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Digest paper

Recent advances in the synthesis and functionalization of 1,2,5-oxadiazole 2-oxides

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ABSTRACT

Among the variety of nitrogen heterocycles, the furoxan (1,2,5-oxadiazole 2-oxide) scaffold has attracted considerable attention owing to its ability to release NO under physiological conditions. Therefore, significant efforts of organic chemists have been directed toward the construction of new drug candidates containing the NO-donor furoxan subunit connected to a known pharmaceutical or a potential pharmacophore by C—C/C—N bonds or through an appropriate linker. This digest summarizes the recent information concerning both new synthetic approaches for the furoxan ring construction and various methods for the functionalized furoxan synthesis with particular focus on the last three years. Methods for the furoxan ring formation including cyclodimerization of nitrile oxides, nitrosation of unsaturated compounds, and acylation of dinitromethane sodium salt are reviewed. The functionalization of furoxan ring is represented by nucleophilic substitution of nitro and arylsulfonyl groups as well as by different condensations of cyano-, carbonyl- and carboxyfuroxan derivatives. Synthesis of hybrid structures combining NO-donor furoxan ring and some pharmacophoric moiety is also considered.

Contents

Introduction

In the late 1990s, Nobel Prize winners Furchgott, Ignarro, and Murad discovered that nitric oxide (NO) is a ubiquitous and crucial regulator for cellular metabolism, affecting various physiological and pathophysiological processes in mammals.[1] An important focus in modern medicinal chemistry is the search for compounds able to release NO (NO-donors) in the body, either enzymatically or independently of NO synthases. Among them, the furoxan moiety has been the subject of increased attention, pioneered by Gasco,[2] owing to a number of interesting biological activities related to the ability of furoxans to exogenous NO release in the presence of thiol cofactors.[3] The incorporation of the furoxan motif as a potential NO-donor into drug candidates with known pharmacological activity has been widely used in the last decade and new furoxan-containing structures with neuroprotective and precognitive,[4] cytotoxic,[5] antihelmintic,[6] antibacterial,[7] and antiaggregant[8]

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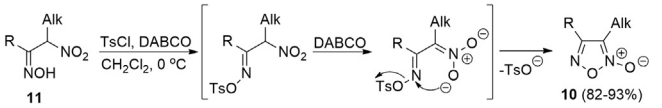
activities were revealed. In addition, furoxans are of interest as potential components of energetic formulations due to a positive formation enthalpy and the presence of two active oxygen atoms in the ring structure.[9] Synthesis of the furoxan derivatives is based either on the furoxan ring formation from acyclic precursors already containing necessary substituents or through the transformation of functional groups attached to the furoxan ring. The chemistry of furoxans, including methods for their preparation and the synthesis of practically oriented structures, has been developed rather intensively in recent years, and several reviews devoted to specific topics of this problem were published.[3,9b,10] Therefore, the current review is focused on the recent advances (mainly, for the last three years) both in the development of new methods for the furoxan ring construction and on various approaches to its regio- and chemoselective functionalization.

Recent approaches to the furoxan ring construction

The widely known methods for the furoxan ring construction include cyclodimerization of nitrile oxides, oxidation of *vic*-glyoximes, and dehydration of α-nitrooximes.[11] Several examples of alkene domino reactions resulting in the furoxan ring formation are also known.[12] In recent years, all these approaches received further development and new methods for the furoxan ring construction were elaborated.

3,4-Bis(azidocarbonyl)furoxan **1** was synthesized through the cycloaddition of azidocarbonylformonitrile oxide **2** generated *via* successive nitrosation of potassium monohydrazinyl malonate **3** to azidocarbonylmalonic acid **4** followed by its nitrosation/nitration/decarboxylation cascade under the action of $NaNO_2$ in conc. HNO_3. However, furoxan **1** is a very dangerous liquid to handle; therefore, it was quickly transformed into 4-amino-3-azidocarbonylfuroxan **5** *via* the Curtius rearrangement[13] (Scheme 1).

[1,4]Dithiino[2,3-*c*:5,6-*c*']bis[1,2,5]oxadiazole di-*N*-oxide as an equilibrium mixture of two isomers **6a** and **6b** was synthesized by oxidation of 1,4-dithiane-2,3,5,6-tetraone tetraoxime **7** with HNO_3. Compound **7** was, in turn, prepared by reaction of dichloroglyoxime **8** with Na_2S. Further oxidation of the **6a** and **6b** mixture to mono- and bis-*S*-oxides gave each derivative as a single isomer, **9a** and **9b**, respectively (Scheme 2).[14]

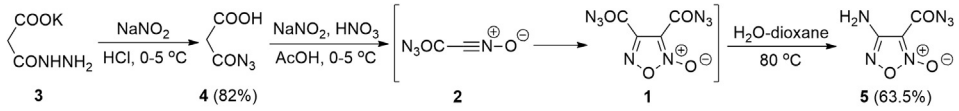


Scheme 3. Synthesis of 3-alkyl-4-arylfuroxans **10** *via* DABCO-mediated sulfonylation/cyclization cascade of α-nitro-ketoximes.

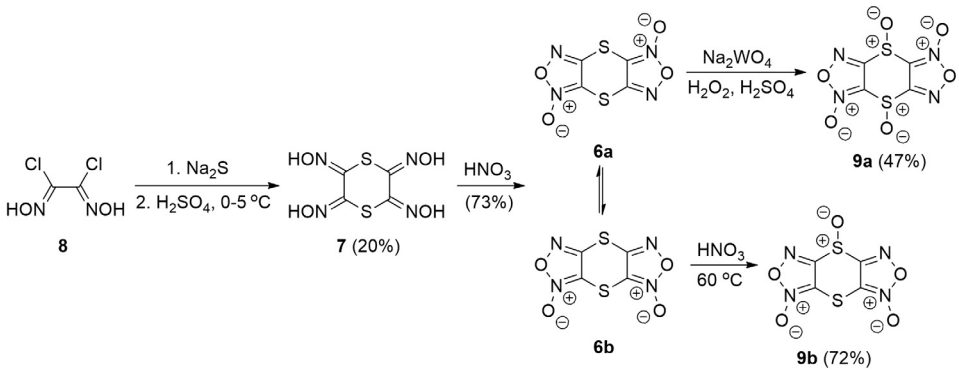
Recently, an efficient and completely regioselective method for the synthesis of 3-alkyl-4-arylfuroxans **10** *via* DABCO-mediated sulfonylation/cyclization cascade of α-nitro-ketoximes **11** under mild reaction conditions has been developed (Scheme 3).[15]

Several approaches for the synthesis of furoxan derivatives were developed on the basis of domino reactions of alkenes induced by nitrosating reagents. In particular, a mixture of isomeric furoxans **12** and **12′** with predominance of isomer **12** was synthesized from the corresponding disubstituted styrenes **13** using nitrosonium tetrafluoroborate in pyridine or in dichloromethane in the presence of an equimolar amount of pyridine. The acid-sensitive functional groups were found to be tolerant to both conditions. In contrast to conventional radical mechanism for the synthesis of disubstituted furoxans **12** in a $NaNO_2/H^+$ system, in this work the ionic mechanism was proposed (Scheme 4). First, a nitrosonium cation interacts with the olefin to afford cationic species **A** or **A′**. Then the pyridine abstracts the acidic proton from **A** and **A′** to afford nitroso alkenes, which react with another nitrosonium cation to afford intermediates **B** and **B′** followed by their cyclization to final furoxans **12** and **12′**. The authors presume that the regioisomers **12** and **12′** ratio is determined by the selectivity of the formation of nitrosonium cations **A** and **A′**. The same nitrosating reagent proved also to be suitable for the regioselective preparation of 4-nitro-3-phenylfuroxan from unsubstituted styrene.[16]

Interestingly, that under the action of sodium nitrite in acidic medium various styrenes substituted in the aromatic ring regioselectively afford 4-nitrofuroxans **14**.[17] This process occurs *via* generation of N_2O_3, which is added to double bond of initial styrene to form pseudonitrosite **C** followed by its nitrosation to dinitroso derivative **D**. The latter is isomerized into nitroglyoxime **D′** which undergoes oxidative cyclization to form the final nitrofuroxan **14** (Scheme 5).



Scheme 1. Synthesis of 3,4-bis(azidocarbonyl)furoxan **1** and 4-amino-3-azidocarbonylfuroxan **5**.



Scheme 2. Synthesis of [1,4]dithiino[2,3-*c*:5,6-*c*']bis[1,2,5]oxadiazole di-*N*-oxide **6a** and **6b** and oxidation to mono- and di-*S*-oxides **9a,b**.