Igor L. Yudin, Aleksei B. Sheremetev*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47, Leninsky Prosp., Moscow 119991, RUSSIA
Fax: (internal) +7 (095) 135 5328
E-mail: sab@ioc.ac.ru

Boris B. Averkiev, Mikhail Yu. Antipin

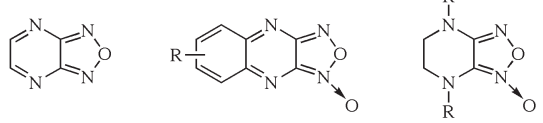
A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
28 Vavilov Street B-334,
Moscow 117813, RUSSIA
Fax: (internal) +7 (095) 135 5085
E-mail: M_Antipin@yahoo.com
Received July 21, 2004

Novel furoxanopyrazines have been synthesized *via* reaction of 2-alkoxy-3,5-dinitro-6-chloropyrazines with sodium azide.

J. Heterocyclic Chem., **42**, 691 (2005).

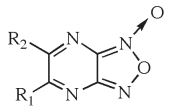
Introduction.

The first synthesis of the heterocyclic ring system furazano[3,4-*b*]pyrazine **1** was reported in 1969 by Gasco and co-workers [1]. The furoxan analogs have been prepared in 1981 and were additionally fused with a benzene ring, furoxano[3,4-*b*]quinoxalines **2** [2]. The bicyclic furoxano[3,4-*b*]pyrazine was only known as the hydrogenated derivatives, furoxano[3,4-*b*]piperazines **3** [3]. It may be noted, that all the furoxans were synthesized by oxidation of the corresponding glyoximes [2-4]. Progress in the synthesis and chemistry of furazano[3,4-*b*]pyrazine derivatives has been the subject of a recent review [5].



1 **2** **3**

During the course of a recent program [6], we were in need of a method to construct a family of furoxano[3,4-*b*]pyrazines **4**. We required a protocol that would tolerate variations in the substituents R_1 and R_2.



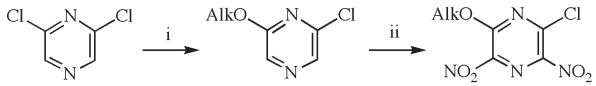
4

A set of methods was reported for the preparation of fused furoxans. One of the most convenient ways to synthesize these compounds is the thermolysis of *o*-azidonitro benzenes and heterocycles [7]. We have examined a sequence assumed initial preparation of *o*-azidonitro pyrazines and following their thermolysis. Our observations have resulted in a novel cascade process and the results are reported herein.

Results and Discussion.

Halobenzenes and heterocycles containing a nitro group, as an activated electron withdrawing function, are versatile synthetic building blocks, because the group facilitates halogen displacement by nucleophiles [8]. There are a few methods for the preparation of nitropyrazines and they are given in a reviewed by Rusinov and Chupakhin [9]. The recent development of nitration of pyrazine derivatives in our laboratory [10] has provided a simple preparation of *o*-chloronitro pyrazines **6a-c** (Scheme 1). These compounds are attractive precursors to synthesize target furoxans.

Scheme 1



5a-c **6a-c**

R = Me (**a**); Et (**b**), Pr (**c**)

Reagents and conditions: (i) NaOAlk/AlkOH, 50-60 °C, 0.5 h (65-95%); (ii) HNO_3/H_2SO_4 (1:1), 40 °C → 70 °C, 1-4.5 h (50-70%).

Thus, nucleophilic displacement of a chlorine atom at the commercially available 2,6-dichloropyrazine was accomplished by treatment with a solution of NaOAlk in corresponding alcohol. Heating the monoalkoxy pyrazines **5a-c** with HNO_3/H_2SO_4 mixture resulted in their clean nitration to the expected dinitro derivatives **6a-c** in good yields [10a].

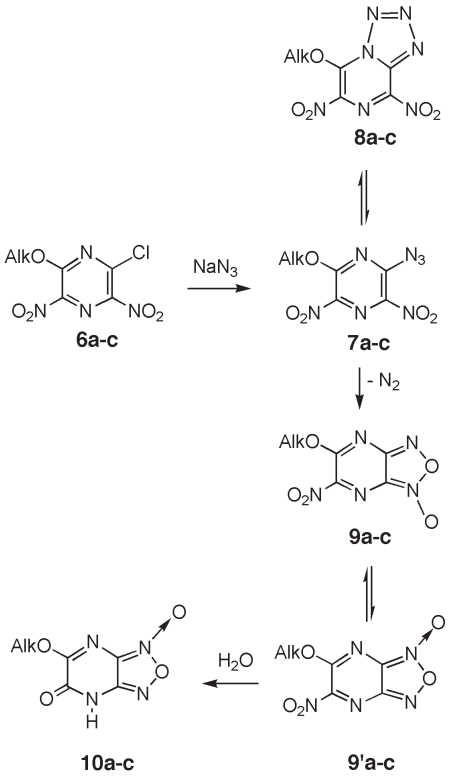
With these *o*-chloronitro pyrazines in hand, we carried out a series of NaN_3 induced reactions. By analogy to the reaction of others halopyrazines with NaN_3 [11], the pyrazine **6a** would be expected to give azidopyrazines **7a** or tautomeric tetrazolo[1,5-*a*]pyrazines **8a**. We were surprised to find that at the reaction of **6a** with NaN_3 in acetonitrile at 50-60 °C for 1 h provide furoxan **10a** (Scheme 2). In the cascade process the chlorine atom is initially replaced by the azide ion. Further reaction can be visualized on the basis of loss of N_2 from the azide **7a-c**, followed by furoxan ring closure and isomerization [12]. The final step is hydrolysis of the nitro group [13]. However, no trace of an azide **7**, a tetrazole **8**, and a nitro derivative from Scheme 2 can be detected in IR or ^{14}N NMR spectra in the reaction mixture.

The nucleophilic reaction was studied under a range of conditions including changes in reaction temperature, a cation in the azidated reagent, solvent systems, and addition of phase transfer catalysts as well as the method of product isolation. At treatment of compound **6a** with LiN_3 in the presence of $BnN(Et)_3Cl$ (TEAC) in CH_2Cl_2 (under anhydrous conditions), the only compound that was additionally isolated was nitro derivative **9'a**. The compound is not stable. Separation of **9'a**, and drying overnight at room temperature resulted in complete transformation to **10a**. It is apparent that the pyrazine ring of furoxano[3,4-*b*]pyrazines is highly π-deficient. As a result, the nitro group of compound **9'a** readily undergoes replacement by hydroxy group with moisture.

Compound **6b** and **6c** were converted to the corresponding pyrazinones **10b** and **10c** in the same manner.

The fused furoxans **10a-c** gave satisfactory elemental analyses and were characterized by IR spectroscopy, mass spectrometry, and ^1H, ^{13}C and ^{14}N NMR spectroscopy. The two characteristic carbon signals of the furoxan ring appeared at δ *ca*. 114 and 148. Both ^1H and ^{13}C NMR spectra of **10a-c** showed a set of signals, indicating a furoxan isomer. The presence of carbonyl absorption at *ca*. 1730 cm^{-1} in the IR spectra of the products **10a-c** supports their formulation as pyrazinones rather than the alternative tautomeric hydroxypyrazines. The structure of the keto tautomer of **10a** was established by X-ray analysis (Figure 1). The molecule is planar, and the N-oxidized nitrogen atom of the furoxan ring is oriented *para* position of the pyrazine ring with respect to the keto group.

Scheme 2



R = Me (**a**), Et (**b**), Pr (**c**)

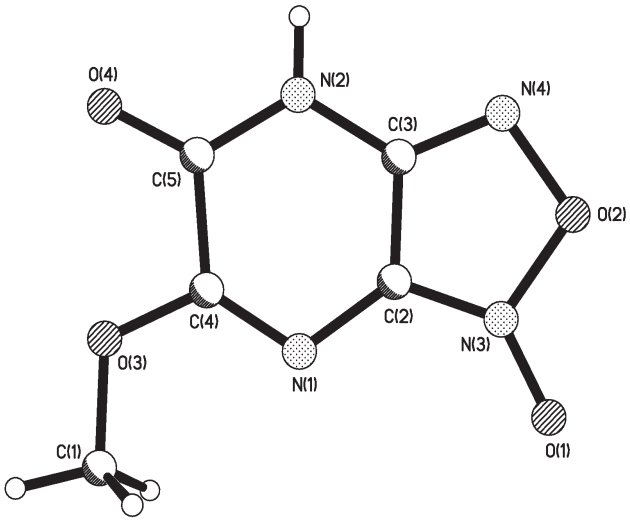


Figure 1. General view of the furoxan **10a**. Selected bond lengths: C(2)-C(3) 1.404(2), C(2)-N(3) 1.320(2), C(3)-N(4) 1.305(2), N(3)-O(1) 1.235(2), N(3)-O(2) 1.447(2), N(4)-O(2) 1.403(2)

Analysis of the Cambridge Structural Database has revealed that there is some lengthening of the N(4)-O(2) bond (1.403Å) in comparison to the average value 1.381Å. This elongation can in explained by the presence of the π-donor NH group taking part in the conjugation with the C(3)N(4)O(2) fragment. Such influence of the donor groups was previously also observed for furazan derivatives with donor and acceptor groups [14].

In crystal molecules form infinite chains along the *b*-axis. These chains are formed by bifurcate H-bonds between the N-H group and oxygen atoms of the C=O and methoxy groups. Parameters of H-bonds are: N(2)…O(4) 2.865(3)Å, H(1)…O(4) 2.04(2)Å, N(2)H(1)O(4) 155(2)°; N(2)…O(3) 3.201(3)Å, H(1)…O(3) 2.51(2)Å, N(2)H(1)O(3) 135(2)°. Oxygen atom O(4) also participates in forming the short intermolecular contact with the furoxan cycles of the neighboring chain. The distance O(4)…N(3) is equial to 3.009(3)Å, and the angle between direction of the contact and the plane of the furoxan ring is equial to 74°. Due to these contacts the chains form «walls» parallel to (0 0 1).

EXPERIMENTAL

Melting points were determined on Gallenkamp melting point apparatus and they are not corrected. Infrared spectra were determined in KBr pellets on a Perkin-Elmer Model 577 spectrometer. Mass-spectra were recorded on a Varian MAT-311A instrument. ^{1}H, ^{13}C and ^{14}N NMR spectra were recorded on a Bruker AM-300 instrument in DMSO-d_6 at 300.13, 75.47 and 21.68 MHz respectively. The chemical shift values (δ) are expressed relative to chemical shifts for the deuterated solvent (2.50 ppm and 39.51 ppm for proton and carbon NMR, respectively) or to an external standard without correction nitromethane (^{14}N). Analytical thin layer chromatography (TLC) was conducted on precoated silica gel plates (Silufol F_{254}). Nitropyrazines **6a-c** were prepared according to the literature procedure [10a].

X-ray Crystallography.

X-Ray quality crystals of the compound **10a** were grown by slow evaporation of a methanol solution at room temperature. At 298 K crystals are orthorhombic, space group $P2_12_12_1$, a=5.769(1)Å, b=8.188(2)Å, c=15.125(3)Å, V=714.5(2)Å^3, Z=4, M=184.12, d_{calc}=1.712 g•cm^{-3}, μ(Mo-K_α)=0.150 mm^{-1}, F(000)=376. Intensities of 2030 reflections were measured with a CAD-4 Enraf Nonius diffractometr at ambient temperature [λ(Mo-K_α)=0.71072, θ/2θ scan, 2θ<62°], and 1915 independent reflections (Rint=0.1153) were used in a further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic approximation for nonhydrogen atoms. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to wR_2=0.1000 and GOF=1.040 for all independent reflections [R_1=0.0363 was calculated against *F* for 1428 observed reflections with $I>2\sigma(I)$]. All calculations were performed using SHELXTL software [15]. Atomic coordinates and thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers 258587.

General Procedure for the Reaction of 2-Chloro-3-nitropyrazine **6a-c** with Sodium Azide.

The reactions were carried out in dry conditions under an argon atmosphere. To a solution of compound **6** (20 mmol) in dry CH_3CN (10 ml) was added NaN_3 (20 mmol) at room temperature. The resulting suspension was stirred 1 h at 50C. The mixture was cooled and after dilution with Et_2O (25 ml) the resulting solid was collected by filtration. The filtrate was evaporated under reduced pressure. The residue was crystallized from $CHCl_3$/AcOH to give **10a**, **10b** and **10c** in 65%, 61%, and 54% yields, respectively.

4*H*-6-Methoxyfuroxano[3,4-*b*]pyrazin-5-one (**10a**).

The compound was obtained as fine colorless crystals, mp 216-218 °C; ir: 3144, 1728, 1652, 1588, 1528, 1200, 976 cm^{-1}; ^{1}H nmr: 3.98; ^{13}C nmr: 56.4, 114.0, 148.3, 151.1, 158.5. ms: (*m/z*) 184 (M^+), 168 (M^+ - O), 154 (M^+ - NO).

Anal. Calcd. for $C_5H_4N_4O_4$ (184.11): C, 32.62; H, 2.19; N, 30.43. Found: C, 32.66; H, 2.18; N, 30.40.

4*H*-6-Ethoxyfuroxano[3,4-*b*]pyrazin-5-one (**10b**).

The compound was obtained as colorless powder; mp 192-193 °C; ir: 3150, 1731, 1647, 1594, 1210, 1180, 968 cm^{-1}; ^{1}H nmr: 4.55 (2H, CH_2), 1.44 (3H, Me); ^{13}C nmr: 14.5, 64.5, 114.4, 148.2, 151.4, 158.7. ms: (*m/z*) 198 (M^+), 182 (M^+ - O), 168 (M^+ - NO) 154 (M^+ - O - C_2H_4).

Anal. Calcd. for $C_6H_6N_4O_4$ (198.14): C, 36.37; H, 3.05; N, 28.28. Found: C, 36.40; H, 3.09; N, 28.25.

4*H*-6-Propoxyfuroxano[3,4-*b*]pyrazin-5-one (**10c**).

A slightly colored amorphous powder; mp 163-166 °C; ir: 3145, 1730, 1645, 1600, 1580, 1205, 1170, 980 cm^{-1}; ms: (*m/z*) 212 (M^+), 196 (M^+ - O).

Anal. Calcd. for $C_7H_8N_4O_4$ (212.16): C, 39.63; H, 3.80; N, 26.41. Found: C, 39.59, H, 3.86; N, 26.36.

6-Methoxy-5-nitrofuroxano[3,4-*b*]pyrazin (**9'a**).

The reactions were carried out in dry conditions under an argon atmosphere. To a solution of compound **6a** (2.6 g, 2 mmol) and TEAC (0.1 g) in dry CH_2Cl_2 (100 ml) was added LiN_3 (20 mmol) at room temperature and the resulting suspension was stirred 10 h. The mixture was diluted with Et_2O (100 ml), cooled to 0 °C and filtered through a pad of silica. The solvent was evaporated *in vacuo* at 0 °C. The residue was purified by freezing from a solution in CCl_4 to give 0.28 g (12%). The compound decomposed when tested for melting point; ^{1}H nmr ($CDCl_3$, δ): 4.29; ^{14}N nmr ($CDCl_3$, δ): -15.5 (NO_2); ms: (*m/z*) 213 (M^+), 197 (M^+ - O), 167 (M^+ - NO_2), 151 (M^+ - O - NO_2), 121 (M^+ - O - NO_2 - NO).

Acknowledgements.

The authors thank the NATO Collaborative Linkage Grant (SSS.CLG.977566) and International Science and Technology Center (ISTC, project no. 1882) for financial support of this work. X-Ray studies are performed under Grant 00-03-32807a from Russian Foundation for Basic Research.

REFERENCES AND NOTES

[1] A. Gasco, G. Rua, E. Menziani, G. M.Nano and G. Tappi, *J. Heterocyclic Chem*., **6**, 769 (1969).

[2] D. N. Nicolaides and J. K. Gallos, *Synthesis*, 638 (1981).

[3] R. L. Willer and D. W. Moore, *J. Org. Chem.*, **50**, 5123 (1985).

[4] J. K. Gallos, P. S. Lianis and D. N. Nicolaides, *J. Heterocyclic Chem.*, **26**, 1415 (1989).

[5] A. B. Sheremetev and I. L. Yudin, *Usp. Khim*., **72**, 93 (2003) (in Russian) [*Russ. Chem. Rev*. (*Engl. Transl*.), **72**, 87 (2003)].

[6a] A. B. Sheremetev, I. L. Yudin, N. N. Makhova, I. V. Ovchinnikov and D. B. Lempert, In Proc. 33st International Annual Conference of ICT - Energetic Materials: Synthesis, Production, and Application., 2002, Karlsruhe, FRG, pp 128/1-12; [b] I. L. Yudin and A. B. Sheremetev, In All-Russian Conference "Energy Condensed Systems", 2002, Chernogolovka, Moscow-Yanus'K, 2002, pp 108-109 (in Russian); [c] N. N. Makhova, A. B. Sheremetev, I. L. Yudin, I. V. Ovchinnikov and D. B. Lempert, In Proc. 35th International Annual Conference of ICT - Energetic Materials: Reactions of Propellants, Explosives and Pyrotechnics, 2004, Karlsruhe, FRG.

[7] For reviews on fused furoxan synthesis, see: [a] A. B. Sheremetev, *J. Heterocyclic Chem.*, **32**, 371 (1995); [b] L. I. Khmelnitskii, S. S. Novikov and T. I. Godovokova, Chemistry of Furoxans. Structures and Synthesis, 2nd Ed. Nauka, Moscow, 1996 (in Russian); [c] L. I. Khmelnitskii, S. S. Novikov and T. I. Godovokova, Chemistry of Furoxans. Reaction and Application, 2nd Ed. Nauka, Moscow, 1996 (in Russian); [d] R. M. Paton, In Comprehensive Heterocyclic Chemistry, Vol. **4**, A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, eds, Pergamon Press, Oxford, 1996, pp 229; [e] A. B. Sheremetev, *Usp. Khim*., **68**, 154 (1999) (in Russian) [*Russ. Chem. Rev*., (*Engl. Transl*.) **68**, 137 (1999)].

[8] F. Terrier. Nucleophilic Aromatic Displacement: The Influence of the Nitro Group.- Organic Nitro Chemistry Series, VCH Publishers, Weinheim, 1991, 460 pp.

[9] V. L. Rusinov and O. N. Chupakhin, *Nitroazines*. Moscow, Nauka, 1991, pp 10 (in Russian).

[10a] V. A. Tartakovskii, O. P. Shitov, I. L. Yudin and V. A. Myasnikov, *USSR Patent* 1703645 (1991); [b] I. L. Yudin, A. B. Sheremetev, O. P. Shitov and V. A. Tartakovskii, *Mendeleev Commun.*, 196 (1995); [c] B. B. Averkiev, M. Yu. Antipin, I. L. Yudin and A. B. Sheremetev, *J. Mol. Struct*., **606**, 139 (2002).

[11] C. Addicott, M. W. Wong and C. Wentrup, *J. Org. Chem*., **67**, 8538 (2002) and references therein.

[12] Following literature analogies the isomers **9'a-c** are more preferable. For reviews that deal with tautomerizm of furoxans, see: ref. [7b,7d,7e].

[13] For view of an extraordinary susceptibility of polynitroazines to ubiquitous environmental contaminants such as water, see: R. D. Chapman, W. S. Wilson, J. W. Fronabarger, L. H. Merwin and G. S. Ostrom, *Thermochim. Acta*, **384**, 229 (2002).

[14] A. S. Batsanov and Yu. T. Struchkov, *Zh. Strukt. Khim*., **26**, 65 (1985) (in Russian).

[15] G. M. Sheldrick, SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI-53719, USA.