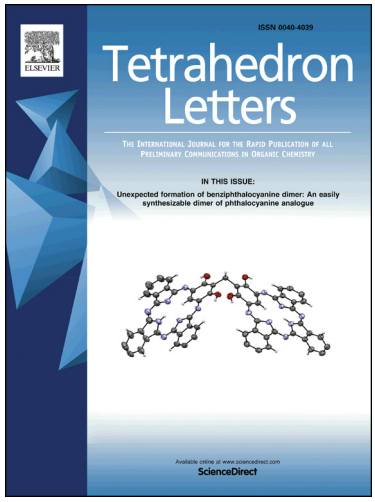

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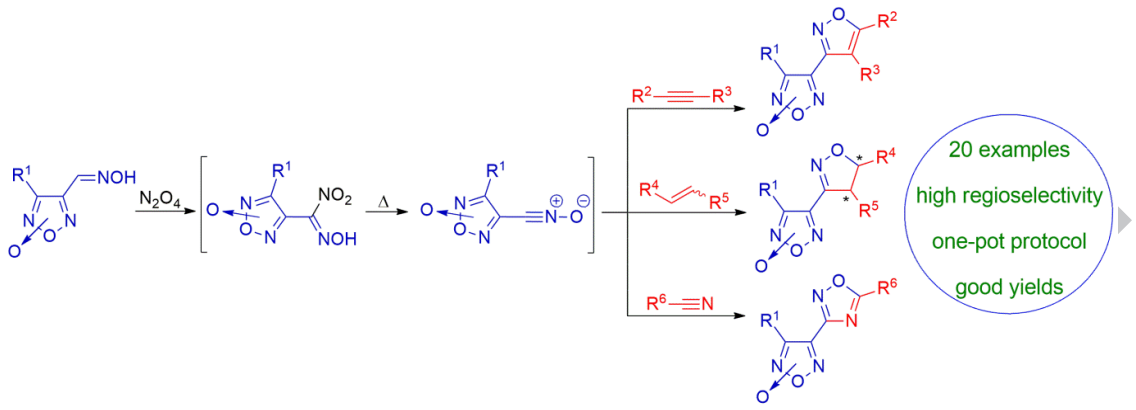

Versatile approach to heteroarylfuroxan derivatives from oximinofuroxans *via* a one-pot, nitration/thermolysis/[3+2]-cycloaddition cascade

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Abstract

A simple, general, and regioselective method has been developed for the synthesis of a series of heteroarylfuroxans, including isoxazolyl-, isoxazolinyl- and (1,2,4-oxadiazolyl)furoxans. The described method is based on a cascade of one-pot processes, including the nitration of furoxancarbaldehyde oximes, thermolysis of the formed nitrolic acids to generate furoxancarbonitrile oxides, and [3+2]-cycloaddition with an appropriate dipolarophile – alkynes, olefins, or activated nitriles.

Keywords: furoxan; isoxazole; nitrolic acids; thermolysis; nitrile oxides; [3+2]-cycloaddition.

The design of potential drugs with improved pharmacokinetic profiles has in recent years been focused on the molecular hybridization of diverse compounds with known pharmacological activities.[1] In particular, special efforts have been directed towards the synthesis of pharmacologically oriented structures comprising of a framework capable of nitric oxide (NO) release, including 1,2,5-oxadiazole 2-oxides (furoxans) which are capable of exogenous NO release in the presence of thiol cofactors.[2] The incorporation of the furoxan motif as a potential

NO donor into drug candidates with known pharmacological activities has been recently explored by a number of research groups,[3] and new hybrid structures with neuroprotective and precognitive,[4] cytotoxic,[5] antihelmintic,[6] antibacterial,[7] and antiaggregant[8] activities have been reported.

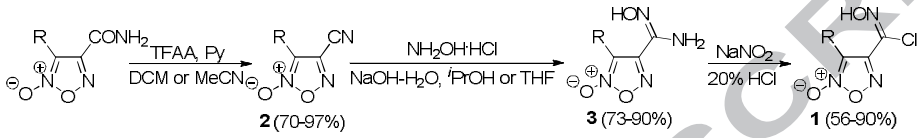
Our research group has significant experience in furoxan chemistry[9] and has developed effective methods for the preparation of new types of hybrid structures, combining a furoxan ring with various pharmacophoric heterocycles (1,2,3-[10a-c] and 1,2,4-triazole,[10d] 1,2,4-,[10e] 1,2,5-[10f,g] and 1,3,4-oxadiazoles,[10h] tetrazole,[10i] pyridines,[10j] tetrahydroisoquinolines,[10j] and others[10k-n]), whereas isoxazolyl- and isoxazolinylfuroxans are practically unknown. Meanwhile, isoxazoles exhibit various biological activities[11] and are a common scaffold of many drugs, such as flucloxacillin, valdecoxib, and dicloxacillin. The isoxazoline core is also found in numerous biologically active compounds,[12] and the 1,2,4-oxadiazole motif is an important subunit in advanced materials and bioactive compounds.[13] A useful approach for the design of such structures might involve the [3+2]-cycloaddition of furoxancarbonitrile oxides with alkynes and olefins, respectively. Additionally, activated nitriles can also be introduced in the cycloaddition protocol to prepare (1,2,4-oxadiazolyl)furoxans.

Herein, we present the development of a versatile approach for the regioselective synthesis of hybrid heterocyclic structures combining, in one molecule, furoxan and isoxazole, isoxazoline, or 1,2,4-oxadiazole heterocycles *via* a cascade of one-pot processes: the nitration of furoxancarbaldehyde oximes, thermolysis of the intermediate nitrolic acids to generate furoxancarbonitrile oxides, and [3+2]-cycloaddition with an appropriate dipolarophile such as alkynes, olefins, or activated nitriles.

Common methods for the preparation of nitrile oxides include the dehydrochlorination of hydroximoyl chlorides under the action of bases,[14] the oxidation of aldoximes,[15] the dehydration of primary nitroalkanes, and the thermal cycloreversion of furoxans, which are dimers of nitrile oxides.[16] The dimerization of nitrile oxides into furoxans is a common side-process in [3+2]-cycloaddition reactions. Over the last years, new methods for the generation of nitrile oxides have been developed. In particular, the water-assisted generation of nitrile oxides from hydroximoyl chlorides under weakly acidic conditions (pH 4–5) was recently reported.[17] Photoredox catalysis was also used for the visible-light-mediated generation of nitrile oxides from hydroxyimino acids.[18] Nitrile oxide intermediates are also formed upon the treatment of substituted aldoximes with alkyl nitrites at 65 ^{o}C.[19] Additionally, a one-pot method for the generation of furoxancarbonitrile oxides by the thermolysis of furoxanylnitrolic acids, resulting in terfuroxan formation, was proposed by Gasco and co-workers.[20] This research group has also

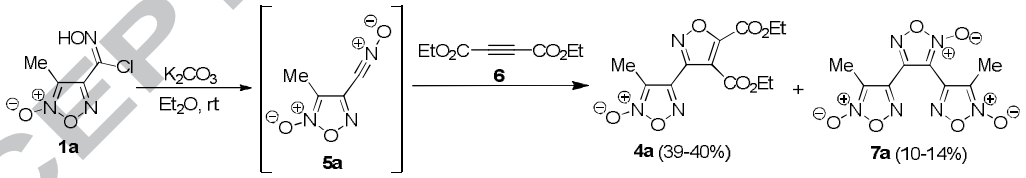
managed to prepare the first and only example of an isoxazolylfuroxan *via* the thermolysis of phenylfuroxanylnitrolic acid in the presence of phenylacetylene.

Recently,[10f] our group has developed a general method for the preparation of (chlorohydroxamoyl)furoxans **1** from readily available cyanofuroxans **2** using a two-step protocol, *via* their reaction with hydroxylamine and subsequent transformation of the resulting (aminohydroxamoyl)furoxans **3** into chlorides **1** under the action of $NaNO_2$ in the presence of HCl (Scheme 1).



Scheme 1. Synthesis of (chlorohydroxamoyl)furoxans **1**

Therefore, we initially studied the dehydrochlorination of compounds **1** for the generation of furoxancarbonitrile oxides using 4-(chlorohydroxamoyl)-3-methylfuroxan **1a** as a model substrate. Detailed screening for the synthesis of furoxanylisoxazole **4a** *via* the base promoted generation of nitrile oxide **5a** from chlorooximinofuroxan **1a** in the presence of diethyl acetylenedicarboxylate **6** is summarized in Table S1 (ESI). Unfortunately, all approaches to generate nitrile oxide **5a** proved to be ineffective. The use of K_2CO_3 in Et_2O in the presence of dipolarophile **6** (3-4 equiv.) at room temperature was somewhat better (ESI; Table S1, entries 11, 12); however, the undesired terfuroxan **7a** was always formed in significant amounts (Scheme 2).

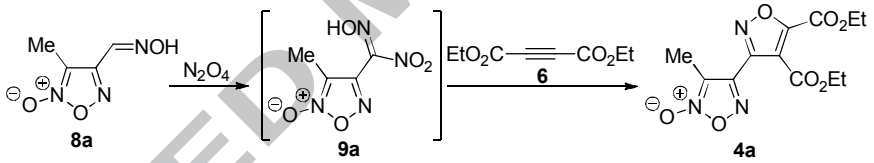


Scheme 2. Generation of nitrile oxide **5a** *via* the dehydrochlorination of furoxan **1a**.

Therefore, we decided to study the possibility for the synthesis of isoxazolylfuroxans **4** *via* generation of nitrile oxides **5** by the thermolysis of furoxanylnitrolic acids **9** in the presence of an appropriate dipolarophile. It is known[20] that nitrolic acids eliminate HNO_2 to give nitrile oxides at elevated temperatures, which was encouraging since nitrile oxide cycloaddition is usually accelerated under such conditions.[15,16] Thus, a set of furoxanylnitrolic acids **9a-c** which were synthesized *via* nitration of the corresponding oximes **8a-c** under the action of N_2O_4 at 0 ^oC, and subjected to further transformations without isolation, were selected for investigation.

Oxime **8a** and diethyl acetylenedicarboxylate **6** were chosen as model substrates for optimization of the reaction conditions. The quantities of N_2O_4 and dipolarophile **6**, the solvent, the temperature, and the reaction time were varied. Nitration of the initial oxime **8a** with a 3-5 molar excess of N_2O_4 in PhH with subsequent heating at reflux in the presence of dipolarophile **6** afforded the target isoxazole **4a** in moderate yield (Table 1, entries 1-3). Replacement of PhH with $CHCl_3$ and performing the reaction at room temperature did not provide the desired product (Entry 4). Increasing the reaction temperature to 60 °C provided isoxazole **4a** and varying the amount of N_2O_4 revealed the necessary use of excess N_2O_4 (Entries 5-7). Increasing the excess of the dipolarophile only slightly altered the yield (Entries 8, 9). At the same time, heating the reaction mixture at reflux with dipolarophile **6** (1 equiv.) for 2 h gave the highest yield of isoxazole **4a** (Entry 10), while an extended reaction time slightly decreased the yield (Entry 11). Therefore, the nitration of oxime **8a** with N_2O_4 (5 equiv.) and dipolarophile **6** (1 equiv.) in $CHCl_3$ for 2 h was the optimal reaction conditions (Entry 10).

Table 1. Reaction conditions screening for the synthesis of isoxazolylfuroxan **4a** based on the [3+2]-cycloaddition of dipolarophile **6** with nitrile oxide **5a**, generated by the thermolysis of furoxanylnitrolic acid **9a**.[a]



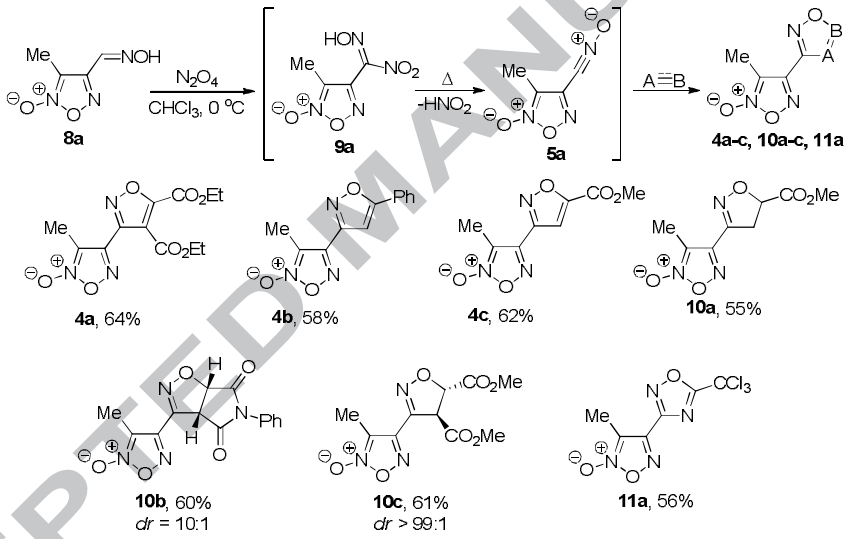
Entry	N_2O_4 (equiv.)	**6** (equiv.)	Solvent	T (°C)	Time (h)	Yield **4a** (%)[b]
1	3	1	PhH	80	1	30
2	5	1	PhH	80	2	20
3	5	3	PhH	80	1	33
4	5	3	$CHCl_3$	20	24	-[c]
5	1	1	$CHCl_3$	60	3	15
6	3	1	$CHCl_3$	60	2	22
7	5	1	$CHCl_3$	60	1	52
8	5	2	$CHCl_3$	60	2	55
9	5	3	$CHCl_3$	60	2	45
10	5	1	$CHCl_3$	60	2	64
11	5	1	$CHCl_3$	60	3	61

[a] Reagents and conditions: oxime **8a** (1 mmol), N_2O_4, solvent (10 mL), 0 °C, 30 min, then dipolarophile **6**, reflux.
[b] Isolated yield.
[c] No reaction.

The optimized conditions were suitable for introduction of the *in situ* formed nitrolic acid **9a** into [3+2]-cycloaddition reactions with various C=C, C≡C, and C≡N dipolarophiles to give

the corresponding isoxazolylfuroxans **4a-c**, isoxazolinylfuroxans **10a-c**, and (1,2,4-oxadiazolyl)furoxan **11a** in good yields. The reaction with terminal olefins and acetylenes proceeded with high regioselectivity; only single regioisomers **4b,c** and **10a** were formed (Table 2). The high regioselectivity for the formation of 3,5-disubstituted isoxazoles and isoxazolines was established on the basis of literature precedence.[19,21] ^{1}H NMR analysis of isoxazoles **4b** and **4c** showed characteristic singlets at 7.66 and 7.48 ppm, respectively, for the isoxazole proton (C^4-H), while for compound **10a** the isoxazoline proton triplet 5.26 ppm (C^5-H) and multiplet 3.72-3.76 ppm (CH_2) were observed. The diastereoselectivity of compounds **10b,c** was reflected by the geometry of the initial olefins.

Table 2. Scope for the synthesis of 4-heteroaryl-3-methylfuroxans *via* the one-pot nitration/thermolysis/[3+2] cycloaddition cascade[a]

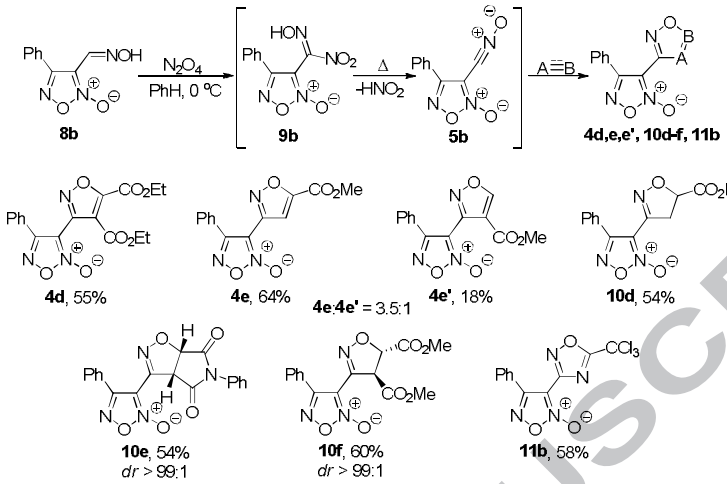


[a] Reagents and conditions: oxime **8a** (1 mmol), N_2O_4 (5 mmol), $CHCl_3$ (10 mL), 0 °C, 30 min, then dipolarophile (1 mmol), reflux.

[b] Isolated yield.

The thermolysis of nitrolic acid **9b** and subsequent cycloaddition of nitrile oxide **5b** with the same dipolarophiles was more successful in benzene at reflux, resulting in good yields of the target heteroarylfuroxans. All reactions proceeded with high regioselectivity; however, in the reaction with methyl propiolate, the second regioisomer **4e'** was also formed in the ratio **4e**:**4e'** = 4:1 (Table 3). The high regioselectivity for the formation of compounds **4d,e** and **10d** as well as the diastereoselectivity of compounds **10e,f** were supported by NMR data (see ESI).

Table 3. Scope for the synthesis of 3-heteroaryl-4-phenylfuroxans *via* the one-pot nitration/thermolysis/[3+2] cycloaddition cascade[a,b]

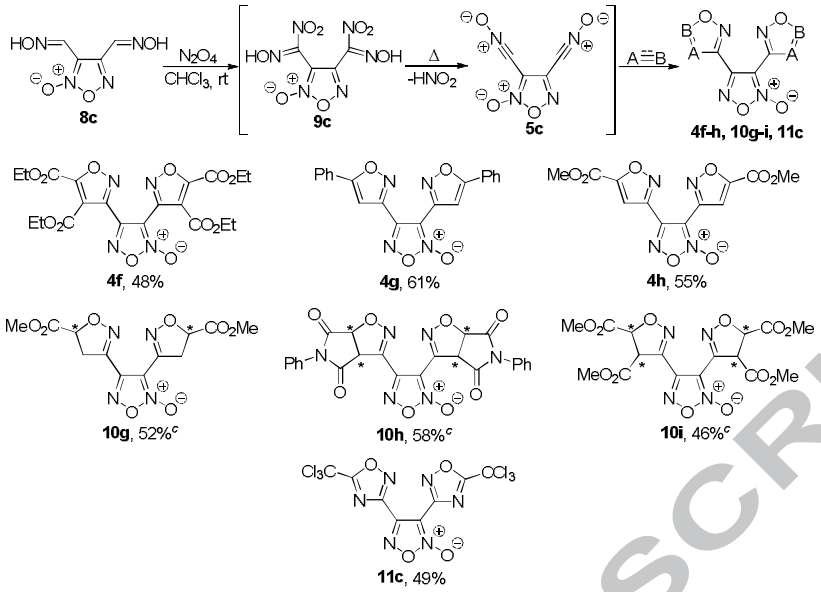


[a] Reagents and conditions: oxime **8b**[20a] (1 mmol), N_2O_4 (5 mmol), PhH (10 mL), 0 °C, 30 min, distillation of excess N_2O_4, then dipolarophile (1 mmol), reflux.

[b] Isolated yields.

Bisnitrolic acid **9c** is described in the literature as an isolated explosive complex with dioxane.[22] Therefore, this nitrolic acid was synthesized *in situ* by the analogous nitration of oxime **8c** under the action of N_2O_4; the best conditions for thermolysis proved to be in $CHCl_3$ at reflux. The one-pot cycloaddition of *in situ* generated bis(nitrile oxide) **5c** with the same dipolarophiles proceeded smoothly and the target products were obtained in good yields (Table 4). In all cases, the cycloaddition occurred at both nitrile oxide motifs and the products of monocycloaddition were not isolated. Thus, it can be concluded that the reactivity of both nitrolic acid and nitrile oxide functionalities under thermal conditions does not depend on their position on the furoxan ring. Compounds **10g-i** could be formed as a mixture of diastereomers (see ESI for the structures of possible stereoisomers), however it was not possible to estimate the diastereoselective ratios due to overlapping of the proton signals in the ^{1}H NMR spectra.

Table 4. Scope for the synthesis of bis(heteroaryl)furoxans *via* the one-pot nitration/thermolysis/[3+2] cycloaddition cascade[a,b]



[a] Reagents and conditions: oxime **8c**[23] (1 mmol), N_2O_4 (10 mmol), $CHCl_3$ (10 mL), rt, 30 min, distillation of excess N_2O_4, then dipolarophile (2 mmol), reflux.

[b] Isolated yields.

[c] Obtained as a mixture of diastereoisomers.

All synthesized isoxazoles **4**, isoxazolines **10**, and 1,2,4-oxadiazoles **11** were characterized by IR, ^{1}H and ^{13}C NMR, and HRMS. The structure of compound **4c** was additionally confirmed by single-crystal X-ray diffraction (Fig. 1).

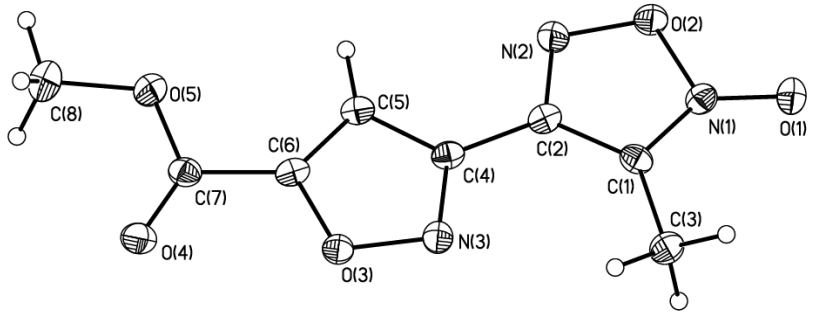


Figure 1. General view of compound **4c**. Atoms are represented by probability ellipsoids of atomic vibrations (ρ=50%).

In summary, a general, highly effective, regio- and diastereoselective method for the synthesis of isoxazolyl-, isoxazolinyl-, and (1,2,4-oxadiazolyl)furoxans has been developed.[24] This method includes a cascade of one-pot reactions: the nitration of furoxancarbaldehyde oximes using dinitrogen tetraoxide, thermolysis of the formed nitrolic acids to generate furoxancarbonitrile oxides, and [3+2]-cycloaddition with an appropriate dipolarophile, containing C≡C, C=C, and

C≡N bonds. It is especially important to note that these reactions are not affected by the position of the functional group at either the C(3) or C(4) furoxan carbon atom. To the best of our knowledge, this study represents the first general and comprehensive investigation of the reactivity of furoxancarbonitrile oxides in cycloaddition processes.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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24. *General procedure for the synthesis of heteroarylfuroxans* **4**, **10**, **11**: A solution of dinitrogen tetraoxide (0.46 g, 5.0 mmol for oximes **8a,b** and 0.92 g, 10.0 mmol for oxime **8c**) in dry $CHCl_3$ or PhH (5 mL) was added dropwise to a magnetically stirred suspension of the corresponding oxime (1.0 mmol) in dry $CHCl_3$ or PhH (5 mL) at 0-5 ^oC. The reaction mixture was stirred at 0-5 ^oC for 30 min, then the cooling bath was removed and the resulting solution concentrated *in vacuo* to remove excess N_2O_4 (final volume 4 mL, in reactions with oxime **8a** excess N_2O_4 was not removed). The appropriate dipolarophile (1.0 mmol) was added and the resulting mixture was heated at reflux for 3 h. The solvent was then evaporated and the residue purified by column chromatography.

Highlights

- The cycloaddition reactions of furoxancarbonitrile oxides have been performed.
- This approach enables to obtain various *N*,*O*-heteroarylsubstituted furoxans.
- Target heteroarylfuroxans are formed in good yields with high regioselectivity.