Russian Chemical Reviews **82** (11) 1007 – 1033 (2013) © 2013 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2013v082n11ABEH004369

Advances in the chemistry of monocyclic amino- and nitrofuroxans †

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Contents

I.	Introduction	1007
II.	Methods of synthesis of aminofuroxans	1007
III.	Reactivity of aminofuroxans	1014
IV.	Methods of synthesis of nitrofuroxans	1023
V.	Reactivity of nitrofuroxans	1027
VI.	Conclusion	1031

Abstract. The review summarizes data on the development of methods of synthesis and reactivity of monocyclic amino- and nitrofuroxans published in the last 20 – 25 years. The details of the synthesis of aminofuroxans based on the Schmidt and Curtius rearrangements involving acetyl- and azidocarbonylfuroxans, respectively, are discussed. Specific features of the transformations of functional substituents in aminofuroxans are described. In consideration of the reactivity of aminofuroxans, the attention is focused on the oxidation, diazotization and the Mannich reaction. Methods of synthesis of nitrofuroxans based on the oxidation of nitroglyoximes and the nitrosation of unsaturated compounds and dipotassium salts of 2-substituted 2-hydroxyimino-1,1-dinitroethanes are covered. The reactivity of nitrofuroxans comprises the nucleophilic substitution, reduction and thermal furoxan ring opening to form nitrile oxides. The bibliography includes 111 references.

I. Introduction

The history of the chemistry of furoxans (1,2,5-oxadiazole 2-oxides) started at the end of the 19th century, when the first approaches to the furoxan ring formation were published. This heterocycle has unique properties distinguishing it from other azoles. First, this heterocycle contains a 'latent' nitro group or two nitroso groups. Some chemical transformations of furoxan are accompanied by the release of the nitro group, whereas other reactions occur with the participation of both nitroso groups. Yet another surprising feature of furoxans is that they are prone to thermal isomerization (at temperatures from 20 to 250 °C), in which the exocyclic oxygen atom migrates from one nitrogen atom to another. This process occurs *via* the formation of the open form, the dinitrosoethylene intermediate, and the susceptibility to this transformation depends on the character of substituents at the carbon atoms of the furoxan ring. The chemistry of furoxans (both the synthesis and reactivity) is summarized in the excellent two-volume monograph by L I Khmel'nitskii and co-workers [1, 2] having two editions (in 1984 and 1996).

Amino- and nitrofuroxans hold a special place among furoxan derivatives. Since this heterocycle furoxan ring has a high enthalpy of formation, its nitro derivatives have attracted interest as potential components of various high energy materials,[3] and aminofuroxans can serve as the starting compounds for the synthesis of nitro derivatives. On the other hand, both amino- and nitrofuroxans exhibit a broad spectrum of biological activity (antibacterial, antihelminthic and fungicidal); some nitrofuroxans are NO donors.[4, 5] Due to such different fields of application, derivatives of amino- and nitrofuroxans have attracted great interest. Data on the chemistry of amino- and nitrofuroxans published before 1995 are covered in the review by Makhova and Godovikova.[6] However, vast new information on methods of synthesis and reactivity of such furoxan derivatives was published since that time and, taking into account the great interest in this type of compounds, it seems reasonable to summarize the latest data. The data considered earlier [6] are partially included in the present review wherever necessary.

II. Methods of synthesis of aminofuroxans

Several approaches are used for the furoxan ring formation. The main methods are based on the oxidation of glyoximes, the cyclodimerization of nitrile oxides and the dehydration

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Received 24 January 2013
Uspekhi Khimii **82** (11) 1007 – 1033 (2013); translated by T N Safonova

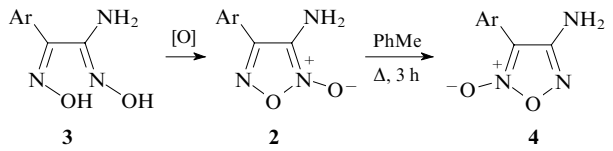
† Dedicated to the memory of Professor Lenor Ivanovich Khmel'nitskii (1927 – 1995).

of α-nitro oximes.[1] Earlier, aminofuroxans have been synthesized mainly by the oxidation of the *amphi* form of aminoglyoximes. In the recent years, new methods of synthesis of aminofuroxans have gained relatively wide application. These are the Curtius and Schmidt rearrangements of azidocarbonyl- and acetylfuroxans, transformations of functional groups at the carbon atom C(3) giving the corresponding 4-aminofuroxan derivatives and the nucleophilic displacement of the 4-nitro group in 4-nitrofuroxans by amino(alkylamino) groups.

1. Oxidation of aminoglyoximes

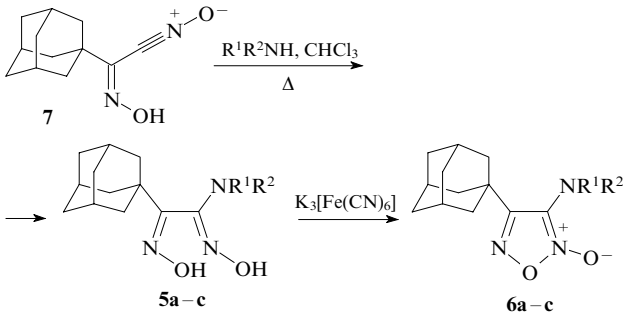
Neither isomeric 3(4)-monoaminofuroxans nor 3,4-diaminofuroxan (**1**) are known, although a rather large number of isomeric 3(4)-aminofuroxans containing various substituents at the second carbon atom of the ring were described. The general method of synthesis of 3-amino-4-arylfuroxans **2** is based on the oxidation of the *amphi*(*Z*,*E*) form of 1-amino-2-arylglyoximes **3** with potassium ferricyanide in an alkaline medium or with bromine in hydrochloric acid.[7] 4-Amino-3-arylfuroxans **4** can be synthesized by the thermal isomerization of 3-aminofuroxans **2** (Scheme 1).

Scheme 1



The oxidation of *amphi*-1-(1-adamantyl)-2-aminoglyoxime (**5a**) with potassium ferricyanide in an excess of ammonia gave 4-(1-adamantyl)-3-aminofuroxan (**6a**) in 37% yield. The starting aminoglyoxime **5a** was synthesized by the reaction of (1-adamantyl)hydroxyiminoacetonitrile oxide (**7**) with an excess of ammonia under reflux in $CHCl_3$. 4-(1-Adamantyl)-3-methylaminofuroxan (**6b**) (in 30% yield) and 4-(1-adamantyl)-3-(dimethylamino)furoxan (**6c**) (in 64% yield) were synthesized in a similar way through the formation of glyoximes **5b**,**c** by the reactions with the use of an excess of methyl- and dimethylamine, respectively (Scheme 2).[8,9]

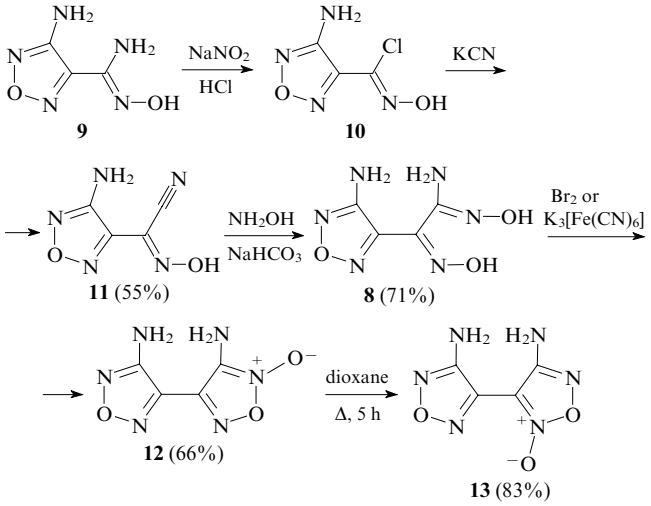
Scheme 2



R^1 = H: R^2 = H (**a**), Me (**b**); R^1 = R^2 = Me (**c**)

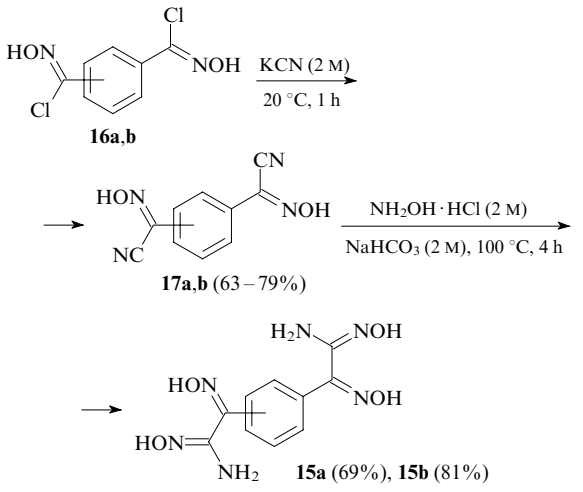
The approach to the synthesis of aminofuroxans by means of oxidation of *amphi*-aminoglyoximes is also described in the work,[10] in which the starting aminoglyoxime **8** contains the aminofurazanyl moiety as the second substituent. Aminoglyoxime **8** was prepared from available (4-aminofurazan-3-yl)hydroxamic acid amide **9**,[11] which was first transformed into the corresponding acid chloride **10** according to a known procedure[12] by the reaction with $NaNO_2$ in hydrochloric acid and then into nitrile **11** by the treatment with KCN. The reaction of compound **11** with hydroxylamine gave the target aminoglyoxime **8**, and the oxidation of the latter with potassium ferricyanide or bromine in hydrochloric acid furnished diaminofurazanylfuroxan **12** containing the amino group in position 3 of the furoxan ring. Isomeric 4-amino derivative **13** was synthesized by the isomerization of diamine **12** in boiling dioxane (Scheme 3).

Scheme 3



Another example of the synthesis of aminofuroxans by the oxidation of aminoglyoximes was described.[13,14] The authors examined the possibility of preparing 1,3- and 1,4-bis(3-aminofuroxan-4-yl)benzenes **14a**,**b**. The starting 1,3- and 1,4-bis[2-amino-1,2-bis(hydroxyimino)ethyl]benzenes (**15a**,**b**) were characterized.[13] These compounds are generated from available[15,16] 1,3- and 1,4-bis[(hydroxyimino)-chloromethyl]benzenes (**16a**,**b**) with KCN in water followed by the binding of hydroxylamine to the nitrile groups in the resulting cyanoximes **17a**,**b** (Scheme 4).

Scheme 4

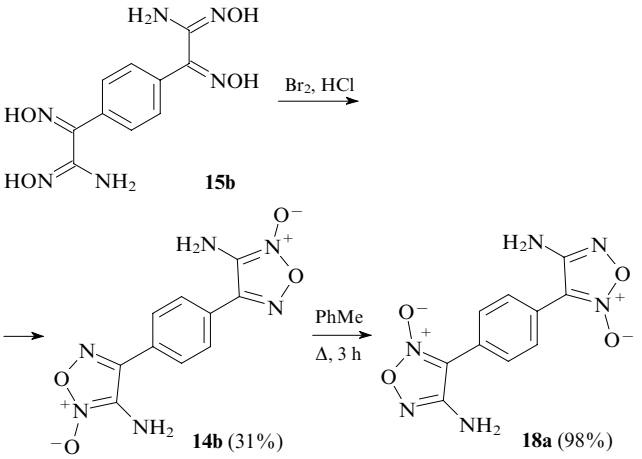


Isomers: 1,3 (**a**), 1,4 (**b**)

With the goal of transforming isomeric 1,3- and 1,4-bis(aminoglyoximes) **15a**,**b** into the corresponding bis(3-aminofuroxan-4-yl)benzenes **14a**,**b**, two oxidizing agents, such as bromine in hydrochloric acid and $K_3[Fe(CN)_6]$ in a

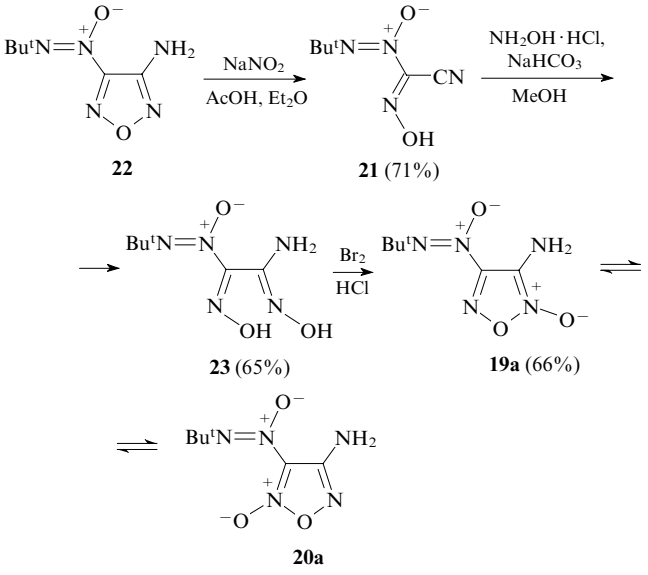
weakly alkaline medium, were investigated.[13, 14] However, satisfactory results were obtained only for 1,4-isomer **15b** using bromine in HCl. 1,4-Bis(3-aminofuroxan-4-yl)benzene (**14b**) was thermally isomerized to thermodynamically more favourable 1,4-bis(4-aminofuroxan-3-yl)benzene (**18a**) (Scheme 5).[14]

Scheme 5



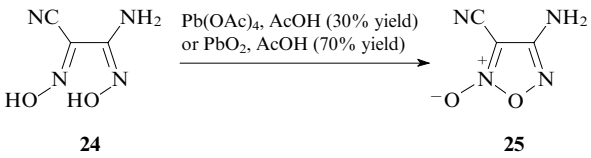
The synthesis of isomeric 3- and 4-aminofuroxans **19a** and **20a** based on the transformation of cyanoxime **21** containing the (*tert*-butyl-NNO-azoxy) group has been described in a recent publication.[17] The starting cyanoxime **21** was prepared by the furazan ring opening in 4-amino-3-*tert*-butyl-NNO-azoxyfurazan **22**[18] with $NaNO_2$ in a mixture of acetic acid and diethyl ether. This reaction resulted in the diazotization of the amino group to form diazonium salt, which is reduced to compound **21** with an excess of $NaNO_2$. The further transformation of the nitrile group into the amidoxime group on treatment with hydroxylamine followed by the oxidation of the resulting glyoxime **23** with bromine in HCl affords 3-aminofuroxan **19a**. An attempt to perform the thermal isomerization of the latter to 4-amino isomer **20a** was not quite successful since the reaction gave an equilibrium mixture of 3- and 4-amino isomers **19a** and **20a** in a ratio of approximately (3–4) : 1 (Scheme 6).

Scheme 6



Among other agents used for the oxidation of aminoglyoximes, let us mention lead tetraacetate and lead(IV) oxide in acetic acid. These reagents were employed to oxidize aminocyanoglyoxime **24**, which is stable only in the complex with AcOH, to 4-amino-3-cyanofuroxan **25**.[19] The best yield of aminofuroxan **25** (70%) was achieved with the use of lead(IV) oxide (Scheme 7).

Scheme 7

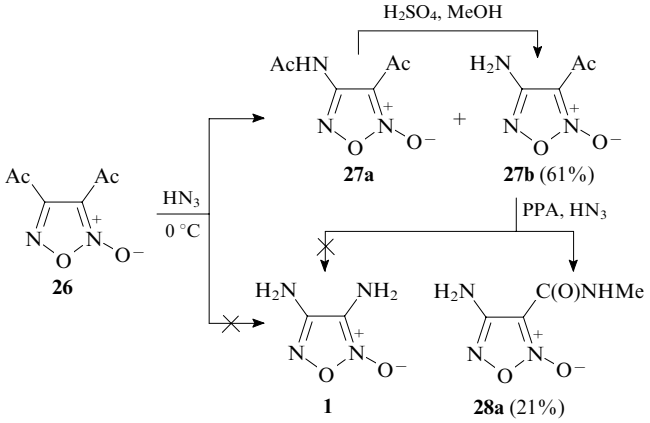


However, aminoglyoximes containing the free amino group and non-aromatic substituents, including 1-amino-2-methyl- and 1,2-diaminoglyoximes, exist mainly in the *anti*(*E*,*E*) form and cannot cyclize to form aminofuroxans by means of the oxidation.[20] Evidently, the *anti* form of these glyoximes is stabilized by a strong hydrogen bond, which hinders the transformation to the *amphi*(*Z*,*E*) form necessary for the cyclization. The synthesis of diaminofuroxan derivatives by the oxidation of glyoximes was successfully performed merely in the case of dialkylaminoglyoximes.[6, 21, 22]

2. Schmidt and Curtius sextet rearrangements involving acetyl- and azidocarbonylfuroxans

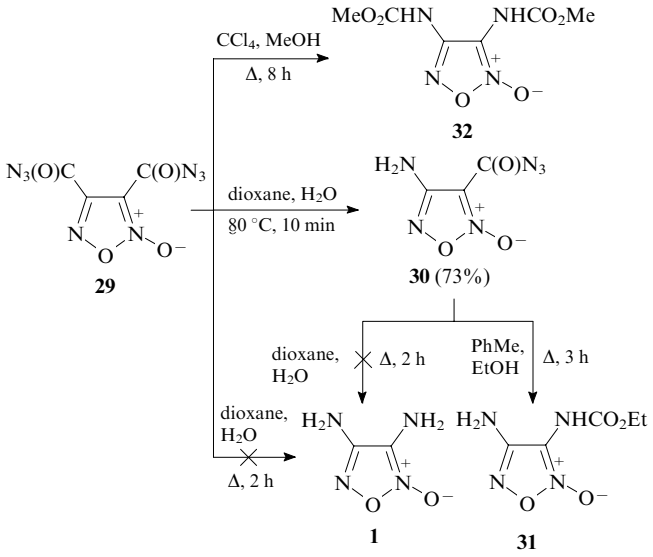
To find a route to 3,4-diaminofuroxan (**1**), in 1995 we developed two new methods for the synthesis of aminofuroxans based on the sextet rearrangements at the nitrogen atom: the Schmidt rearrangement of methyl furoxanyl ketones[23] and the Curtius rearrangement of azidocarbonylfuroxans.[24] It appeared that only one acetyl group of diacetylfuroxan **26** undergoes the Schmidt rearrangement even with the use of a large excess of HN_3 in $CHCl_3$ (or in CH_2Cl_2) in the presence of concentrated H_2SO_4 to form 3-acetyl-4-aminofuroxan (**27b**) through the formation of intermediate 3-acetyl-4-acetylaminofuroxan (**27a**). The 3-acetyl group in compound **27b** undergoes the Schmidt rearrangement in the presence of polyphosphoric acid (PPA) as the catalyst. However, only one possible rearrangement product, 4-aminofuroxan-3-carboxylic acid *N*-methylamide (**28a**), was isolated in low yield instead of the expected diaminofuroxan **1** although the starting amine **27b** was completely consumed (Scheme 8).

Scheme 8



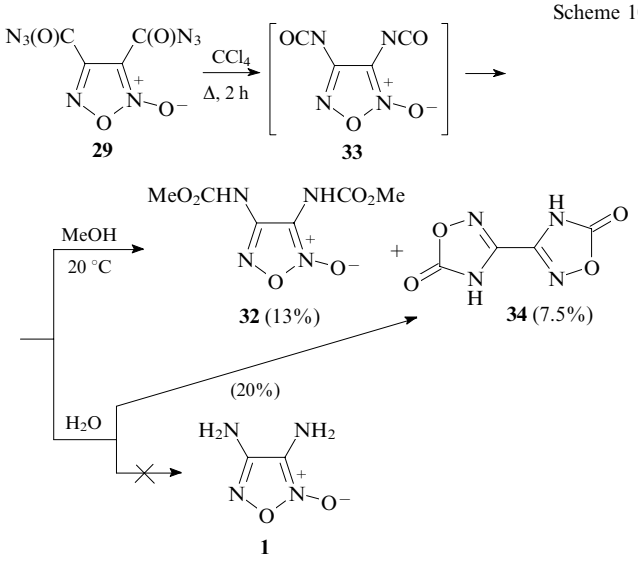
The Curtius rearrangement of 3,4-bis(azidocarbonyl)furoxan (**29**) was performed in a dioxane–water mixture at 80 °C in order to synthesize 3,4-diaminofuroxan (**1**).[24] The reaction was completed in 10 min. However, only one of the two azidocarbonyl groups underwent the rearrangement to give 4-amino-3-azidocarbonylfuroxan (**30**). The second azidocarbonyl group was subjected to the Curtius rearrangement under more drastic conditions by refluxing in a toluene–EtOH mixture for 3 h to form 4-amino-3-ethoxycarbonylaminofuroxan (**31**). The Curtius rearrangement of 3,4-bis(azidocarbonyl)furoxan (**29**) in a CCl_4–MeOH mixture for 8 h furnished 3,4-bis(methoxycarbonylamino)furoxan (**32**). The heating of compound **29** or **30** in a dioxane–water mixture at 100 °C resulted in the complete decomposition of both starting compounds, whereas compound **1** was not formed (Scheme 9).

Scheme 9



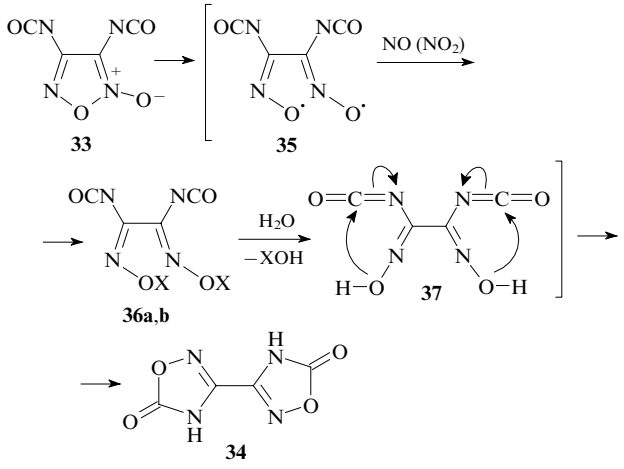
These results indicate that 3,4-diaminofuroxan (**1**) is unstable both in the presence of acids (Schmidt rearrangement) and at high temperatures (Curtius rearrangement). Hence, an attempt was made to synthesize the precursor of diaminofuroxan — 3,4-di(isocyanato)furoxan (**33**) — based on the Curtius rearrangement of 3,4-bis(azidocarbonyl)furoxan (**29**). The reaction was performed at elevated temperature (refluxing in dry CCl_4) followed by the cooling of the reaction mixture. The reaction of compound **33** with water was carried out at room temperature. The evolution of various gases was observed on refluxing. Their nature (N_2O_4, NO, N_2O, CO_2) was determined by the IR spectroscopic study of the reaction in a 0.6 mm CaF_2 cell on a UR-20 infrared spectrometer at 65 °C in the same solvent. The formation of gases is evidently due to the decomposition of diisocyanatofuroxan **33** on heating. The formation of diisocyanate **33** was confirmed by the isolation of 3,4-bis(methoxycarbonylamino)furoxan (**32**) in 13% yield after the treatment of the cooled reaction mixture with methanol. In addition to diurethane **32**, a new compound, 3,3′-bi(1,2,4-oxadiazole)-5,5′(4*H*,4′*H*)-dione (**34**), was isolated in 7.5% yield. The treatment of the reaction mixture with water afforded compound **34** in 20% yield instead of the expected diaminofuroxan **1** (Scheme 10).[25]

Scheme 10



Hypothetical Scheme 11 was proposed[25] to explain the formation of 3,3′-bi(1,2,4-oxadiazole)-5,5′(4*H*,4′*H*)-dione (**34**). It is known[1,2] that the O(1)–N(2) bond is the weakest one in the furoxan ring. On heating, this bond in compound **33** is apparently cleaved to generate biradical **35**. The biradical can react with NO or NO_2, which are eliminated as a result of thermal decomposition of compound **33**, to form esters **36a** or **36b**. When treated with water, these esters can be hydrolyzed to 1,2-diisocyanatoglyoxime **37**, which undergoes cyclization to bicyclic compound **34.** The above results show that 3,4-diaminofuroxan (**1**) cannot be synthesized either at elevated temperature in an acidic medium or under neutral conditions at room temperature.

Scheme 11



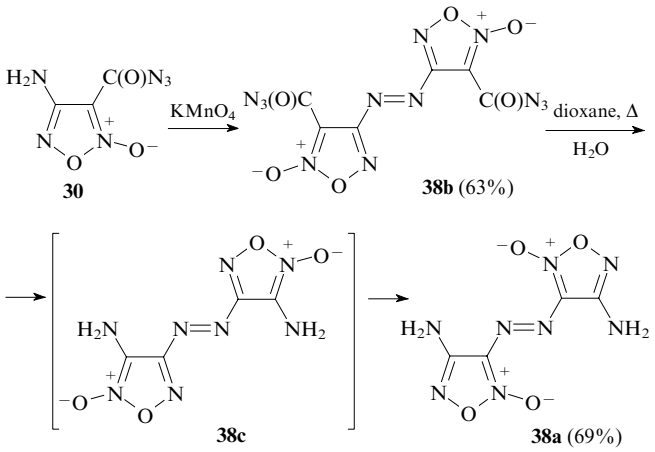
X = NO (**a**), NO_2 (**b**)

The possible factors responsible for low thermal stability of diaminofuroxan **1** were investigated by mathematical and quantum chemistry.[26] In these calculations, the structural isomers of diaminofuroxan were generated, and the most stable forms in the gas phase and in aqueous solution were screened by quantum chemical calculations [DFT B3LYP 6-31G(d) and MP2 6-31G(d) methods]. It was shown that diaminofuroxan **1** is not the thermodynamically most stable compound among the structural isomers. The results of this study suggest that the failure of the synthesis of diaminofuroxan is apparently due to its thermodynamic instability.

3. Synthesis of 4-aminofuroxans based on the transformation of the second substituent in aminofuroxans

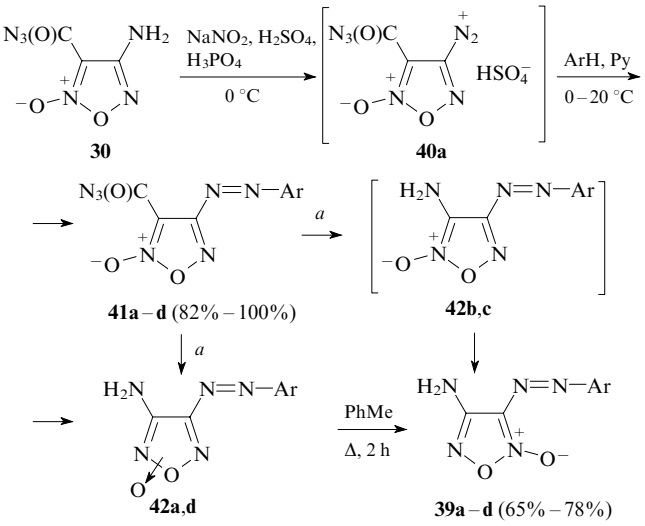
4-Amino-3-azidocarbonylfuroxan (**30**) proved to be a convenient substitute of diaminofuroxan **1**. In this compound, the azidocarbonyl group acts as the latent amino group. After various reactions at the free amino group in compound **30**, the products containing the azidocarbonyl groups were subjected to the Curtius rearrangement to form the second amino group, which can be involved in the same or other reactions. This scheme was used to synthesize 4,4′-diamino-3,3′-azofuroxan (**38a**) through intermediate 3,3′-bis(azidocarbonyl)-4,4′-azofuroxan (**38b**). It should be noted that under the conditions of the Curtius rearrangement, 3,3′-diamino-4,4′-azofuroxan (**38c**) that is formed in the first step undergoes isomerization to thermodynamically more favourable 4,4′-diamino isomer **38a** (Scheme 12).[27]

Scheme 12



A series of 4-amino-3-arylazofuroxans **39a**–**d** was synthesized according to the same scheme. Thus, the diazotization of the amino group in 4-amino-3-azidocarbonylfuroxan (**30**) was followed by the azo coupling of the resulting diazonium salt **40a** with alkoxybenzenes, *m*-xylene and mesitylene.[28] Azo-coupling products **41a**–**d** were subjected to the Curtius rearrangement involving the azidocarbonyl group to form 3-amino-4-azofuroxans **42b**,**c**. Under the reaction conditions, these products were thermally isomerized to 4-amino isomers **39b**,**c**. Under these conditions, compounds **41a**,**d** gave mixtures of 3- and 4-amino isomers **42a**,**d**, which were transformed into amino derivatives **39a**,**d** by refluxing in toluene (Scheme 13).

Scheme 13

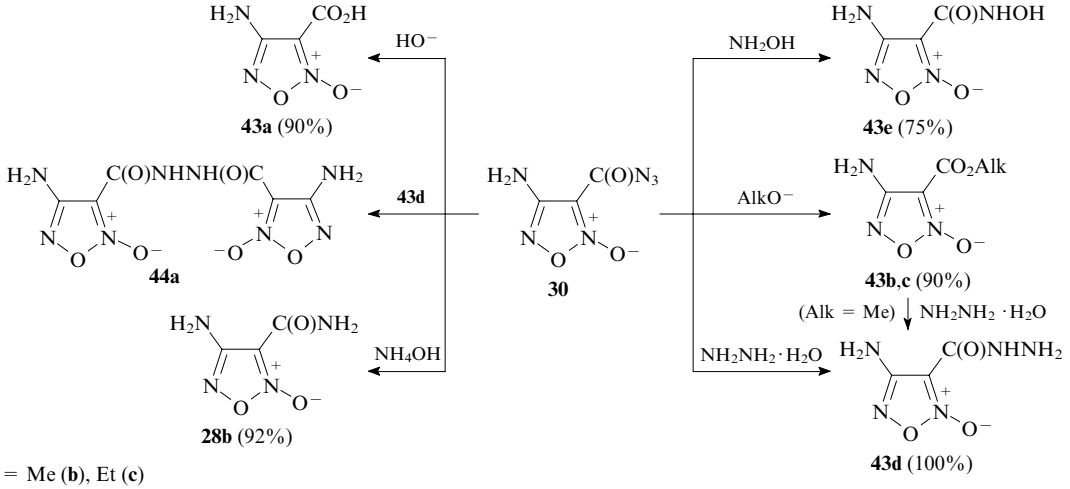


Ar = 4-$MeOC_6H_4$ (**a**), 4-$EtOC_6H_4$ (**b**), 2,4-$Me_2C_6H_3$ (**c**), 2,4,6-$Me_3C_6H_2$ (**d**); (*a*) dioxane, H_2O, 80 °C, 15 min

A series of new 4-aminofuroxans was synthesized by the nucleophilic substitution of the azido group in 4-amino-3-azidocarbonylfuroxan (**30**) using various N- and O-nucleophiles to form 4-amino-3-furoxancarboxylic acid (**43a**) and its derivatives: alkyl esters **43b**,**c**, amide **28b**, hydrazide **43d**, hydroxylamino derivative **43e** and 1,2-bis(4-aminofuroxan-3-ylcarbonyl)hydrazine (**44a**).[29] Besides, hydrazide **43d** was synthesized by the reaction of ester **43b** with hydrazine hydrate (Scheme 14).

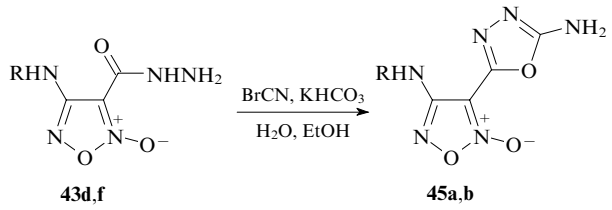
4-Aminofuroxan-3-carboxylic acid hydrazide (**43d**) and its *N*-acetyl derivative **43f** proved to be convenient starting compounds for the synthesis of (5-amino-1,3,4-oxadiazol-2-yl)furoxans **45a**,**b**. For this purpose, the heterocyclization of the hydrazides was perfromed using bromocyane in aqueous ethanol in the presence of $KHCO_3$ (Scheme 15).[30]

Scheme 14



43: Alk = Me (**b**), Et (**c**)

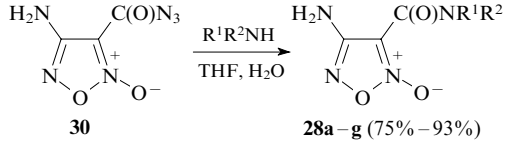
Scheme 15



R = H (**43d**; **45a**, 71%), Ac (**43f**; **45b**, 92%)

Amides **28a–g** were synthesized by the nucleophilic substitution of the azido group in compound **30** with various aliphatic and alicyclic amines (Scheme 16).[31]

Scheme 16



NR^1R^2 = NHMe (**a**), NH_2 (**b**), $NHPr^n$ (**c**), $NHBu^n$ (**d**), $NH(CH_2)_2OH$ (**e**), NHCy (**f**), $N(CH_2)_5$ (**g**); Cy is cyclohexyl

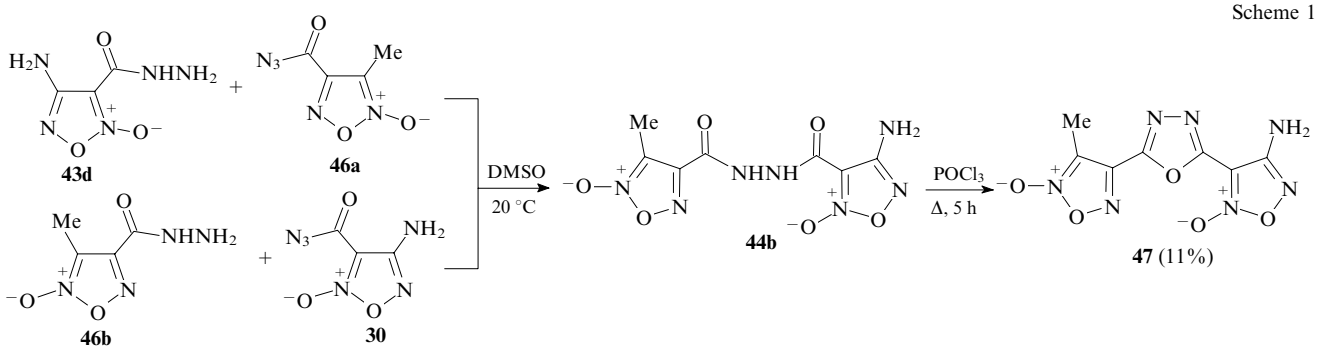
The acylation of hydrazide **43d** with 3-methylfuroxan-4-carboxylic acid azide (**46a**) (or of hydrazide **46b** with azide **30**) gave 1-(4-aminofuroxan-3-ylcarbonyl)-2-(3-methylfuroxan-4-ylcarbonyl)hydrazine (**44b**). The latter was subjected to the dehydration with $POCl_3$ on heating. Unfortunately, the final 2,5-bis(furoxanyl)-1,3,4-oxadiazole **47** was obtained in low (11%) yield because of the presence of the amino group in the starting compound **44b**. Under these conditions, symmetric hydrazide **44a** decomposed. The use of other dehydrating reagents also did not lead to a success (Scheme 17).[30]

In addition to the reactions involving the azidocarbonyl group, new functional derivatives of 4-aminofuroxans were synthesized by various transformations of the cyano group in 3-cyano-4-aminofuroxan (**25**). The reactivity of the CN group in this compound is high due to the effect of the electron-withdrawing furoxan ring.[22] Thus, aminocyanofuroxan **25** adds hydroxylamine and hydrazine at the cyano group to form amidoxime **48a** and amidrazone **48b**, respectively, and the reaction of amidoxime **48a** with $HC(OEt)_3$ furnishes a mixture of isomeric 4-amino-3-(1,2,4-oxadiazol-3-yl)furoxan (**49a**) and bicyclic system **49b** in a 2 : 1 ratio.[19] The reaction of compound **25** with sodium azide in the presence of $ZnBr_2$ affords 4-amino-3-(tetrazol-5-yl)furoxan **49c** (Scheme 18).[32]

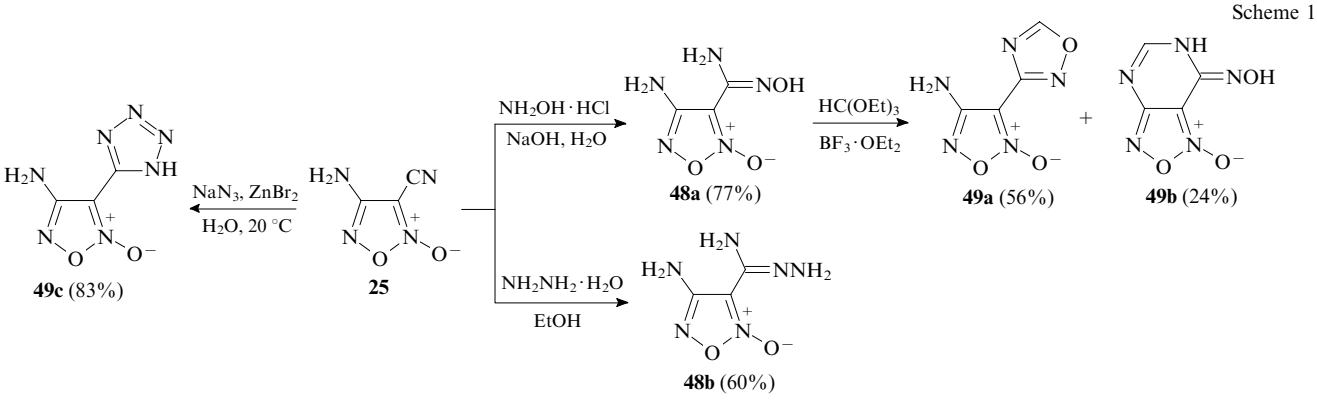
4-Aminofuroxans **27b**,**c** and **43c** containing the acetyl, benzoyl or ethoxycarbonyl group in position 3 are easily reduced with $NaBH_4$ in ethanol to give 4-amino-3-[α-hydroxyalkyl(benzyl)]furoxans **50a–c**. The replacement of the hydroxy group in compounds **50a**,**b** by the chlorine atom under the action of thionyl chloride in pyridine gave chloroalkyl derivatives **51a**,**b**, in which the halogen atom is susceptible to nucleophilic substitution. In particular, the chlorine atom in compound **51b** was successfully replaced by the azide group to form 4-amino-3-(1-azidoethyl)furoxan **52** (Scheme 19).[33]

In addition to the reduction, 3-acetyl-4-aminofuroxan **27b** was brominated at the acetyl group in acetic acid resulting in the formation of 4-amino-3-bromoacetyl derivative **53**.[34] The bromine atom in the latter compound was easily replaced under the action of S-nucleophiles, such as thiourea and heterocyclic thiolates (Scheme 20).[35]

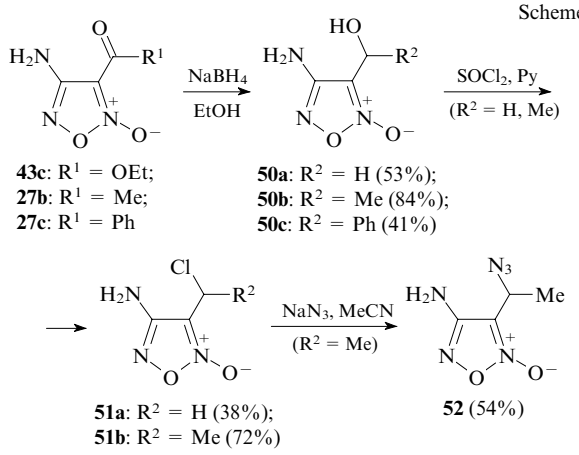
Scheme 17



Scheme 18



Scheme 19



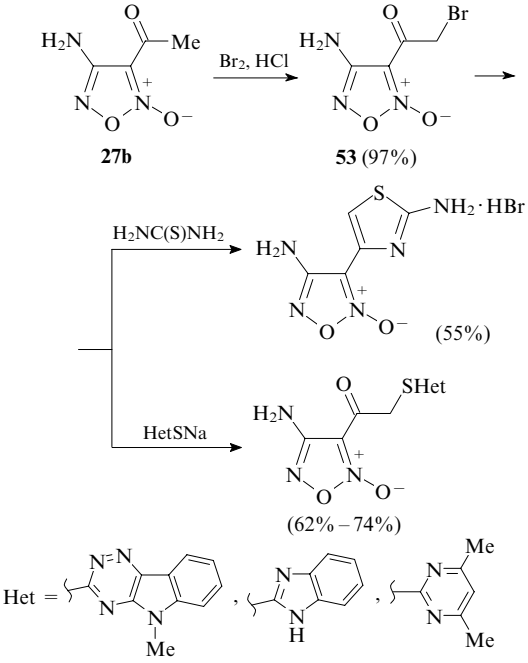
43c: R^1 = OEt;
27b: R^1 = Me;
27c: R^1 = Ph

50a: R^2 = H (53%);
50b: R^2 = Me (84%);
50c: R^2 = Ph (41%)

51a: R^2 = H (38%);
51b: R^2 = Me (72%)

52 (54%)

Scheme 20



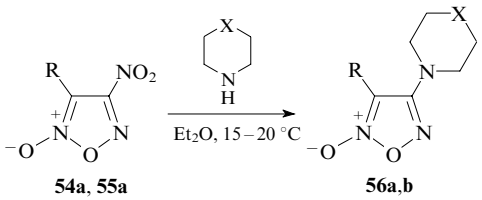
27b

53 (97%)

4. Synthesis of aminofuroxans by nucleophilic substitution or reduction of the nitro group in nitrofuroxans

Some aminofuroxans can be easily synthesized by the nucleophilic substitution of nitro groups in nitrofuroxan derivatives. In particular, the nitro group in 3-methyl-4-nitrofuroxan (**54a**) and 4-nitro-3-phenylfuroxan (**55a**) is replaced under mild conditions by secondary cyclic amines to form aminofuroxans **56a**,**b** (Scheme 21).[36–38]

Scheme 21



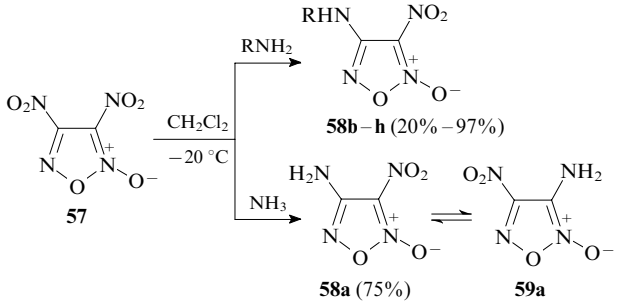
54a, **55a**

56a,**b**

R = Me (**54a**, **56a**), Ph (**55a**, **56b**); X is absent (**56a**, 75%), NMe (**56b**, 64%)

3-Nitrofuroxans are not involved in the reactions with amines accompanied by the replacement of the nitro group; however, these compounds react with stronger nucleophiles, for example, with alkali metal alkoxides resulting in the replacement by the alkoxy group.[6,39,40] The different behaviour of the nitro groups in positions 3 and 4 of the furoxan ring toward nucleophilic agents is associated with the electronic structure of furoxan. The CNDO/2 quantum chemical calculations for dinitrofuroxan **57** showed that the charge distribution among the carbon atoms of this compound is non-uniform. Thus, the C(3) atom is negatively charged, whereas the C(4) atom bears a positive charge.[41] The nitro group in position 4 of the ring in dinitrofuroxan **57** is replaced by the amino or alkylamino group in the reaction with ammonia or alkylamines in CH_2Cl_2 already at −20 °C to form 4-amino(alkylamino)-3-nitrofuroxans **58a**–**h** (Scheme 22).[41,42] 4-Amino-3-nitrofuroxan (**58a**) proved to be thermally unstable in $CDCl_3$ in a ampoule placed in an NMR spectrometer (28 °C), and it was already transformed into a mixture of 4- (**58a**) and 3-amino isomers (**59a**) in a ratio of 7 : 3 within 2 h.[39]

Scheme 22



57

58b–**h** (20%–97%)

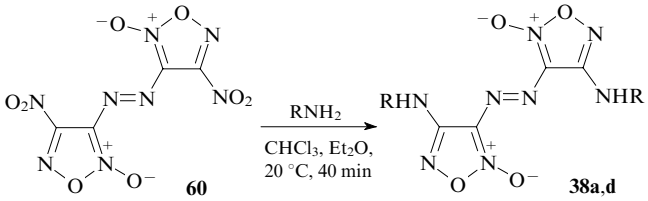
58a (75%)

59a

58: R = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**), Bn (**e**), Ph (**f**), CH_2CH_2OH (**g**), CH_2CH_2CN (**h**)

The 4-nitro groups in 4,4′-dinitro-3,3′-azofuroxan (**60**) are easily replaced by amino or methylamino groups to give 4,4′-diamino-3,3′-azofuroxan (**38a**) and its *N*,*N*′-dimethyl analogue **38d** (Scheme 23).[43]

Scheme 23



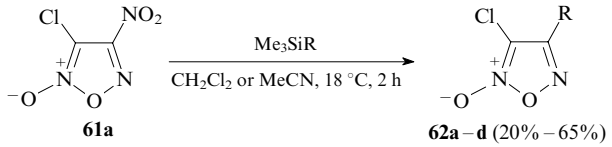
60

38a,**d**

R = H (**a**, 71%), Me (**d**, 75%)

A method based on the use of dialkyl(trimethylsilyl)-amines as nucleophiles was developed for the selective replacement of the nitro group (rather than the more active Cl atom) in 3-chloro-4-nitrofuroxan (**61a**) by the dialkyl-

Scheme 24



61a

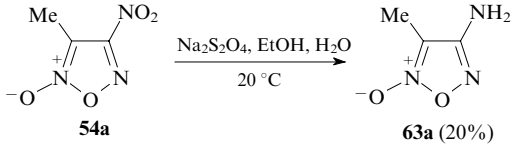
62a–**d** (20%–65%)

62: R = NMe_2 (**a**), NEt_2 (**b**), $N(CH_2)_5$ (**c**), $N(CH_2CH_2)_2O$ (**d**)

amino group to form 4-dialkylamino-3-chlorofuroxans **62a–d** (Scheme 24).[44, 45]

Several examples of the synthesis of aminofuroxans by the reduction of the nitro group in nitrofuroxans were documented. For instance, the treatment of 3-methyl-4-nitrofuroxan (**54a**) with $Na_2S_2O_4$ in an aqueous ethanol led to its reduction to 4-amino-3-methylfuroxan (**63a**) (Scheme 25).[46]

Scheme 25



54a **63a** (20%)

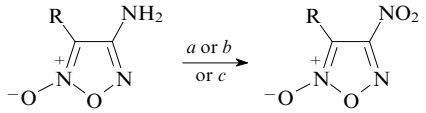
III. Reactivity of aminofuroxans

Aminofuroxans, being analogues of aromatic amines, can participate in the reactions typical of aromatic amines. However, due to a very low basicity of these substrates,[46, 47] most of the reactions proceed under more drastic conditions. Thus, the oxidation of the majority of aminofuroxans to nitro derivatives requires the use of concentrated H_2O_2 in a mixture with concentrated H_2SO_4. The diazotization of aminofuroxans takes place only in a strongly acidic medium. However, the N–N unit is retained in the reactions of the resulting diazonium salts (azo coupling, the formation of triazenes). The replacement of the diazonium moiety by the nitro group in two furoxanyldiazonium salts was recently documented. Amino groups in aminofuroxans are susceptible to acylation, and the resulting derivatives can undergo azole–azole rearrangements. The conditions of the Mannich reaction of aminofuroxans with formaldehyde and trinitroethanol giving methylenebis(aminofuroxans) and trinitroethylaminofuroxans, respectively, were found, and the amino groups in the Mannich bases were nitrated to form the corresponding nitramines. The nitration of the amino group in 3- and 4-aminofuroxans and the reduction of aminofuroxans to aminofurazans were described.

1. Oxidation of aminofuroxans to nitro-, azo- and azoxyfuroxans

The study[48] of isomeric 4(3)-amino-3(4)-phenylfuroxans **4a** and **2a** showed that only 4-amino isomer **4a** can be oxidized to 4-nitro-3-phenylfuroxan (**55a**). The reaction was performed with the use of trifluoroperoxyacetic acid in CH_2Cl_2 as the oxidant. This reagent was also employed to oxidize 3-acetyl-4-aminofuroxan (**27b**) and 4-amino-3-bromoacetylfuroxan (**53**) to the corresponding 4-nitrofuroxans **64a**,**b**.[23, 34] However, more drastic conditions (a mixture of concentrated H_2O_2 and sulfuric acid) are required for the oxidation of other aminofuroxans (compounds **28b**, **30**, **43c** and **50a**,**b**).[24, 32, 48, 49] These approaches were employed to synthesize a series of 4-nitrofuroxans **64c–h** containing various substituents at the C(3) atom. It should be noted that the 4-amino group in 4-amino-3-hydroxyalkylfuroxans **50a**,**b** can be oxidized to the nitro group with peroxides to form the corresponding nitro derivatives **64f**,**g**, in which the hydroxyalkyl moiety remains intact (Scheme 26).[33]

Scheme 26



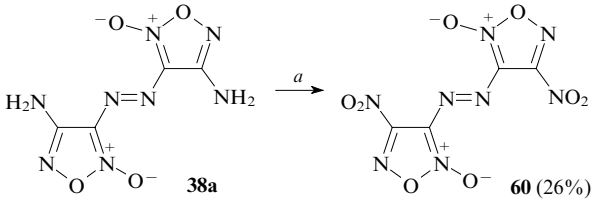
4a, **27b**, **28b**, **30**, **43c**, **49c**, **50a**,**b**, **53** **55a**, **64a–h**

(*a*) CF_3CO_3H, CH_2Cl_2, 20–45 °C; (*b*) 80%–90% H_2O_2, H_2SO_4, 20 °C; (*c*) 50% H_2O_2, H_2SO_4, Na_2WO_4

Substrate	R	Conditions	Product	Yield (%)
4a	Ph	*a*	**55a**	50
27b	Ac	*a*	**64a**	55
53	$C(O)CH_2Br$	*a*	**64b**	48
28b	$C(O)NH_2$	*b*	**64c**	46
30	$C(O)N_3$	*b*	**64d**	48
43c	CO_2Et	*b*	**64e**	75
50a	CH_2OH	*b*	**64f**	81
50b	CH(OH)Me	*b*	**64g**	41
49c	tetrazol-5-yl	*c*	**64h**	45

The oxidation of 4-amino groups in 4,4′-diamino-3,3′-azofuroxan (**38a**) furnished 4,4′-dinitro-3,3′-azofuroxan (**60**), which is one of the most powerful explosives known to date.[27, 50–52] The oxidation of the amino groups in diamine **38a** required very drastic conditions (85% H_2O_2 in concentrated H_2SO_4 in the presence of Na_2WO_4) because of the strong electron-withdrawing effect of the azofuroxanyl moiety (Scheme 27).

Scheme 27



38a **60** (26%)

(*a*) 85% H_2O_2, Na_2WO_4, 96% H_2SO_4, 30–35 °C, 1.5 h

The detonation rate of compound **60** at a density of 1.97 g cm^{-3} was experimentally determined. This value extrapolated to the density of a single crystal (2.002 g cm^{-3} according to the X-ray diffraction data) reaches 10.0 km s^{-1} (Table 1).

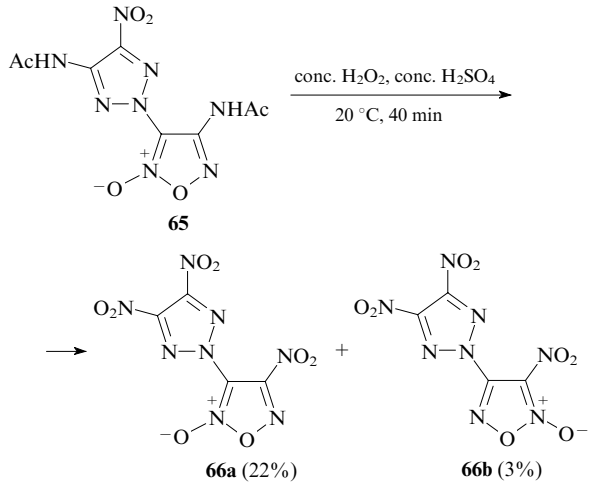
Not only aminofuroxans containing free amino groups but also acetyl derivatives can be oxidized. Thus, the

Table 1. Comparative characteristics of compound **60**, octogen and hexanitrobenzene.[27]

Compound	Density /g cm^{-3}	Detonation rate /km s^{-1}	Heat of explosion /kal g^{-1}	Detonation pressure /GPa	Misile capacity (%)
60	1.97	9.70	1788	47	111
Octogen	1.9	9.15	1340	40	100
Hexanitrobenzene	2.0	9.45	1640	44	105.5

acetamide group in 4-acetylamino-3-(5-acetylamino-4-nitro-1,2,3-triazol-2-yl)furoxan (**65**) is oxidized to the nitro group with a mixture of concentrated H_2O_2 and concentrated H_2SO_4 at 20–22 °C. The acetylamino group bound to the triazole ring is simultaneously oxidized in this reaction, resulting in the formation of a mixture of isomeric trinitro derivatives **66a**,**b** in a ratio of ~7 : 1 (Scheme 28).[43]

Scheme 28

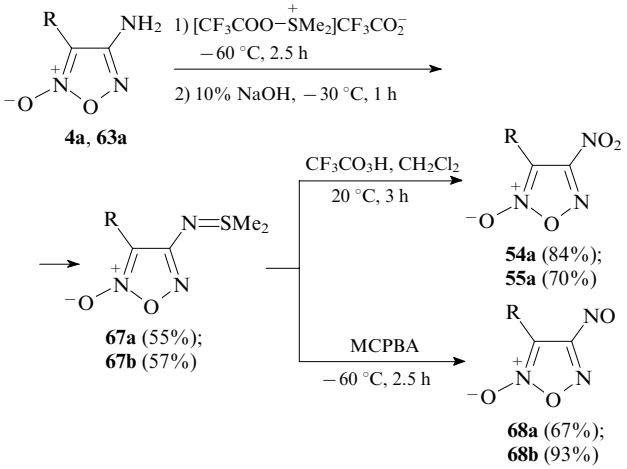


65

66a (22%) **66b** (3%)

In addition to the direct oxidation of 4-amino- or 4-acetylaminofuroxans, the oxidative transformation of the amino group was performed according to another approach. Thus, the amino group in compounds **63a** and **4a** was initially transformed into the sulfylimino group to form sulfylimino derivatives **67a**,**b**. The latter were oxidized by peroxide oxidizing agents under mild conditions. It should be noted that the reactions with trifluoroperoxyacetic acid gave 4-nitrofuroxans **54a** and **55a**, whereas the oxidation with *m*-chloroperoxybenzoic acid (MCPBA) on cooling produced the corresponding 4-nitroso derivatives **68a**,**b** (Scheme 29).[53]

Scheme 29



4a, **63a**

67a (55%); **67b** (57%)

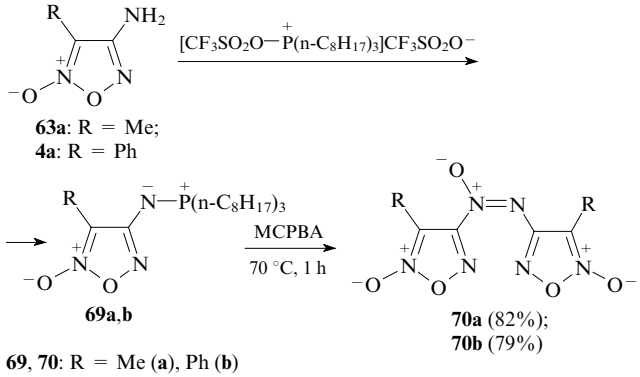
54a (84%); **55a** (70%)

68a (67%); **68b** (93%)

R = Me (**63**, **54a**), Ph (**4a**, **55a**); **67**, **68**: R = Me (**a**), Ph (**b**)

The oxidative transformation of phosphiniminofuroxans **69a**,**b**, which were synthesized by the reaction of 4-amino-3-methyl(phenyl)furoxans **63a** and **4a** with trioctylphosphine bis(trifluoromethylsulfonate), was studied. Azoxyfuroxans **70a**,**b** were synthesized for the first time by the oxidation of compounds **69a**,**b** with *m*-chloroperoxybenzoic acid under rather mild conditions (Scheme 30).[54]

Scheme 30



63a: R = Me;
4a: R = Ph

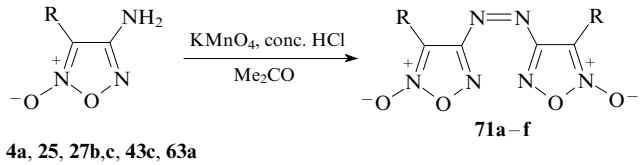
69a,**b**

70a (82%); **70b** (79%)

69, **70**: R = Me (**a**), Ph (**b**)

Both 4- and 3-aminofuroxans undergo the oxidative condensation to form the corresponding azofuroxans **71** and **72**. This reaction proceeds with the use of $KMnO_4$ in a mixture of hydrochloric acid and aprotic organic solvents miscible with water (for example, acetone). The final outcome depends only slightly on the electronic effect of the second substituent in the furoxan ring (Scheme 31).[27, 29, 31, 55] Besides, 4,4′-diphenyl-3,3′-azofuroxan (**72a**) is generated by the oxidation of amine **2a** with dibromoisocyanurate (DBI) (95% yield).[56]

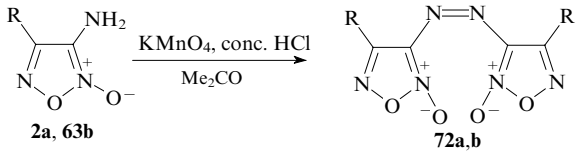
Scheme 31



71a–**f**

4a, **25**, **27b**,**c**, **43c**, **63a**

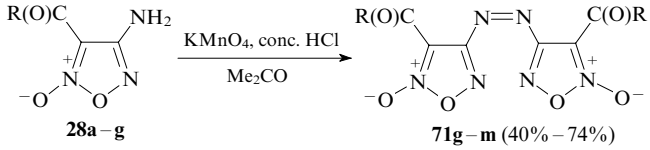
R = Ph (**4a**, **71a**), Me (**63a**, **71b**), CO_2Et (**43c**, **71c**), Ac (**27b**, **71d**), Bz (**27c**, **71e**), CN (**25**, **71f**)



2a, **63b**

72a,**b**

R = Me (**63b**, **72a**), Ph (**2a**, **72b**)



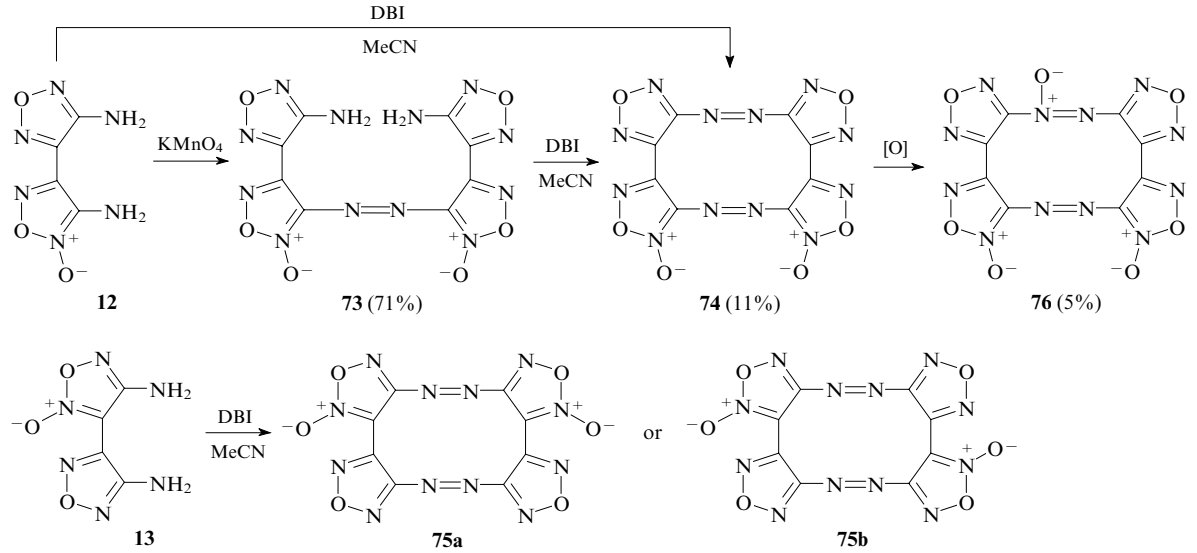
28a–**g**

71g–**m** (40%–74%)

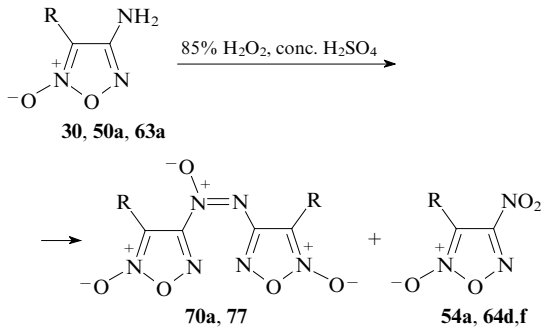
71: R = NHMe (**g**), NH_2 (**h**), $NHPr^n$ (**i**), $NHBu^n$ (**j**), $NH(CH_2)_2OH$ (**k**), NHCy (**e**), $N(CH_2)_5$ (**m**)

The oxidation of diaminofurazanylfuroxan **12** containing the amino group at the C(3) atom performed under similar conditions proceeds with high regioselectivity to give azo derivative **73** as a result of the oxidation of only the amino group bound to the furoxan ring. The oxidation of diamine **12** (like azo derivative **73**) with the use of dibromoisocyanurate as the oxidizing agent furnished macrocycle **74**. The reactions of isomeric diamine **13** containing the

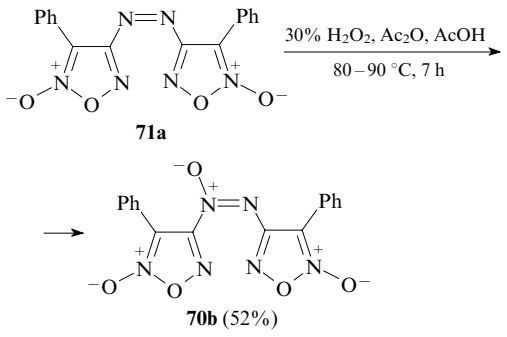
Scheme 32



Scheme 33



Starting amine	R	Bis-product	Yield (%)	Nitro compound	Yield (%)
63a	Me	**70a**	33	**54a**	12
30	$C(O)N_3$	–	–	**64d**	65
50a	CH_2OH	**77**	27	**64f**	16



amino group in position 4 of the furoxan ring with $KMnO_4$ in water or with its mixtures with various organic solvents did not generate azo derivatives. The oxidation of diamine **13** with DBI in acetonitrile gave macrocyclic compound **75** (in 12% yield). However, it was impossible to assign one of the two probable isomeric structures (the product of either head-to-head or head-to-tail cyclization of two starting molecules **75a** or **75b**, respectively) to macrocyclic compound **75** based on spectroscopic characteristics. Attempts to oxidize azo groups to azoxy groups in macrocycles **74** and **75** led to a success only in the case of macrocycle **74**, only the azo group bound to the furazan rings being oxidized to produce macrocycle **76**. Of the studied oxidizing agents, only 85% H_2O_2 in 20% oleum in the presence of $Na_2WO_4 \cdot 2\,H_2O$ appeared to be suitable for the oxidation of macrocycle **74** (Scheme 32).[10]

The direct oxidation of 4-aminofuroxans **30**, **50a** and **63a** to azoxy derivatives with peroxide oxidizing agent was successful only for aminofuroxans containing electron-donating substituents (**50a** and **63a**). These reactions afforded compounds **77** and **70a** along with nitrofuroxans **54a** and **64d**. The ratio of azoxy to nitro derivatives depends on the character of the substituent at the carbon atom C(3) of the furoxan ring. The independent synthesis of azoxy derivative **70b** by the oxidation of azofuroxan appeared to be possible only for 3,3′-diphenyl-4,4′-azofuroxan (**71a**) (Scheme 33).[55]

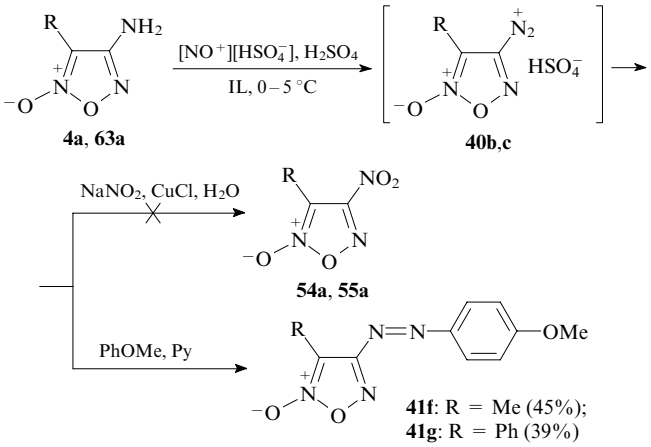
2. Diazotization of aminofuroxans and reactions of furoxanyldiazonium salts

4-Aminofuroxans belong to weakly basic amines.[46, 47, 57] Earlier,[58] the diazotization of aminofuroxans was performed with the use of sodium nitrite in a mixture of concentrated H_2SO_4 and H_3PO_4. It was found that the reactions of diazonium salts **40** proceed with the retention of the N – N group (azo coupling, the formation of triazenes and azides; see, in particular, Scheme 13 and the review [6]). An attempt to perform the Sandmeyer reaction of diazonium salts **40** with neutral solutions of halides or alkali metal nitrites in the presence of copper salts led to their complete decomposition with the ring opening, which is apparently associated with instability of 1,2,5-oxadiazole radicals that are formed after the elimination of the nitrogen molecule.

The diazotization of aminofuroxans **63a** and **4a** followed by the azo coupling of diazonium salts **40b**,**c** with anisole to form azo derivatives **41f**,**g** can be accomplished with the use of so-called acidic ionic liquids instead of mixtures of

inorganic acids and the employment of nitrosylsulfuric acid as the nitrosating agent. However, an attempt to perform the Sandmeyer reaction under strongly acidic or weakly acidic conditions by pouring the reaction mixture to an aqueous solution of an excess of $NaNO_2$ in the presence of CuCl resulted in the complete decomposition of diazonium salts **40b**,**c** without the formation of any products detected by TLC (Scheme 34).[59]

Scheme 34



R = Me (**63a**, **40b**, **54a**); Ph (**4a**, **40c**, **55a**);

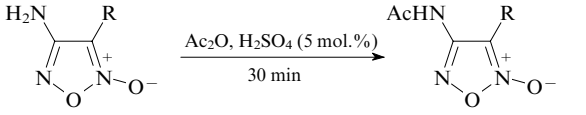
IL = HSO_4^- ([bmim][HSO_4]), $CF_3SO_3^-$ ([bmpyrr][CF_3SO_3])

The diazonium ion in furoxanyldiazonium salts **40b**,**c** was replaced by the nitro group *in situ* (at the instant of the formation) by performing the diazotization of aminofuroxans in a water–DMF mixture in a weakly acidic medium (pH 4–5) in the presence of a large excess of $NaNO_2$ in the reaction mixture at 0–2 °C.[59] Unfortunately, only aminofuroxans **63a** and **4a** containing Me and Ph substituents were introduced into this reaction. 4-Aminofuroxans containing electron-withdrawing substituents [CO_2Et, $C(O)N_3$, $C(O)NH_2$] decomposed under the reaction conditions. The reaction of furoxan **63a** afforded target compound **54a** along with 1,3-bis(3-methylfuroxan-4-yl)triaz-1-ene (**78**) as the by-product. It is known that triazenes are generated by the reactions of diazonium salts that are formed with unconsumed amine. Hence, the isolation of compound **78** from the reaction mixture is an additional evidence for the formation of diazonium salts **40b**,**c** under weakly acidic conditions. It was suggested that the reaction proceeds *via* the S_NAr mechanism through the formation of intermediates **79f**,**g** and anionic Meisenheimer-type σ-complexes **80f**,**g**, although it is most likely that these products can be represented as mesoionic structures **81f**,**g** (Scheme 35).

3. Acylation of aminofuroxans and azole–azole rearrangements of acetylamino(ureido, thioureido, amidino) derivatives of furoxan

Various 4-aminofuroxan derivatives (4-acetylamino-, 4-ureido-, 4-thioureido- and 4-amidinofuroxans) were synthesized in order to study azole–azole rearrangements.[60,61] The acetylation of 4-aminofuroxans was performed using an excess of acetic anhydride at 20 °C in the presence of a catalytic amount of sulfuric acid, which is associated with low basicity of aminofuroxans. Under these conditions, *N*-acetyl derivatives **82a**–**f** are produced in high yields, and 4-amino-3-(arylazo)furoxans **39a**–**d** are easily acetylated to form the corresponding *N*-acetyl derivatives **82g**–**j** also in high yields[28] (Scheme 36).

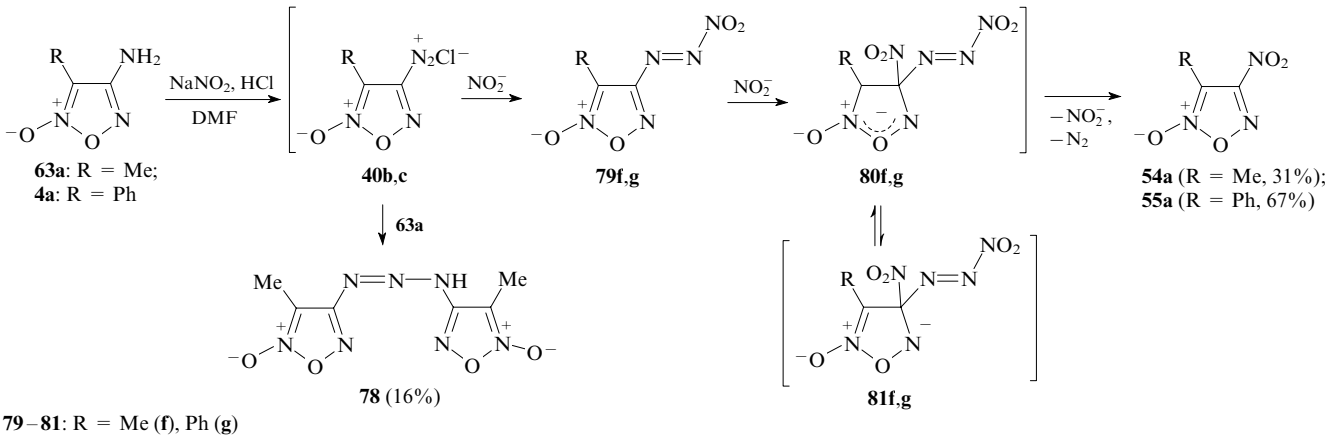
Scheme 36



R = Me (**63a**, **82a**), Ph (**4a**, **82b**), Ac (**27b**, **82c**), CO_2Me (**43b**, **82d**), Bz (**27c**, **82e**), $C(O)NH_2$ (**28b**, **82f**), $X_nC_6H_{5-n}N{=}N$ [X = 4-OMe (**39a**, **82g**), 4-OEt (**39b**, **82h**), 2,4-Me_2 (**39c**, **82i**), 2,4,6-Me_3 (**39d**, **82j**)]

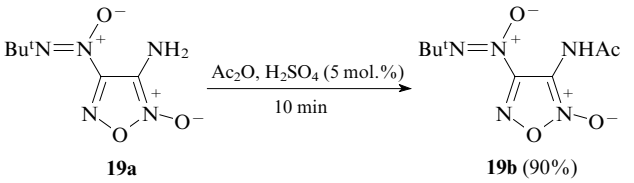
The acetylation of 3-aminofuroxan was performed under similar conditions. This reaction was described only for 3-amino-4-(*tert*-butyl-NNO-azoxy)furoxan (**19a**). The yield of acetylamino derivative **19b** was 90% (Scheme 37).[17]

Scheme 35



79–**81**: R = Me (**f**), Ph (**g**)

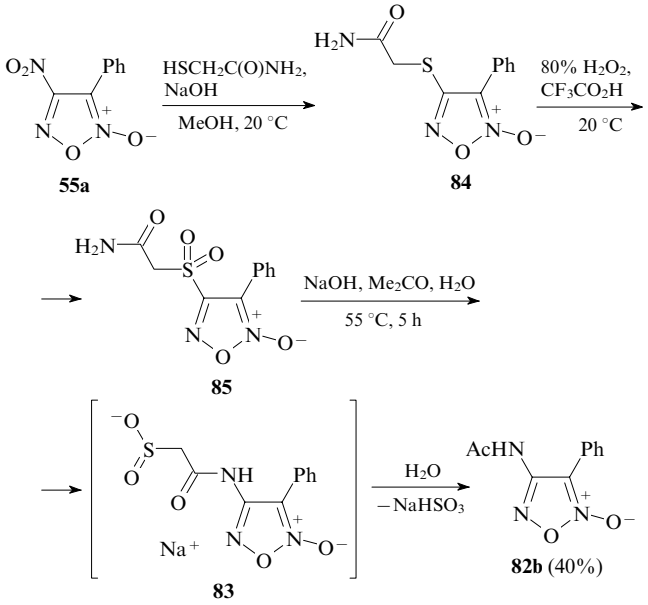
Scheme 37



19a **19b** (90%)

The unusual approach to the synthesis of 4-acetylamino-3-phenylfuroxan (**82b**) was described.[62] This acetamide was generated by the hydrolysis of Smiles rearrangement product **83**. The latter was prepared by the nucleophilic displacement of the nitro group in 4-nitro-3-phenylfuroxan (**55a**) by the carbomoylmethylsulfonyl group followed by the oxidation of compound **84** to sulfone **85** and the reaction of the latter with 50% NaOH in acetone, resulting in the intramolecular nucleophilic *ipso*-substitution (Scheme 38).

Scheme 38

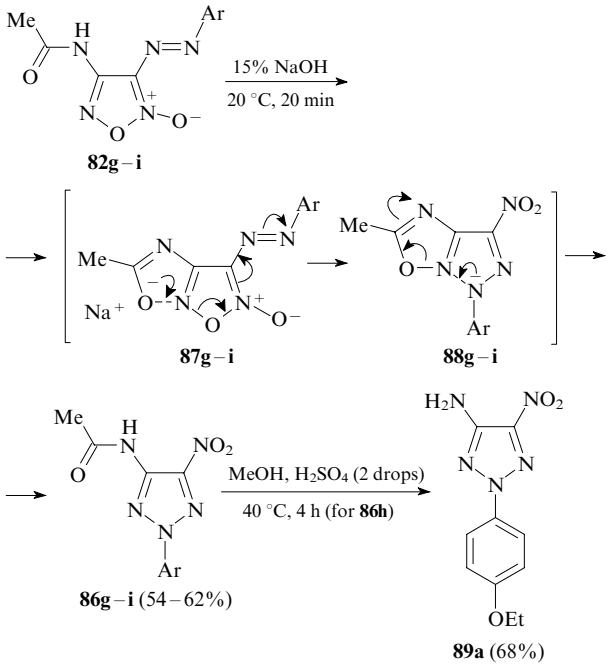


55a **84** **85** **83** **82b** (40%)

The treatment of 4-(*N*-acetylamino)-3-arylazo derivatives of furoxan **82g–i** with dilute aqueous alkali gave 4-acetylamino-2-aryl-5-nitro-2*H*-1,2,3-triazoles **86g–i**. The formation of these compounds can be represented by two successive (cascade) rearrangements, resulting in the transformation of one five-membered nitrogen-containing heterocycle into another one (so-called azole–azole rearrangements). The first rearrangement proceeds through intermediates **87g–i** to give 1,2,4-oxadiazole derivatives **88g–i**. In this step, the 'latent' nitro group of the furoxan ring is released as the 1-nitroalkyl moiety. 1,2,4-Oxadiazole derivatives **88g–i** undergo *in situ* the second rearrangement involving the azo group to form 4-acetylamino-2-aryl-5-nitro-1,2,3-triazoles **86g–i**, in which the nitro group is bound directly to the triazole ring. 4-Amino-2-aryl-5-nitrotriazole **89a** was obtained after the hydrolytic removal of the acetyl protecting group from rearrangement product **86h** (Scheme 39).[28]

These rearrangements are relatively common for azoles and, in some cases, provide convenient routes to various heterocycles, which are difficult to prepare by other procedures.[63–67] However, such reactions were described mainly for benzannulated derivatives of furoxans (Boulton–Katritzky rearrangement).[2,63] Earlier, the rearrangement of monocyclic derivatives of furoxan has been performed only for benzoylfuroxan oxime, which gave 3-(1-nitroethyl)-4-phenylfurazan.[67] Hence, we examined the possibility of performing azole–azole rearrangements for other acylated aminofuroxans.

Scheme 39



82g–i **87g–i** **88g–i** **86g–i** (54–62%) **89a** (68%)

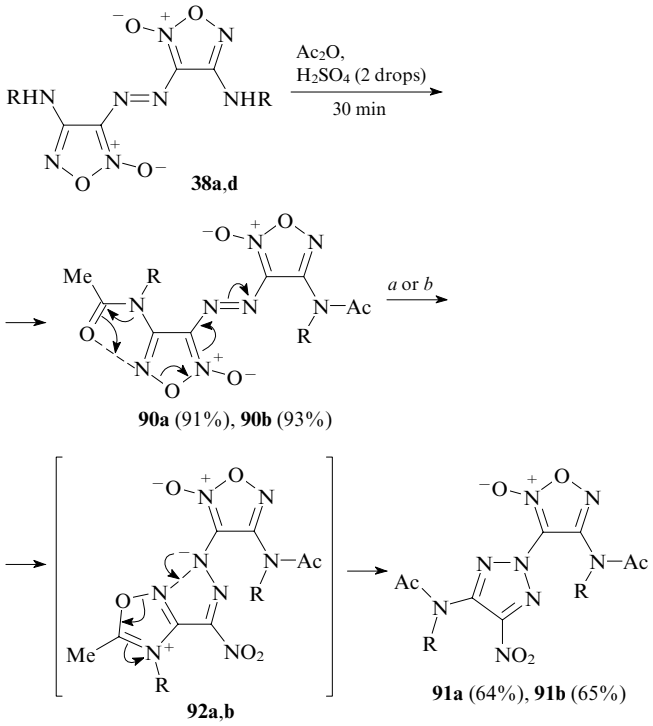
82, **86–88**: Ar = 4-MeOC$_6$H$_4$ (**g**), 4-EtOC$_6$H$_4$ (**h**), 2,4-Me$_2$C$_6$H$_3$ (**i**)

Of aminofuroxan derivatives, 4,4′-diamino(di-*N*-methylamino)-3,3′-azofuroxans **38a**,**d** were acetylated with Ac_2O in the presence of H_2SO_4. The resulting 4,4′-bis(acetylamino)-3,3′-azofuroxan (**90a**) and its *N*,*N*′-dimethyl analogue **90b** were also subjected to cascade rearrangements. However, they proceeded thermally on heating in acetic acid or ethyl acetate in the absence of catalysts to yield 5-nitro-2-furoxanyl-1,2,3-triazole derivatives **91a**,**b**. The reaction mechanism is apparently analogous to the mechanism of the rearrangement of compounds **82** and involves the formation of 1,2,4-oxadiazole derivatives **92a**,**b** (Scheme 40).[43]

Along with the formation of the target 4-acetylamino derivative **20b**, the thermal isomerization of 3-acetyl derivative **19b** was found to be accompanied by the cascade azole–azole rearrangement to give finally triazole 1-oxide derivative **93**. However, in this case intermediate 1,2,4-oxadiazole **94** was isolated and characterized and was then transformed into final triazole 1-oxide **93** both under thermal conditions and in the presence of bases (Scheme 41).[17]

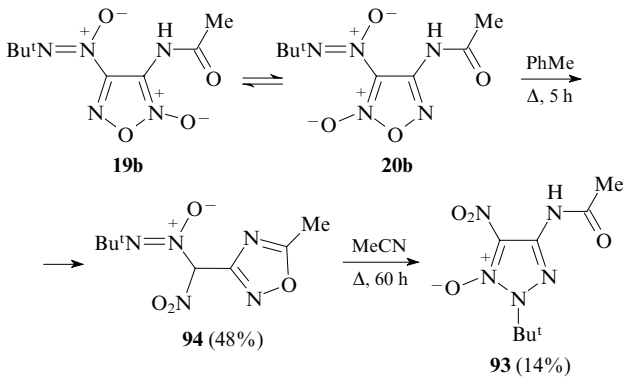
The reaction of aminofuroxans with various isocyanates was investigated in order to find a route to carbamoyl derivatives. Phenyl isocyanate did not react with 4-aminofuroxans either in organic solvents or in melt. Only highly reactive ethoxycarbonyl isocyanate was successfully introduced into the reaction. The reaction was performed without heating in anhydrous organic solvents (chloroform, diethyl ether, ethyl acetate or benzene) depending on the solubility of the starting aminofuroxans. For the aminofuroxan series, the reaction was carried out with 3-R-4-ami-

Scheme 40



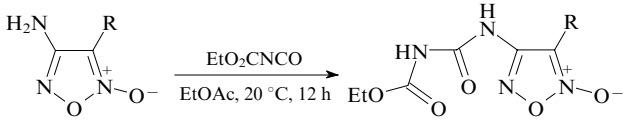
34: R = H (**a**), Me (**d**); **90**–**92**: R = H (**a**), Me (**b**);
(*a*) Ac_2O, AcOH, 50 °C, 3 h (for **90a**);
(*b*) Ac_2O (or EtOAc), 80–100 °C, 1.5–2 h (for **90b**)

Scheme 41



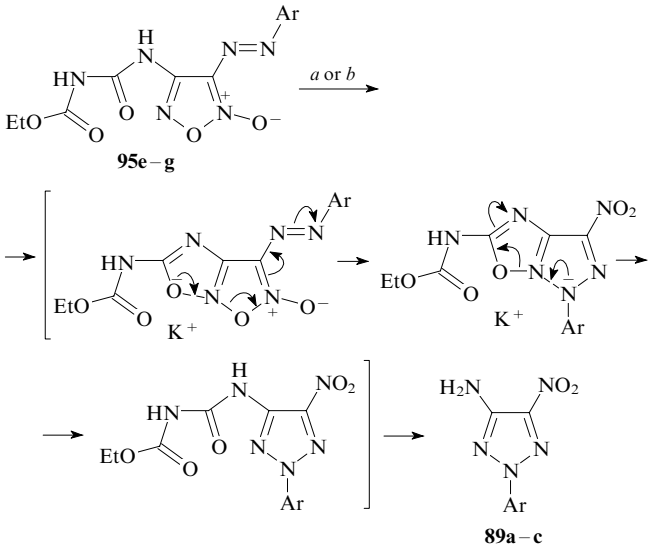
nofuroxans containing various substituents (R = Me, Ph, Ac, CO_2Me, 4-$MeOC_6H_4N{=}N$, 4-$EtOC_6H_4N{=}N$, 2,4,6-$Me_3C_6H_2N{=}N$). Ureido derivatives **95a**–**g** were obtained in high yields (Scheme 42).[61,68]

Scheme 42



R = Me (**63a**, **95a**), Ph (**4a**, **95b**), Ac (**27b**, **95c**), CO_2Me (**43b**, **95d**), 4-$MeOC_6H_4N{=}N$ (**39a**, **95e**), 4-$EtOC_6H_4N{=}N$ (**39b**, **95f**), 2,4,6-$Me_3C_6H_2N{=}N$ (**39d**, **95g**)

Scheme 43



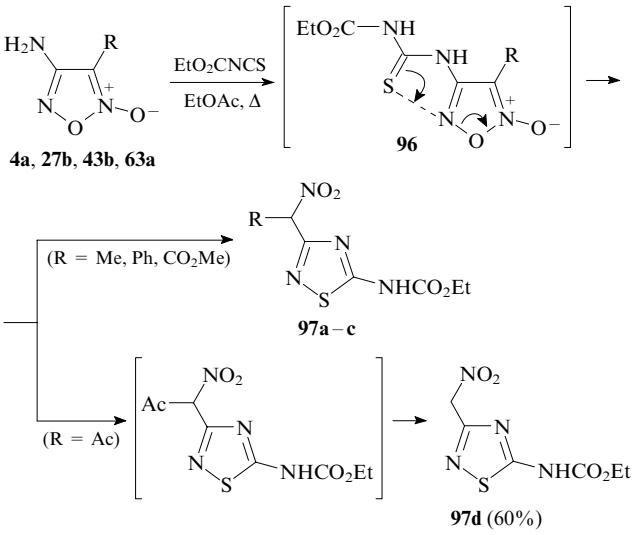
Compound **89**	Ar	Yield (%)	
		conditions *a*	conditions *b*
a	4-$EtOC_6H_4$	65	–
b	4-$MeOC_6H_4$	50	32
c	2,4,6-$Me_3C_6H_2$	45	65

Among the synthesized ureido derivatives **95**, only arylazo derivatives **95e**–**g** undergo the rearrangement, the recyclization being initiated both thermally [heating in DMSO at 120 °C (conditions *a*)] and using a base catalyst [Bu^tOK in DMF, 100 °C (conditions *b*)].[61,68] This is also a cascade rearrangement. This reaction proceeds by the mechanism similar to that shown in Schemes 40 and 41 to form 5-amino-2-aryl-4-nitrotriazoles **89a**–**c**, the carbamoyl protecting group being removed in the reaction (Scheme 43).

The reactions of isothiocyanates with aminofuroxans are even more difficult to perform. The most active isothiocyanate containing the ethoxycarbonyl substituent was introduced into the reaction with 3-R-4-aminofuroxans (R = Me, Ph, Ac, Ar–N=N). However, its reactivity proved to be lower than that of the corresponding isocyanate. Hence, the prolonged refluxing of the reactants in ethyl acetate was necessary for the reaction to occur. The reaction did not afford the expected thioureidofuroxans **96**; instead, it gave products of their azole–azole rearrangement **97**. The reactions of aminofuroxans with R = Me, Ph, CO_2Me (compounds **63a**, **4a** and **43b**, respectively) furnished 5-ethoxycarbonylamino-3-(1-nitro-1-R-methyl)-1,2,4-thiadiazoles **97a**–**c**. In the reaction of 3-acetyl derivative **27b**, the acetyl group was hydrolyzed in the course of the isolation to form nitromethyl derivative **97d**. Therefore, this rearrangement involves the transformation of the 'latent' nitro group of the furoxan ring into the nitromethyl group (Scheme 44).[69]

An unexpected result was obtained in the reaction of ethoxycarbonyl isothiocyanate with arylazo-substituted aminofuroxans **39a**,**d**. Thus, the expected cascade rearrangement to nitrotriazole derivatives **89** did not occur, and the reaction stopped at the first rearrangement giving

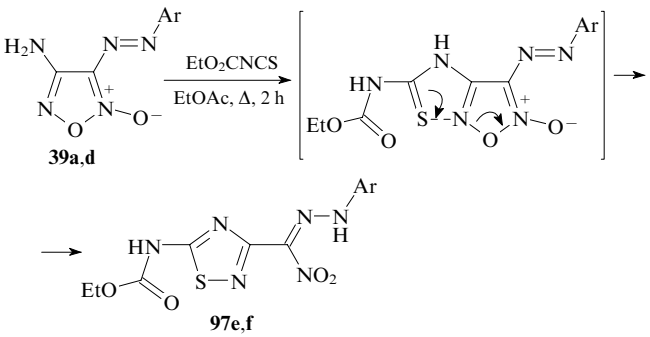
Scheme 44



R = Me (**63a**; **97a**, 47%), Ph (**4a**; **97b**, 40%), CO_2Me (**43b**; **97c**, 39%), Ac (**27b**, **97d**)

1,2,4-thiadiazolylnitroformaldehyde arylhydrazones **97e**,**f** (Scheme 45).[69]

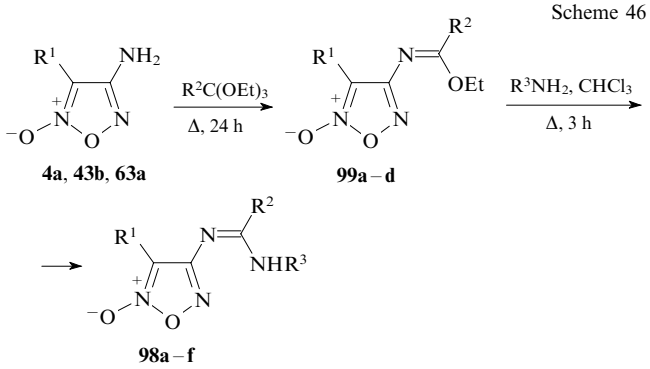
Scheme 45



Ar = 4-$MeOC_6H_4$ (**39a**; **97e**, 60%), 2,4,6-$Me_3C_6H_2$ (**39d**; **97f**, 52%)

Another base-induced azole–azole rearrangement of aminofuroxan derivatives was performed after their transformation into amidines **98**. These compounds were synthesized in two steps by the reaction of the corresponding aminofuroxans with triethyl orthoformate or triethyl orthoacetate to form imino ethers **99a–d** followed by their reaction with aliphatic or aromatic amines (Scheme 46).[60, 61]

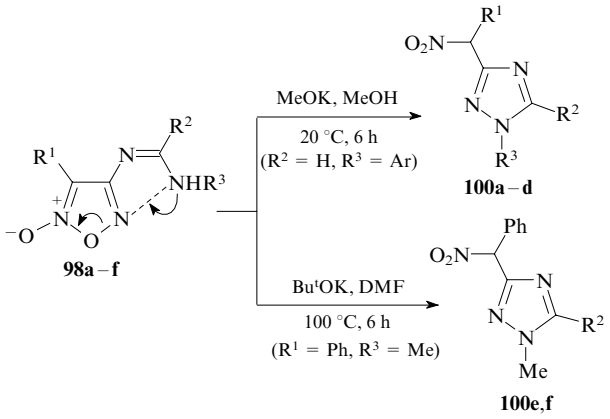
Scheme 46



R^1 = Me (**63a**, **98a**, **99a**), Ph (**4a**, **98b**,**c**,**e**,**f**, **99b**,**c**), CO_2Me (**43b**, **98d**, **99d**); R^2 = H (**98a–e**, **99a**,**b**,**d**), Me (**98f**, **99c**); R^3 = 4-MeC_6H_4 (**98a**,**b**,**d**), 4-$EtOC_6H_4$ (**98c**), Me (**98e**,**f**)

The resulting amidines **98a–f** were subjected to the rearrangement in the presence of various bases. 1-Aryl-3-(1-nitroalkyl)-1,2,4-triazoles **100a–d** were synthesized by refluxing arylamidines **98a–d** in methanol in the presence of an equimolar amount of sodium methoxide, and alkyl amidines **98e**,**f** underwent the rearrangement on heating in DMF in the presence of Bu^tOK to form 1-alkyl-3-(1-nitroalkyl)-1,2,4-triazoles **100e**,**f** (Scheme 47).[60, 61]

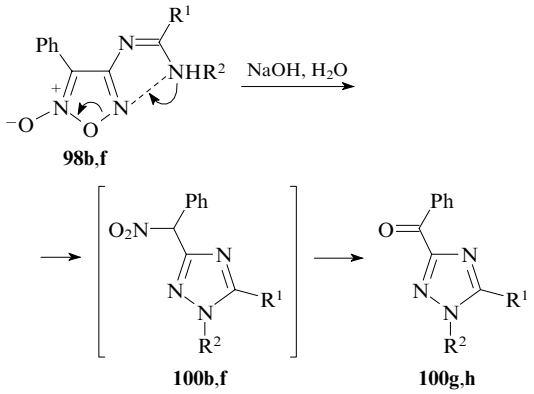
Scheme 47



100: R^2 = H, R^3 = 4-MeC_6H_4: R^1 = Me (**a**, 86%), Ph (**b**, 92%), CO_2Me (**d**, 68%); R^1 = Ph, R^2 = H, R^3 = 4-$EtOC_6H_4$ (**c**, 95%); R^2 = H (**e**, 70%), Me (**f**, 58%)

An aqueous-alkaline medium also proved to be suitable for the rearrangement of amidines **98** (as exemplified by compounds **98b**,**f**). However, 3-benzoyl-1,2,4-triazoles **100g**,**h** were obtained as the reaction products even upon storage of the starting furoxans under these conditions without heating. Evidently, under the reaction conditions, 3-(1-nitroalkyl)-1,2,4-triazoles **100b**,**f** formed in this rearrangement were hydrolyzed to the corresponding ketones by the Nef reaction (Scheme 48).[60, 61]

Scheme 48



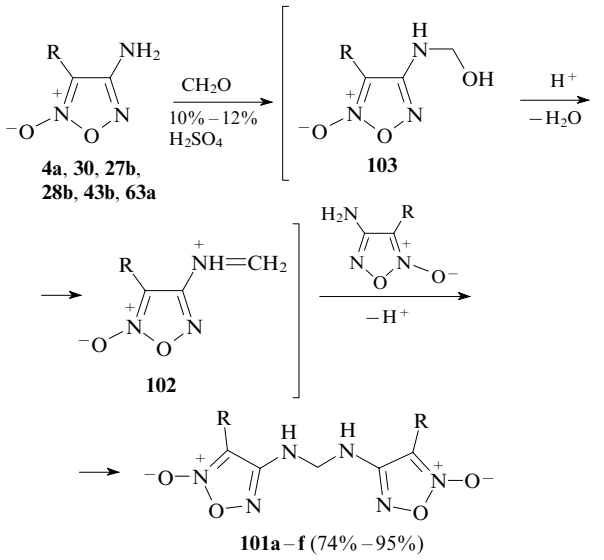
100: R^1 = H, R^2 = 4-MeC_6H_4 (**g**, 56%); R^1 = R^2 = Me (**h**, 51%)

4. Aminofuroxans in the Mannich reaction

The Mannich reaction is one of the most commonly used reactions of different types of amines. In particular, derivatives of methylene-bis-amines are widely used in synthetic organic chemistry, for example, as aminomethylating agents.[70] The conditions of this reactions vary in a wide range and depend, in particular, on the basicity of the amines used.[71] This method was employed to synthesize aminofurazan derivatives, which are close analogues of aminofuroxans, *N*,*N*′-bis(furazanyl)methylenediamines and *N*,*N*′-dinitro-*N*,*N*′-bis(furazanyl)methylenediamines.[72–76]

However, aminofuroxans were introduced into the Mannich reaction quite recently because aminofuroxans containing functional substituents are difficult to synthesize. The approach to the synthesis of the latter compounds was developed with our participation (see Schemes 3, 5, 8 and 9). It was found that only 4-aminofuroxans can be subjected to the Mannich reaction with formaldehyde.[77] Due to low basicity of aminofuroxans,[46,47] the synthesis of methylenediamino derivatives **101** required higher acidity of the reaction medium compared to that used for analogous aminofurazan derivatives. The reaction performed in 10% sulfuric acid at 20 °C overnight gave the best results.[77] Apparently, only under these conditions, iminium ion **102** can be generated through the protonation of hydroxymethylamino derivative **103** (Scheme 49).

Scheme 49

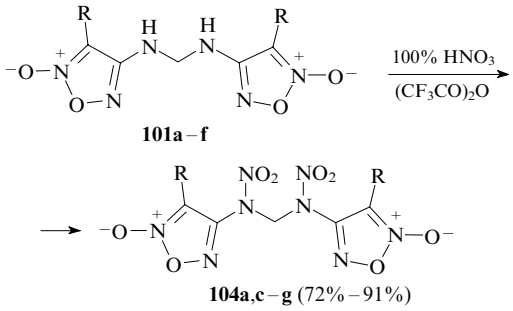


R = Me (**63a**, **101a**), Ph (**4a**, **101b**), Ac (**27b**, **101c**), CO_2Me (**43b**, **101d**), $C(O)N_3$ (**30**, **101e**), $C(O)NH_2$ (**28b**, **101f**)

The HNO_3–$(CF_3CO)_2O$ mixture proved to be the most efficient among the studied nitrating mixtures for the nitration of methylenediaminofuroxans **101a**–**f**. *N*,*N*′-Dinitro derivatives **104a**,**c**–**g** were prepared in rather high yields. The nitration of *N*,*N*′-bis(3-phenylfuroxan-4-yl)methylenediamine **101b** occurs at both the NH groups and the phenyl substituent to form *N*,*N*′-dinitro-*N*,*N*′-bis[3-(4-nitrophenyl)furoxan-4-yl]methylenediamine **104g** (Scheme 50).[77]

Methylenediaminofuroxans **101** and 4-aminofuroxans themselves, were introduced into the Mannich reaction

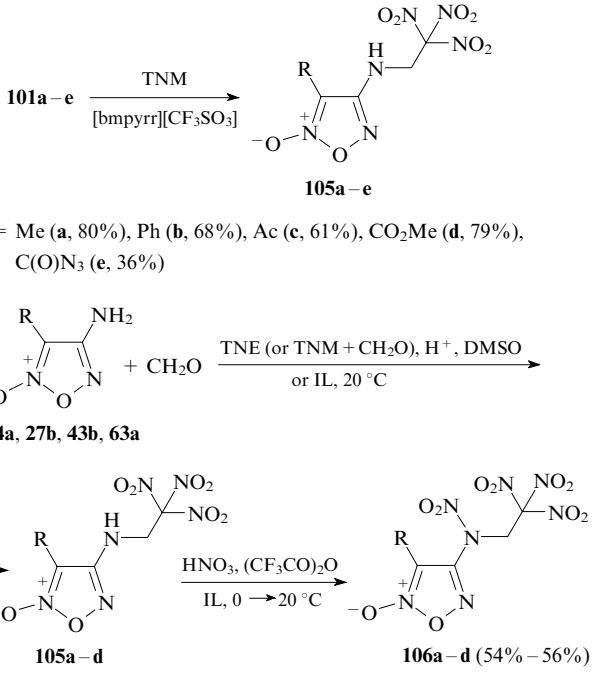
Scheme 50



R = Me (**a**), Ph (**b**), Ac (**c**), CO_2Me (**d**), $C(O)N_3$ (**e**), $C(O)NH_2$ (**f**), 4-$O_2NC_6H_4$ (**g**)

with trinitroethanol (TNE) [or a mixture of trinitromethane (TNM) and formaldehyde] in acidic ionic liquids or in DMSO in the presence of H_2SO_4 to form 3-R-4-(2,2,2-trinitroethylamino)furoxans **105a**–**e**. These Mannich bases were successfully nitrated with a HNO_3–$(CF_3CO)_2O$ mixture to the corresponding nitramines **106a**–**d**. However, of all the nitramines, which were isolated in these reactions, only nitramine derivative **106a** with R = Me proved to be stable in the presence of atmospheric moisture. Other compounds **106** are highly sensitive to hydrolysis during storage (Scheme 51).[78]

Scheme 51



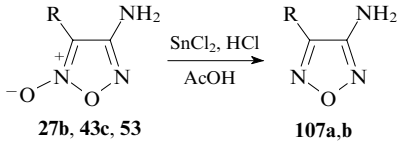
R = Me (**63a**), Ph (**4a**), Ac (**27b**), CO_2Me (**43b**);
105, **106**: R = Me (**a**), Ph (**b**), Ac (**c**), CO_2Me (**d**);
IL = [bmpyrr][CF_3SO_3], [emim][HSO_4]

5. Other reactions of aminofuroxans

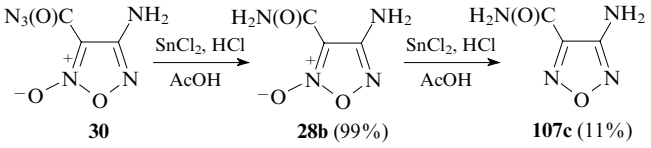
Some carbonyl-substituted aminofuroxans, in particular, compounds **27b** and **43c**, can be reduced to the corresponding furazans **107a**,**b** using $SnCl_2$ in a mixture of hydrochloric and acetic acids (the yields of the products are 42% and 40%, respectively).[79] Under these conditions, the reduction of the furoxan ring in 4-amino-3-(bromoa-

cetyl)furoxan (**53**) is accompanied by the reduction of the bromoacetyl group to the acetyl one (the yield of compound **107a** is 36%), and the azidocarbonyl group in 4-amino-3-azidocarbonylfuroxan (**30**) is reduced to the amide group. The reduction proceeds in steps to give initially furoxan **28b** and then furazan **107c** (Scheme 52).

Scheme 52



R = Ac (**27b**, **107a**), CO_2Et (**43c**, **107b**), $C(O)CH_2Br$ (**53**)

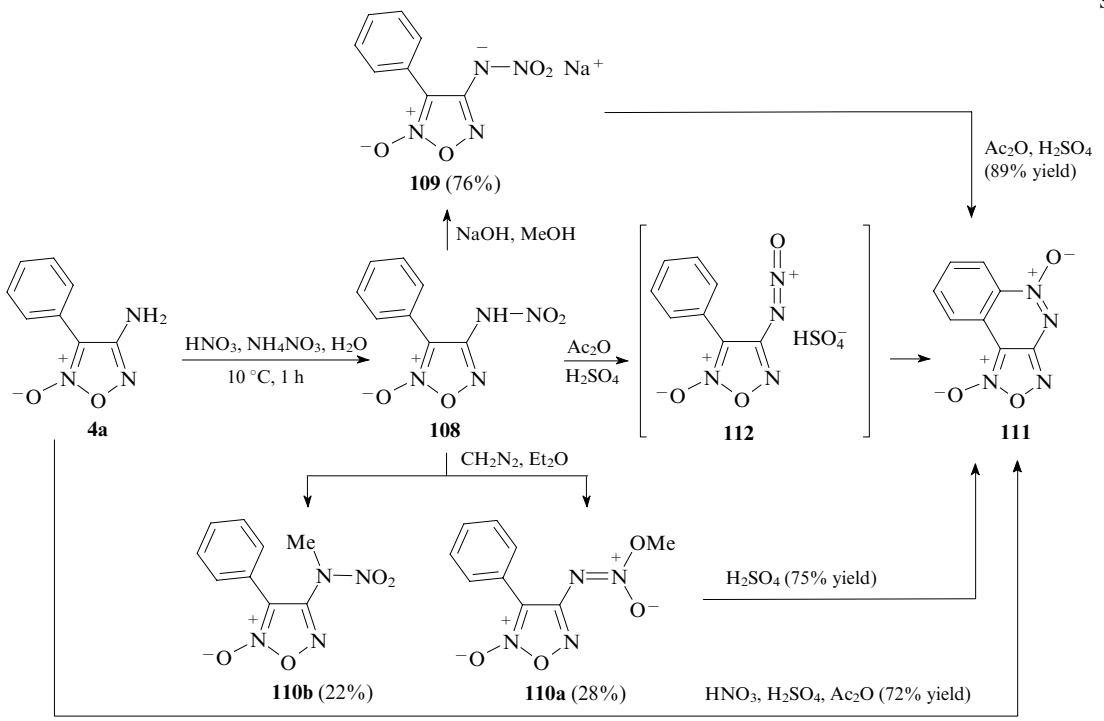


The nitration of the amino group and subsequent transformations of the resulting nitramino derivatives were studied for isomeric 4(3)-amino-3(4)-phenylfuroxans **4a** and **2a**.[80] 4-Amino-3-phenylfuroxan (**4a**) was nitrated to nitramine **108** in 72% yield with the use of the mixture composed of HNO_3 (70%), NH_4NO_3 (20%) and H_2O (10%). Nitramine **108** proved to be unstable. Its sodium salt **109** and diazomethane methylation products, which were obtained as a mixture of OMe and NMe derivatives **110a**,**b**, with the former slightly predominating, are more stable. The reaction of sodium salt **109** with a $Ac_2O-H_2SO_4$ mixture gave the fused system, 1,2,5-oxadiazolo[3,4-*c*]cinnoline 1,5-dioxide (**111**) (89% yield). It was suggested that the reaction proceeds through the formation of oxodiazonium ion **112** and its subsequent condensation with the benzene ring (Scheme 53).[80] The synthesis of an analogous heterocyclic system based on amino(phenyl)furazan was documented.[81,82]

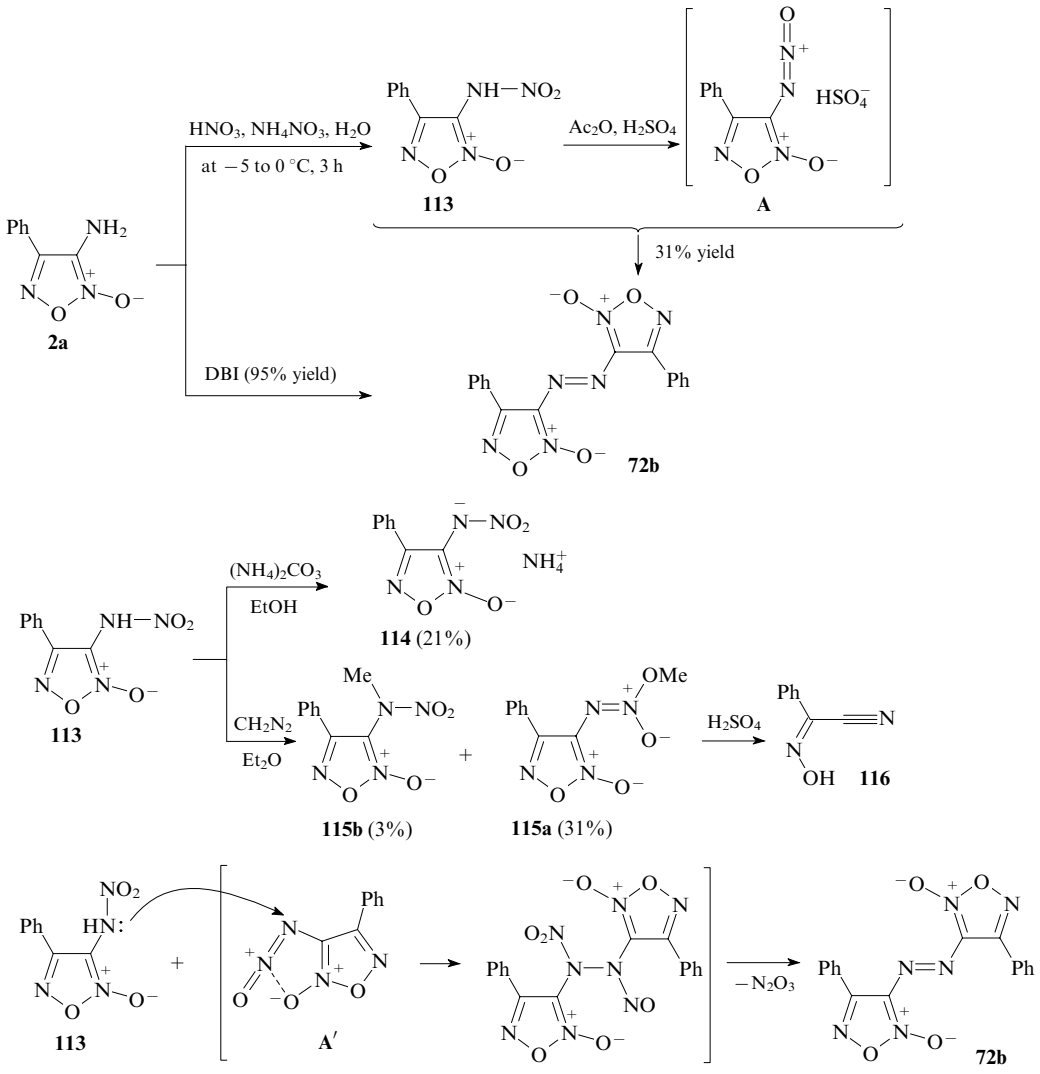
Compound **111** can be synthesized in 72% yield directly from 4-amino-3-phenylfuroxan (**4a**) by the addition of an equimolar amount of HNO_3 to a solution of **4a** followed by the addition of the resulting mixture to a mixture of an equimolar amount of H_2SO_4 in Ac_2O. In this case, the reaction also proceeds through the formation of nitramine **108** and oxodiazonium ion **112.** The reaction of O-methylated nitramine **110a** with 93% H_2SO_4 also furnishes compound **111** (75% yield) (see Scheme 53).[80]

A somewhat different situation was observed in attempting to prepare a fused system analogous to heterocycle **111** starting from 3-amino-4-phenylfuroxan (**2a**). The nitration of this amine with the same nitrating mixture afforded unstable nitramine **113**, which can be stabilized as ammonium salt **114** by the reaction with ammonium carbonate and as O- and N-methyl derivatives **115a**,**b** by the reaction with diazomethane. However, attempts to generate the oxodiazonium ion **A** in order to prepare a cinnoline derivative both from amine **2a** through the formation of nitramine **113** and from O-methyl derivative **115a** failed. In the former case, 4,4′-diphenyl-3,3′-azofuroxan (**72b**) was obtained instead of the expected fused system. In the latter case, 2-hydroxyimino-2-phenylacetonitrile (**116**) was produced. It was suggested that the formation of azo compound **72b** is associated with the fact that the oxodiazonium ion has the conformation **A′** stabilized by an intramolecular interaction with the N-oxide oxygen atom and it cannot be subjected to the condensation with the phenyl ring. The mechanism of the formation of compound **116** remains unclear (Scheme 54).[56]

Scheme 53



Scheme 54



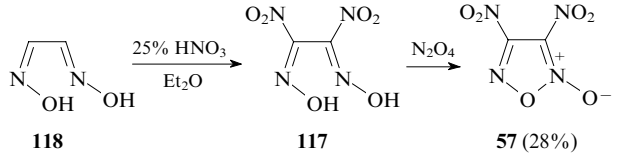
IV. Methods of synthesis of nitrofuroxans

Nitrofuroxans can be synthesized using both traditional approaches, in particular, the furoxan ring formation *via* the oxidation of nitroglyoximes, the cyclodimerization of nitrile oxides, the dehydration of α-nitro oximes or the oxidation of aminofuroxans to nitrofuroxans, and the recently developed methods based on transformations of precursors, which already contain the nitro group, for instance, the nitrosation of dipotassium salts of 2-substituted 2-hydroxyimino-1,1-dinitroethanes. The synthesis of nitrofuroxans from alkene and alkyne derivatives was investigated in sufficient detail.

1. Synthesis of nitrofuroxans by oxidation of nitroglyoximes

It is the oxidation of nitroglyoxime that was used to prepare for the first time dinitrofuroxan **57**. For this purpose, dinitroglyoxime **117**, which was synthesized by the nitration of glyoxime **118** with dilute nitric acid, was oxidized to dinitrofuroxan **57** with N_2O_4 under mild conditions (Scheme 55).[6, 39, 40]

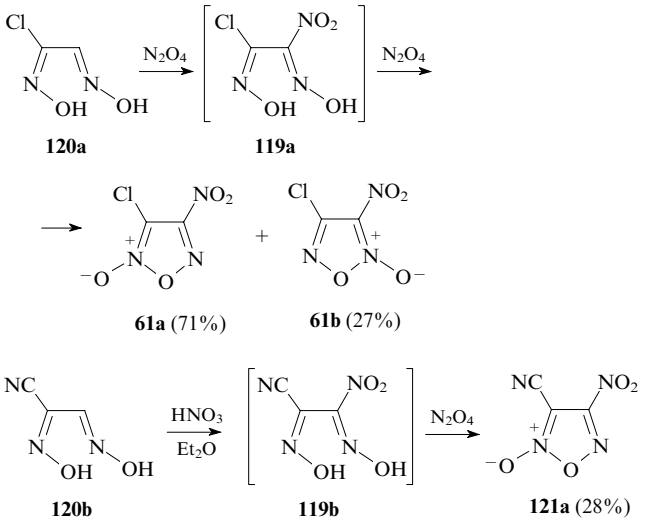
Scheme 55



In addition to the oxidation of dinitroglyoxime, the cyclodimerization of nitroformonitrile oxide was also employed to synthesize furoxan **57**. The following two methods were developed for the generation of nitroformonitrile oxide: the dehydration of dinitromethane and the nitration of 2-methyl-1-nitroprop-1-ene.[83, 84] Both approaches were described in detail in the review.[6]

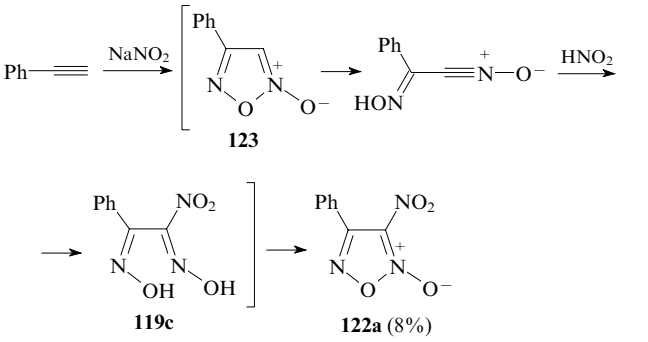
The oxidation of mononitro-substituted glyoximes **119a–c** with N_2O_4 furnished other nitrofuroxans as well. Thus, chloronitrofuroxan is generated as a mixture of 3- and 4-isomers **61a,b** (in a ratio of 7 : 3) in the reaction of *amphi*(*Z*,*E*)-chloroglyoxime **120a** with N_2O_4 in diethyl ether.[85, 86] The reaction apparently proceeds through the intermediate formation of chloronitroglyoxime **119a**. Under similar conditions, cyanonitroglyoxime **119b** was oxidized to 3-cyano-4-nitrofuroxan **121a**. The starting glyoxime **119b** was prepared by the nitration of cyanoglyoxime **120b** with nitric acid in diethyl ether (Scheme 56).[87]

Scheme 56



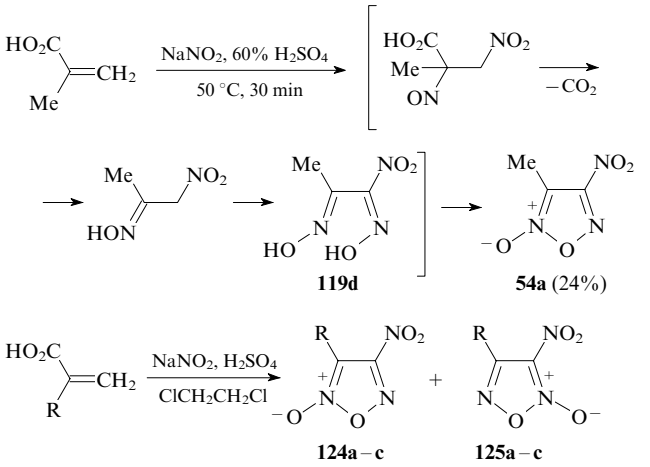
The formation of 3-nitro-4-phenylfuroxan (**122a**) by the reaction of phenylacetylene with $NaNO_2$ in AcOH apparently occurs through the oxidation of the corresponding nitroglyoxime **119c**. Evidently, the first step affords 4-phenylfuroxan (**123**), which is followed by the ring opening in the latter to form 2-hydroxyimino-2-phenylacetonitrile oxide. In this case, $NaNO_2$ or AcONa can act as the base. Then HNO_2 binds to the nitrile oxide moiety to give the *amphi* form of phenylnitroglyoxime **119c**, and the latter is oxidized to the final nitrofuroxan **122a** in low yield (Scheme 57).[88]

Scheme 57



It was suggested that the synthesis of nitrofuroxans from unsaturated compounds can also proceed through the formation of nitroglyoxime **119d**. In particular, the reaction of $NaNO_2$ in H_2SO_4 with methacrylic acid yielded methylnitrofuroxan **54a**.[89] Evidently, the reaction involves the addition of N_2O_3 at the double bond as the first step and the subsequent decarboxylation. This reaction appeared to be also suitable for the synthesis of nitrofuroxans from other 2-substituted acrylic acids [R = Et, $(CH_2)_2OMe$, CH_2CO_2Me].[88] The reaction was performed in a H_2SO_4 – dichloroethane mixture at 50 °C. It proceeds regioselectively and affords a mixture of the corresponding 4- (**124a – c**) and 3-nitrofuroxans (**125a – c**), with the 4-nitro isomers predominating (Scheme 58). The content of the 3-nitro isomer in the mixture increases with increasing electronegativity of the substituent R.

Scheme 58

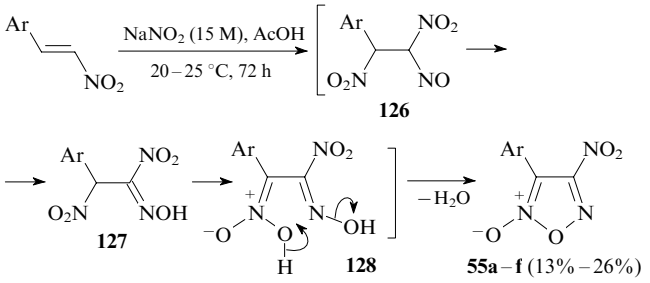


Compound	R	Yield of **124** (%)	Yield of **125** (%)
a	Et	27	0
b	$(CH_2)_2OMe$	22	5
c	CH_2CO_2Me	21	9

2. Dehydration of α-nitro oximes

As a method of synthesis of disubstituted furoxans, the dehydration of α-nitro oximes is widely used for the preparation of alkylaryl-, dialkyl- and cycloalkyl-substituted furoxans (see Ref. 1, p. 250). This approach was successfully employed to synthesize 3-aryl-4-nitrofuroxans **55**. The reaction of β-nitrostyrenes with $NaNO_2$ in acetic acid affords pseudo-nitrosites **126** through the addition of N_2O_3 at the double bond. Under the reaction conditions, compounds **126** are isomerized to α-nitro oximes **127** and their *aci*-form **128**. The latter is dehydrated even at 20 – 25 °C to form 3-aryl-4-nitrofuroxans **55a – f**. The reaction proceeds very slowly (is completed in several days) and in low yields (Scheme 59).[88] Other examples of the dehydration of α-nitro oximes are described in the review.[6]

Scheme 59



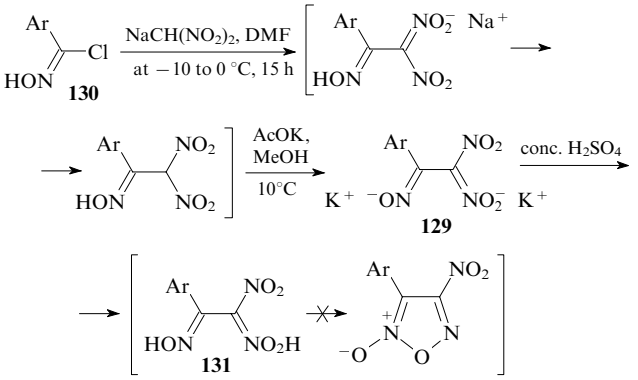
Ar = Ph (**a**), 2-$O_2NC_6H_4$ (**b**), 3-$O_2NC_6H_4$ (**c**), 4-$O_2NC_6H_4$ (**d**), 4-BrC_6H_4 (**e**), 4-MeO-3,5-$(O_2N)_2C_6H_2$ (**f**)

3. Nitrosation of dipotassium salts of 2-substituted 2-hydroxyimino-1,1-dinitroethanes

Isomeric α-nitro oximes in the form of dipotassium salts **129** containing two nitro groups at the carbon atom were synthesized by the reaction of hydroxamic acid chlorides **130** with dinitromethane sodium salt. However, attempts to perform the dehydration of salts **129** with concentrated

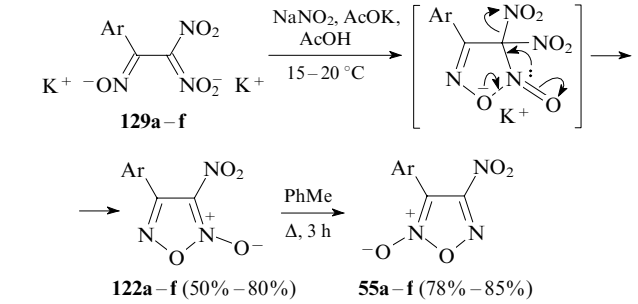
sulfuric acid to prepare nitrofuroxans failed due apparently to instability of the *aci*-form of the nitro group in intermediate **131** necessary for the dehydration (Scheme 60).[90]

Scheme 60



Dipotassium salts **129a–f** were transformed into 4-aryl-3-nitrofuroxans **122** on treatment with $NaNO_2$ in AcOH.[90,91] This reaction proceeds apparently through the nitrosation of the anion of the dinitromethyl moiety in salts **129a–f** followed by the attack of the anion of the oxime group on the nitrogen atom of the nitroso group to form 3-nitrofuroxans **122**. 3-Nitrofuroxans **122a–f** are completely isomerized to thermodynamically more favourable 4-nitro isomers **55a–f** on heating in boiling toluene for 3 h (Scheme 61).

Scheme 61



Ar = Ph (**a**), 2-$O_2NC_6H_4$ (**b**), 3-$O_2NC_6H_4$ (**c**), 4-$O_2NC_6H_4$ (**d**), 4-BrC_6H_4 (**e**), 4-MeO-3,5-$(O_2N)_2C_6H_2$ (**f**)

This approach to the synthesis of isomeric 3- and 4-nitrofuroxans was investigated in sufficient detail. In particular, hydroxamic acid chlorides containing not only aromatic substituents (Ar = 3-AcHN-5-$O_2NC_6H_3$, for example)[92] but also Ac and EtO_2C substituents were introduced into the reaction.[91] In the latter case, N_2O_4 was used as the nitrosating agent.

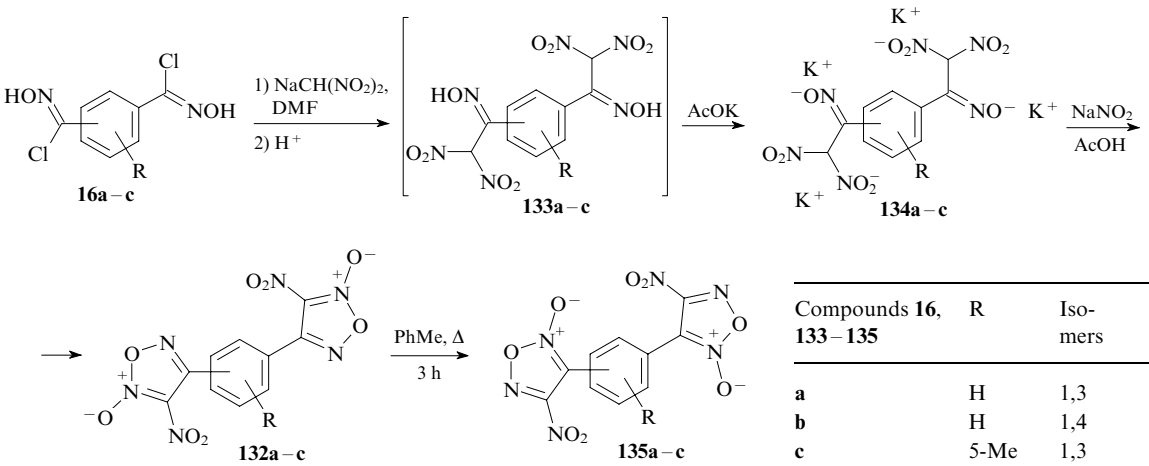
In addition to the synthesis of monocyclic nitrofuroxans, this reaction was successfully employed to prepare isomeric 1,3- and 1,4-bis(3-nitrofuroxan-4-yl)benzenes **132a–c**. To synthesize these compounds, the reactions of acid bischlorides **16a–c** were performed with dinitromethane sodium salt in DMF, the resulting 1,3- and 1,4-bis(1-hydroxyimino-2,2-dinitroethyl)benzenes **133a–c** were transformed into tetrapotassium salts **134a–c**, and the latter were subjected to nitrosation with $NaNO_2$ in AcOH in the presence of AcOK. Target 1,3- and 1,4-bis(3-nitrofuroxan-4-yl)benzenes **132a–c** were obtained in good yields. 3-Nitro isomers **132a–c** were thermally isomerized to the corresponding thermodynamically more stable 4-nitro isomers **135a–c** in high yields (Scheme 62).[13,91]

The above-considered reaction provides a new route to the furoxan ring formation. A hypothetical mechanism of this reaction was proposed.[93] This mechanism was experimentally confirmed by two methods: the determination of the ionization constants of the dinitromethyl and oxime groups in the starting salts [for dipotassium salt **129f**, Ar = 4-MeO-3,5-$(O_2N)_2C_6H_2$] and the ^{13}C, ^{14}N, ^{15}N NMR spectroscopic and mass spectrometric studies of isomeric 4(3)-(4-bromophenyl)-3(4)-nitrofuroxans **55e** and **122e** containing the ^{15}N-labelled endocyclic nitrogen atoms N(5) and N(2), respectively, and 3,4-bis(4-bromophenyl)furoxan **136** with both ^{15}N-labelled endocyclic nitrogen atoms.

The ionization constants of the oxime and dinitromethyl groups were determined by the standard UV spectrophotometric method from the dependence of the molar absorption coefficients on the relative contents of the protonated, half-protonated and ionized forms in acid–base equilibrium. The values of pK_{a1} (oxime group) and pK_{a2} (dinitromethyl group) were determined by the graphic method using the standard equation

$$\log \frac{\varepsilon_B - \varepsilon}{\varepsilon - \varepsilon_{BH}} = pK - H_X$$

Scheme 62

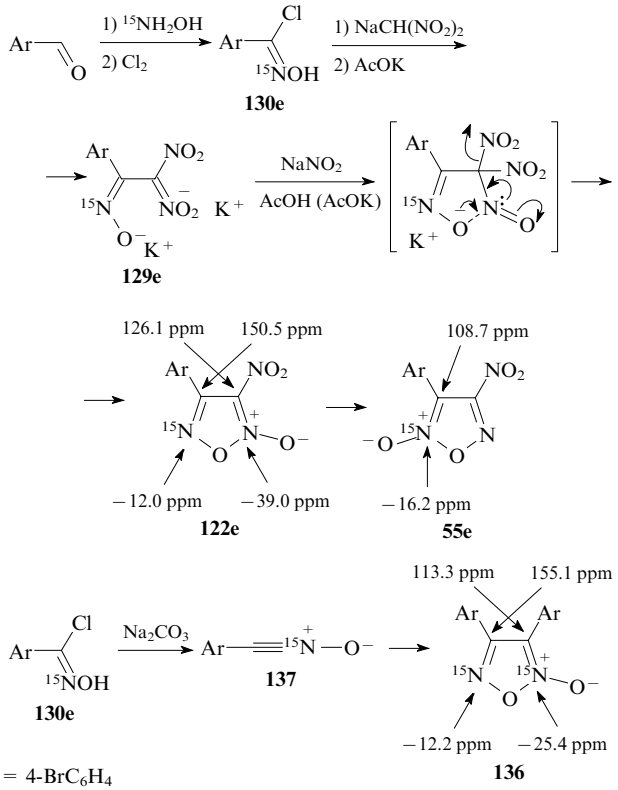


Compounds **16**, **133–135**	R	Isomers	Yield (%)	
			132	**135**
a	H	1,3	56	91
b	H	1,4	45	90
c	5-Me	1,3	90	70

where ε_B, ε and ε_{BH} are the molar absorption coefficients of the completely ionized, half-protonated and protonated forms, respectively, and H_X is the Hammett acidity function. These constants are 4.43 and 2.23, respectively. Therefore, these data confirm the proposed mechanism. Actually, the anion of the dinitromethyl group should be subjected to nitrosation in the first step.

To investigate the mechanism of this reaction by NMR spectroscopy and mass spectrometry using ^{15}N-labelled compounds, acid chloride **130e** (R = 4-BrC_6H_4) was synthesized starting from nitrogen-labelled hydroxylamine ($^{15}NH_2OH$) and then it was converted into the corresponding 3- and 4-nitrofuroxans **122e** and **55e**. In addition, the dehydrochlorination of ^{15}N-labelled acid chloride **130e** furnished nitrile oxide **137**, and the dimerization of the latter afforded bis(4-bromophenyl)furoxan **136**, in which both endocyclic nitrogen atoms were ^{15}N-labelled (Scheme 63).[93]

Scheme 63



Ar = 4-BrC_6H_4

A comparison of the ^{15}N and ^{13}C NMR spectra of compound **122e**, **55e** and **136** shows that the spin-spin coupling constants between the nitrogen atom ^{15}N and adjacent carbon atoms of the furoxan ring ($J_{^{13}C-^{15}N}$) and the chemical shifts in the NMR spectra of furoxans **122e** and **55e** correlate with the chemical shifts and the coupling constants ($J_{^{13}C-^{15}N}$) in the NMR spectra of furoxan **136**.

Compound	Chemical shift of N(5) /ppm	$J_{^{13}C-^{15}N}$ /Hz	Compound	Chemical shift of N(2) /ppm	$J_{^{13}C-^{15}N}$ /Hz
122e	−12.0	6.3	**55e**	−16.2	24.5
136	−12.2	2.6	**136**	−25.4	24.6

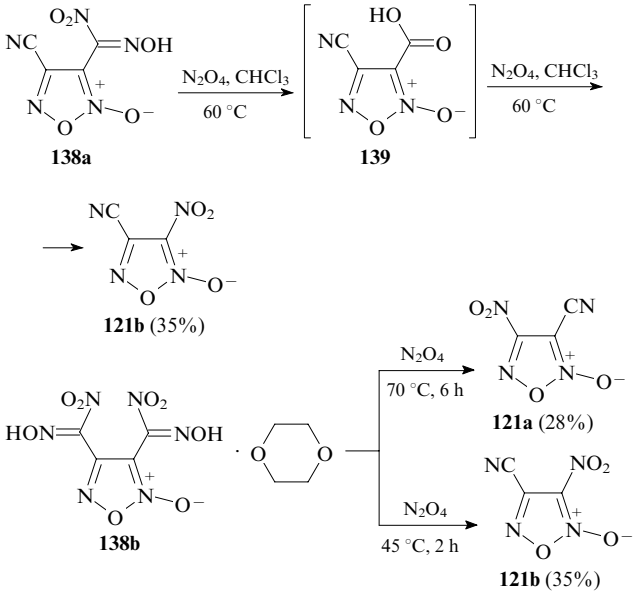
Consequently, the label completely migrates to the furoxan ring in the course of the synthesis of furoxan **122e**. In this nitrofuroxan, the endocyclic nitrogen atom N(5) was labelled, whereas the N(2) atom was labelled in isomeric nitrofuroxan **55e**. The fragmentation of the molecules of all three compounds (**122e** and **55e**, **136**) in the mass spectra also corresponds to the proposed ^{15}N-labelled structures.

Therefore, the results obtained in the study [93] completely confirmed the proposed earlier hypothetical mechanism of the synthesis of 4-R-3-nitrofuroxans **122** by the nitrosation of dipotassium salts of 2-R-2-hydroxyimino-1,1-dinitroethanes **129**.

4. Other methods of synthesis of nitrofuroxans

The unusual method for the formation of the nitro group in position 3 of the furoxan ring [synthesis of 4-cyano-3-nitrofuroxan (**121a**)] is based on the transformation of 3-furoxannitrolic acid **138a** in the presence of an excess of N_2O_4 in an aprotic organic solvent at 60 °C.[87] This process apparently proceeds *via* the destructive (or substitutive) nitration of 3-furoxancarboxylic acid **139**. The carboxy group can be generated *via* the oxidative deoximination, as was described for alkanenitrolic acids.[94] An analogous transformation of one of the units of the nitrolic acid is observed in the reaction of furoxandinitrolic acid **138b** with N_2O_4 under similar conditions. This reaction yields two isomers of cyanonitrofuroxan (**121a** and **121b**) depending on the reaction conditions. Thus, the 3-NO_2 isomer is generated at 45 °C, whereas the 4-NO_2 isomer is produced at 70 °C (Scheme 64).[87]

Scheme 64

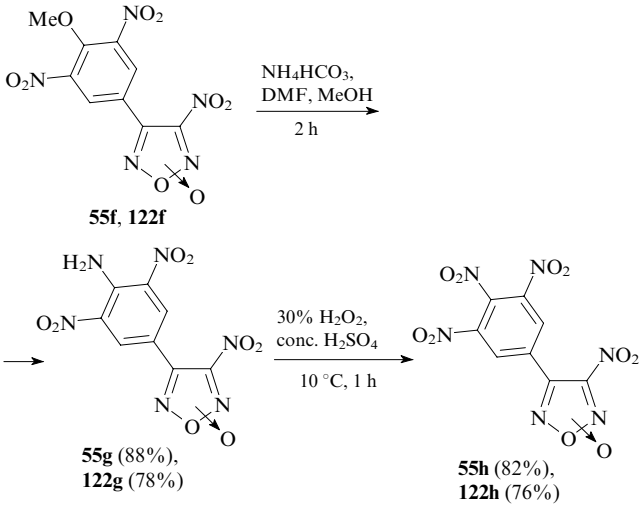


5. Transformations of substituents in nitrofuroxans

Several functionalized nitrofuroxans were synthesized by the transformation of the substituents at the second carbon atom of the furoxan ring. Thus, 3(4)-nitro-4(3)-(3,5-dinitro-4-methoxyphenyl)furoxans **55f** and **122f** were transformed into isomeric 3(4)-nitro-4(3)-(3,4,5-trinitrophenyl)furoxans **55h** and **122h** (see Scheme 61) through intermediate 3(4)-nitro-4(3)-(4-amino-3,5-dinitrophenyl)furoxans **55g** and **122g**. The comparative kinetics of the hydrolysis of the NO_2 group in position 4 of the aromatic ring of these

compounds and the analogous NO_2 group in position 2 of 1,2,3,5-tetranitrobenzene (TNB) was studied.[95,96] It appeared that the hydrolysis rate of TNB is much (100 times) higher than the hydrolysis rate of the studied furoxans. Hence, this type of compounds can be recommended for the design of high energy compounds (Scheme 65).

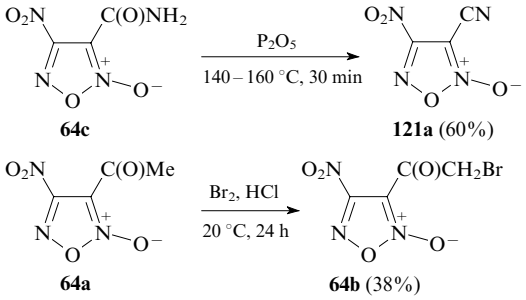
Scheme 65



Isomers: 3-nitro (**f**), 4-nitro (**g**)

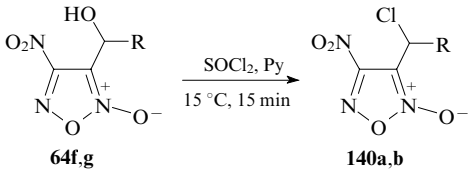
4-Nitrofuroxan-3-carboxylic acid amide (**64c**) was subjected to dehydration with phosphoric anhydride to form 3-cyano-4-nitrofuroxan (**121a**) in 60% yield.[29] Unstable 3-bromoacetyl-4-nitrofuroxan (**64b**) was synthesized in 38% yield by the bromination of 3-acetyl-4-nitrofuroxan (**64a**) (Scheme 66).[34]

Scheme 66



The hydroxy group in alcohols **64f**,**g** is easily replaced with a chlorine atom under the action of the $SOCl_2$–pyridine complex in CH_2Cl_2 or dioxane to form α-chloroalkyl derivatives of 4-nitrofuroxans **140a**,**b** in preparative yields (Scheme 67).[33]

Scheme 67



R = H (**64f**; **140a**, 51%), Me (**64g**; **140b**, 86%)

The method of the preparation of nitrofuroxans by the oxidation of aminofuroxans is described in Section III.

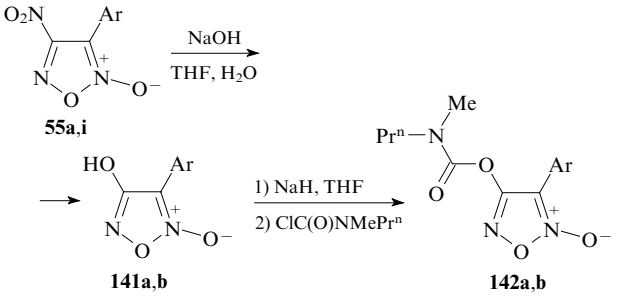
V. Reactivity of nitrofuroxans

Investigations of the reactivity of nitrofuroxans were started relatively recently after the development of methods for their synthesis. The nucleophilic substitution of the nitro group in positions 3 and 4 in the reactions with O-, N- and S-nucleophiles was studied most comprehensively. These investigations revealed a new rearrangement in the series of non-fused furoxan derivatives, *viz.*, the recyclization of the furoxan ring to 1,2,3-triazole 1-oxide. Dinitrofuroxan was subjected to thermal decomposition giving rise to two molecules of nitroformonitrile oxide. Data on these reactions are discussed in detail in the review.[6] However, new information on both the transformations of nitrofuroxans and their reactivity has been published in recent years.

1. Nucleophilic substitution of the nitro group

The nucleophilic displacement of the nitro group in nitrofuroxans by amino, alkylamino, dialkylamino and other groups (RS, OR, N_3) is described in the section devoted to the synthesis of aminofuroxans (see Section II). However, new examples of such reactions were reported in the last years. Most of these reactions were performed in order to prepare new biologically active compounds. For instance, it was shown that the 4-nitro group in 3-aryl-4-nitrofuroxans **55a**,**i** is replaced by the OH group to form 4-hydroxyfuroxans **141a**,**b** on treatment with aqueous alkali in a mixture with THF. These compounds were acylated at the hydroxy group with carbamoyl chloride in the presence of NaH to prepare urethanes **142a**,**b** exhibiting anti-HIV activity (Scheme 68).[97]

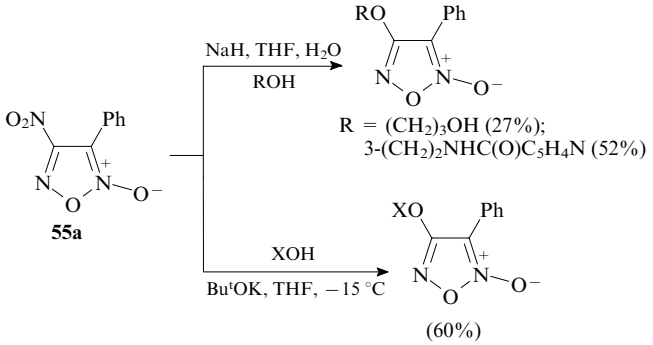
Scheme 68



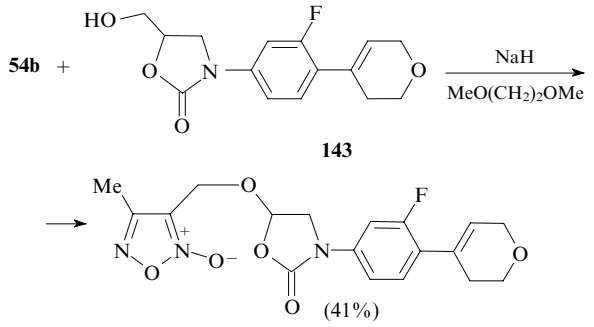
Ar = Ph (**55a**, **141a**, **142a**), 2,6-$Cl_2C_6H_3$ (**55i**, **141b**, **142b**)

The nucleophilic displacement of the nitro group in 4-nitrofuroxans by alkoxy groups is usually performed in the presence of strong bases capable of forming alkoxides. For example, propylene glycol replaces the nitro group in 4-nitro-3-phenylfuroxan (**55a**) in the presence of NaOH in THF at 20 °C.[98] Under similar conditions, this nitro group is replaced by *N*-(2-hydroxyethyl)nicotinamide.[99] The replacement of the nitro group under the action of tetraethyl-5-hydroxypentylidene phosphonate was performed in the presence of Bu^tOK.[100] The nucleophilic substitution of the 3-nitro group in 4-methyl-3-nitrofuroxan (**54b**) by the hydroxymethyl derivative of N-substituted oxazolidinedione **143** was carried out in the presence of NaH in dimethoxyethane (Scheme 69).[101]

Scheme 69

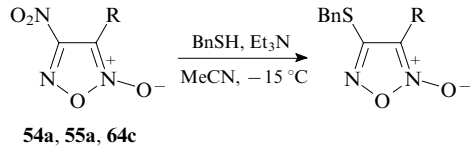


X = $[(EtO)_2PO]_2CH(CH_2)_4$



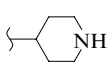
Thiols are stronger nucleophiles than alcohols. Hence, the nucleophilic displacement of the nitro group in nitrofuroxans by the alkylthio or arylthio moiety is usually performed under milder conditions. For example, the replacement of the 4-nitro group in 3-methyl-, 3-phenyl- and 3-aminocarbonylnitrofuroxans **54a**, **55a** and **64c** by the benzylthio group takes place in MeCN in the presence of triethylamine at low temperature.[102, 103] Under somewhat more drastic conditions (aqueous alkali, 20 °C), the nitro group in 4-nitro-3-phenylfuroxan (**55a**) is replaced under the action of 4-sulfanylpiperidine, amide and ethyl sulfanylacetate (Scheme 70).[104]

Scheme 70



R = Me (**54a**), Ph (**55a**), $C(O)NH_2$ (**64c**)



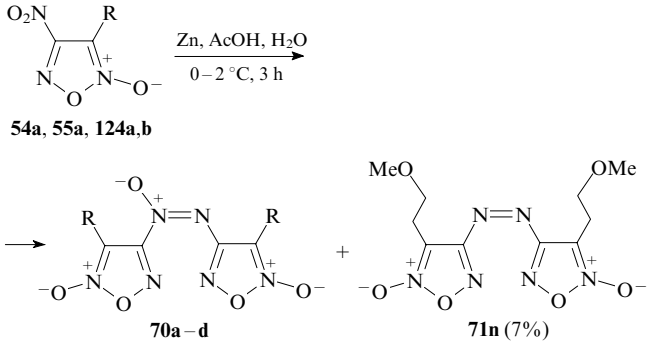
R = $CH_2C(O)NH_2$, CH_2CO_2Et, 

The 3-nitro group in 4-ethoxy-3-nitrofuroxan (**58i**) was replaced by the dimethylaminoethylthio group using a $NaOH–H_2O–THF$ mixture (25% yield).[105]

2. Reactions of nitrofuroxans with reducing agents

Studies of the reactions of nitrofuroxans with various reducing agents showed that the use of Zn dust in AcOH leads to the reductive condensation of 4-nitrofuroxans **54a**, **55a**, **124a**,**b** to give 4,4′-azoxyfuroxans **70a–d**. In the case of R = $(CH_2)_2OMe$, a small amount of 4,4′-azofuroxan **71n** was obtained. 3-Nitrofuroxans are not involved in this reaction (Scheme 71).[55]

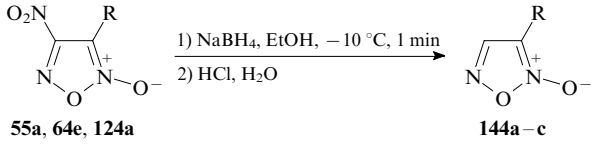
Scheme 71



R = Me (**54a**; **70a**, 58%), Ph (**55a**; **70b**, 52%), Et (**124a**; **70c**, 49%), $(CH_2)_2OMe$ (**124b**, **70d**; 17%)

The nitro group in 3-substituted 4-nitrofuroxans can be replaced by the hydride ion under the action of $NaBH_4$ in ethanol. It should be emphasized that the substituent at the C(3) atom of the furoxan ring remains intact. Hence, this reaction is a convenient route to 3-monosubstituted furoxans **144a–c** (Scheme 72).[106]

Scheme 72

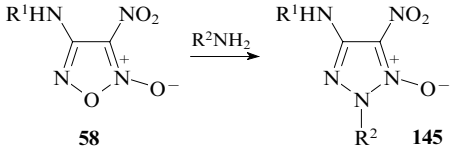


R = Ph (**55a**, **144a**, 89%), Et (**124a**, **144b**, 49%), CO_2Et (**64e**, **144c**, 53%)

3. Recyclization of the furoxan ring to 1,2,3-triazole 1-oxide

Studies of the nucleophilic substitution of the 4-nitro group in dinitrofuroxan under the action of various primary amines revealed a new reaction. This is the transformation of 4-(alkyl)amino-3-nitrofuroxans **58** into 2-alkyl-5-nitro-1,2,3-triazole 1-oxides **145** (Scheme 73).[40, 107, 108] This reaction was described for the first time in the paper[40] and in the review.[6]

Scheme 73

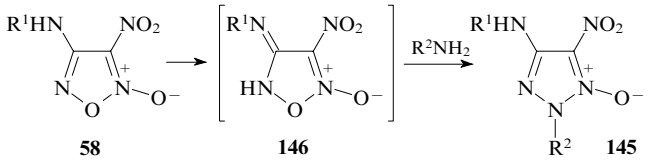


R^1 = H, Alk; R^2 = Alk

In more recent studies,[107, 108] the same research team described the main specific features of this reaction. It was found that the presence of an electron-withdrawing substituent at the C(3) atom of the furoxan ring (NO_2, Ph) and the amino or alkylamino group at the C(4) atoms is a necessary condition for this reaction to occur. The CNDO/2 quantum chemical calculations showed that it is this combination of the substituents that provides a sufficiently high charge on the N(2) atom of the starting furoxan

necessary for its attack by primary aliphatic amines. Another necessary condition for this reaction is the presence of at least one hydrogen atom in the 4-amino group of the starting furoxan, which facilitates the generation of imino form **146** under the reaction conditions. This form was detected in the reaction of 4-amino-3-nitrofuroxan (**58a**) with methylamine studied by IR and UV spectroscopy and by ^{13}C and $^{14/15}N$ NMR spectroscopy immediately after the mixing of the reactants.[107] Under the optimal conditions, a series of primary aliphatic amines was introduced into the reactions with this furoxan and other alkylaminofuroxans resulting in the formation of 1,2,3-triazole 1-oxides **145** containing various alkyl substituents at the N(2) atom (Scheme 74).

Scheme 74



58 **146** **145**

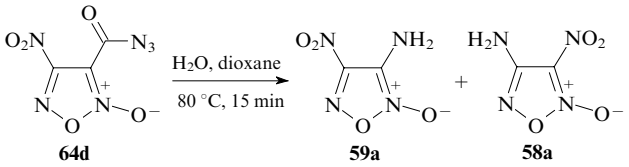
R^1 = H: R^2 = Me, Et, n-C_6H_{13}, n-C_7H_{15}, n-C_8H_{17}, n-$C_{12}H_{25}$, Pr^i, Bu^i, $(CH_2)_2OH$, $(CH_2)_2CN$, Bn; R^1 = R^2 = Me, Et, Pr^n;
R^2 = Me: R^1 = $(CH_2)_2CN$, $(CH_2)_2OH$

4. Other reactions of nitrofuroxans

Attempts to synthesize 3-amino-4-nitrofuroxan (**59a**) by the Schmidt rearrangement of the corresponding 3-acetyl-4-nitrofuroxan (**64a**) in the presence of either H_2SO_4 or polyphosphoric acid (PPA) failed. The use of H_2SO_4 resulted in the isolation of a mixture of 4-nitrofuroxan-3-carboxylic acid *N*-methylamide (**147**) and 5-methyl-1-(4-nitrofuroxan-3-yl)tetrazole (**148**) in low yields, whereas the reaction in the presence of polyphosphoric acid gave only product **147**. Nevertheless, the formation of tetrazole **148** attests to the migration of the furoxan moiety. Low yields of compounds **147** and **148** indicate that the possible products of the main reaction path — *N*-acetyl derivative of aminonitrofuroxan **149** or parent aminonitrofuroxan **59a** — can be generated but were unstable under the reaction conditions (Scheme 75).[23]

The Curtius rearrangement of 3-azidocarbonyl-4-nitrofuroxan (**64d**) affords a mixture of isomeric aminonitrofuroxans **58a** and **59a**, with the 4-isomer substantially predominating (Scheme 76).[24]

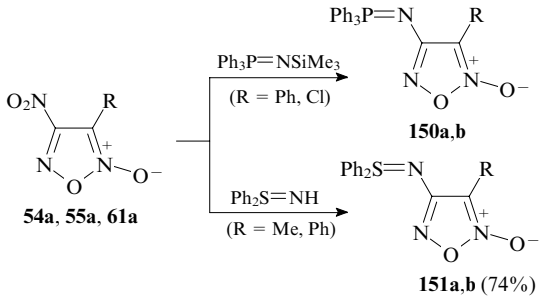
Scheme 76



64d **59a** **58a**

Recently, new facile methods were developed for the synthesis of heterocyclic triphenylphosphinimines[109] and diphenylsulfylimines[110] based on the condensation of the corresponding nitrogen heterocycles with *N*-trimethylsilyl-*P,P,P*-triphenylphosphinimine and *S,S*-diphenylsulfylimine, respectively. The reactions were performed under mild conditions in dichloromethane at 20 °C. The products were obtained in high yields. It should be noted that nitrofuroxans are also involved in these reactions. Thus, 3-chloro- (**61a**) and 3-phenyl-4-nitrofuroxans (**55a**) gave triphenylphosphinimine derivatives **150a**,**b**, and the reactions of 3-methyl- (**54a**) and 3-phenyl-4-nitrofuroxans (**55a**) produced diphenylsulfyliminofuroxans **151a**,**b** (Scheme 77).

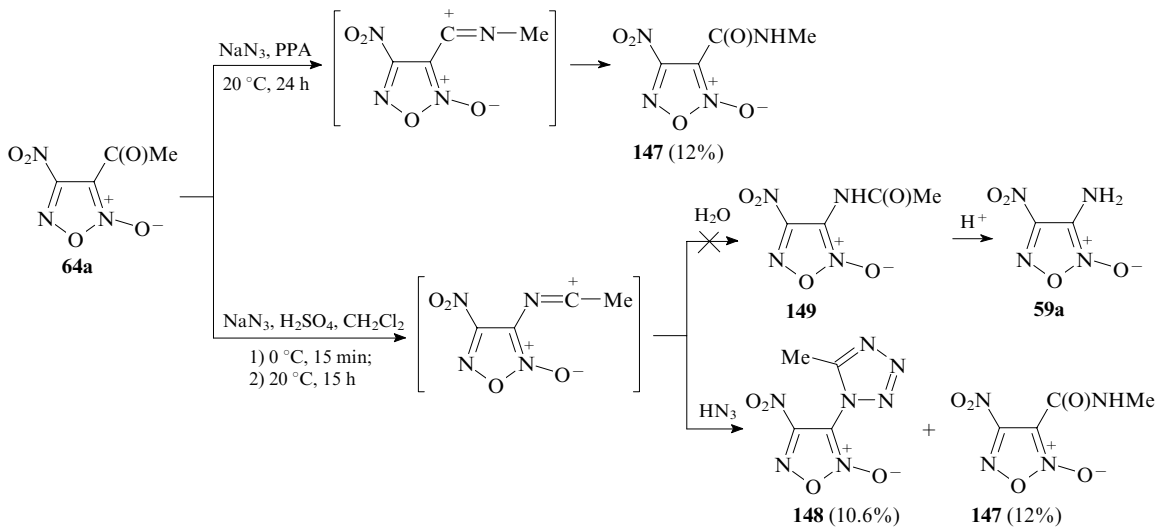
Scheme 77



54a, **55a**, **61a** **150a**,**b** **151a**,**b** (74%)

R = Me (**54a**; **151a**), Ph (**55a**; **150a**, 44%; **151b**), Cl (**61a**; **150b**, 30%)

Scheme 75



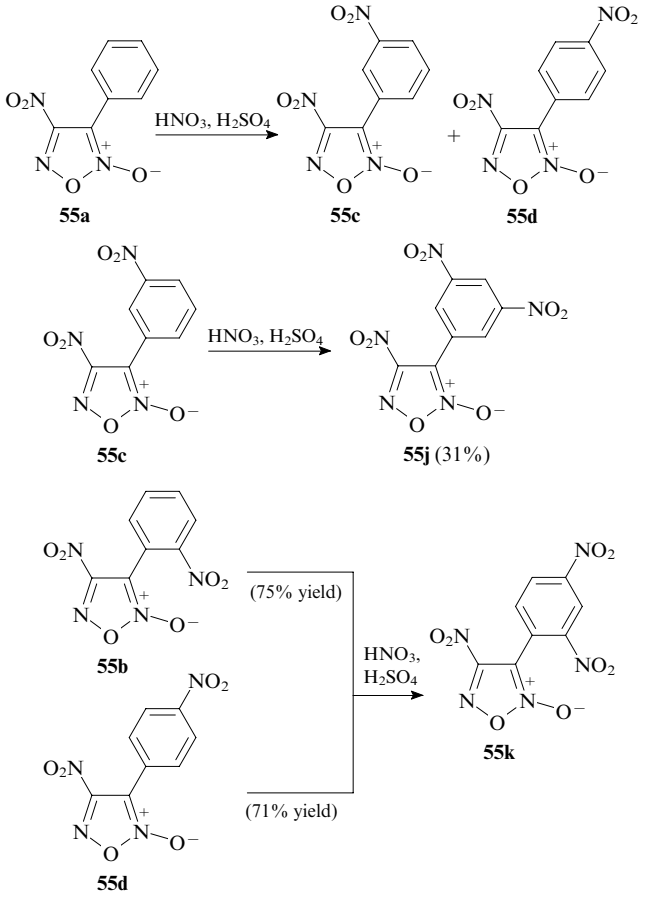
64a **147** (12%) **149** **59a** **148** (10.6%) **147** (12%)

5. Orientation effect of the nitrofuroxanyl moiety on the nitration of the aromatic ring

It was shown [111] that the unsubstituted furoxan ring acts as the *ortho*, *para* directing group in the nitration of the phenyl group in 3-phenylfuroxan. More recently, the nitration of monoarylnitrofuroxans was investigated [88] using 3-aryl-substituted [phenyl- (**55a**), 2-nitrophenyl- (**55b**), 3-nitrophenyl- (**55c**) and 4-nitrophenyl- (**55d**)] 4-nitrofuroxans. In all cases, the nitration was performed with a mixture of equal volumes of 100% nitric and concentrated sulfuric acid (the molar ratio substrate : HNO_3 = 1 : 10). It was shown that the nitration of 4-nitro-3-phenylfuroxan (**55a**) proceeds in high yield already at 0 °C and affords a mixture of 4-nitro- and 3-nitrophenyl derivatives **55d** and **55c** in approximately equal amounts (the total yield was 86%).

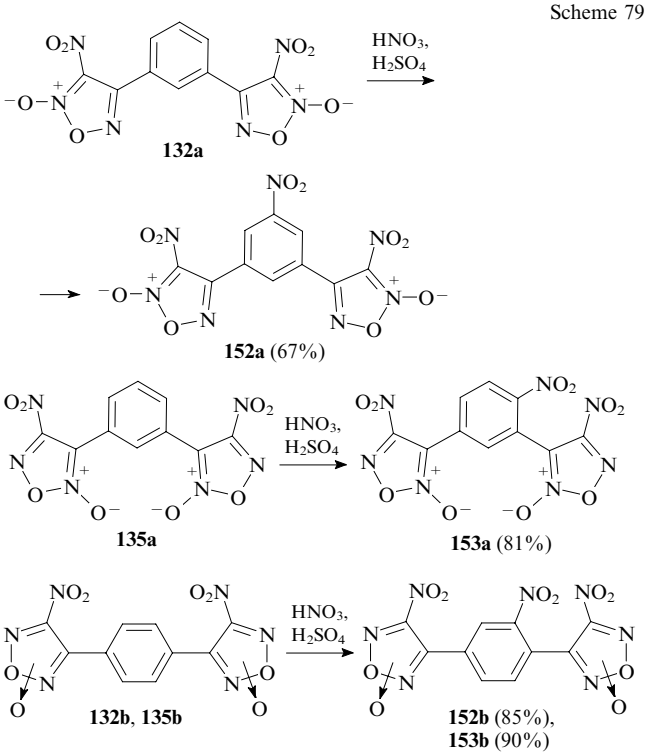
Therefore, the 4-nitrofuroxan moiety acts as a mixed *ortho*(*para*) direcror and *meta* direvtor in the nitration of the 3-phenyl group. In the nitration of 2-, 3- and 4-nitrophenyl derivatives **55b**–**d**, the direction of the insertion of the second nitro group is always determined exclusively by the nitro group at the benzene ring, resulting in the formation of dinitro derivatives **55j**,**k**, in which the second nitro group is attached in the *meta* position with respect to the first nitro group. Due to the deactivating effect of the nitro group in compounds **55b**–**d**, the introduction of the second nitro group required an increase in the temperature to 35–45 °C for 3-nitrophenyl derivative **55c** and to 25–30 °C for 2- and 4-nitrophenyl derivatives **55b**,**d** (Scheme 78).[88]

Scheme 78



A somewhat different directing effect of the nitrofuroxan moiety was observed in the nitration reactions of 1,3- and 1,4-bis(nitrofuroxanyl)benzenes **132a**–**c** and **135a**–**c**.[14] The nitration of 1,3-bis(3-nitrofuroxan-4-yl)benzene (**132a**), in which the furoxan ring is attached to the aromatic ring at the C(4) atom, furnishes only 5-nitro isomer **152a**. By contrast, the nitration of 1,3-bis(4-nitrofuroxan-3-yl)benzene (**135a**), in which the furoxan ring is bound to the aromatic ring at the C(3) atom, gives 4-nitro derivative **153a**. Therefore, two 4-nitrofuroxan-3-yl moieties in the 1,3 positions exhibit the concerted *ortho*(*para*) directing effect, unlike the 3-nitrofuroxan-4-yl moieties providing the concerted *meta* direction.

Scheme 79

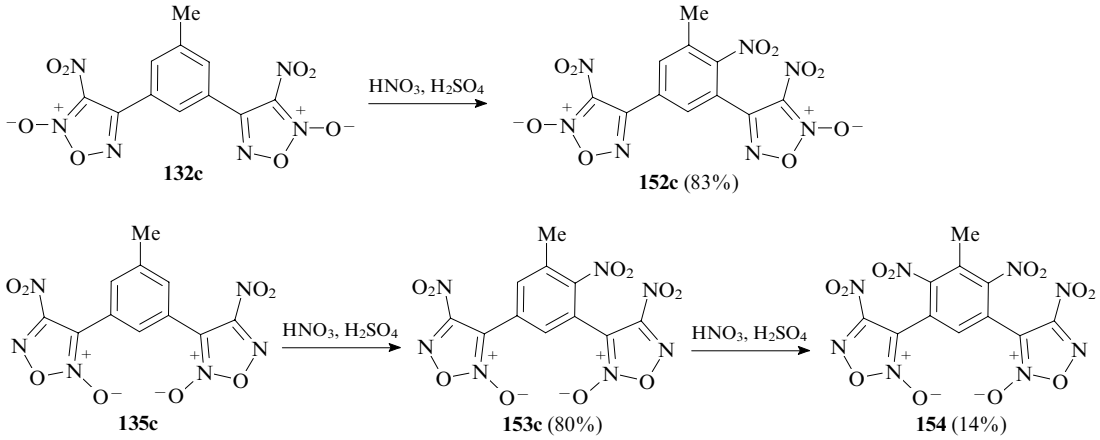


Isomers: 3-nitro (**132b**, **152b**), 4-nitro (**135b**, **153b**)

The difference in the orientation effect of different isomers of nitrofuroxan is associated with the specific features of the electron density distribution in the furoxan ring. The furoxan ring has a pronounced electron-withdrawing character; however, due to the resonance effect of the N-oxide group, the C(3) atom of the furoxan ring has high electron density, resulting in the activation of the *ortho* and *para* protons of the aromatic ring for the electrophilic attack. Since the regioselectivity of the nitration of 1,4-isomers **132b** and **135b** is invariant, the NO_2 groups occupied only position 2 of the aromatic ring to form compounds **152b** and **153b** regardless of the position of the nitro group in the nitrofuroxan moieties of the starting compounds (Scheme 79).

The direction of the insertion of the NO_2 group in the nitration reaction of methyl-substituted bis(3-nitrofuroxan) **132c** and bis(4-nitrofuroxan) **135c** was determined exclusively by the electron-donating effect of the methyl group, resulting in the formation of the corresponding 4-nitro derivatives at the benzene ring **152c** and **153c**. The nitration of compound **135c** produced also dinitro derivative **154** in low yield. However, the exhaustive transformation of compound **135c** into dinitro derivative **154** by the nitration was

Scheme 80



not achieved due to the deactivating effect of the already introduced nitro group (Scheme 80).

The synthesized isomeric bis(nitrofuroxanyl)benzenes are of practical interest. In particular, derivatives **153a**,**b** can be investigated as potential high energy materials because they have high enthalpy of the formation (297 kJ mol^{-1}) and high thermal stability (the temperature of the onset of decomposition is higher than 180 °C). Compounds **132a** and **135a** exhibit high inhibitory and bactericidal activity against *Staphylococcus aureus* and *Escherichia coli*.

VI. Conclusion

As can be seen from the data presented in this review, the chemistry of amino- and nitrofuroxans has received great attention from researchers. In the last years, this field has been extensively developed. In addition to the known methods (oxidation of amino- and nitroglyoximes, the dehydration of α-nitro oximes), fundamentally new approaches were elaborated for the formation of both types of these compounds: sextet rearrangements at the nitrogen atom for the synthesis of aminofuroxans and the nitrosation of substituted acrylic acids and salts of 2-hydroxyimino-1,1-dinitroethanes for the synthesis of nitrofuroxans. The mechanism of the furoxan ring formation for the latter process giving nitrofuroxans was determined. This reaction provides a route to the previously unknown isomeric 1,3- and 1,4-bis(nitrofuroxanyl)benzenes and their nitroaryl derivatives. The latter, along with 3,3′-azo-4,4′-dinitrofuroxan, are of interest as high energy materials. Methods for the transformation of aminofuroxans into nitro derivatives by means of the oxidation with peroxide oxidizing agents and of nitrofuroxans into amino derivatives by the nucleophilic displacement of the nitro group with an amino group are well developed. A multitude of functional derivatives of both amino- and nitrofuroxans were synthesized using the transformation of the second substituent of the furoxan ring, in particular, by means of the nucleophilic substitution of the azido group in azidocarbonylfuroxans or the reduction of carbonyl or ester groups in acylfuroxans or esters of furoxancarboxylic acids.

In addition to the oxidation to nitrofuroxans, both isomers of aminofuroxans can be oxidized to azo derivatives with one-electron oxidants, and azofuroxans containing electron-donating substituents can be oxidized to azoxy derivatives. On the other hand, azoxyfuroxans can be synthesized by the reductive condensation of nitrofuroxans. One of the quite new transformations of acylated derivatives of aminofuroxans, which are generated on treatment with Ac_2O, isocyanates or isothiocyanates, are azole–azole rearrangements giving other heterocycles (various triazoles and thiadiazoles) accompanied by the release of the latent nitro group of the furoxan ring. The conditions of the previously unknown transformation of furoxanyldiazonium derivatives into nitrofuroxans were found based on the results of detailed investigations of the Mannich reaction with aminofuroxans.

A new field of application of aminofuroxans was found in the very recent past. This is the transformation of these compounds into a new heterocyclic system, *viz*., 1,2,5-oxadiazolo[3,4-*c*]cinnoline 1,5-dioxide, based on nitraminofuroxans. Along with the replacement by the amino group, the nitro group in nitrofuroxans can be replaced under the action of other nucleophiles, for example, with thioalkyl(thioaryl) or alkoxy groups and even a hydride ion. The detailed investigations of the rearrangement of aminonitrofuroxans to 1,2,3-triazole 1-oxides resulted in the experimental detection of an intermediate, the reaction of which with amine gives rearrangement products. Unfortunately, attempts to synthesize diaminofuroxan **1** failed, but new information shedding light on the factors responsible for its low stability was obtained. New biologically active compounds were found among nitrofuroxan derivatives. It is quite evident that the chemistry of amino- and nitrofuroxans is far from being exhausted. Taking into account the results of investigations performed in the past years, new practically important results will be expected to be obtained for this series of compounds.

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