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The first synthesis of 3-nitro-4-[(*s*-tetrazin-3-yl)amino]furazans

Aleksei B. Sheremetev,* Nadezhda V. Palysaeva and Marina I. Struchkova

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation.
Fax: +7 499 135 5328; e-mail: sab@ioc.ac.ru

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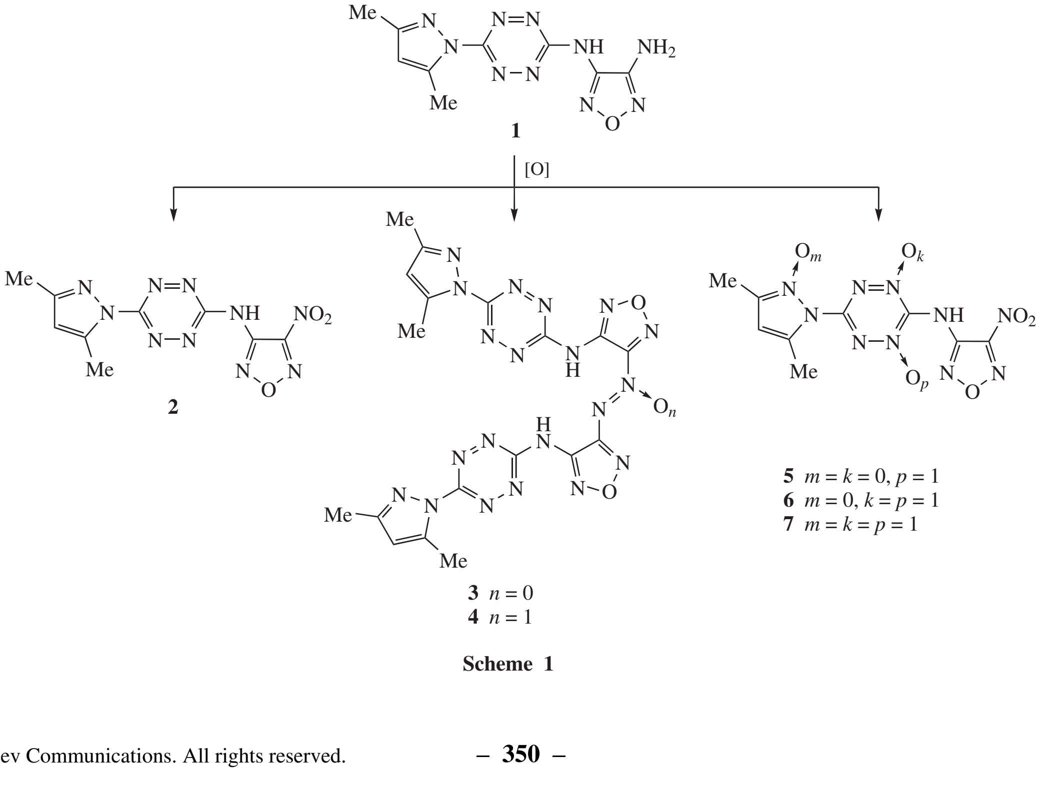
Oxidation of 3-amino-4-[(*s*-tetrazin-3-yl)amino]furazans with peroxy acids or 30% $H_2O_2/Na_2WO_4/H_2SO_4$ system results in transformation of the amino group into the nitro one and is accompanied by formation of *N*-oxides at tetrazine moiety.

Five- and six-membered nitrogen rich heterocycles,[1] *e.g.*, furazans (1,2,5-oxadiazoles)[2] and *s*-tetrazines,[3] have found widespread application in high energy material chemistry. The presence of nitro groups in their molecules provides a better oxygen balance. However, *s*-tetrazine bearing nitro group at carbon atom displayed poor thermal and chemical stability.[3(*a*)] Nitrofurazans, on the other hand, exhibit good thermal stability (for example, 3,4-dinitrofurazan can be distillated at atmosphere pressure at 168 °C[1(*e*),2(*e*)] without decomposition). Furazans with NH or NH_2 groups display diverse physico-chemical properties depending on the specific substitution within the molecule.[4] Thus, the amino group and the adjacent nitro group can form intramolecular hydrogen bond similar to ones observed for 1,3,5-triamino-2,4,6-trinitrobenzene (TATB) molecule as well as for various similar thermostable explosives.[1(*h*),(*j*)] In our continuing interest in the development of efficient protocols to construct new energetic materials, we have now synthesized secondary amines incorporating nitrofurazan and *s*-tetrazine moieties.[†]

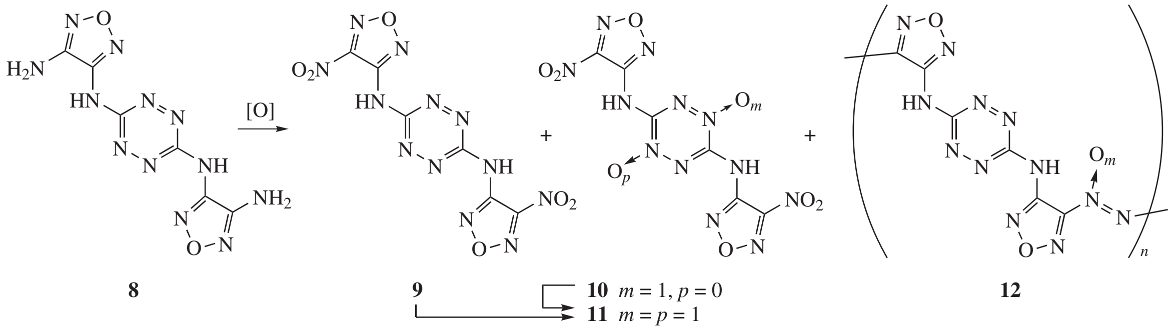
The oxidation of amines into the corresponding nitro compounds is an important reaction in synthetic organic chemistry.[5] Within the furazan series, this transformation is usually carried out with peroxy acids[2(*d*),(*i*),6] or $H_2O_2/Na_2WO_4/H_2SO_4$. The same oxidants, however, are prone to transform tetrazine into its *N*-oxides.[3(*a*)–(*d*),(*g*),(*l*)]

Our initial studies focused on the oxidation of readily available 3-amino-4-[6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]aminofurazan **1**.[7] A variety of reagents were screened in order to find effective conditions to promote the formation of nitro compound **2** (Scheme 1). Attempts to oxidize amine **1** were made in the past including the use of large excess of both AcOOH and MCPBA, but even after prolonged reaction times only traces of the desired **2** were formed without any traces of tetrazine-*N*-oxides. Treatment of amine **1** with 5 equiv. CF_3COOOH at ambient temperature for 3 h gave 16% of the nitro product **2** and 12% of azoxy compound **3**. Prolongation of the reaction time to 24 h did not improve the conversion. The use of 10 and 20 equiv. CF_3COOOH increased the yield of compound **2** to 21 and 27%, respectively, and a mixture of inseparable *N*-oxides was also formed.

Application of system 30% $H_2O_2/Na_2WO_4/H_2SO_4$ (10 equiv.) at 22 °C and pH 1 provided 31% yield of nitro compound **2** after flash chromatography. The separation also gave unreacted starting amine **1** (28%), azoxy compound **3** (12%) and azo compound **4** (15%). Azo- and azoxyfurazan formation is a well documented side-reaction for oxidation with $H_2O_2/Na_2WO_4/H_2SO_4$.[6] However, we were pleased to find that the treatment of amine **1** with 1 equiv. Na_2WO_4, using a 4:1 mixture of 35% H_2O_2 (40 mol equiv.) and 96% H_2SO_4 at room temperature for



Scheme 1



8 **9** **10** $m = 1, p = 0$ **11** $m = p = 1$ **12**

Scheme 2

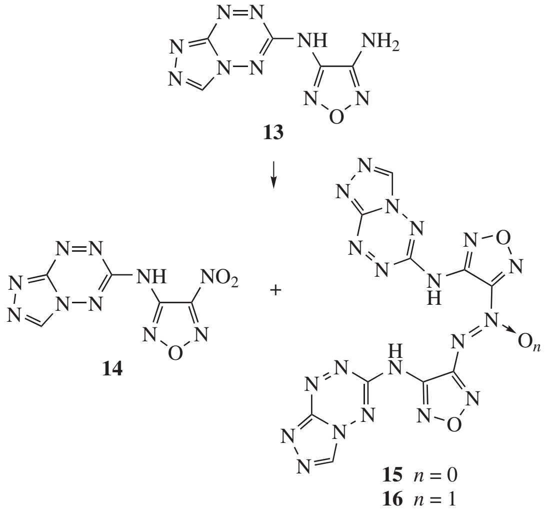
2.5 h improved the yield of the desired nitrofurazan **2** to 43%, while the amounts of the azo **3** (5%) and azoxy **4** (8%) products were lower. *N*-oxides **5**, **6** and **7** were also formed;[‡] they are easily separated by column chromatography.

The protocol[§] was examined and found to be effective for the oxidation of aminofurazans with various types of *s*-tetrazine substituents (Scheme 2). Oxidation of 3,6-bis(3-aminofurazan-4-ylamino)-*s*-tetrazine **8**[7] produced a 6:2:1 mixture of nitro compound **9** with mono- and di-*N*-oxides **10** and **11**, respectively (Scheme 2). An insoluble oligomer **12** was also obtained. The product **9** was isolated in 34% yield by chromatography. *N*-Oxides **10** and **11** proved inseparable by column chromatography. The major *N*-oxide **10** (11%) could be isolated by fractional crystallization of this mixture, while pure di-*N*-oxide **11** could be obtained only by the further oxidation of isolated nitro compounds **9** or **10** in the similar fashion.

To further highlight the applicability of this method, the triazolotetrazine-substituted aminofurazan **13** was oxidized into the nitro analogue **14** in 52% yield (Scheme 3). Again, a mixture of azo **15** (3%) and azoxy **16** (12%) by-products were formed. However, no oxidation of the triazolotetrazine moiety occurred here.

All of the nitro-, azo- and azoxyfurazans thus prepared are new, and their structures were proved by mass spectrometry, IR and ^{1}H, ^{13}C and ^{14}N NMR spectroscopy and elemental analyses.[¶]

The synthesized nitro compounds are strong NH-acids;[††] parent tetrazines are stronger acids than their *N*-oxides. The acidity of these compounds allows a large variety of energetic salts to be prepared. For example, the synthesis of 3,6-bis-(3-nitrofurazan-4-ylamino)-*s*-tetrazine salts (salts of **9**) was accomplished by reacting compound **9** with stoichiometric amounts of guanidine carbonate, aminoguanidine bicarbonate, ammonia, hydrazine, 3,3-dinitroazetidine,[8] 1,5-diamino-1*H*-tetrazole,[9] 3,6-dihydrazino-1,2,4,5-tetrazine,[3(*c*)] and 4,8-diamino-4*H*,8*H*-bisfurazano[3,4-*b*:3′,4′-*e*]pyrazine.[10] The high thermal stability of the parent NH-acids as well as the strongly marked hydrogen bonding in the salts provide their good resistance to temperature; typically, the salts decompose well above their relatively high melting points.



13 **14** **15** $n = 0$ **16** $n = 1$

Scheme 3

In summary, the chemistry here developed may be useful in the synthesis of libraries of nitrogen- and oxygen-rich functionalized heterocycles of high diversity, especially targeted on new energetic materials.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.11.017.

[†] To study the structure–properties relationships within furazan–tetrazine series, we recently investigated the structural requirements of the bridge that links these heterocycles and synthesized compounds with azoxy bridging unit. The preparation and evaluation of a series of 1-(6-R-*s*-tetrazin-3-yl)-2-(4-R′-furazan-3-yl)diazene oxides were presented at the All-Russian Conference on Chemistry of Nitrocompounds and Related Nitrogen–Oxygen Systems, Moscow, October 2009 (*Book of Abstracts*, p. 129).

[‡] The structures of the tetrazine-*N*-oxides given in Schemes 1 and 2 present the most plausible positions of *N*-oxides. According to the literature, oxidation of 3-(R-amino)-*s*-tetrazines leads to the formation of *N*-oxides in which the oxide moiety is in α-position with respect to the amino group. In the case of 3,6-di(R-amino)-*s*-tetrazine, *N*-oxide groups are formed at the 1- and 4-positions,[3(*a*),(*b*),(*g*)] whereas with 3-(R-amino)-6-R′-*s*-tetrazine (R′ = H, Cl, NO_2), N-oxidation occurs at two ring nitrogen atoms in α-position with respect to the amino group.[3(*a*),(*d*),(*l*)] In the ^{13}C NMR spectra, signals for carbon atoms of tetrazine *N*-oxides are shifted upfield by 7–16 ppm compared to those for the corresponding tetrazines.

[§] *General procedure for the preparation of nitrofurazans*. A mixture of sodium tungstate (0.05 mol) and the corresponding aminofurazan (0.05 mol) was added in small portions to a solution of 35% hydrogen peroxide (2 mol) and 96% H_2SO_4 (0.5 mol) with stirring and cooling at 10 °C. After stirring for 0.5 h at 10 °C the temperature was raised to 25 °C over a period of 0.5 h. The reaction mixture was stirred at room temperature until the complete consumption of the starting amine (2.5–5.5 h, according to TLC and NMR). The oxidation products were separated from the solution by filtration or extraction with EtOAc. The combined extracts were dried with $MgSO_4$ and evaporated. The residue was separated by column chromatography.

[¶] For characteristics of compounds **2–4**, **9–11** and **14–16**, see Online Supplementary Materials.

[††] For example, the pK_a value determined spectrophotometrically for compound **14** in water is 4.81.

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