **j** (54% – 93%)

183a – **j** (53% – 88%) **184c** – **i** (64% – 98%)

R^1 = Ph (**171h**, **182a**, **183a**), Bu^t (**171k**, **182b**, **183b**), C_6H_4OMe-4 (**171l**, **182c** – **184c**), $C_6H_3(OMe)_2$-3,4 (**171m**, **182d** – **184d**), $C_6H_2(OMe)_3$-3,4,5 (**171n**, **182e** – **184e**), $C_6H_3(OCH_2O)_3$-3,4 (**171o**, **182f** – **184f**), C_6H_4OEt-4 (**171p**, **182g** – **184g**), C_6H_4F-4 (**171q**, **182h** – **184h**), C_6H_4Cl-4 (**171r**, **182i** – **184i**), 2-Th (**171s**, **182j**, **183j**); R^2 = OMe, OEt

Some triazolylaminofurazan derivatives were studied in oxidation reactions. The amino group basicity in such heterocyclic systems is noticeably reduced due to the strong electron-withdrawing character of the furazan ring. A rather severe oxidizing system consisting of concentrated hydrogen peroxide, sulfuric acid and sodium tungstate was required to oxidize the amino groups in compounds **165a**, **165′a**, **165″a** and **183k** to nitro groups to form nitro derivatives **185a** – **d**.[159] The oxidation of compound **167b** to nitrofurazan **185e** by a similar reaction was performed using trifluoroperoxyacetic acid, which was generated *in situ* from hydrogen peroxide and trifluoroacetic anhydride (Scheme 75).

Scheme 75



185a – **d** (52% – 89%)

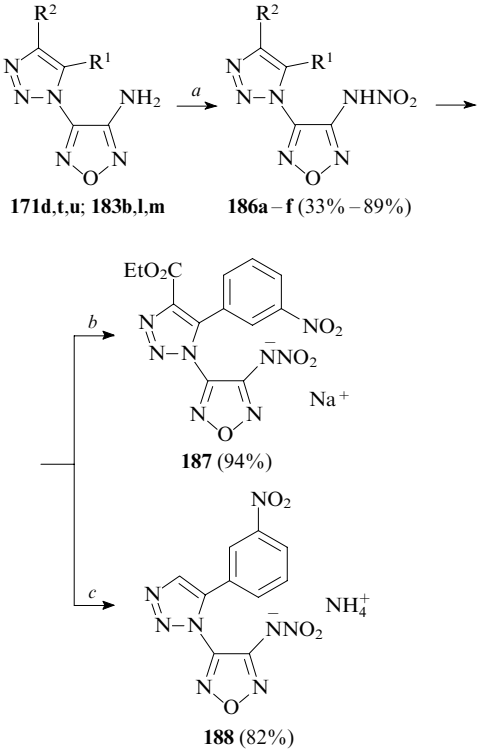
165a, **165′a**, **165″a**, **167b**, **183k**

185e (70%)

R^1 = CH_2OH: R^2 = CH_2OH (**165a**, **185a**), H (**165′a**, **185b**); R^1 = H: R^2 = CH_2OH (**165″a**, **185c**), Ph (**183k**, **185d**); (*a*) 85% – 90% H_2O_2, 98% H_2SO_4, Na_2WO_4; (*b*) for **167b** (R^1 = H, R^2 = NO_2): 85% H_2O_2, TFAA

The treatment of amino derivatives **171d**,**t**,**u** and **183b**,**l**,**m** with $NaNO_3$ in 98% sulfuric acid yields nitroamines **186a** – **f**; triazolylfurazans containing aromatic substituents also undergo benzene ring nitration in the *meta*-position to the triazole ring. Compounds **186b**,**e** were then converted to sodium salt **187** and ammonium salt **188**, respectively (Scheme 76).[151]

Scheme 76



171d,**t**,**u**; **183b**,**l**,**m** **186a** – **f** (33% – 89%)

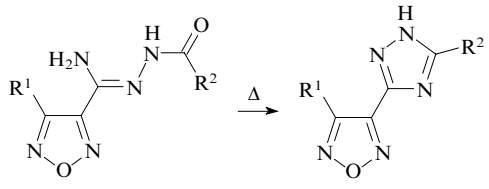
187 (94%)

188 (82%)

R^2 = CO_2Et: R^1 = Me (**171d**, **186a**), $C_6H_4NO_2$-3 (**171t**, **186b**), $C_6H_3NO_2$-3-Cl-4 (**171u**, **186c**); R^2 = H: R^1 = Bu^t (**183b**, **186d**), $C_6H_4NO_2$-3 (**183l**, **186e**), $C_6H_3NO_2$-3-Cl-4 (**183m**, **186f**); (*a*) $NaNO_3$, 98% H_2SO_4; (*b*) for **186b**: $NaHCO_3$, H_2O – Me_2CO; (*c*) for **186e**: NH_3, H_2O, EtOH

1,2,4-Triazolylfurazans are far less accessible than their 1,2,3-triazolyl analogues, as they cannot be obtained by dipolar cycloaddition. One of the few methods known for the preparation of 5-substituted 1,2,4-triazolylfurazans **189a** – **g** is based on the intramolecular cyclodehydration of *N*-acylamidrazones **190a** – **g**, which are heated to temperatures 2 – 10 °C above their melting points (Scheme 77).[135, 160] The second approach to the synthesis

Scheme 77

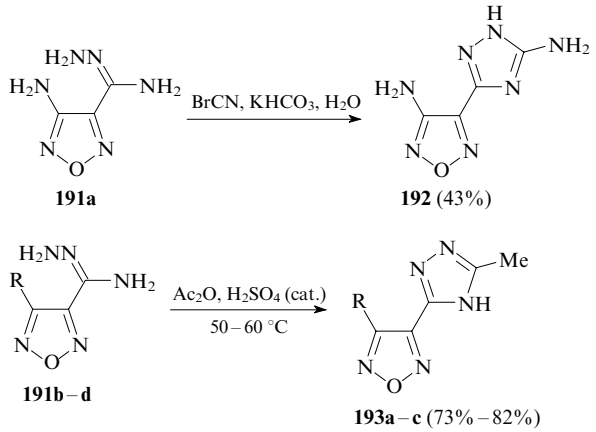


190a – **g** **189a** – **g** (60% – 84%)

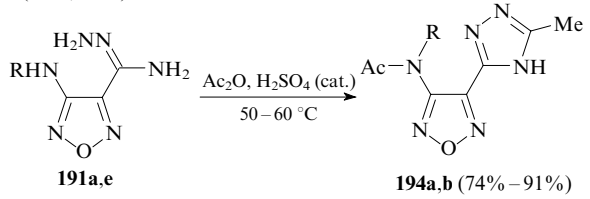
R^1 = Me: R^2 = Me (**a**), CH_2Cl (**b**), Ph (**c**); R^1 = NH_2: R^2 = CH_2OMe (**d**), $(CH_2)_5OH$ (**e**), (4-aminofurazan-3-yl)methyl (**f**); 4-methylfurazan-3-yl (**g**)

of 1,2,4-triazolylfurazans is based on the condensation of furazanylamidrazones **191** with electrophilic reagents. In particular, the heterocyclization of amidrazone **191a** with cyanogen bromide yields 3-amino-4-(5-amino-1*H*-1,2,4-triazol-3-yl)furazan (**192**) (Scheme 78).[161]

Scheme 78



R = NMe_2 (**191b**, **193a**), $N(CH_2CH_2)_2O$-cyclo (**191c**, **193b**), OMe (**191d**, **193c**)

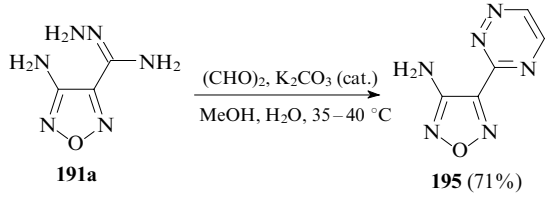


R = H (**a**), Me (**191e**, **194b**)

The 1,2,4-triazole ring can also be formed in the reaction of amidrazones **191b – d** with acetic anhydride in the presence of a catalytic amount of sulfuric acid with the formation of compounds **193a – c**.[162] In the case of substrates **191a**,**e**, acylation of free NH moieties also takes place, resulting in the formation of *N*-acetylfurazanyl-1,2,4-triazoles **194a**,**b** (see Scheme 78), followed by the acetyl deprotection by concentrated hydrochloric acid in methanol.

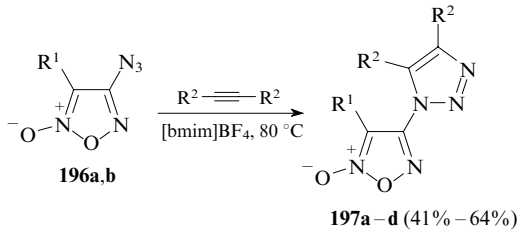
Stepanov *et al.*[162] also synthesized the first representatives of 1,2,4-triazinylfurazans **195** *via* the condensation of amidrazone **191a** with glyoxal (Scheme 79).

Scheme 79



Recently, a method was proposed for preparing 1,2,3-triazolylfuroxans by means of azide – alkyne cycloaddition in ionic liquids.[163] The reaction of 4-azidofuroxans **196a**,**b** with symmetrically disubstituted acetylenes resulted in (1*H*-1,2,3-triazol-1-yl)furoxan **197a – d** formation in moderate yields (Scheme 80).

Scheme 80

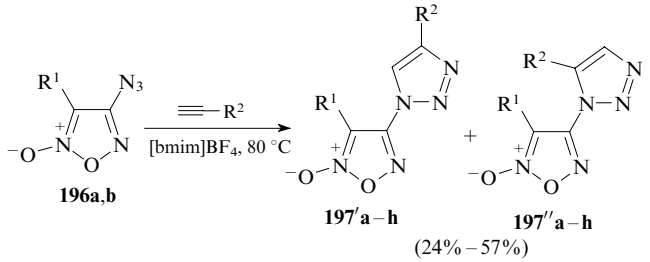


R^1 = Ph (**196a**; **197a**,**b**), Pr^n (**196b**; **197c**,**d**);
R^2 = CO_2Et (**197a**,**c**), CH_2OH (**197b**,**d**)

A similar reaction of azidofuroxans **196a**,**b** with terminal acetylenes proceeds regioselectively to yield preferably 1,4-disubstituted triazoles (Scheme 81). The ratio of regioisomers **197′a – h** and **197″a – h** was determined from the integrated intensity ratio of the ^{1}H NMR signals for the CH groups of triazole rings and ranged from 3 : 1 to 6 : 1.[163]

In common organic solvents, the reaction of azidofuroxans with acetylenes did not occur even under prolonged heating.

Scheme 81



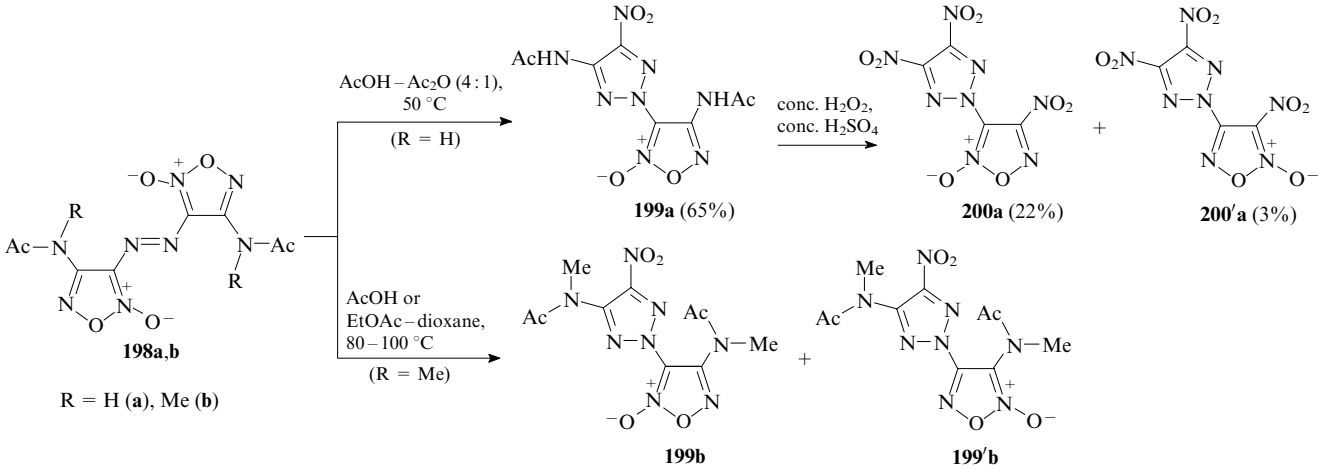
197′, **197″**: R^1 = Ph (**a** – **d**), Pr^n (**e** – **h**); R^2 = CO_2Me (**a**, **e**), CH_2OH (**b**, **f**), Ac (**c**, **g**), Ph (**d**, **h**)

Some synthetic routes to 1,2,3-triazolylfuroxans are based on substrate-specific approaches. One of these approaches implies the azole – azole rearrangement of one of the furoxan rings in diacetamido- and di(*N*-methylacetamido)azofuroxans **198a**,**b** to give heterocyclic system **199a** and a mixture of isomers **199b** and **199′b** (1 : 2, 38% yield) (Scheme 82).[164] The acetamide groups in compound **199a** are then additionally oxidized to obtain a mixture of polynitro derivative isomers **200a** and **200′a** in the 8 : 1 ratio.

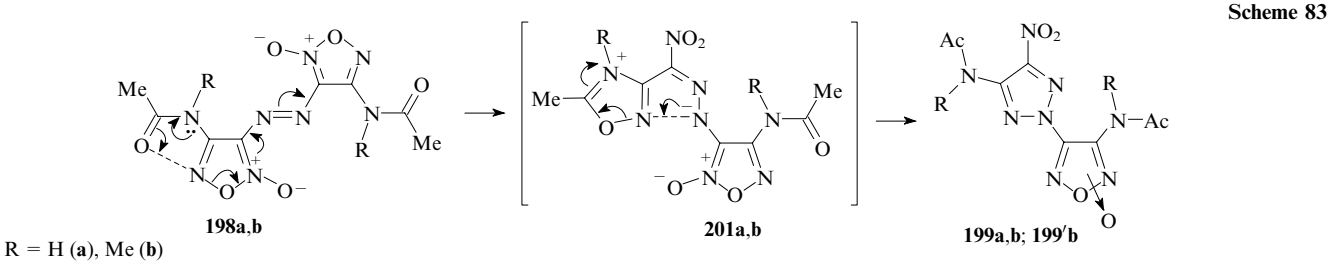
In the authors' opinion,[164] the presence of acetamide groups in starting azofuroxans **198a**,**b** is the key condition for the rearrangement to occur. According to this, they proposed a tandem reaction mechanism composed of two consecutive rearrangements. The first rearrangement comprises the conversion of one acetamide moiety in compounds **198a**,**b** to the 1,2,4-oxadiazole ring upon O(1) – N(5) bond cleavage in the furoxan ring with the simultaneous release of the nitrohydrazone moiety in intermediates **201a**,**b**. The second rearrangement includes thermal cleavage of the O(1) – N(2) bond in the 1,2,4-oxadiazole ring, followed by the attack of the acyclic nucleophilic nitrogen atom of the nitrohydrazone moiety on the nitrogen atom of the heterocycle to yield 1,2,3-triazole furoxan derivatives **199a**, **199b** and **199′b** (Scheme 83).

Later, another type of rearrangement of azofuroxans under oxidizing conditions was discovered.[165] During the reaction, one of the furoxan rings in compounds **202a – d** is thermally opened to yield vicinal dinitrosoethylene intermediates **203a – d** in which one of the nitroso groups is then

Scheme 82

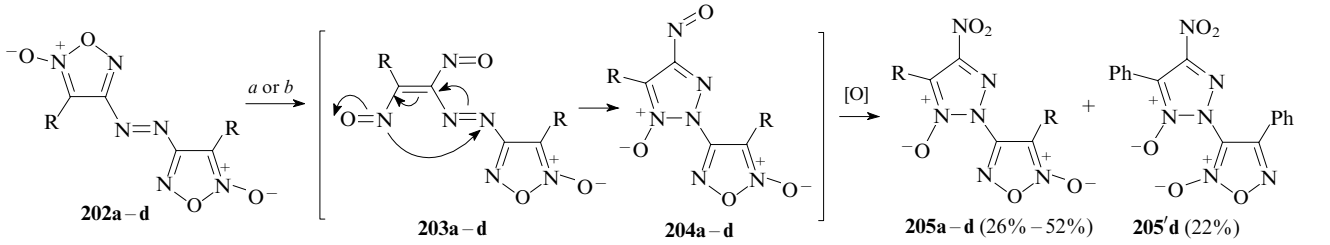


Scheme 83



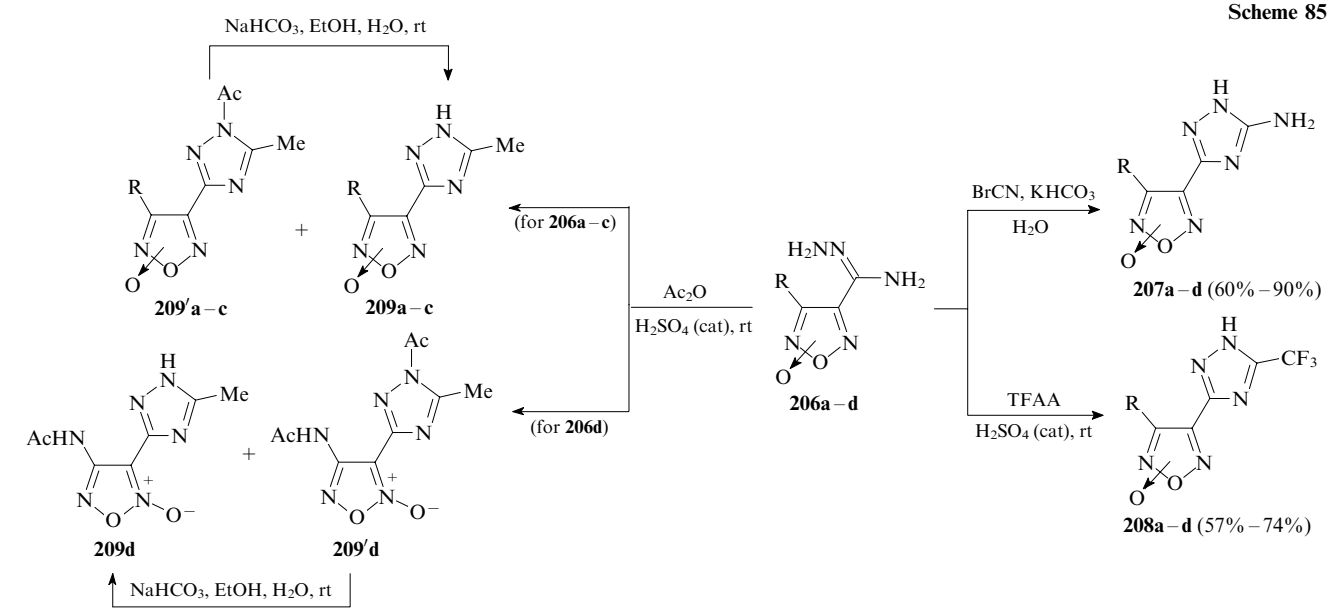
R = H (**a**), Me (**b**)

Scheme 84



R = CO_2Me (**a**), $C(O)NH_2$ (**b**), Me (**c**), Ph (**d**); (*a*) for **202a – c**: 85% H_2O_2, TFA, Δ; (*b*) for **202d**: 30% H_2O_2, AcOH, Ac_2O, Δ

Scheme 85



R = 3-Me (**a**), 4-Ph (**b**), 3-CN (**c**), 4-NH_2 (**d**)

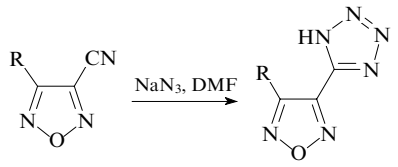
condensed with the azo group to yield triazole *N*-oxide derivatives **204a – d**. At the final stage, the remaining nitroso group in compounds **204a – d** is oxidized under those conditions to the nitro group to yield nitro derivatives **205a – d** (Scheme 84). To perform the rearrangement, azofuroxans **202a – c** were subjected to reaction with the *in situ* generated trifluoroperacetic acid, whereas for diphenylazofuroxan **202d**, peracetic acid was employed in both cases, the reaction gave a mixture of isomeric furoxans **205d** and **205′d**.

A series of 1,2,4-triazolylfuroxans were prepared by reactions of furoxan amidrazones **206a – d** with electrophilic agents. The cyclization of substrates **206a – d** with cyanogen bromide and trifluoroacetic anhydride proceeded selectively under mild conditions to yield 5-amino- (**207a – d**) and 5-trifluoromethyl-1,2,4-triazoles (**208a – d**), respectively. The reaction of amidrazones **206a – c** with acetic anhydride yielded a mixture of NH-acetyltriazoles (**209a – c**) and *N*-acetyltriazoles (**209′a – c**); amidrazone **206d**, which contains the amino group at the C(4) atom of the furoxan ring, was also acylated to yield a mixture of derivatives **209d** and **209′d**. Mixtures of compounds **209** and **209′** were not separated, but treated with sodium bicarbonate in aqueous alcohol to remove the acetyl protecting group (Scheme 85).[166] The yields of compounds **209a – c** and **209d** were 64% – 86% and 81%, respectively.

III.5. Preparation of furazans and furoxans with tetrazolyl substituents

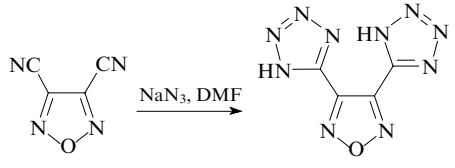
Apart from the preparation of 1,2,3-triazolyl-1,2,5-oxadiazoles, 1,3-dipolar cycloaddition is also used to obtain tetrazolyl-1,2,5-oxadiazoles. Furazancarboxylic acid nitriles **210a – e** reacted successfully with sodium azide to yield furazanyl-substituted 1*H*-tetrazoles **211a – e** (Scheme 86).[167 – 169] With a higher molar excess of sodium azide, the addition occurred at both nitrile groups of dicyanofurazan **210c** to yield bis(tetrazolyl)furazan **211f**.[167]

Scheme 86

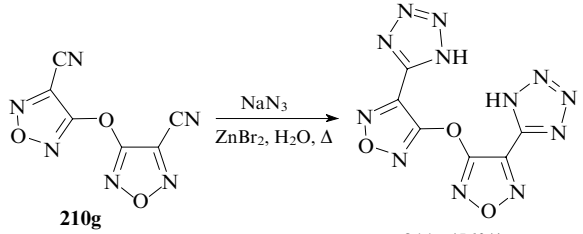


210a – e **211a – e** (74% – 91%)

R = Me (**a**), NH_2 (**b**), CN (**c**), $C(NH_2)NOH$ (**d**), $C(=NH)NHNH_2$ (**e**)



210c **211f** (82%)

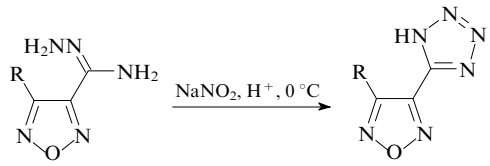


210g **211g** (56%)

To perform cycloaddition with dicyanofurazanyl ether **210g**, Lewis acids were required.[170]

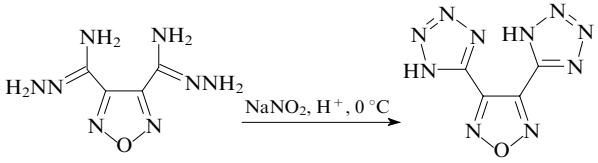
Another two-step approach to the preparation of tetrazolylfurazans **211a – d**,**f**,**h – k** is based on the nitrosation of available amidrazones **191a – i** (Scheme 87).[162, 167, 168]

Scheme 87



191a – h **211a – d**,**h – k** (62% – 77%)

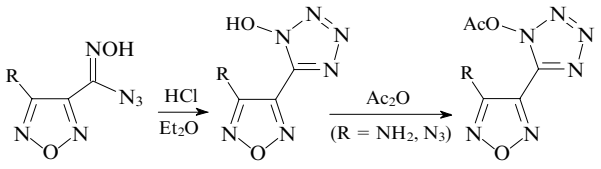
R = Me (**191f**, **211a**), NH_2 (**191a**, **211b**), CN (**191g**, **211c**), $C(NH_2)NOH$ (**191h**, **211d**), NHMe (**191e**, **211h**), NMe_2 (**191b**, **211i**), $N(CH_2CH_2)_2O$-cyclo (**191c**, **211j**), OMe (**191d**, **211k**)



191i **211f** (78%)

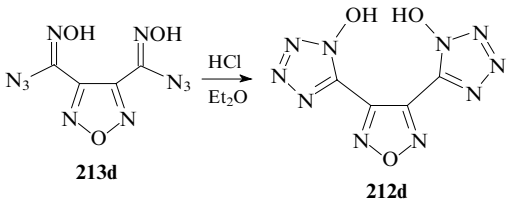
The precursors in the synthesis of *N*-hydroxy-substituted tetrazoles **212a – d** are hydroxyiminocarbazides **213a – d**, which cyclize in high yields in acidic medium.[136, 171, 172] The hydroxy group in compounds **212a**,**b** can be acylated by acetic anhydride to give structures **214a**,**b** (Scheme 88).[171]

Scheme 88



213a – c **212a – c** (83% – 86%) **214a**,**b** (70%)

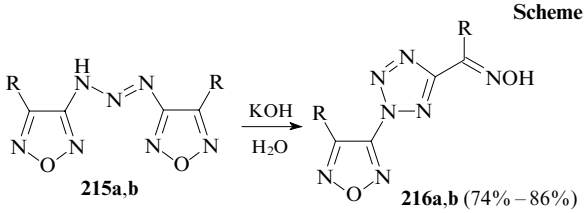
R = NH_2 (**a**), N_3 (**b**), $N(CH_2CH_2)_2O$-cyclo (**c**)



213d **212d**

N-Furazanyl-substituted tetrazoles are far less accessible. One of the methods for the synthesis of this type of heterocyclic assembly is outlined in Scheme 89. In alkaline medium, difurazanyltriazenes **215a**,**b** undergo the Boulton–Katritzky rearrangement to tetrazolylfurazans **216a**,**b**.[173]

Scheme 89

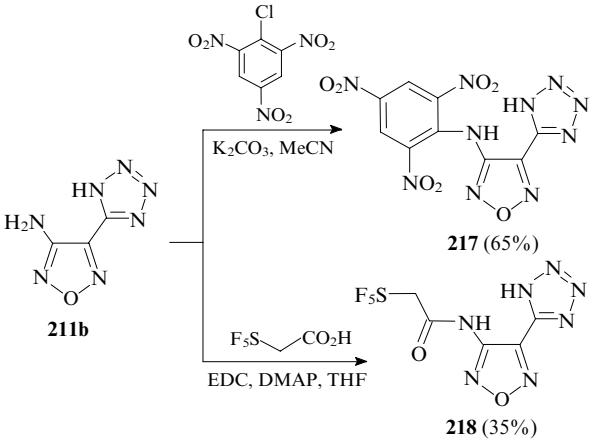


215a,**b** **216a**,**b** (74% – 86%)

R = Me (**a**), NH_2 (**b**)

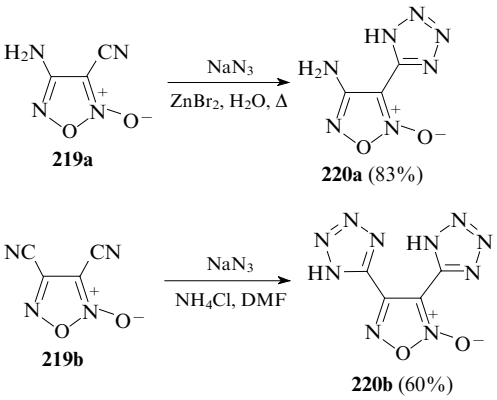
The presence of a tetrazole ring and a furazan ring, which are both electron-withdrawing, significantly decreases the reactivity of the amino group in aminofurazan **211b**. Nevertheless, this compound is capable of acting as the substrate in aromatic nucleophilic substitution reactions; in particular, the reaction with 2,4,6-trinitrochlorobenzene yields secondary amine **217**. In the presence of 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (EDC) and catalytic amounts of 4-dimethylaminopyridine (DMAP), aminofurazan **211b** reacts with pentafluorosulfonylacetic acid to yield amide **218** (Scheme 90).[174]

Scheme 90



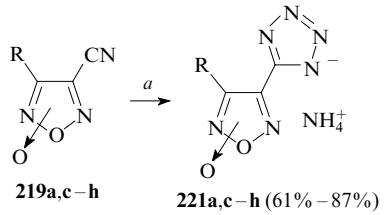
Until recently, only two representatives of tetrazolylfuroxans were synthesized based on the [3 + 2]-cycloaddition of cyanofuroxans to sodium azide. The reaction of aminocyanofuroxan **219a** or dicyanofuroxan **219b** with sodium azide in the presence of zinc bromide or ammonium chloride yielded tetrazolylfuroxans **220a**,**b** (Scheme 91).[175 – 177]

Scheme 91

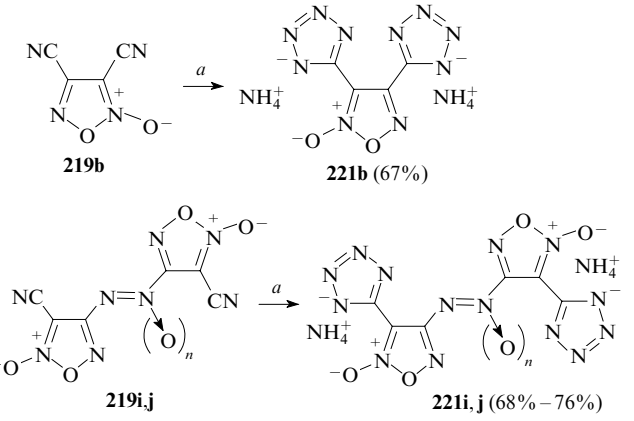


A wider use of this reaction was obviously hampered by high sensitivity of furoxan derivatives to alkaline agents. However, a recent modification of this method with the use of trimethylsilyl azide and ammonium fluoride makes it possible both to perform the cycloaddition reaction under mild conditions and to prepare ammonium salts of tetrazolylfuroxans **221a** – **k** in a one-pot process.[178] The reaction of 4-nitro-3-cyanofuroxan (**219k**) also resulted in nucleophilic substitution of azide group for the nitro group and selectively gives 4-azido-3-(1*H*-tetrazol-5-yl)furoxan ammonium salt (**221k**) in a high yield (Scheme 92). All of the salts prepared in this way are hydrolyzed to free NH-tetrazoles under mild conditions.

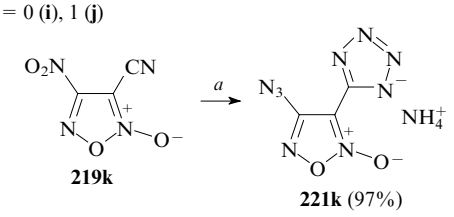
Scheme 92



R = NH_2 (**a**), Me (**c**), Ph (**d**), CO_2Me (**e**), NHAc (**f**), N=NC_6H_4OMe-4 (**g**), N=$NC_6H_2Me_3$-2,4,6 (**h**)



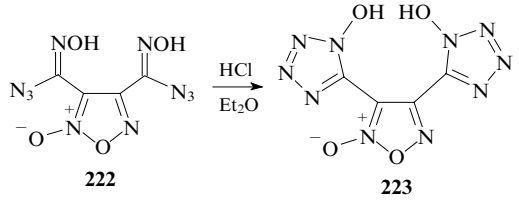
n = 0 (**i**), 1 (**j**)



(*a*) $TMSN_3$, NH_4F, MeCN, rt

The cyclization of bis(hydroxyiminocarbazide) **222** induced by gaseous HCl yields bis(1-hydroxytetrazolyl)furoxan **223** (Scheme 93).[172]

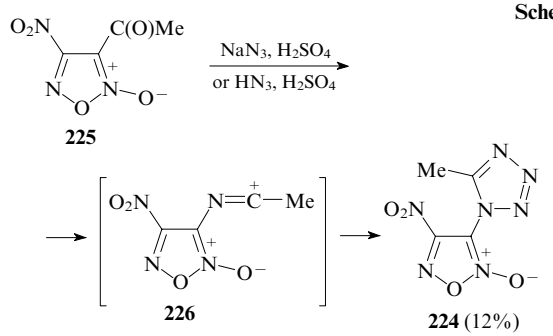
Scheme 93



5-Methyl-1-(4-nitrofuroxan-3-yl)tetrazole (**224**) formed unexpectedly in an insignificant yield in an attempt to perform the Schmidt rearrangementent of 3-acetyl-4-nitrofuroxan (**225**).[179] The reaction mechanism includes migration of the furoxanyl moiety to the electron-deficient nitrogen atom to generate iminocarbenium intermediate **226** and the subsequent addition of the azide ion (Scheme 94).

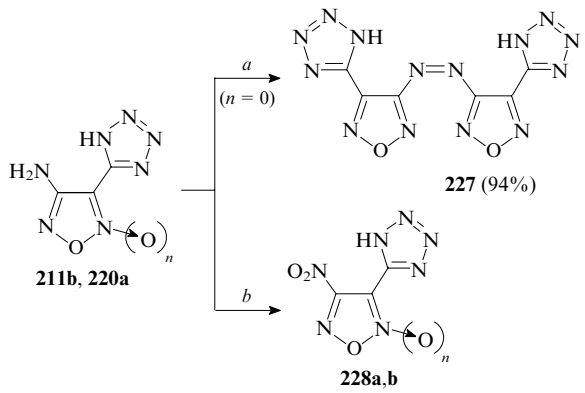
The oxidation of amino(tetrazolyl)furazan **211b** by a single-electron oxidant ($KMnO_4$) yields polyheterocyclic system **227** in high yield.[169, 180] At the same time, the amino groups of 1,2,5-oxadiazoles **211b** and **220a** are oxidized to nitro groups by 50% hydrogen peroxide and

Scheme 94



sodium tungstate in sulfuric acid to yield nitro derivatives **228a**,**b** (Scheme 95).[175, 180]

Scheme 95



n = 0 (**211b**; **228a**, 45% yield), 1 (**220a**; **228b**, 83%);
(*a*) for **211b**: $KMnO_4$, HCl; (*b*) 50% H_2O_2, Na_2WO_4, H_2SO_4

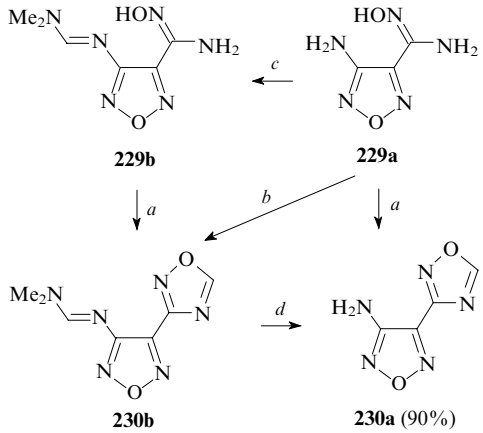
The NH moiety in tetrazolyl-substituted furazans and furoxans has a relatively high acidity, and this is used to prepare high-energy salts based on these compounds. There are many examples of syntheses of ionic structures where tetrazolyl-1,2,5-oxadiazoles act as anions and protonated polynitrogen-containing organic bases are the cations (*e.g.*, guanidine and its mono-, di- and triamino derivatives; 3-amino-, 3,5-diamino- and 3,4,5-triamino-1,2,4-triazoles).[170, 175 – 177, 180 – 184]

III.6. Heterocyclic assemblies of 1,2,4- and 1,2,5-oxadiazoles

The preparation of heterocyclic assemblies comprising two or more consecutively linked 1,2,4-, 1,3,4- and 1,2,5-oxadiazole rings in various combinations is important in the context of practical application. Structures of this type were mostly designed based on furazans; however, new methodologies have recently been proposed for preparing relevant furoxan derivatives.

1,2,4-Oxadiazolylfurazans were obtained using the strategy based on heterocyclization of 1,2,5-oxadiazole amidoximes with electrophilic agents. For example, the reaction of amidoxime **229a** with orthoesters catalyzed by boron trifluoride etherate yields heterocyclic structure **230a**. Under the Vilsmeier – Haack reaction conditions, amidoxime **229a** cyclizes to 1,2,4-oxadiazole, but along with this, the amino group is modified to give product **230b** in 72% yield. Compound **230b** can also be prepared in the two-step cascade that comprises the reaction of aminofurazan **229a** with dimethylformamide dimethylacetal (DMF-DMA) followed by cyclization of the amidoxime moiety to dimethylaminomethyleneaminofurazan **229b** with trimethyl orthoformate in the presence of Lewis acid (82% yield). The acid hydrolysis of compound **230b** produces amino(1,2,4-oxadiazolyl)furazan **230a** in 74% yield (Scheme 96).[162, 185]

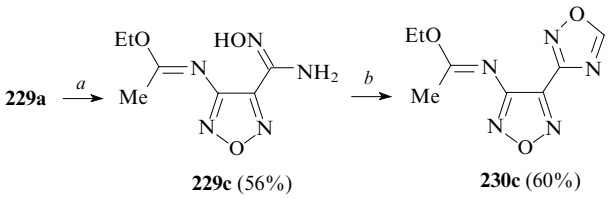
Scheme 96



(*a*) $HC(OMe)_3$, $BF_3 \cdot Et_2O$, Δ; (*b*) $POCl_3$, DMF, 100 °C;
(*c*) DMF-DMA; (*d*) 5% HCl, H_2O

A similar two-step process using amidoxime **229a** was utilized to prepare 1,2,4-oxadiazolylfurazan **230c**. The first step provided iminoester **229c** under the action of triethyl orthoacetate, and then the amidoxime moiety of the iminoester cyclized to structure **230c** (Scheme 97).[185]

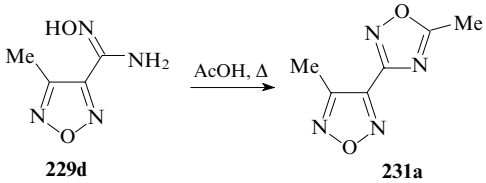
Scheme 97



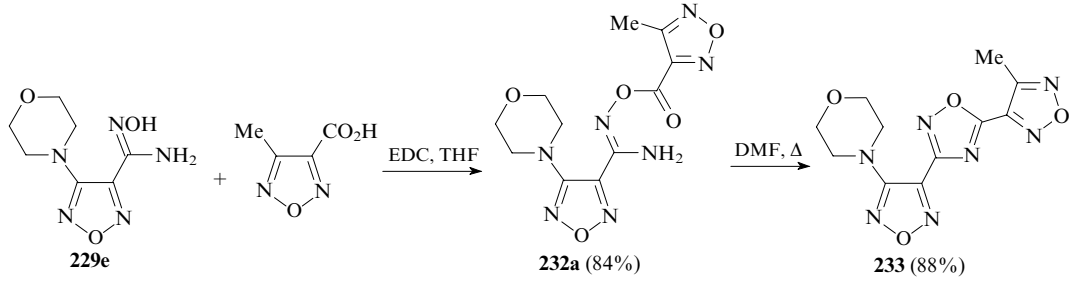
(*a*) $MeC(OEt)_3$; (*b*) $HC(OEt)_3$, $BF_3 \cdot Et_2O$

The cyclization of amidoximes with orthoesters is suitable for the synthesis of only monosubstituted 1,2,4-oxadiazoles with hydrogen atom as the substituent at the 1,2,4-oxadiazole ring C(5) atom. In order to introduce an aliphatic, aromatic or heterocyclic substituent into this position of oxadiazole, carboxylic acids or their derivatives are cyclized with amidoximes of the furazan series. Thus, the total synthesis of 1,2,4-oxadiazolylfurazans comprises two consecutive steps: the acylation of amidoxime by electrophilic agents and cyclodehydration. For example, refluxing of methylfurazanylcarboxamidoxime **229d** in acetic acid results in 1,2,4-oxadiazole ring closure and gives compound **231a** (Scheme 98).[153]

Scheme 98



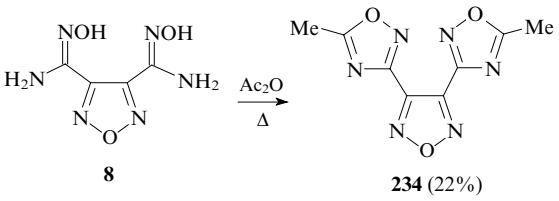
Scheme 99



The reaction of amidoxime **229e** with 4-methylfurazan-3-carboxylic acid in the presence of 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide yields *O*-acylated adduct **232a**. Upon short refluxing in DMF, the adduct cyclizes to heterocyclic assembly **233**, which contains two furazan rings linked *via* a 1,2,4-oxadiazole bridge (Scheme 99).[136]

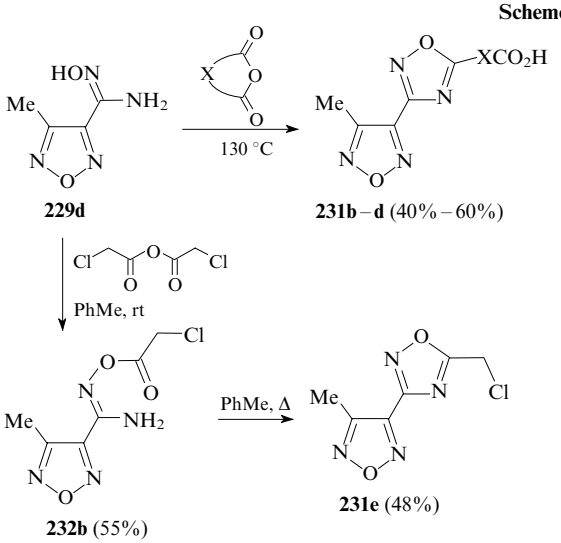
However, carboxylic acids are rarely used as acylating agents because of their low reactivity, so in most cases, carboxylic acid anhydrides or chlorides are employed in the reactions with amidoximes. The formation of the 1,2,4-oxadiazole ring proceeds at both functional groups of bis(amidoxime) **8** under reflux in acetic anhydride giving bis(1,2,4-oxadiazolyl)furazan **234** (Scheme 100).[76]

Scheme 100



Heating of amidoxime **229d** with succinic, glutaric or phthalic anhydride in a solid-phase variant provides 1,2,4-oxadiazolylfurazans **231b**–**d** in satisfactory yields. However, attempts to prepare 5-chloromethyl-1,2,4-oxadiazole **231e** in the same way were unsuccessful, because of decomposition of the final product under the reaction conditions. Therefore, compound **231e** was obtained using a two-step

Scheme 101

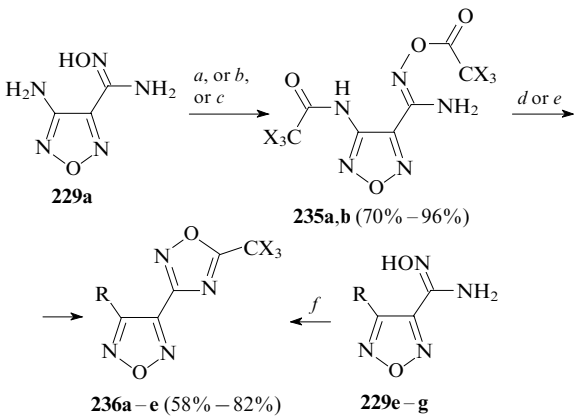


231: X = $(CH_2)_2$ (**b**), $(CH_2)_3$ (**c**), *o*-phenylene (**d**)

strategy based on acylation of starting amidoxime **229d** by chloroacetic anhydride followed by refluxing of the resulting acylated adduct **232b** in toluene (Scheme 101).[186]

The treatment of amidoxime **229a** with trifluoroacetic anhydride or trichloroacetyl chloride yields N,O-diacylated adducts **235a**,**b**, which are thermally cyclized to 1,2,4-oxadiazolylfurazans **236a**,**b** with simultaneous removal of the trihaloacetyl protection from the amino group.[132, 185] Meanwhile, heating of furazan amidoximes **229e**–**g** with trichloroacetyl chloride in butyl acetate immediately yields 5-trichloromethyl-1,2,4-oxadiazole **236c**–**e** (Scheme 102). The treatment of 1,2,4-oxadiazolylfurazans **236b**,**c** with aqueous alkali or ammonia results in hydrolysis of the trichloromethyl moiety to yield furazanyl-1,2,4-oxadiazol-5(4*H*)-ones **237a**,**b**.[132, 136]

Scheme 102



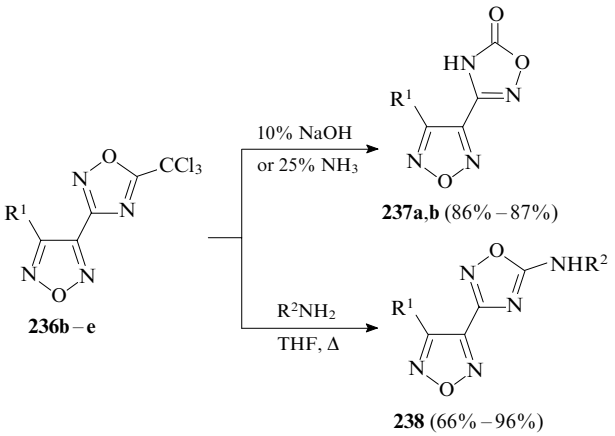
X = F (**235a**, **236a**), Cl (**235b**, **236b**–**e**); R = NH_2 (**236a**,**b**), $N(CH_2CH_2)_2O$-cyclo (**229e**, **236c**), NHC_6H_4OMe-4 (**229f**, **236d**), $NHCH_2C_6H_4OMe$-4 (**229g**, **236e**); (*a*) TFAA, 120 °C; (*b*) $Cl_3CC(O)Cl$, 120 °C; (*c*) $(Cl_3CCO)_2O$, 120 °C; (*d*) PhMe, Δ; (*e*) 4-$H_2NC_6H_4Me$, EtOH, Δ; (*f*) $Cl_3CC(O)Cl$, Bu^nOAc, Δ

The reactions of compounds **236b**–**e** with aliphatic, aromatic or heterocyclic amines lead to nucleophilic substitution of the CCl_3 group, resulting in the synthesis of a series of N-substituted 5-amino-1,2,4-oxadiazolylfurazans **238** (Scheme 103).[136, 187]

Heating of mixtures of aminofurazanylamidoxime **229a** with carboxylic acid amides to 160–180 °C in the absence of a solvent affords 1,2,4-oxadiazolylfurazans **239a**–**c**. In the same manner, compound **229a** and 2-cyanopyridine are converted to structure **239d** (Scheme 104).[161]

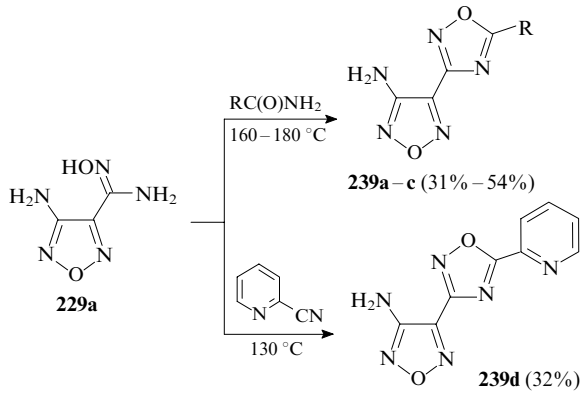
To increase the efficiency of reactions between amidoxime **229a** and nitriles, the reactions are carried out in the presence of an equimolar amount of zinc chloride and gaseous HCl; this provides 5-aryl- and 5-hetarylamino-

Scheme 103



237: $R^1 = NH_2$ (**a**), $N(CH_2CH_2)_2O$-cyclo (**b**); **238**: $R^1 = NH_2$, $N(CH_2CH_2)_2O$-cyclo, NHC_6H_4OMe-4, $NHCH_2C_6H_4OMe$-4; R^2 = H, Alk, Ar, Het

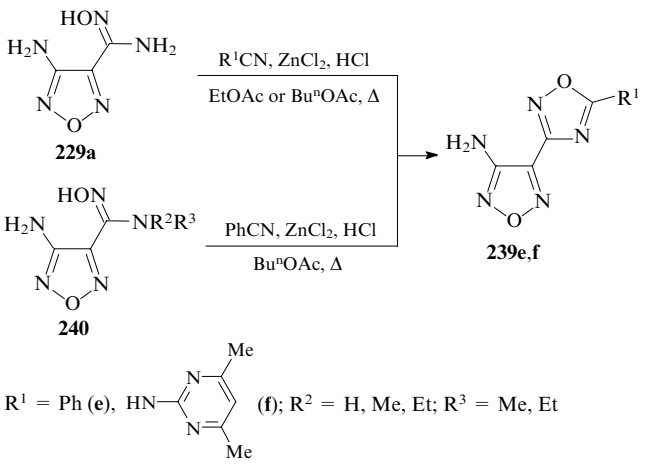
Scheme 104



239: R = Me (**a**), 4-Py (**b**), 4-aminofurazan-3-yl (**c**)

1,2,4-oxadiazolylfurazans **239e**,**f** in 65% – 67% yields.[188 – 190] *N*-Mono- and *N*,*N*-disubstituted amidoximes **240** react successfully with benzonitrile under the same conditions to give in all cases heterocyclic system **239e** in 40% – 47% yield (Scheme 105).[188]

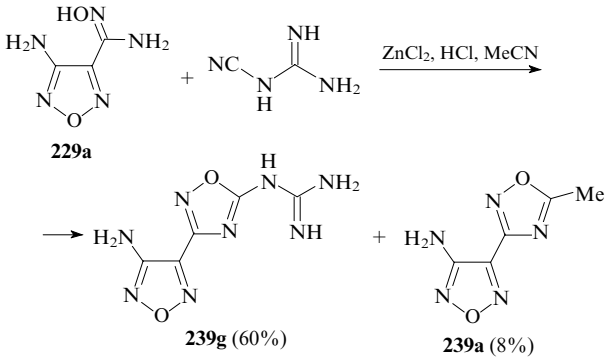
Scheme 105



R^1 = Ph (**e**), HN(Me)(N=C(Me)N=C(Me)) (**f**); R^2 = H, Me, Et; R^3 = Me, Et

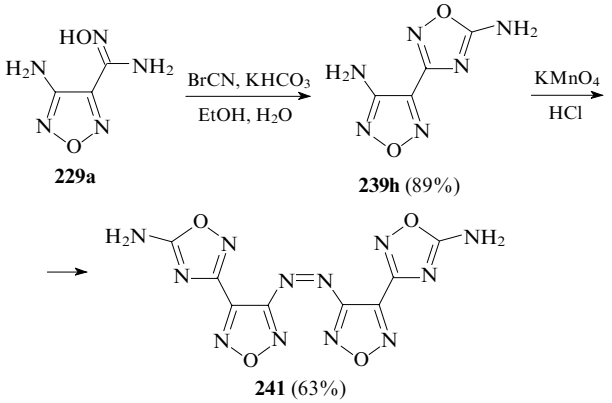
The reaction of amidoxime **229a** with cyanoguanidine in acetonitrile furnished not only 5-guanidino-1,2,4-oxadiazolylfurazan **239g**, but 5-methyl-1,2,4-oxadiazolylfurazan **239a** is also formed (in a minor yield) upon reaction of starting compound **229a** with acetonitrile (Scheme 106).[190]

Scheme 106



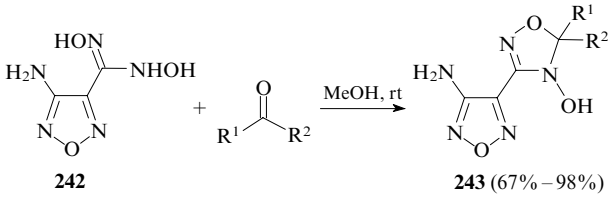
Cyanogen bromide can be used as the electrophilic agent in reaction with amidoxime **229a**, providing 3-amino-4-(5-amino-1,2,4-oxadiazol-3-yl)furazan (**239h**) in high yield. Compound **239h** is oxidized to azo derivative **241** on subsequent treatment with potassium permanganate in hydrochloric acid (Scheme 107).[161]

Scheme 107



Reactions of *N*-hydroxyamidoxime **242** with aldehydes or ketones under very mild conditions provide the formation of the 4-hydroxy-1,2,4-oxadiazoline ring to yield heterocyclic compounds **243** (Scheme 108).[191]

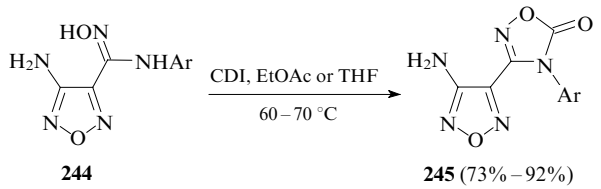
Scheme 108



R^1, R^2 = H, Alk (13 examples)

N-Arylamidoximes **244** are precursors in the synthesis of an extensive series (comprising 40 compounds) of 4-aryl-3-(furazan-3-yl)-1,2,4-oxadiazolones **245** *via* condensation with the CO moiety, the synthetic equivalent of which is 1,1′-carbonyldiimidazole (CDI) (Scheme 109).[192 – 195]

Scheme 109



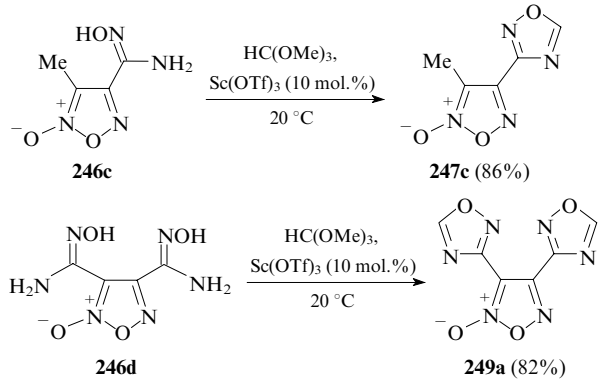
244 **245** (73% – 92%)

When a furoxanylamidoxime of series **246a**, containing an amino group at the C(4) atom of the furoxan ring, participates in a similar cyclization with an orthoester, the product is a mixture of two regioisomers, namely, expected 1,2,4-oxadiazolylfuroxan **247a** and pyrimidofuroxan **248**.

The formation of bicyclic structure **248** can be attributed to interaction of the electrophilic carbon atom of the orthoester with two amino groups. To avoid this competing process, the amino group linked to the furoxan ring can be selectively converted to the dimethylaminomethylene moiety. The amidoxime **246b** thus formed is readily converted to desired 1,2,4-oxadiazolylfuroxan **247b** (Scheme 110).[196]

$Sc(OTf)_3$ (where OTf stands for trifluoromethanesulfonate, triflate) turned out to be a more efficient Lewis acid as a catalyst in the reactions of furoxanyl amidoximes with orthoesters. In its presence, substrates **246c**,**d** reacted with trimethyl orthoformate in few minutes to give 1,2,4-oxadiazolylfuroxans **247c** and **249a** in high yields (Scheme 111).[197]

Scheme 111

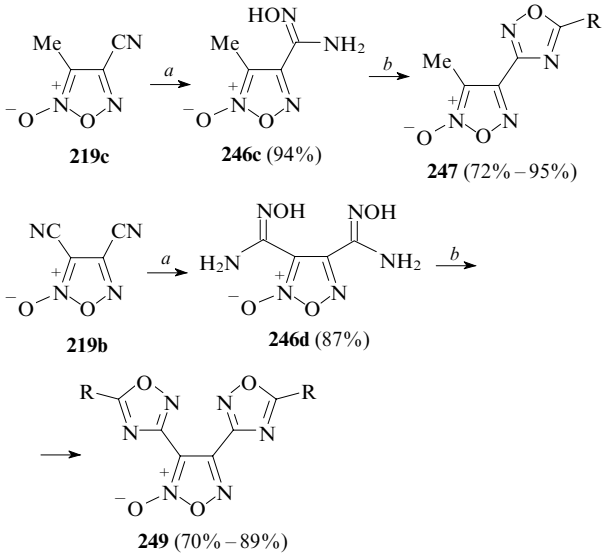


246c **247c** (86%)

246d **249a** (82%)

Fershtat *et al.*[197] also proposed a general and efficient method for preparing 1,2,4-oxadiazolylfuroxans that contain an aliphatic, aromatic or heterocyclic substituent at the C(5) atom of the 1,2,4-oxadiazole ring. This method comprises the one-pot acylation of furoxanylamidoximes **246c**,**d**, which were prepared from cyanofuroxans **219c**,**b**, by carboxylic acid chlorides followed by caesium carbonate-promoted cyclodehydration under mild conditions. 3-Methyl-4-(1,2,4-oxadiazol-3-yl)furoxans **247** and bis(1,2,4-oxadiazol-3-yl)furoxans **249** were prepared within 10 – 24 and 24 – 48 h, respectively, in good or high yields (Scheme 112).

Scheme 112

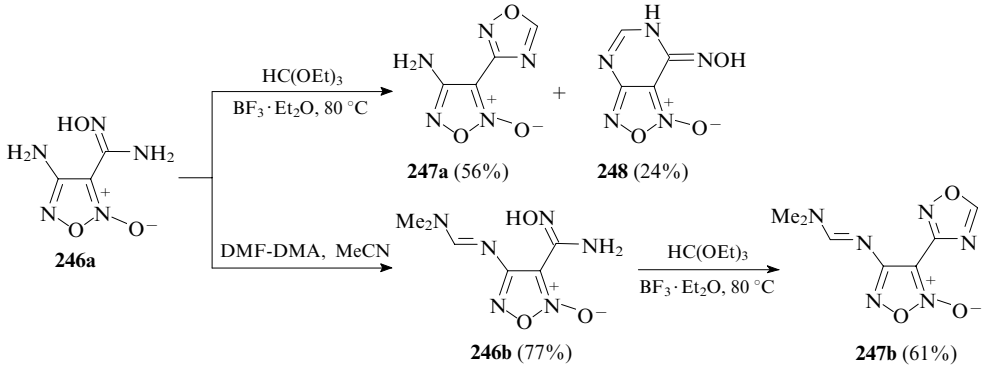


R = CH_2OMe, CH_2OBn, Ph, C_6H_4OMe-4, $C_6H_4NO_2$-2, $C_6H_4NO_2$-3, $C_6H_4NO_2$-4, 2-Fu, 4-Py, 5-methyl-1-phenylpyrazol-4-yl, 3-methylfuroxan-4-yl; (*a*) $NH_2OH \cdot HCl$, K_2CO_3, H_2O; (*b*) RC(O)Cl, Cs_2CO_3, MeCN, rt

Another approach to prepare 1,2,4-oxadiazolylfuroxans, which is rarely encountered, consists of the cycloaddition of furoxancarbonitrile oxides to dipolarophiles. Nitrolic acid **250** generates thermally nitrile oxide **251**, which is so reactive that undergoes 1,3-dipolar cycloaddition even with acetonitrile to yield 1,2,4-oxadiazolylfuroxan **252**.[198] Along with compound **252**, however, 4-nitro-3-cyanofuroxan **253** was formed as a result of oxygen atom elimination from intermediate **251** under the action of nitrogen(III) oxide (N_2O_3), which was present in the reaction medium due to the decomposition of nitrous acid (Scheme 113).

The furoxan ring can also be contained in a dipolarophile molecule. Cyanoformonitrile oxide (**254**) generated *in situ* from cyanoacetic acid, adds to dicyanofuroxan **255** at one of its nitrile groups.[199]

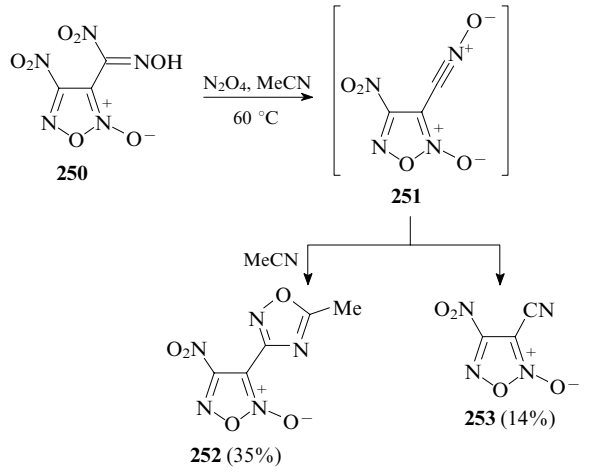
Scheme 110



246a **247a** (56%) **248** (24%)

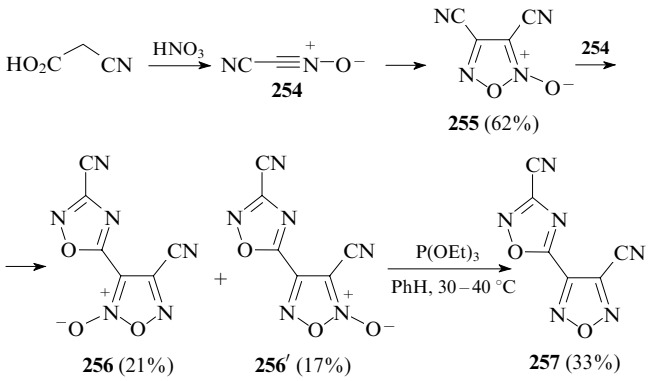
246b (77%) **247b** (61%)

Scheme 113



Isomeric cyanofuroxans **256** and **256′** were separated by HPLC, but they were used as a mixture in the reduction reaction to obtain furazan derivative **257** (Scheme 114).

Scheme 114

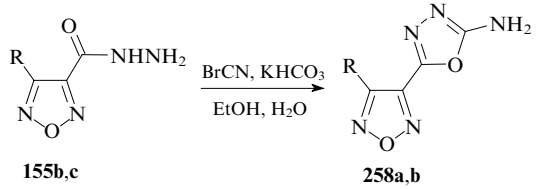


III.7. Heterocyclic assemblies of 1,3,4- and 1,2,5-oxadiazoles

The published data on the preparation of heterocyclic assemblies consisting of 1,3,4- and 1,2,5-oxadiazole rings are scarce for both furazans and furoxans. The only approach used to design this type of heterocyclic system is based on the heterocyclization of hydrazides of furazan- and furoxancarboxylic acids with electrophilic agents.

The reaction of furazancarboxylic acid hydrazides **155b**,**c** with cyanogen bromide results in the formation of 5-amino-1,3,4-oxadiazolylfurazans **258a**,**b** in good yields (Scheme 115).[161,200]

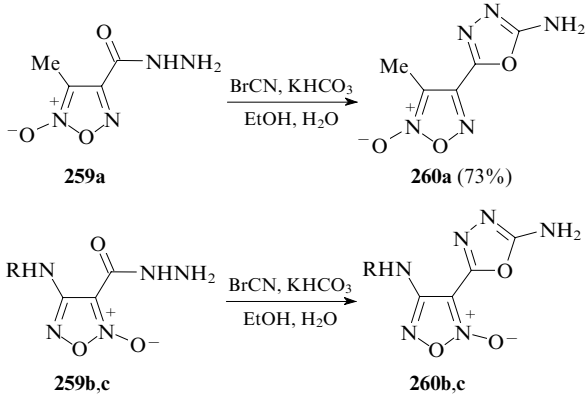
Scheme 115



R = NH_2 (**155b**; **258a**, 84% yield), $NHCO_2Bu^t$ (**155c**; **258b**, 50%)

Hybrid molecules consisting of furoxan and 1,3,4-oxadiazole rings were recently prepared by two methods where furoxancarboxylic acid hydrazides **259** were also employed as precursors. One approach is an analogue of the conversion depicted in Scheme 115; it consists of the heterocyclization of compounds **259a** – **c** with cyanogen bromide in aqueous ethanol in the presence of potassium hydrogencarbonate (Scheme 116).[201] (5-Amino-1,3,4-oxadiazol-2-yl)furoxans **260a** – **c** are thus produced in high yields. The nitramino derivative (the furazan analogue of product **260b**) prepared from compound **258a** was used to produce a series of high-energy salts.[202]

Scheme 116



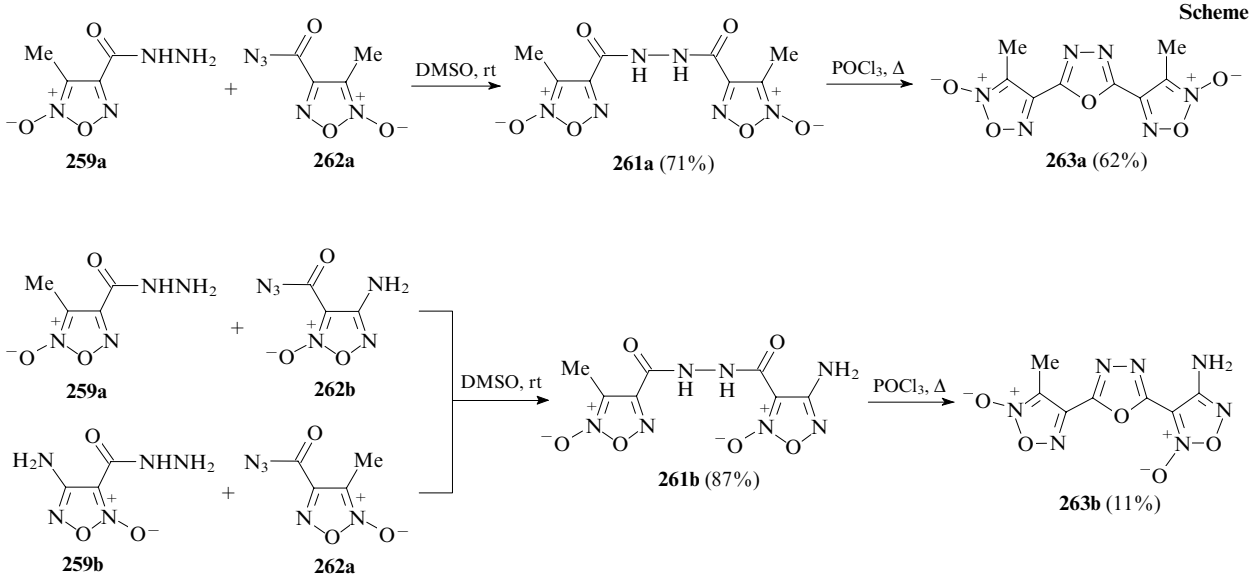
R = H (**b**, 84% yield), Ac (**c**, 81%)

Recently,[201] one more method for the formation of assemblies that contain two furoxan rings linked by a 1,3,4-oxadiazole bridge in one molecule has been described. In this case, the initial compounds were 1,2-bis-(furoxanoyl)hydrazines **261a**,**b**. They were obtained by acylation of furoxancarboxylic acid hydrazides **259a**,**b** with carbonyl azides **262a**,**b** in DMSO (Scheme 117). Compounds **261a**,**b** were dehydrated to yield 2,5-disubstituted 1,3,4-oxadiazoles **263a**,**b**. $SOCl_2$, conc. H_2SO_4, $POCl_3$ and 1,3-dimethyl-2-chloroimidazolium chloride were tested as dehydrating agents. The most successful dehydration was achieved by refluxing compounds **261a**,**b** in an excess of $POCl_3$. The yield of final 1,3,4-oxadiazole derivative **263b** decreased appreciably because of the presence of an amino group in starting 1,2-bis(furoxanoyl)hydrazine **261b**.

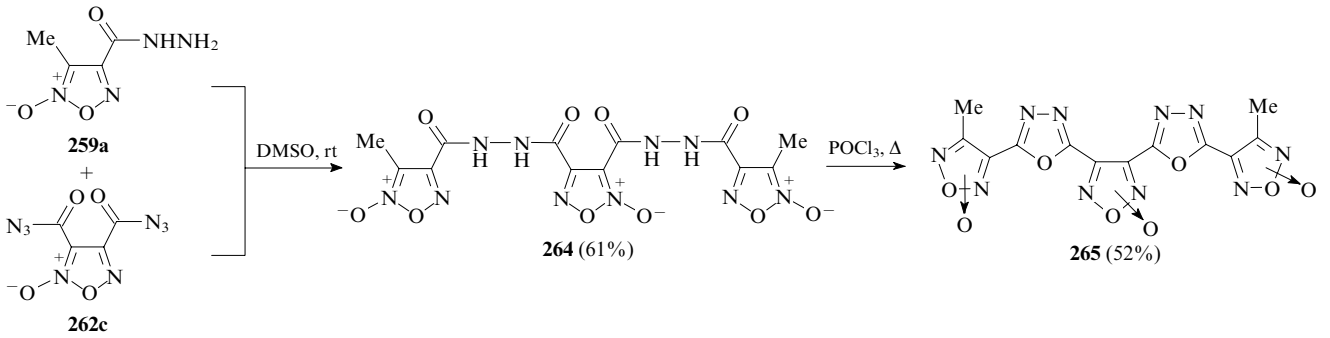
3-Methylfuroxan-4-carboxylic acid hydrazide (**259a**) served as the starting compound for generating assemblies where three furoxan rings are linked *via* two 1,3,4-oxadiazole bridges. Its reaction with bis(azidocarbonyl)furoxan **262c** yielded furoxandicarboxylic acid dihydrazide **264** acylated by the 3-methyl-4-furoxanoyl moiety at both amino groups. The prolonged refluxing of compound **264** in an excess of $POCl_3$ led to the isomerization of furoxan rings and yielded a mixture of isomers **265**, which could not be separated (Scheme 118).[201]

In order to provide a wider range of assemblies of furoxan and 1,3,4-oxadiazole rings, hydrazide **259a** was introduced into $POCl_3$-induced condensation with carboxylic acids. In the course of this reaction, carboxylic acids were converted to acid chlorides, which acylated initial hydrazide **259a** through the generation of 1,2-diacylhydrazine intermediates **266a** – **h**. Intermediates **266a** – **h** were cyclodehydrated *in situ* to desired 1,3,4-oxadiazolylfuroxans **267a** – **h** in moderate yields (Scheme 119).[128] This is a general approach to prepare assemblies of furoxan and

Scheme 117

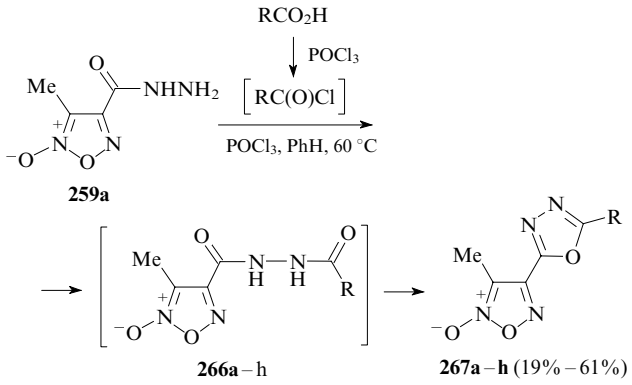


Scheme 118



1,3,4-oxadiazole rings, as the reaction can involve aliphatic, aromatic or heterocyclic carboxylic acids.

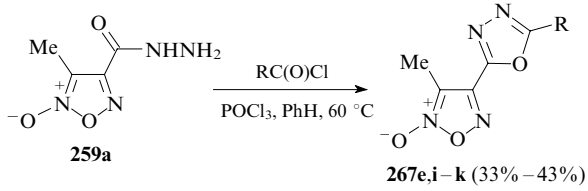
Scheme 119



266, **267**: R = Bn (**a**), CH_2Cl (**b**), Ph (**c**), $C_6H_4NO_2$-3 (**d**), $C_6H_4NO_2$-4 (**e**), C_6H_4OMe-4 (**f**), $C_6H_3(OMe)_2$-3,4 (**g**), 2-Fu (**h**)

An alternative route to prepare this type of compound was utilization of carboxylic acid chlorides rather than carboxylic acids. The condensation was performed for a number of substituted aromatic and aliphatic acid chlorides (Scheme 120).[128] With the use of carboxylic acid chlorides, the required amount of dehydrating agent was decreased.

Scheme 120



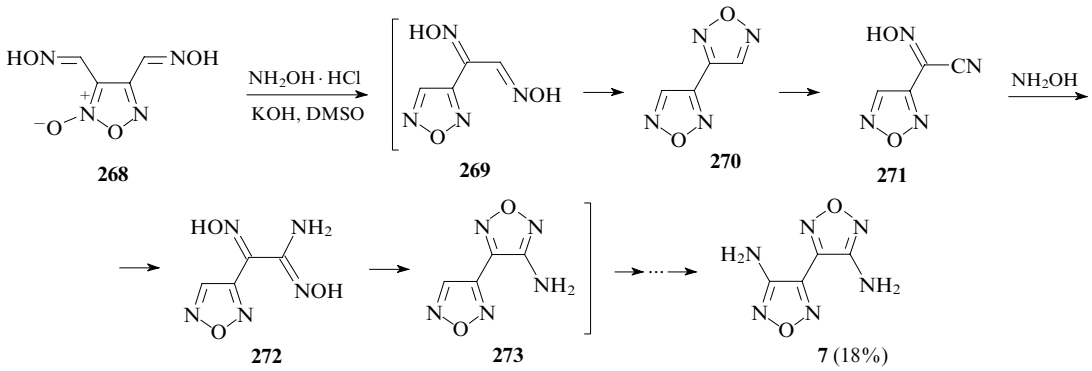
267: R = $C_6H_4NO_2$-4 (**e**), $C_6H_2(OMe)_3$-3,4,5 (**i**), CH_2OMe (**j**), CH_2Th-2 (**k**)

III.8. Heterocyclic assemblies of 1,2,5-oxadiazoles

This Section presents data pertaining to the preparation of heterocyclic assemblies that comprise two or three of furazan and furoxan rings consecutively linked to one another in various combinations. The focus will be on difurazanylfuroxan derivatives for the reason that such structures are of great interest as potential high-energy compounds.

3,4-Bis(hydroxyiminomethyl)furoxan **268** (its trivial name is α-isocyanilic acid) serves as a substrate in the domino reaction of the synthesis of 4,4′-diamino-3,3′-bifurazan (**7**) under the action of hydroxylamine in alkaline medium.[203] The first step of this process is the Boulton–Katritzky rearrangement of compound **268** to give furazanylglyoxime intermediate **269**, which is then dehydrated to bifurazan **270** under the reaction conditions. Further, inter-

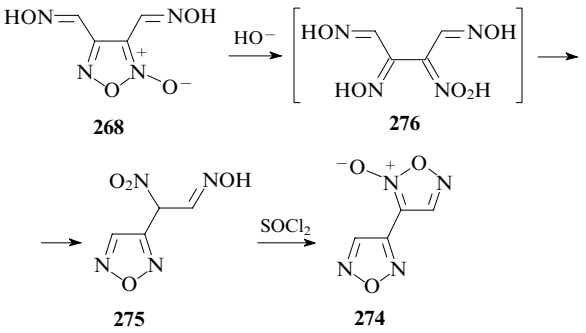
Scheme 121



mediate **270** undergoes opening of one furazan ring to yield cyanoxime **271**, which then adds a hydroxylamine molecule to afford aminoglyoxime **272**; dehydration of the latter gives aminofurazanylfurazan **273**. Repeating the last three steps with the second monosubstituted furazan ring produces desired compound **7** in 18% yield (Scheme 121). The researchers cited [203] mention that the use of bifurazan **270** in the domino reaction, instead of α-isocyanilic acid (**268**), increased the yield of final product **7** to 39%.

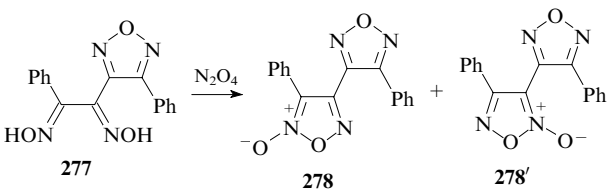
The first example of heterocyclic assembly comprised of furazan and furoxan rings is 3-furazanylfuroxan **274**, which can be produced from β-isocyanilic acid (**275**) under the action of thionyl chloride. Compound **275** is obtained upon the alkali-induced hydrolysis of α-isocyanilic acid (**268**) to give cyclic intermediate **276** in which the glyoxime moiety is closed to form a furazan ring and the furoxan ring is constructed upon dehydration of the α-nitro oxime group (Scheme 122).[14]

Scheme 122



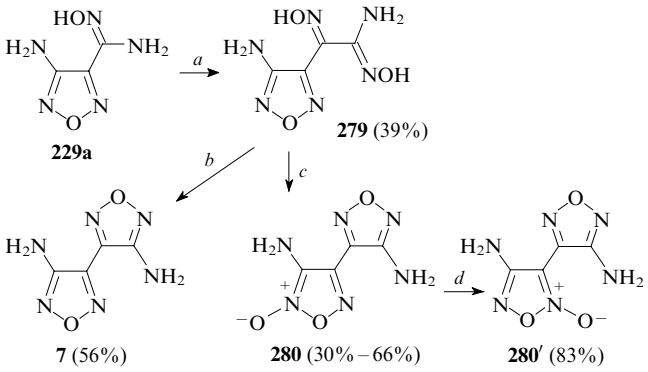
The oxidation of glyoxime **277** by nitrogen(IV) oxide was used to prepare representatives of isomeric furazanylfuroxans, but the yields of compounds **278** and **278′** were not reported (Scheme 123).[14]

Scheme 123



The oxidation of aminoglyoxime **279**, which was prepared *via* the three-step conversion of furazanyl amidoxime **229a** in a one-pot variant, yields 3-amino-4-(3-aminofurazan-4-yl)furoxan (**280**) which is then refluxed in dioxane to isomerize into thermodynamically more favourable 4-aminofuroxan **280′**. The dehydration of aminoglyoxime **279** under heating in aqueous alkali yields 4,4′-diamino-3,3′-bifurazan (**7**) in 56% yield (Scheme 124).[204] Recently,[204] 12- and 18-membered macrocyclic systems, in which bifurazanyl or furazanylfuroxanyl moieties were linked through an azo group, **280** and **280′**, were prepared by dibromoisocyanurate-induced oxidative cyclocondensation of compounds **7**.

Scheme 124

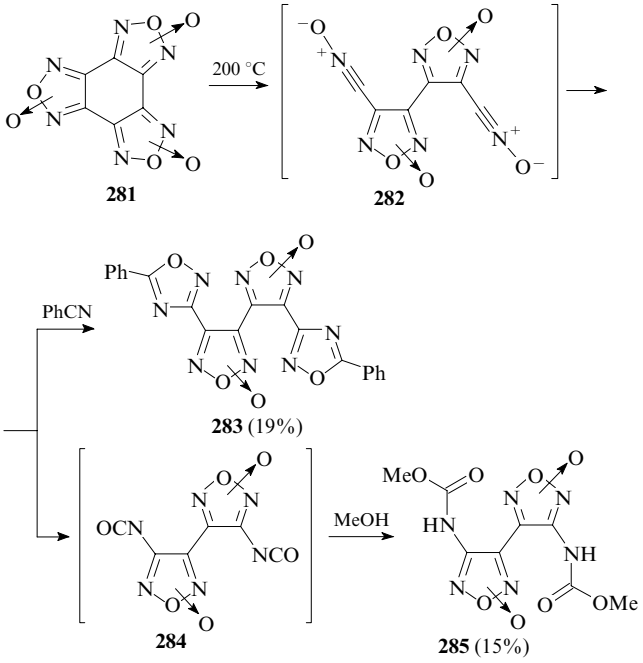


(*a*) 1) $NaNO_2$, HCl; 2) KCN, EtOAc, H_2O; 3) $NH_2OH \cdot HCl$, $NaHCO_3$, MeOH, H_2O; (*b*) NaOH, H_2O, Δ; (*c*) $K_3Fe(CN)_6$ or Br_2, HCl; (*d*) dioxane, Δ

Derivative **7** can serve as the precursor for high-energy compounds. Klapötke and co-workers [205] recently showed that the nitration of compound **7** by fuming nitric acid gives 4,4′-dinitramino-3,3′-bifurazan, which reacts with inorganic or organic bases to yield a large series of metal salts and salts of polynitrogen high-energy cations with 4,4′-dinitramino-3,3′ -bifurazanyl dianion.

One of the first methods used to prepare derivatives of bifuroxan systems is based on transformations of benzotrifuroxan **281**. The thermolysis of compound **281**, in which positions of all three N-oxide groups are unfixed, gives bis(nitrile oxide) **282**, which participates in the [3 + 2]-cycloaddition reaction in the presence of benzonitrile as the dipolarophile to yield two 1,2,4-oxadiazole rings at the ends of bifuroxan system **283**. At high temperatures, the nitrile oxide moiety of intermediate **282** tends to isomerize to isocyanate **284**, which cannot be isolated in an individual form but can be detected by reaction with methanol giving dimethyl ester of dicarbamic acid **285** (Scheme 125).[206]

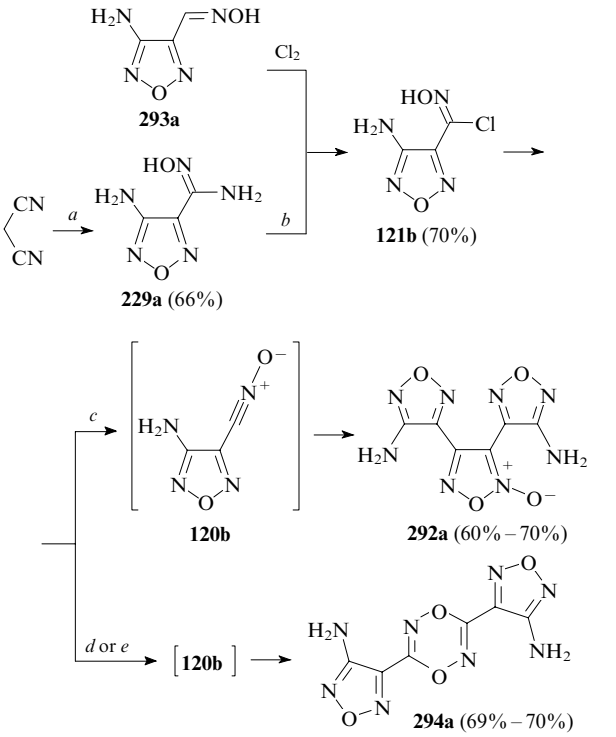
Scheme 125



Trimethylsilyldimethylfurazan derivative **286** was used in the synthesis of heterocyclic oligomer **287**. The deprotonation of the methyl group in starting **286** induced by n-butyllithium and followed by passing gaseous carbon dioxide results in lithium furazancarboxylate **288** in a nearly quantitative yield. Nitrogen(IV) oxide treatment of salt **288** promotes the formation of dinitrolic acid **289**, which then eliminates nitrous acid *in situ* to afford bisnitrile oxide **290**. The intermolecular dimerization of nitrile oxide moieties in intermediate **290** yields poly(furazanylfuroxan) **287** with alternating positions of furazan and furoxan rings (Scheme 126).[207] When compound **286** participates in a similar synthetic sequence consisting of nitrosation and N_2O_4-induced substitution nitration, bis(4-methylfurazan-3-yl)furoxan **291** can be prepared in a commensurate yield.[207] Obviously, this reaction also involves the generation of a methylfurazanylcarbonitrile oxide intermediate.

Hydroxamoyl chlorides serve as precursors for 1,2,5-oxadiazoles in the synthesis of 3,4-bis(4-aminofurazan-3-yl)furoxan (**292a**), an important high-energy compound having low sensitivity, good thermal stability and high detonation performance.[208] In the publication describing compound **292a** for the first time,[209] initial hydroxamoyl chloride **121b** was prepared by chlorinating furazan aldoxime **293a**. Treatment of the chloride with Na_2CO_3 in diethyl ether yielded nitrile oxide **120b**, which dimerized *in situ* to final furoxan **292a** (Scheme 127). In later studies,[210–212] chloride **121b** was generated in a one-pot process by the reaction of sodium nitrite in hydrochloric acid with malononitrile through 4-aminofurazan-3-carboxamidoxime intermediate (**229a**). However, the conversion of chloride **121b** to nitrile oxide **120b** can yield symmetric dioxadiazine adduct **294a** as a minor product. Furoxan **292a** is the major product under heterogeneous conditions (in the presence of sodium or potassium carbonate in diethyl ether, methylene chloride or ethyl acetate), whereas in a homogeneous medium (triethylamine in diethyl ether or acetonitrile), an inverted regioselectivity is observed and dioxadiazine **294a** is formed.[210] The dimerization regiochemistry of aminofurazanylcarbonitrile oxide **120b** also strongly depends on the solvent: potassium carbonate in THF promotes the formation of only **294a**, despite the heterogeneity of the medium.[211]

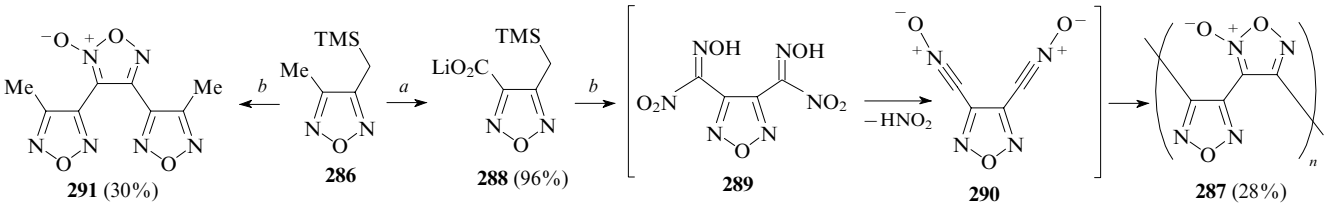
Scheme 127



(*a*) 1) $NaNO_2$, HCl; 2) $NH_2OH \cdot HCl$, Na_2CO_3; (*b*) $NaNO_2$, HCl; (*c*) Na_2CO_3, Et_2O; (*d*) K_2CO_3, THF; (*e*) Et_3N, MeCN

An improved synthetic scheme for bis(aminofurazanyl)-furoxan **292a** was proposed more recently (see Scheme 128).[213] The yield of amidoxime **229a** increased due to the replacement of hydrochloric acid with acetic

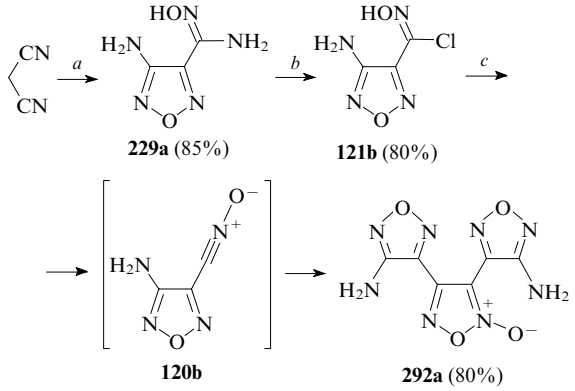
Scheme 126



(*a*) 1) Bu^nLi, 2) CO_2; (*b*) N_2O_4, CH_2Cl_2

acid in the first step and of sodium carbonate with alkali in the second one. At the final stage of synthetic strategy, the formation of the second regioisomer upon dimerization of nitrile oxide **120b** (dioxadiazine **294a**) was completely avoided by using silver carbonate as the dehydrohalogenating agent. The overall yield of desired compound **292a** was 54%. When stored at room temperature, acid chloride **121b** spontaneously eliminates an HCl molecule to give furoxan **292a** in 35% yield.[210]

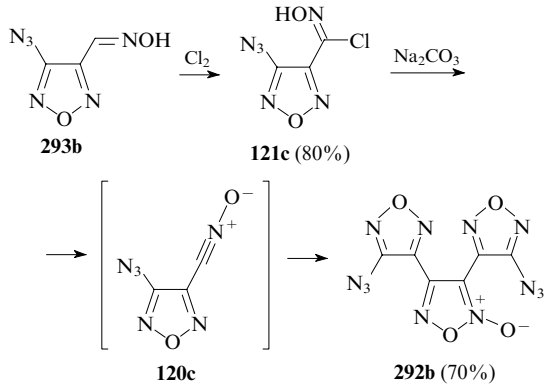
Scheme 128



(*a*) 1) $NaNO_2$, AcOH, H_2O; 2) NH_2OH, NaOH; (*b*) $NaNO_2$, HCl; (*c*) Ag_2CO_3, THF

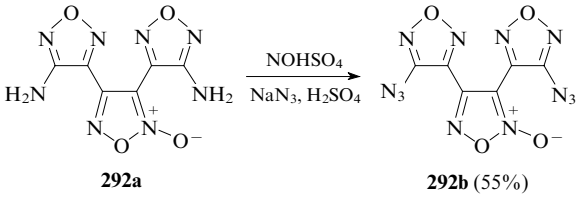
The chlorination of aldoxime **293b** followed by treatment of hydroxamoyl chloride **121c** with a base yields azidofurazanylcarbonitrile oxide **120c**, which dimerizes to give very labile 3,4-bis(4-azidofurazan-3-yl)furoxan (**292b**) (Scheme 129).[209]

Scheme 129



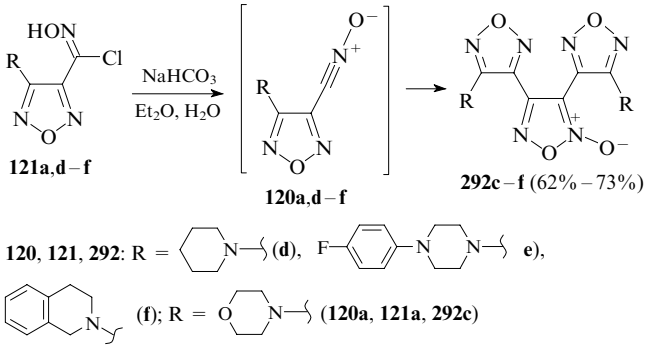
An alternative route to prepare compound **292b** consists of nitrosating bis(aminofurazanyl)furoxan **292a** through a bisdiazonium salt intermediate, which reacts (without being isolated) with sodium azide in a sulfuric acid solution (Scheme 130).[214]

Scheme 130



Chloroximes **121a,d–f**, which are derived from furazans linked to saturated nitrogen-containing heterocycles, are also converted in the presence of a base to nitrile oxides **120a,d–f**, which then dimerize *in situ* to furoxans **292c–f** (Scheme 131).[136]

Scheme 131

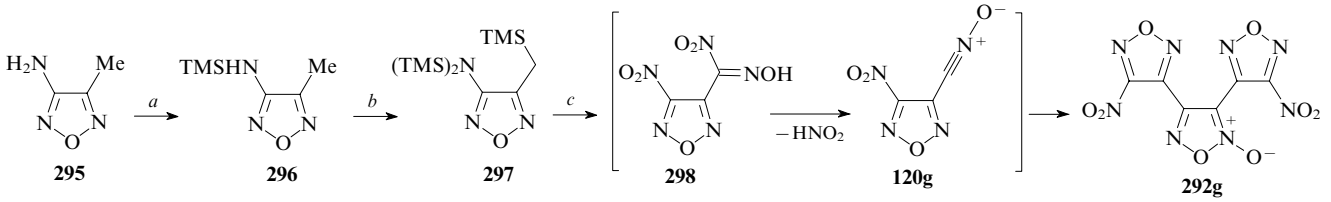


120, 121, 292: R = (**d**), **e**), (**f**); R = (**120a**, **121a**, **292c**)

The use of nitrolic acid as the key intermediate served to prepare 3,4-bis(4-nitrofurazan-3-yl)furoxan **292g**, one more important high-energy derivative. Compound **292g** attracts attention owing to its good thermal stability, low melting point (110 °C) and high density (1.875 g ml^{-1}).[213, 215, 216] Aminomethylfurazan **295** was chosen as the starting compound to prepare furoxan **292g**; compound **295** was silylated by hexamethyldisilazane (HMDS) to give mono(trimethylsilyl) derivative **296**,[217] which was introduced into the lithiation–silylation tandem process to afford tris(trimethylsilyl) derivative **297**; this product can be regarded as the C,N,N-silylation product of starting aminomethylfurazan **295** (Scheme 132). The subsequent nitration of compound **297** with N_2O_5 in the presence of a catalytic amount of sodium fluoride yields nitrolic acid **298**, which then eliminates nitrous acid to generate nitrile oxide **120g**, subsequently dimerizing to furoxan **292g** in an overall yield of 23%.

3,4-Bis(4-nitrofurazan-3-yl)furoxan (**292g**) can also be prepared *via* the oxidation of both amino groups in 3,4-bis(4-aminofurazan-3-yl)furoxan (**292a**) by a mixture of trifluoroacetic anhydride and 60% H_2O_2.[211] To oxidize bis(aminofurazanyl)dioxadiazine **294a** to dinitro derivative **294b**, a stronger three-component system of oxidants was required, which consisted of ammonium persulfate or

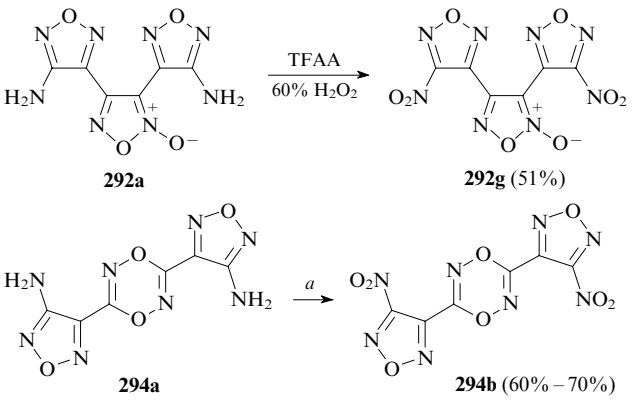
Scheme 132



(*a*) HMDS; (*b*) 1) Bu^nLi; 2) TMSCl; (*c*) N_2O_5, NaF (cat)

sodium tungstate, 60% – 90% H_2O_2 and concentrated sulfuric acid (Scheme 133).[212, 218]

Scheme 133

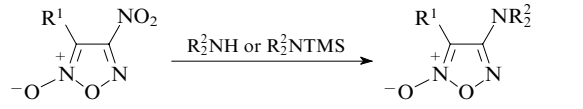


(*a*) $(NH_4)_2S_2O_8$ or Na_2WO_4, 60% – 90% H_2O_2, 98% H_2SO_4

The nitro groups in compound **292g** are very susceptible to nucleophilic substitution by N- and O-nucleophiles due to the strong electron-withdrawing effect of the heterocyclic assembly composed of two furazan rings and one furoxan ring. 3,4-Bis(4-nitrofurazan-3-yl)furoxan (**292g**) possesses high reactivity towards nucleophilic substitution; the process cannot be stopped after the monosubstitution, so the nucleophilic agent is used in excess to obtain disubstituted products in higher yields. In addition, dibasic nucleophiles (like primary amines) offer a means to prepare difurazanofuroxanoazepine heterocyclic systems, and heating of compound **292g** with potassium carbonate in anhydrous acetonitrile yields similar annelated oxepine structures.[214, 219 – 221]

Other nitrofuroxans and nitrofurazans can also take part in nucleophilic substitution reactions owing to the electron-withdrawing effect of the 1,2,5-oxadiazole ring. So, the 4-nitro group in dinitrofuroxan **299a** can efficiently be displaced by piperidine, whereas the 3-nitro group is retained in final structure **300a**.[222] To accomplish a similar conversion in 4-nitro-3-chlorofuroxan (**299b**), *N*-trimethylsilyl-substituted piperidine and morpholine were required; the reactions gave heterocyclic assemblies **300b**,**c**, respectively (Scheme 134).[223, 224]

Scheme 134

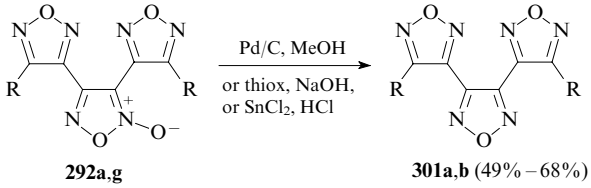


R^1 = NO_2 (**299a**, **300a**), Cl (**299b**, **300b**,**c**); NR^2_2 = $N(CH_2)_5$-cyclo (**300a**,**b**), $N(CH_2CH_2)_2O$-cyclo (**300c**)

In the same manner, various nitrofurazans undergo nucleophilic substitution reactions induced by cyclic secondary amines to yield heterocyclic assemblies of the furazan series linked to saturated nitrogen-containing heterocyclic moieties.[136, 150]

Furoxan rings in bis(aminofurazanyl)- and bis(nitrofurazanyl)furoxans **292a**,**g** can be selectively reduced to furazans by various agents [palladium on coal, formamidine sulfinic acid (thiox) or tin dichloride in hydrochloric acid] to yield assemblies **301a**,**b** (Scheme 135).[225, 226]

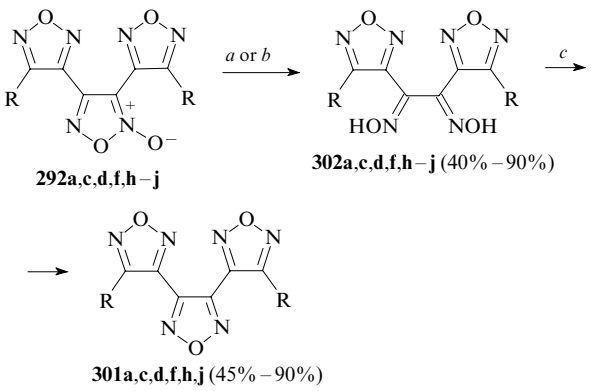
Scheme 135



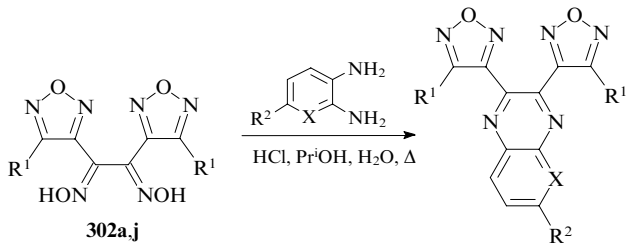
R = NH_2 (**a**), NO_2 (**292g**, **301b**)

However, Stepanov *et al.*[227] failed to reduce the furoxan ring in compounds **292a**,**c**,**d**,**f**,**h** – **j** to furazan ring by palladium on carbon or in the presence of hydrazine. In all cases, they obtained glyoximes **302a**,**c**,**d**,**f** ,**h** – **j** instead of difurazanylfurazans, and the dehydration of compounds **302a**,**c**,**d**,**h**,**j** yielded 3,3′:4′,3″-terfurazans **301a**,**c**,**d**,**h**,**j**. At the same time, glyoximes **302a**,**j** react with aromatic (including heterocyclic) *ortho*-substituted diamines to yield bicyclic structures **303** (Scheme 136).

Scheme 136



R = NH_2 (**a**), $N(CH_2CH_2)_2O$-cyclo (**c**), $N(CH_2)_5$-cyclo (**d**), 1,2,3,4-tetrahydroisoquinolin-2-yl (**f**), NHAc (**h**), $N(CH_2CH_2)_2NMe$-cyclo (**i**), OMe (**j**); (*a*) NH_2NH_2, Pd/C, Pr^iOH, 60 °C; (*b*) Pd/C, Pr^iOH, 30 – 45 °C; (*c*) 1) 10% NaOH; 2) Ac_2O

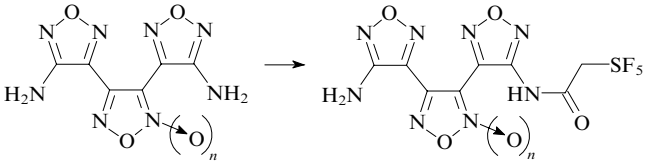


R^1 = NH_2, OMe; R^2 = H, F, Me; X = CH, N

On treatment with trichloroisocyanuric acid, bis(aminofurazanyl)furazan **301a** and bis(aminofurazanyl)furoxan **292a** are converted to 16-membered macrocyclic systems. In these systems, two heterocyclic sequences, each consisting of three 1,2,5-oxadiazole rings, are linked by azo bridges.[228]

One of the amino groups in heterocyclic structures **292a** and **301a** can be functionalized by a pentafluorosulfanyl group. In the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and a catalytic amount of 4-dimethylaminopyridine, compounds **292a** and **301a** react with pentafluorosulfanylacetic acid to yield amides **304a**,**b** (Scheme 137).[174]

Scheme 137



292a, **301a** **304a**,**b** (35% – 45%)

n = 1 (**292a**, **304a**), 0 (**301a**, **304b**);
(*a*) $F_5SCH_2CO_2H$, EDC, DMAP, THF

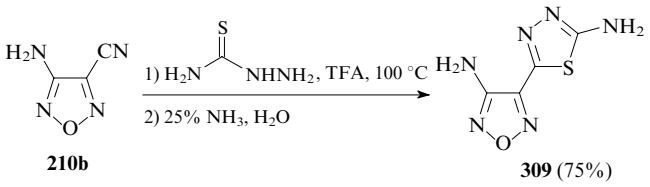
There are only few studies dealing with the synthesis of heterocyclic assemblies that consist of three consecutively linked furoxan rings. The reactions of furoxanyl aldoximes **305a** – **g** and **305′a** – **e** with N_2O_4 yield nitrolic acids **306a** – **g** and **306′a** – **e**, which can be converted to nitrile oxides **307a** – **g** and **307′a** – **e** upon refluxing in diethyl ether or chloroform in a one-pot process. The dimerization of intermediates **307a** – **g** and **307′a** – **e** yields furoxan assemblies **308a** – **g** and **308′a** – **e** (Scheme 138).[42]

Isomeric 3(4)-bis[chloromethylfuroxan-4(3)-yl)furoxans **308d** and **308′d** undergo S_N2 reaction under the action of bromide anion. The resulting bromomethyl derivatives **308h** and **308′h** can be efficiently converted to tertiary amines **308i**, **308′i** and nitro esters **308j**, **308′j** in the course of similar transformations (Scheme 139).[42]

III.9. Preparation of furazans and furoxans linked to other azole substituents

3-Amino-4-(5-amino-1,3,4-thiadiazol-2-yl)furazan (**309**), the only currently known representative of 1,3,4-thiadiazolyl-substituted furazans, was prepared by cyclization of aminocyanofurazan **210b** with thiosemicarbazide in the presence of trifluoroacetic acid (Scheme 140).[229]

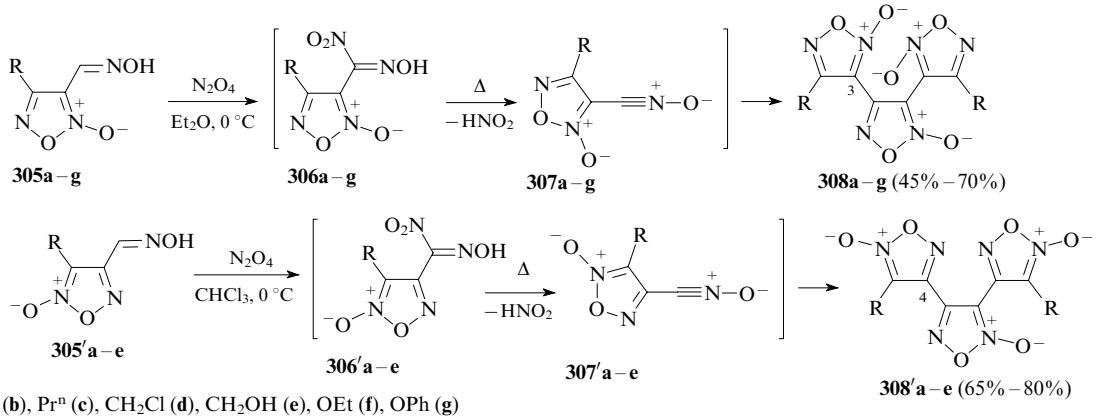
Scheme 140



210b **309** (75%)

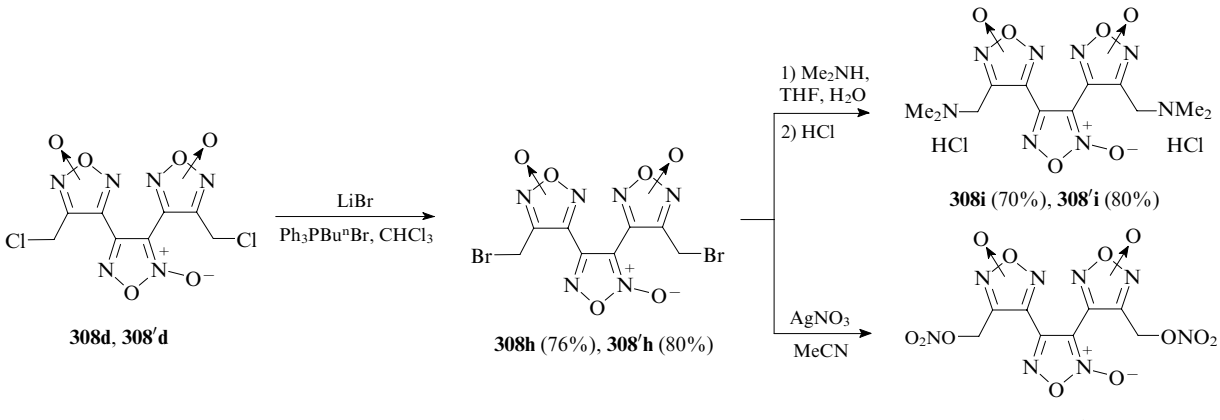
The unique feature of dinitrofuroxan **299a** consists in its ability to exist at room temperature in equilibrium with its monomeric form, *i.e.*, nitroformonitrile oxide **310**. This fact was used to prepare the first 1,4,2-dioxazolylfuroxan **311** by the [3 + 2]-cycloaddition of intermediate **310** to 4-amino-3-acetylfuroxan (**312**) catalyzed by an ionic liquid (Scheme 141).[230] The ability of dinitrofuroxan **299a** to cycloreversion also served as the basis to develop a general synthetic strategy for the preparation of 3-nitroazoles *via* the cycloaddition of nitrile oxide **310** to various dipolarophiles.[231]

Scheme 138



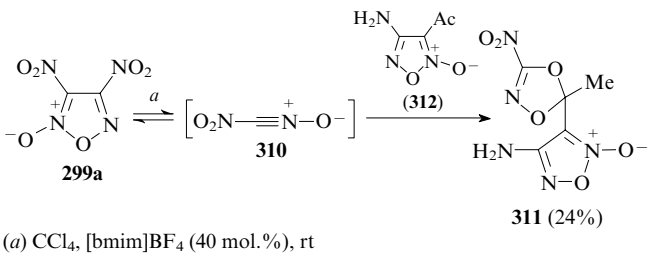
R = Ph (**a**), Me (**b**), Pr^n (**c**), CH_2Cl (**d**), CH_2OH (**e**), OEt (**f**), OPh (**g**)

Scheme 139



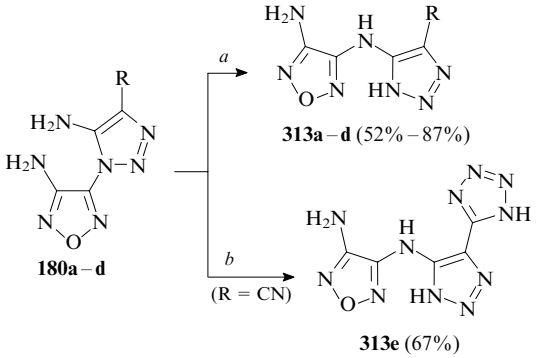
Isomers: furoxan-3-yl (**308**), furoxan-4-yl (**308′**)

Scheme 141



(*a*) CCl_4, [bmim]BF_4 (40 mol.%), rt

Scheme 142



R = CN (**a**), C(O)NH_2 (**b**), $C_6H_4NO_2$-4 (**c**), C_6H_4Cl-4 (**d**);
(*a*) DMF, 90 °C; (*b*) for **180a**: NaN_3, $ZnBr_2$, 130 °C, sealed tube

IV. Synthesis of 1,2,5-oxadiazoles linked by heteroatomic bridges to other heterocycles

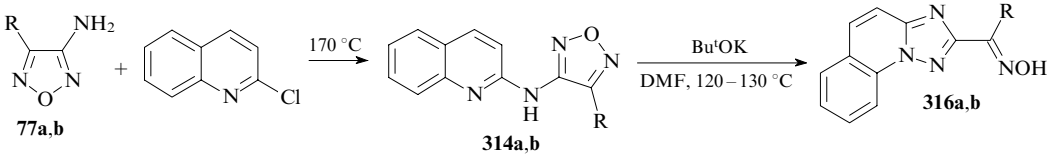
IV.1. Synthesis of furazans linked by NH bridges to other heterocycles

There are very few publications pertaining to the synthesis of heterocyclic assemblies where NH bridges link 1,2,5-oxadiazole rings to other heterocycles. Furthermore, all compounds prepared hitherto contain exclusively furazan rings as structural elements, and there are no furoxan analogues.

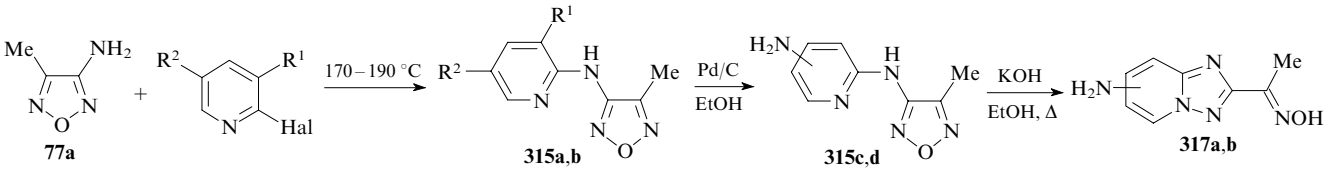
One approach to the synthesis of title systems is to use 3-amino-4-(5-amino-4-R-1*H*-1,2,3-triazol-1-yl)furazans **180a** – **d** as the starting compounds. The Dimroth rearrangement of heterocycles **180a** – **d** on heating in dipolar aprotic solvents yields N-triazolyl-substituted diaminofurazans **313a** – **d** (Scheme 142); however, the process does not proceed when the substrate has a thioamide moiety (triazole **180e**).[158] The Dimroth rearrangement of aminotriazole **180a** in a sealed tube at 130 °C in the presence of sodium azide and $ZnBr_2$ promotes tetrazole ring formation at the free nitrile group of compound **313a** to yield heterocyclic **313e**.[232]

The key step of another synthetic strategy to prepare furazans linked to heterocyclic substituents *via* NH bridges is the nucleophilic displacement of the halogen atom in a 2-halo-substituted heterocycle by aminofurazans **77a**,**b** at high temperatures, resulting in quinolinylaminofurazans **314a**,**b** and pyridylaminofurazans **315a**,**b**.[233] Under the action of a strong base, heterocyclic system **314a**,**b** is rearranged with furazan ring cleavage to give the 1,2,4-

Scheme 143

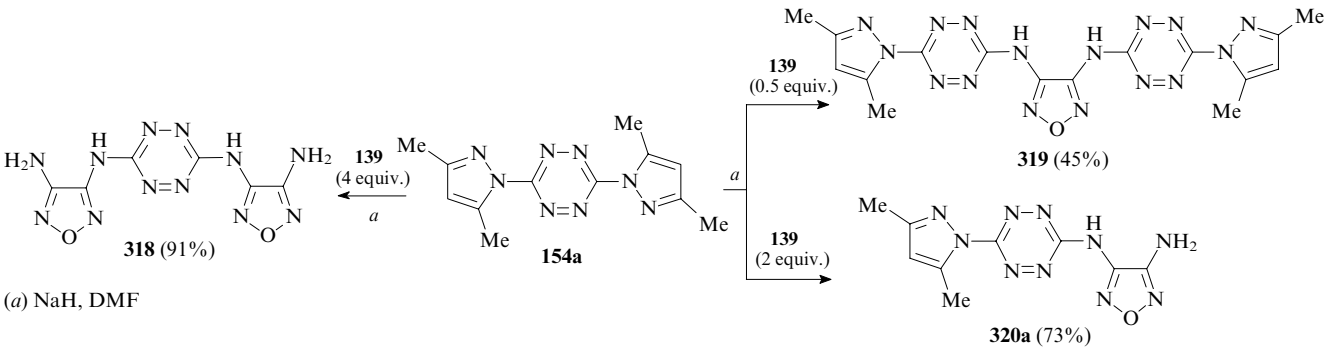


R = Me (**77a**; **314a**, 70% yield; **316a**, 66%), Ph (**77b**; **314b**, 87%; **316b**, 70%)



R^1 = NO_2, R^2 = H (**315a**, 58% yield); R^1 = H, R^2 = NO_2 (**315b**, 53%); Hal = Cl, Br;
NH_2 position: 3 (**315c**, 92%), 5 (**315d**, 90%), 8 (**317a**, 68%), 6 (**317b**, 32%)

Scheme 144



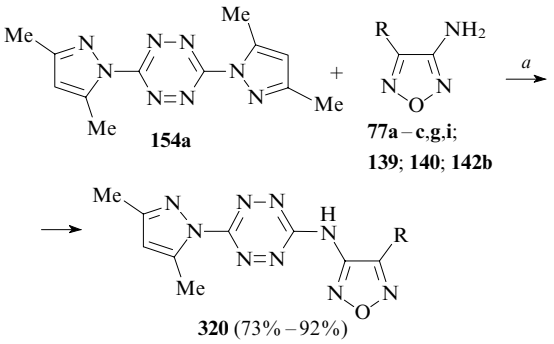
(*a*) NaH, DMF

triazole ring in compounds **316a**,**b**. However, this reaction does not proceed for pyridylaminofurazans **315a**,**b**, as the nucleophilicity of the pyridine nitrogen atom is lowered due to the presence of the nitro group. This drawback can be avoided by the nitro group reduction. The resulting amino(furazanylamino)pyridines **315c**,**d** rearrange under milder conditions to yield triazolopyridines **317a**,**b** (Scheme 143).

The reaction of 3,4-diaminofurazan (**139**) with 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (**154a**) results in the nucleophilic displacement of one or two dimethylpyrazole moieties involving one or two amino groups depending on the reactant ratio. This reveals the route to the regioselective synthesis of polynitrogen heterocyclic structures **318**, **319** and **320a** (Scheme 144).[234]

3,6-Bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (**154a**) can successfully react with other aminofurazans (**77a**–**c**,**g**,**i**, **139**, **140** and **142b**) in the presence of alkali metal carbonates allowing a selective displacement of only one dimethylpyrazole moiety to yield heterocyclic structures **320** (Scheme 145).[235]

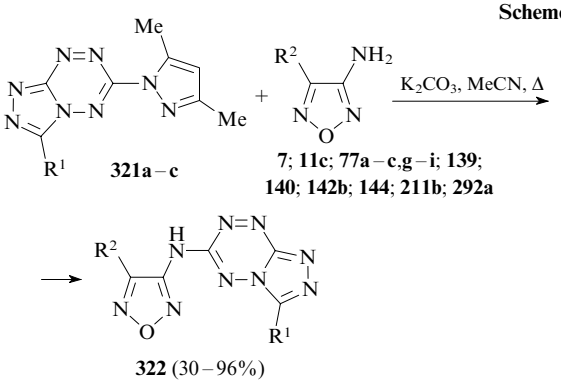
Scheme 145



R = Me, OMe, CO_2Me, Ph, NH_2, NO_2, N_3, (4-aminofurazan-3-yl)diazenyl, (4-aminofurazan-3-yl)diazenoxido; (*a*) K_2CO_3 or Cs_2CO_3, MeCN, Δ

It was shown later that 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazines **321a**–**c** [R^1 = H (**a**), CF_3 (**b**) and 4-methylfurazan-3-yl (**c**)] also undergo nucleophilic substitution under the action of aminofurazans **7**, **11c**, **77a**–**c**,**g**–**i**, **139**, **140**, **142b**, **144**, **211b** and **292a** in the presence of potassium carbonate as the base.[236] This approach is general and can be used to prepare a library of high-energy compounds **322** (33 compounds) comprising a furazan heterocycle and a triazolotetrazine heterocycle linked *via* an NH bridge (Scheme 146).

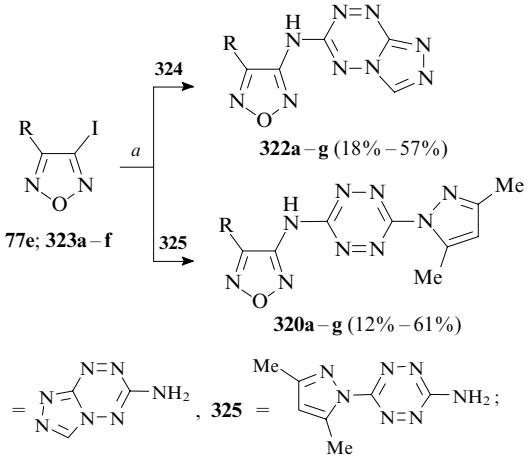
Scheme 146



R^1 = H, CF_3, 4-methylfurazan-3-yl; R^2 = Me, OMe, CO_2Me, CN, NH_2, N_3, NO_2, Ph, C_6H_4Me-2, C_6H_4F-4, 3-Py, tetrazol-5-yl, 4-methylfurazan-3-yl, (4-aminofurazan-3-yl)diazenyl, (4-aminofurazan-3-yl)diazenoxido, *etc*.

An alternative approach to prepare this type of compound was the cross-coupling of iodofurazans **77e**, **323a**–**f** with aminotriazolotetrazine **324** and aminotetrazine **325**.[237] The authors cited [237] utilized copper acetate in combination with acetylcyclohexanone as the chelating agent to yield heterocyclic structures **320a**–**g** and **322a**–**g** (Scheme 147). More frequently used palladium-based catalysts were unsuitable for this reaction. Attempts at functionalizing the amino group in compound **322g** to the tetranitroethylamine moiety did not lead to the desired result.[238]

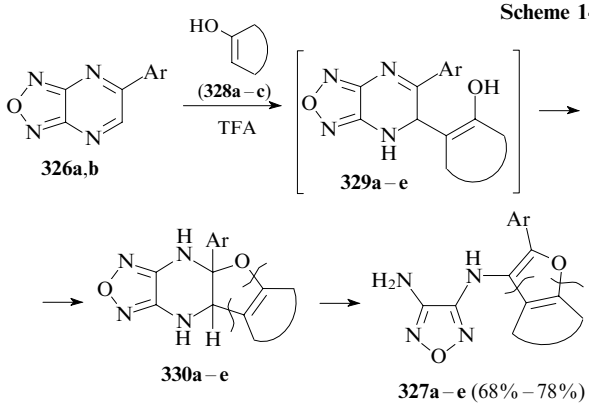
Scheme 147



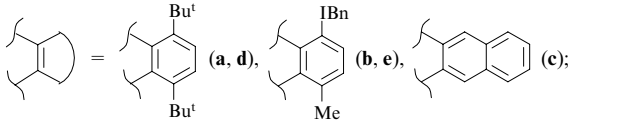
320, **322**, **323**: R = Me (**a**), OMe (**b**), Ph (**c**), N_3 (**d**), NO_2 (**e**), 4-iodofurazan-3-yldiazenyl (**f**); R = NH_2 (**77e**, **320g**, **322g**); (*a*) 2-acetylcyclohexanone, $Cu(OAc)_2$, K_2CO_3, PhMe, DME, 50 °C

Furazanopyrazines **326a**,**b** can in some cases serve as the starting compounds in the synthesis of (furazanylamino)-benzofurans **327a**–**e**.[239] Substrates **326a**,**b** react with 2,4-di-*tert*-butylphenol (**328a**), 2-isobornyl-4-methylphenol (**328b**)

Scheme 148



Ar = Ph (**326a**), 3-Th (**326b**); **327**, **329**, **330**: Ar = Ph (**a**–**c**), 3-Th (**d**, **e**);

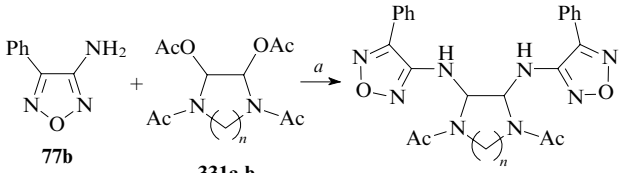


IBn is isobornyl

or β-naphthol (**328c**) in trifluoroacetic acid generating the expected S_N^H adducts **329a – e**, which are then cyclize under the reaction conditions to tetracyclic systems **330a – e**. However, due to instability of the intermediates **330a – e** in acid media, the pyrazine ring is opened to yield final structures **327a – e** (Scheme 148).

The nucleophilic substitution involving two acetoxy groups in imidazolidine (**331a**) and piperazine (**331b**) derivatives on treatment with aminophenylfurazan **77b** yielded heterocyclic systems **332a**,**b** incorporating furazan moieties linked to saturated nitrogen-containing heterocycles through NH bridges (Scheme 149).[240]

Scheme 149



77b **331a**,**b** **332a**,**b** (89%)

331, **332**: n = 1 (**a**), 2 (**b**); (*a*) TsOH, MeCN, rt

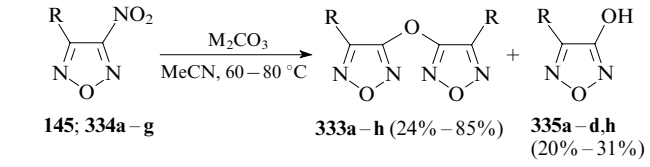
IV.2. Synthesis of furazans and furoxans linked by O bridges to heterocyclic substituents

Most papers concerning the preparation of 1,2,5-oxadiazoles with heterocyclic substituents linked *via* oxygen bridges deal with hetaryl furazanyl and difurazanyl ethers. Publications concerning hetaryl furoxanyl ethers appeared only in the last decade.

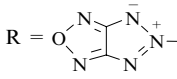
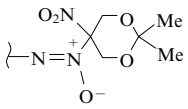
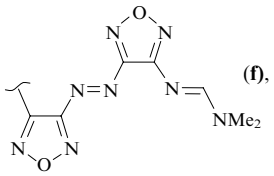
The key route to prepare difurazanyl ethers **333a – h** is based on the use of nitrofurazans **145** and **334a – g** as the precursors. On heating in anhydrous acetonitrile in the presence of sodium or potassium carbonate, these precursors are converted to target ethers **333a – h** (Scheme 150).[241 – 246] The 4*H*,8*H*-bisfurazano[3,4-*b*;3′,4′-*e*]pyrazine dianion (**163**) can also serve as the base.[145] In some cases, hydroxyfurazans **335a – d**,**h** were isolated as side products. The amount of hydroxyfurazans was increased because of the presence of trace wate. In addition, hydroxyfurazans formed regioselectively when crystalline hydrates of inorganic salts were used.[247]

The conversion of nitrofurazans to difurazanyl ethers under the action of a weak base is not a trivial process. A suggested mechanism of this reaction is depicted in Scheme 151. Sheremetev *et al.*[241] suggest that a base induces

Scheme 150

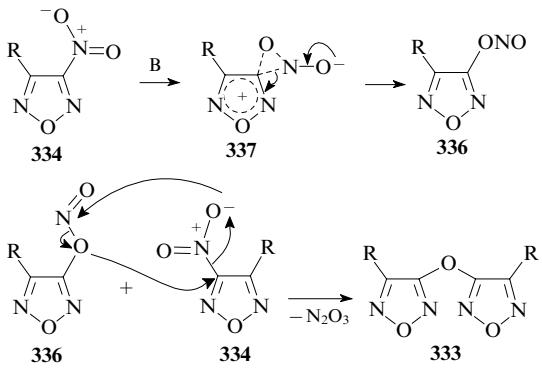


145; **334a – g** **333a – h** (24% – 85%) **335a – d**,**h** (20% – 31%)

R =  (**145**, **333h**, **335h**); **333 – 335**: R = NO_2 (**a**), CN (**b**), Ac (**c**), N(O)=NBu^t (**d**),  (**e**),  (**f**), N=N(O)C$(NO_2)_2$F (**g**); M = Na, K

the nitro – nitrite rearrangement of nitrofurazan **334** to nitroso ester **336** through the generation of oxaziridine spirocyclic intermediate **337**. Nitroso ester **336** further reacts with the second molecule of nitrofurazan **334** to yield desired difurazanyl ether **333** with simultaneous elimination of an N_2O_3 molecule.

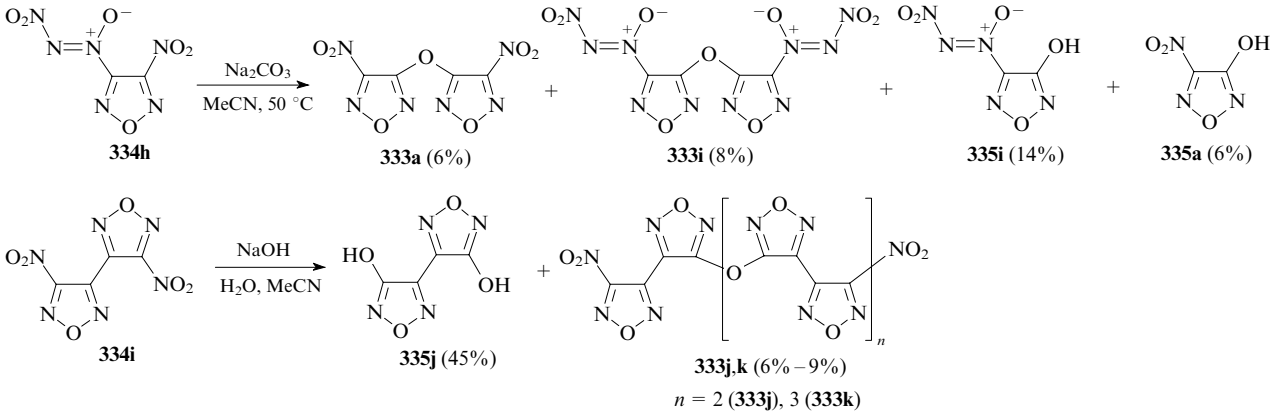
Scheme 151



334 **337** **336** **336** **334** **333**

The reaction of nitrofurazan **334h** containing an N-nitroazoxy group with sodium carbonate resulted in a mixture of four products: two difurazanyl ethers (**333a**,**i**) and two hydroxyfurazans (**335a**,**i**).[242] Notably, the treatment of dinitrobifurazan **334i** with aqueous alkali yields not only the dihydroxy derivative, but also a mixture of two polyfurazanyl ethers **333j**,**k** (Scheme 152).[243] Similar trends

Scheme 152



334h **333a** (6%) **333i** (8%) **335i** (14%) **335a** (6%)

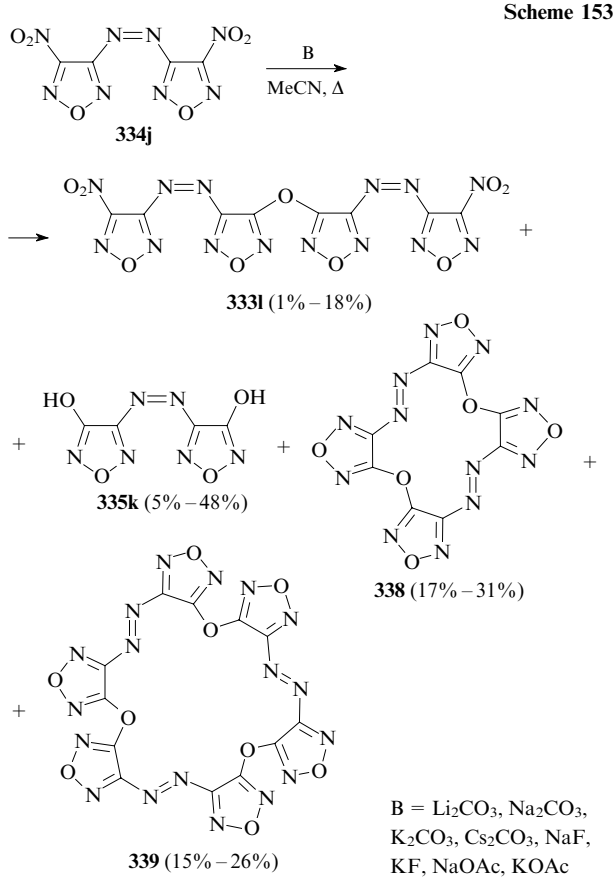
334i **335j** (45%) **333j**,**k** (6% – 9%)

n = 2 (**333j**), 3 (**333k**)

were observed in the reaction of dinitroazoxyfurazan[248] or 4-nitro-3-[4-chlorofurazanyl-3-N(O)N-azoxy]furazan.[249]

The conversion of dinitroazofurazan **334j** in a basic medium followed a peculiar pathway. Regardless of the type of base, the reaction resulted in a mixture of four products, namely difurazanyl ether **333l**, dihydroxy derivative **335k** and two macrocyclic structures **338** and **339** formed upon linking of two or three substrate molecules *via* oxygen bridges (Scheme 153).[250]

Scheme 153



In some cases, an approach based on the reaction of nitrofurazans **334a**,**b**,**j** with hydroxyfurazan salts **340a – c** is used for the regioselective preparation of difurazanyl ethers. This modification can provide heterocyclic assemblies **333m – o** in good yields (Scheme 154).[251, 252]

Dinitrofurazan **334a** reacts with dihydroxyfurazan disodium salt **340b** to furnish a mixture of a linear product and a cyclic product resulting from nitro group displacement, namely compounds **333p** and **341**.[251] This reaction also produced a small amount of dinitrofurazanyl ether **333a** owing to compound **340b** functioning as the base (Scheme 155).

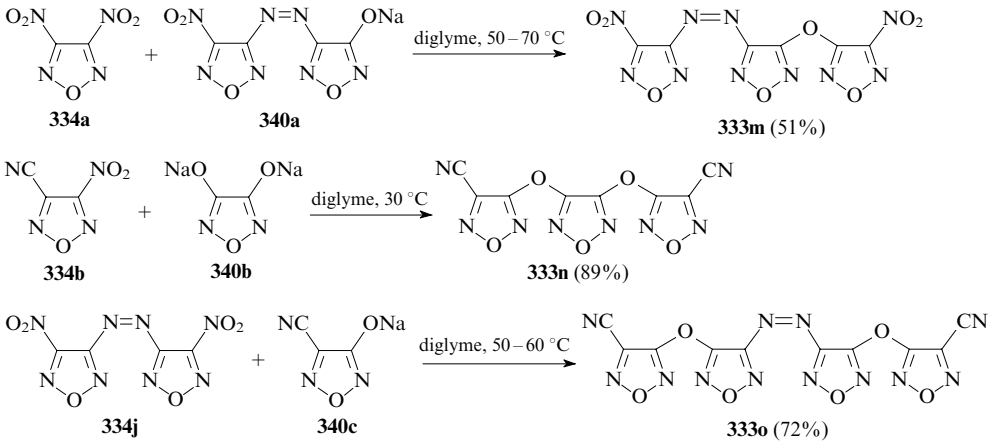
An intriguing feature was found in an attempt to displace nitro groups in dinitrofurazanyl ether **333a** under the action of hydroxycyanofurazan sodium salt **340c**.[253] The starting furazanyl ether **333a** was trans-etherified under the reaction conditions to yield unsymmetrically substituted derivative **333q**, with subsequent replacement of remaining nitrofurazanyloxy group under the action of a second molecule of salt **340c** providing dicyano derivative **333b** (Scheme 156). Mixed difurazanyl ethers **333r – u** were prepared in the same way.

Difurazanyl ethers, especially containing explosophoric groups (NO_2, N=N or CN), are regarded to be potential components of high-energy formulations. Some difurazanyl ether derivatives are used to prepare high-energy salts.[254, 255]

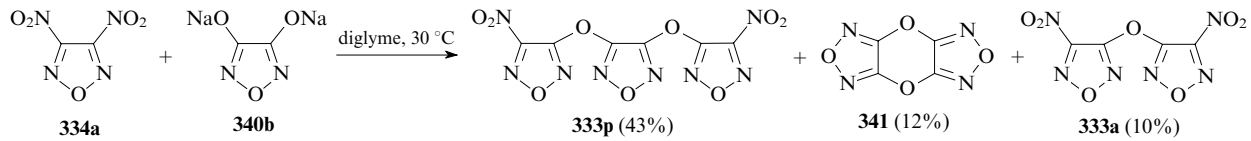
O-Nucleophiles can substitute the phenylsulfonyl group in furazan derivatives (*e.g.*, in compound **342**). In particular, this method was used to prepare quinuclidinyloxyfurazan **343** (Scheme 157).[256]

The first representative of hetaryl furoxanyl ethers was prepared in 2004.[257] The 3,4-bis(phenylsulfonyl)furoxan (**344**) served as the initial compound. The phenylsulfony group at the C(4) atom of **344** was efficiently substituted

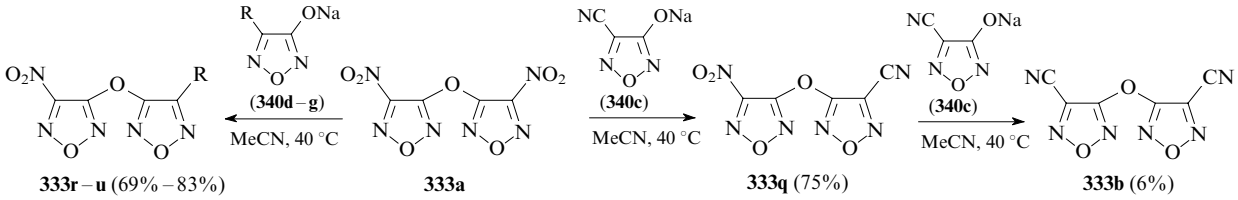
Scheme 154



Scheme 155



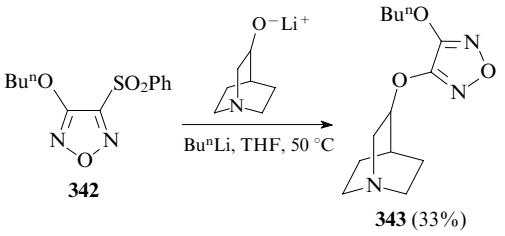
Scheme 156



333r – u (69% – 83%) **333a** **333q** (75%) **333b** (6%)

R = Me (**333r**, **340d**), NHMe (**333s**, **340e**), N(CH$_2$CH$_2$)$_2$O-cyclo (**333t**, **340f**), 1,2,3,4-tetrahydroxyisoquinolin-2-yl (**333u**, **340g**)

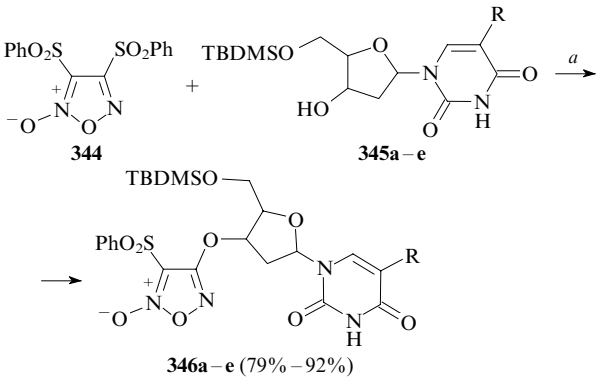
Scheme 157



342 **343** (33%)

under the action of hydroxy nucleophiles **345a – e**. As a result, tetrahydrofuranyl furoxanyl ethers **346a – e** were formed in high yields (Scheme 158).

Scheme 158

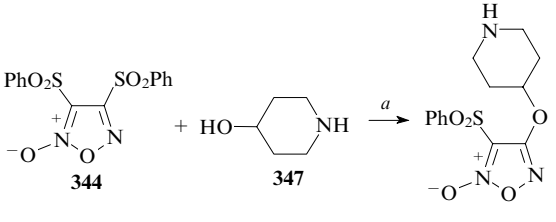


344 **345a – e** **346a – e** (79% – 92%)

R = H (**a**), Me (**b**), I (**c**), F (**d**), CF$_3$ (**e**);
(*a*) 50% NaOH, H$_2$O, THF, 0 °C; TBDMS = SiMe$_2$Bu^t

A similar reaction of 4-hydroxypiperidine (**347**) proceeds regioselectively with displacement of the sulfonyl group in position 4 of the ring to yield piperidinyloxyfuroxan **348** (Scheme 159).[258] Recent studies showed the feasibility of nucleophilic displacement of the nitro group in 4-nitrofuroxans **349a – c** under the action of hydroxy-substituted heterocycles **350a – e** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base.[259]

Scheme 159

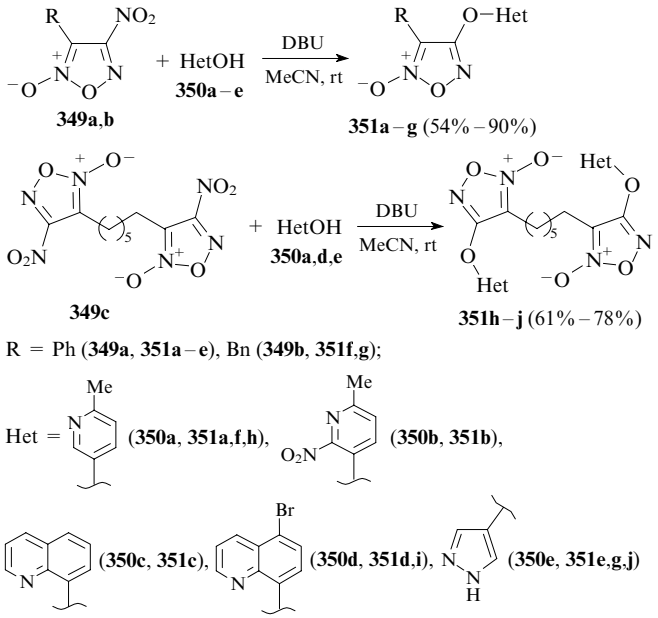


344 **347** **348** (61%)

(*a*) 30% NaOH, H$_2$O, THF, rt

Nitrofuroxans bearing an aliphatic or aromatic substituent at the C(3) atom of the furoxan ring were studied in this reaction.[260] A series of hetaryl furoxanyl ethers **351a – j**, which contained a pyridine, quinoline or pyrazole moiety, were thus obtained (Scheme 160).

Scheme 160



349a,**b** **351a – g** (54% – 90%)

349c **351h – j** (61% – 78%)

R = Ph (**349a**, **351a – e**), Bn (**349b**, **351f**,**g**);

Het = (**350a**, **351a**,**f**,**h**), (**350b**, **351b**),

 (**350c**, **351c**), (**350d**, **351d**,**i**), (**350e**, **351e**,**g**,**j**)

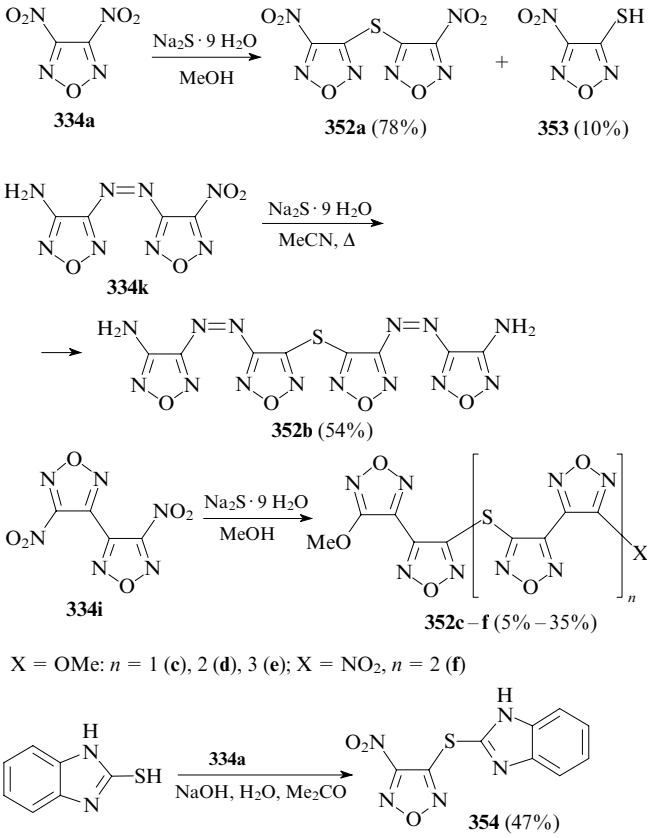
IV.3. Synthesis of furazans and furoxans linked by S bridges to heterocyclic substituents

The reaction of dinitrofurazan **334a** with sodium sulfide offers a means to prepare difurazanyl thioether **352a** along with a monosubstituted side product, furazanylthiol **353**.[261] Aminonitroazofurazan **334k** reacts in the same manner to yield thioether **352b**.[244] Dinitrobifurazan **334i**, however, reacts with sodium sulfide to yield a mixture of four products **352c – f**, each containing a bridging sulfur atom. The highest yield is achieved for oligomer **352e** (Scheme 161).[261] One of the nitro groups in dinitrofurazan **334a** can also be displaced under the action of benzimidazole-2-thiol in alkaline medium to yield heterocyclic structure **354**.[261]

Dinitrofurazanyl thioether **352a** is oxidized by Caro's acid to yield a mixture of sulfoxide **355** (in 52% yield) and sulfone **356** (23%).[261] The use of fuming nitric acid produces a mixture of the same products but in appreciably lower yields of 7% and 5%, respectively (Scheme 162).[262]

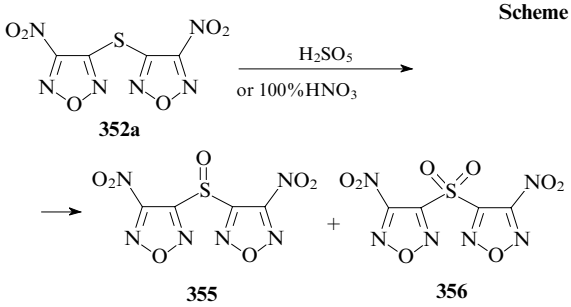
Not only nitrofurazan **357**, but also nitrofuroxan **349a** is capable of the nucleophilic substitution with 4-sulfanylpiperidine to yield heterocyclic assemblies **358a**,**b**, which

Scheme 161



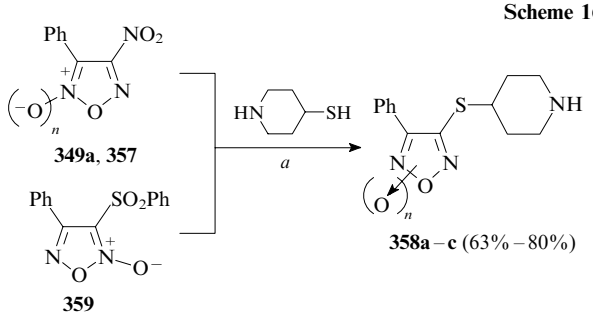
X = OMe: *n* = 1 (**c**), 2 (**d**), 3 (**e**); X = NO_2, *n* = 2 (**f**)

Scheme 162



comprise S-bridged 1,2,5-oxadiazole and piperidine rings. Phenylsulfonyl furoxan **359** undergoes a similar conversion to compound **358c** (Scheme 163).[263]

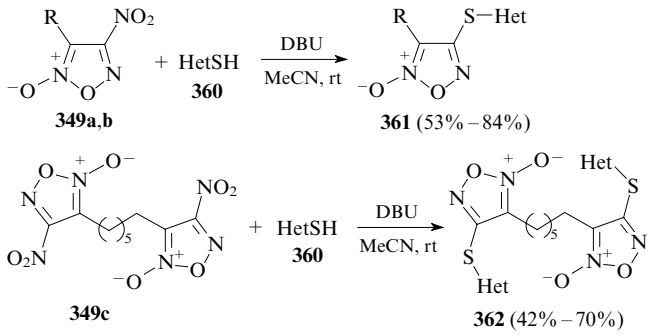
Scheme 163



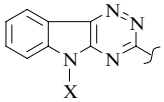
n = 0 (**357**, **358a**), 1 (**349a**, **358b**,**c**); isomers **358**: 2-oxido (**b**), 5-oxido (**c**); (*a*) Aliquat 336 [methyltri(n-octyl)ammonium chloride], NaOH, PhH, H_2O

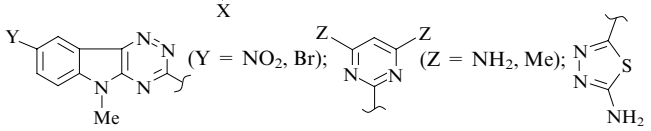
The nucleophilic displacement of a nitro group in nitrofuroxans **349a**–**c** under the action of hetarylthiols **360** recently served to prepare a library of hetarylsulfanylfuroxans **361** (38 compounds) and **362** (11 compounds) (Scheme 164),[259,264] which contained a heterocyclic (indolotriazine, pyrimidine or aminothiadiazole) pharmacophoric moiety.

Scheme 164



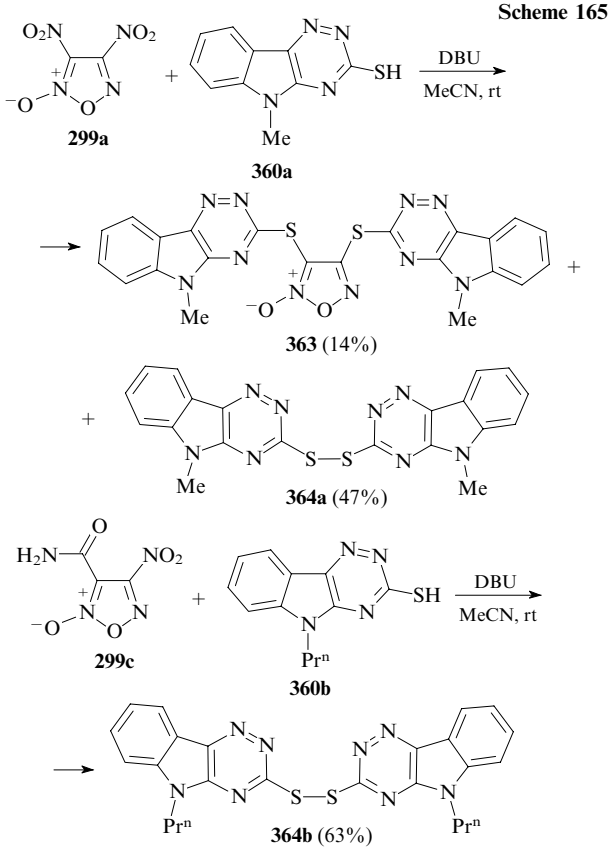
349: R = Ph (**a**), Bn (**b**);

360–**362**: Het =  (X = H, Me, Et, Pr^n, Pr^i, Bu^n, Bn, CH_2Bn, All);

 (Y = NO_2, Br); (Z = NH_2, Me);

The behaviour of 4-nitrofuroxans with the electron-withdrawing substituents at the C(3) ring atom differed from the behaviour of furoxans **349a**–**c**. 3,4-Dinitrofuroxan **299a** reacted with hetarenethiol **360a** to generate bis(hetar-

Scheme 165



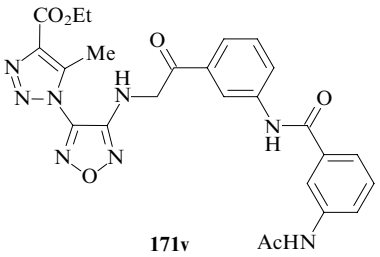
ylsulfanyl)furoxan **363** in low yield. The major product of this reaction was disulfide **364a**; that is, dinitrofuroxan **299a** acted as an oxidant in the reaction. 4-Nitrofuroxan-3-carboxylic acid amide (**299c**) behaves in a similar manner in reaction with indolotriazinylthiol **360b**: instead of the expected nitro-group substitution product, only disulfide **364b** was obtained (Scheme 165).[259, 264]

V. Pharmacological activity of polynuclear heterocyclic structures based on 1,2,5-oxadiazoles

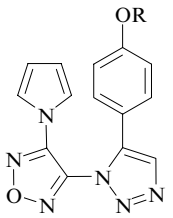
Among the heterocyclic systems containing the 1,2,5-oxadiazole ring considered in this review, there are compounds that have various types of pharmacologic activities, primarily anticancer activity. 3-(Pyrrol-1-yl)-4-(1*H*-1,2,3-triazol-1-yl)furazans **184c**,**g** in relatively low concentrations showed antitumour activity against leukaemia SR cells, melanoma MDA-MB-435 cells and colon cancer cells.[152] Aminofurazanylazabenzimidazoles **14** were capable of inhibiting a family of protein kinases B (including those encoded by AKT1, AKT2 and AKT3 genes), and, hence, they could be useful for cancer therapy.[84, 85] N-Substituted 5-amino-1,2,4-oxadiazolylfurazans **238a** – **d** showed antitumour properties in *in vivo* studies on sea urchin embryos.[187] Piperidinyloxyfuroxan **348** was used to design new antiproliferative agents against liver cancer and non-small cell lung cancer.[258, 265]

In addition, aminofurazanylazabenzimidazole derivatives **14** constitute a new class of inhibitors of mitogen-activated protein kinase 1 (MSK-1), which is responsible for the destruction of hippocampal neurons and leads to cerebrovascular ischemia.[81, 82] One 1,2,3-triazolylfurazan derivative, namely compound **171v**, was shown to be a highly efficient inhibitor of the severe acute respiratory syndrome (SARS) coronavirus cysteine protease in micromolar concentrations.[155] Quinuclidinyloxyfurazan **343** showed a moderate activity against neurotoxins.[256]

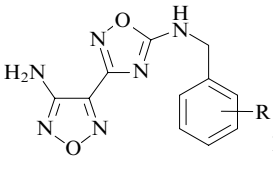
Structures of active compounds



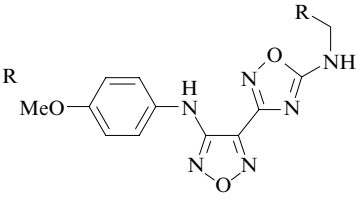
171v



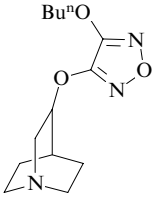
184c (R = Me);
184g (R = Et)



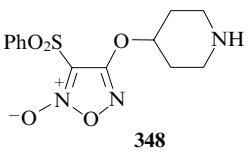
238a (R = 3-OMe);
238b (R = 4-OMe)



238c (R = 3,4-(MeO)$_2$C$_6$H$_3$);
238d (R = 3-Py)



343



348

VI. Conclusion

The data summarized in this review demonstrate the great interest of researchers in the chemistry of non-annelated polynuclear heterocyclic systems comprising 1,2,5-oxadiazole (furazan and furoxan) rings. This interest is due to high application potential of these systems, primarily, as physiologically active compounds and as components of high-energy formulations. Both conventional methods and new strategies were used in recent years to prepare these systems, including most efficient one-pot processes which can be conducted under mild conditions without isolating intermediate products.

One of the conventional methods used to synthesize heterocyclic furazan derivatives is dehydration of mono- and disubstituted glyoximes that are formed *in situ* from available initial compounds. Most of the new approaches to the synthesis of hetaryl-substituted furazans discovered in recent years are based on transformations of functional groups in appropriate furazan derivatives. In particular, the pyrrole, dihydropyrrole, 1,2,3-triazole or 1,2,3-triazolo[4,5-*c*]-1,2,5-oxadiazole moiety can be added to the furazan ring of aminofurazans. However, most new methods for preparing hetarylfurazans are based on reactions of available derivatives of alkyl furazanyl ketones and furazancarboxylic acids. Indolyl-, indolizinyl- and thiazolylfurazans were prepared from bromoacetylfurazans. Nitrofurazanylacetic acid is a suitable precursor for the preparation of pyrazolylfurazans. Furazanylamidrazones served to prepare (1,2,4-triazol-3-yl)furazans, tetrazolyl- and triazinylfurazans, while furazanylamidoximes can be converted to (1,2,4-oxadiazolyl)furazans. A unique reaction of nitrofurazans under the action of weak inorganic bases was unexpectedly discovered to yield difurazanyl ethers. A method has been developed to prepare difurazanyl thioethers. New heterocyclic systems have been synthesized on the basis of 1,2,5-oxadiazoles (*e.g.*, 4*H*-furazano[3,4-*e*]-1,3,4-oxadiazine), as well as polycyclic structures and unique heterocyclic assemblies that contain up to 5 – 7 heterocycles in one molecule.

The earlier popular approach to furoxan ring formation *via* the oxidation of hetaryl-substituted glyoximes has recently been employed only rarely to prepare hetarylfuroxans as the appropriate glyoximes are hardly available. These compounds were more frequently prepared by the heterocyclization of hetarylcarbonitrile oxides, which yielded symmetrically substituted 3,4-bis(hetaryl)furoxans. Along with well-known methods for generation of nitrile oxides, a new approach was proposed to generate these intermediates *in situ* by reactions of hetaryl-substituted dinitromethane salts with N_2O_4.

To construct a furoxan ring with the goal of preparing unsymmetrically substituted hetarylfuroxans, new methods have been developed comprising the transformations of functional groups in furoxan derivatives. These methods were, however, less useful than for similar furazan derivatives. This was due to the lower availability of the relevant functional derivatives, the synthesis of which has started to be developed only recently, and to a considerable difference between the reactivities of furazan and furoxan derivatives caused by the effect of the N-oxide moiety. So, the methods for the synthesis of amino-substituted furoxans have been created quite recently, and the reactivities of amino and other functional groups linked to the C(3) and C(4) atoms of the furoxan ring are strongly dependent on conditions.

For example, the [3 + 2]-cycloaddition of azidofuroxans with acetylenes to form (1,2,3-triazolyl)furoxans was accomplished only in ionic liquids. Efficient methods for preparing tetrazolylfuroxans and their ammonium salts, 1,2,4-triazolylfuroxans, 1,2,4- and 1,3,4-oxadiazolylfuroxans have recently been developed at the Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, and relevant studies are now in progress.[266]

The synthesis of structures based on 1,2,5-oxadiazoles receives currently great attention with the view of preparing new high-energy compounds. Among these compounds, worth noting are dinitrobifuroxanyl- and 3,4-bis(nitrofurazanyl)furoxans, a series of polyheterocyclic structures in which two, three or more furazan rings are linked *via* azo or azoxy bridges, as well as difurazanyl ethers and assemblies of five heterocycles containing three furoxan rings bridged by 1,2,4- and 1,3,4-oxadiazole rings. Pyrazolylfurazans unsubstituted at the pyrazole nitrogen atom and tetrazolylfurazans and tetrazolylfuroxans unsubstituted at the tetrazole nitrogen atom were used to prepare a series of high-energy salts containing an ammonium cation, a guanidine cation or its mono-, di- and triamino derivatives. In addition, 3-amino-, 3,5-diamino- and 3,4,5-triamino-1,2,4-triazolyl analogues of these compounds were synthesized, and high-energy structures were found among them.

Furazan rings can be linked to other heterocycles through NH bridges. A library of high-energy compounds where the furazan and triazolotetrazine ring are linked by this bridge have been prepared. Heterocyclic systems in which furoxan rings are combined with other heterocycles *via* S and O bridges have been prepared only recently, while difuroxanyl ethers and difuroxanyl thioethers, like also their analogues with NH bridges, remain unknown. Compounds with diverse pharmacological activities have been found among the obtained structures.

The data presented in this review clearly demonstrate that the chemistry of non-annelated polynuclear heterocyclic systems comprising 1,2,5-oxadiazole rings is far from being exhausted. The great contribution of Russian chemists to the development of synthetic methods and studies of these structures deserves special mention. The set of studies performed in recent years gives hope for new results that would be of scientific and applied value.

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