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Synthesis of novel polycyclic heterosystems based on 5-nitro[1,2,5]thiadiazolo[3,4-*e*]benzofuroxan

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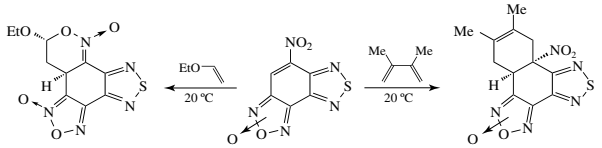
The Diels–Alder and Michael reactions of 5-nitro[1,2,5]-thiadiazolo[3,4-*e*]benzofuroxan afforded complex polycyclic compounds with potential NO-donor activity containing furoxan moiety along with another heterocyclic pharmacophoric fragments.

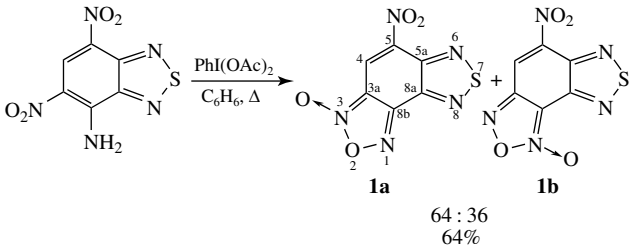


This work is a part of our ongoing research on application of nitroarene cyclodearomatization methodology towards complex hybrid molecules,[1] pharmacology-oriented nitrogen–oxygen systems with potential NO-donor activity containing furoxan ring and adjacent another aromatic heterocycle. The methodology deals with annelation of a furoxan ring to the nucleus of nitrobenzoazole or nitrobenzoazine followed by pericyclic [4+2]-cycloaddition (*e.g.*, the Diels–Alder reaction) at C=C bond activated by the nitro group. Recently we have thus obtained polycyclic compounds on the basis of 5-nitrofuroxanoquinoline[2] and isoxazolobenzofuroxan.[3] These compounds contain furoxan together with another heterocyclic pharmacophore.

Here we report on the synthesis of polycyclic furoxans on the basis of the previously unknown 5-nitro[1,2,5]thiadiazolo-[3,4-*e*]benzofuroxan. Furoxan derivatives are of interest as compounds possessing diverse biological activity,[4] including anti-HIV activity.[5] One of the most promising applications of furoxan compounds in medicine is based on their ability to be exogenous nitric oxide (NO) donors,[6] therefore, transformations of furoxans are intensively investigated (*e.g.*, ref. 7).

Versatile biological activity of 1,2,5-thiadiazole derivatives caused a considerable interest to their intense study and synthesis of their new representatives. Thus, thiadiazolo[3,4-*e*]benzofuroxan was found to be potent *in vivo* and *in vitro* vasodilator with activity similar to glyceryl trinitrate.[8] Many types of activities were found among monocyclic 1,2,5-thiadiazoles, including non-nucleoside HIV-1 reverse transcriptase inhibitors,[9] antitumor agents,[10] muscarinic agonists with analgesic[11] or antipsychotic-like activity.[12]

Annulation of a furoxan ring leading to the previously unknown 5-nitrothiadiazolo[3,4-*e*]benzofuroxan **1** was accomplished according to Scheme 1 *via* oxidative cyclization of 7-amino-4,6-dinitro[2,1,3]benzothiadiazole[13] under the action of $PhI(OAc)_2$.†



Scheme 1

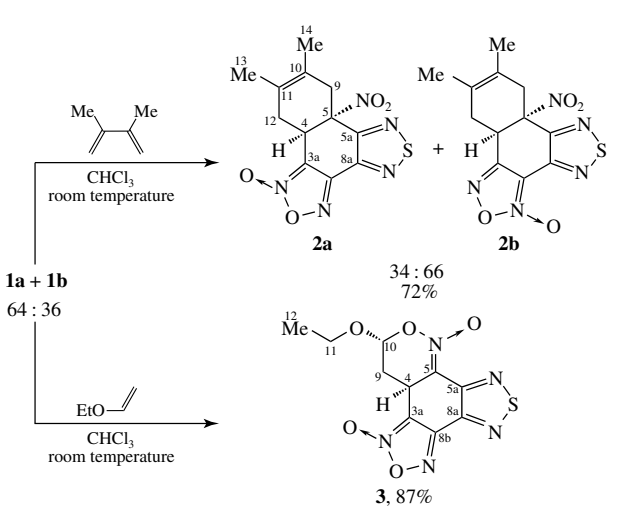
The product was an inseparable mixture of isomers **1a** and **1b**. According to results of 2D NMR experiments, **1a** was proved to be the major isomer.

Reaction of furoxans **1a/1b** with 2,3-dimethylbutadiene in $CHCl_3$ at room temperature (Scheme 2) leads to [4+2]-cycloadducts **2a/2b** in 72% yield.‡ In this case C=C−NO_2 fragment

† All chemicals were of commercial grade and used directly without purification. Melting points were measured on a Stuart SMP20 apparatus. The ^{1}H and ^{13}C NMR spectroscopic data were recorded on a Bruker Avance 600 FT-spectrometer (600 and 150 MHz, respectively). IR spectra were recorded on a Bruker Alpha spectrometer in KBr pellets. HRMS were measured on a Bruker maxis apparatus (ESI). All reactions were monitored by TLC analysis using ALUGRAM SIL G/UV254 plates, which were visualized by UV light. 4-Amino-5,7-dinitrothiadiazole was synthesized as previously described.[13]

*5-Nitro[1,2,5]thiadiazolo[3,4-*e*][1,2,5]benzoxadiazole 3-oxide* **1a** and *5-nitro[1,2,5]thiadiazolo[3,4-*e*][1,2,5]benzoxadiazole 1-oxide* **1b**. $PhI(OAc)_2$ (0.84 g, 2.6 mmol) was added to a suspension of 4-amino-5,7-dinitro[2,1,3]benzothiadiazole (0.48 g, 2 mmol) in benzene (50 ml) and the mixture was heated under reflux for 10 h, evaporated to dryness and the residue was thoroughly washed with hexane and MeOH to give a mixture of compounds **1a** and **1b** (0.31 g, 64%, ratio **1a**:**1b** = 64:36) as yellow solid, mp 162–163 °C. ^{1}H NMR (DMSO-d_6) δ: **1a**: 8.90 (s, 1H, 4-H); **1b**: 9.17 (s, 1H, 4-H). ^{13}C NMR (DMSO-d_6) δ: **1a**: 112.50 (C^{3a}), 116.70 (C^4), 142.16 (C^{5a}), 145.50 (C^{8a}), 146.70 (C^{8b}), 149.32 (C^5); **1b**: 106.40 (C^{8b}), 119.80 (C^4), 142.53 (C^{8a}), 145.43 (C^{5a}), 147.66 (C^{3a}), 151.39 (C^5). IR (KBr, ν/cm^{-1}): 1339 and 1545 (NO_2), 1630 (C=N→O).

‡ *8,9-Dimethyl-6b-nitro-6b,7,10,10a-tetrahydro[1,2,5]thiadiazolo-[3',4':3,4]naphtho[1,2-*c*][1,2,5]oxadiazole 1-oxide* **2a** and *8,9-dimethyl-6b-nitro-6b,7,10,10a-tetrahydro[1,2,5]thiadiazolo[3',4':3,4]naphtho-[1,2-*c*][1,2,5]oxadiazole 3-oxide* **2b**. 2,3-Dimethyl-1,3-butadiene (1.13 ml, 10 mmol) was added to a suspension of compounds **1a/1b** (0.24 g, 1 mmol) in $CHCl_3$ (10 ml) and the mixture was stirred for 24 h at 20 °C. The reaction mixture was poured to hexane (50 ml), filtered, cooled and



Scheme 2

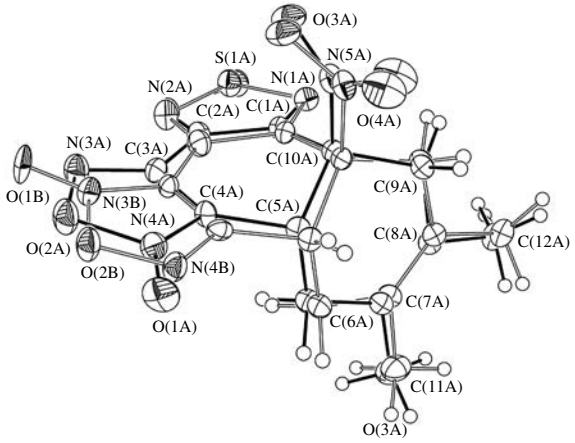


Figure 1 General view of one of two independent pairs of isomers occupying the same crystallographic position in the crystal of **2a/2b**, in thermal ellipsoids representation (p = 50%). The whole numbering scheme is shown for isomer **2a**.

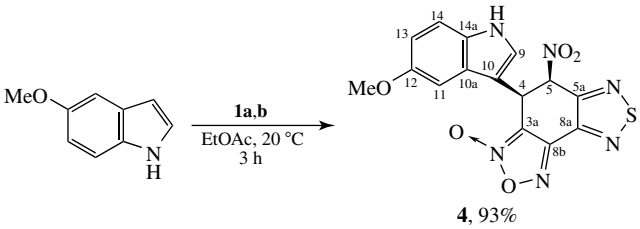
acts as dienophile and the reaction proceeds according to normal electron demands. The structure of **2a/2b** was confirmed by NMR experiments (HSQC, HMBC, COSY, NOESY). It should be stressed that the ratio of isomers **2a** and **2b** is completely inversed with respect to the ratio of initial furoxans **1a/1b**.

In addition, the structure of compounds **2a/2b** was confirmed by X-ray diffraction study (Figure 1).§ In a crystal two independent crystallographic positions (Z' = 2) are occupied by both isomers in different ratios. The refined ratios of **2a/2b** are 0.58 : 0.42 and 0.12 : 0.88 for the first and the second positions, respectively. Such type of the disorder is common for this type of compounds [for example, see ref. 2(*b*)]. It is expected that the ratios of isomers in a crystal vary if they form a solid solution, but in this particular case the total ratio of **2a/2b** equal to 35 : 65 virtually coincides with the value from NMR data. The restraints applied in the refinement of the structure due to close atomic positions do not allow analyzing molecular geometry in detail, but the refined bond lengths and angles are close to the average values for similar fragments of structures of known compounds.

Reaction of **1a/1b** with excess of ethyl vinyl ether at room temperature afforded the cyclic nitronate **3** in high yield (see Scheme 2).¶ In this case C=C−NO_2 fragment serves as heterodiene and the reaction proceeds according to inversed electron demands. ^{1}H NMR spectrum of the product contains trace signals of another isomer. Stereochemistry of the major (> 90%) cycloadduct was established on the basis of 2D NOESY spectrum. This crystalline compound was found to be unstable in common organic solvents and decomposed completely after 24 h of standing at room temperature.

In addition to high Diels–Alder reactivity furoxan **1a/1b** was found to exhibit the nitroolefinic properties. It reacts with 5-methoxyindole to give Michael-type adduct **4** (Scheme 3) containing three pharmacophoric fragments in a molecule (furoxan, thiadiazole and biologically important indole system).††

The *cis* stereochemistry of **4** was established by means of NMR experiments. Compound **4** readily decomposes in solutions (DMSO, $CHCl_3$, MeCN), therefore the ^{1}H NMR spectrum always



Scheme 3

the precipitate deposited was collected by filtration. Yield: 0.23 g, 72%, mp 115–118 °C. ^{1}H NMR ($CDCl_3$) δ: **2a**: 1.57 (s, 3H, 13-H), 1.70 (m, 1H, 12′-H), 1.76 (s, 3H, 14-H), 2.66 (m, 1H, 12-H), 3.16 (d, 1H, 9′-H, J 13.6 Hz), 3.62 (d, 1H, 9-H, J 17.1 Hz), 4.31 (dd, 1H, 4-H, J 7.0 Hz, J 10.4 Hz); **2b**: 1.59 (s, 3H, 13-H), 1.76 (s, 3H, 14-H), 1.97 (m, 1H, 12′-H), 2.66 (m, 1H, 12-H), 3.16 (d, 1H, 9′-H, J 13.6 Hz), 3.46 (d, 1H, 9-H, J 17.2 Hz), 4.44 (dd, 1H, 4-H, J 7.2 Hz, J 9.8 Hz). ^{13}C NMR ($CDCl_3$) δ: **2a**: 18.21 (C^{13}), 18.72 (C^{14}), 33.45 (C^{12}), 35.03 (C^4), 36.90 (C^9), 88.33 (C^5), 111.87 (C^{3a}), 122.46 (C^{10}), 123.21 (C^{11}), 146.00 (C^{8a}), 146.16 (C^{8b}), 155.92 (C^{5a}); **2b**: 18.21 (C^{13}), 18.72 (C^{14}), 34.75 (C^{12}), 36.90 (C^9), 37.20 (C^4), 88.50 (C^5), 105.63 (C^{3a}), 122.24 (C^{10}), 123.21 (C^{11}), 142.88 (C^{8a}), 154.82 (C^{5a}), 155.32 (C^{3a}). IR (KBr, ν/cm^{-1}): 1328 and 1550 (NO_2), 1646 (C=N→O). MS (ESI), m/z: 344.0422, (calc. for $C_{12}H_{11}N_5NaO_4S$, m/z: 344.0424 [M + Na]$^+$).

§ *Crystallographic data for* **2a/2b**: at 120(2) K yellow crystals of $C_{12}H_{11}N_5O_4S$ are triclinic, space group $P\bar{1}$, a = 8.7066(11), b = = 11.3434(14) and c = 14.2748(17) Å, α = 72.521(2), β = 85.405(2) and γ = 87.479(3)°, V = 1340.1(3) Å^3, Z = 4 (Z' = 2), d_{calc} = 1.593 g cm^{-3}. Intensities of 17974 reflections were collected on a Bruker SMART APEX II diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, 2θ < 60.00°], and 7822 independent reflections (R_{int} = 0.0425) were used in the structure solution and refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic approximation for all non-hydrogen atoms. The positions of hydrogen atoms were calculated. Hydrogen atoms were refined in riding model with U_{iso}(H) equal to 1.5U_{eq}(C) and 1.2U_{eq}(C) of the connected methyl and other carbon atoms. For one of the crystallographically independent sites with the ratio of isomers of *ca*. 0.58 : 0.42 we were able to split the positions of all atoms of the isomers using ISOR and EADP instructions for close atomic positions. For the second pair, the ratio of the minor isomer (*ca*. 0.12) was too low, and only furoxan moiety was disordered. The refinement converged to R_1 = 0.0558 [calc. for 5423 observed reflections with $I > 2\sigma(I)$], wR_2 = 0.1349 and GOF = 1.007. All calculations were performed with SHELX software package.[15]

CCDC 1450757 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

¶ *9-Ethoxy-10,10a-dihydro-9*H*-[1,2,5]oxadiazolo[3,4-*f*][1,2,5]thiadiazolo[3,4-*h*][2,1]benzoxazine 1,7-dioxide* **3**. Ethyl vinyl ether (1 ml, 10 mmol) was added to a suspension of compounds **1a/1b** (0.24 g, 1 mmol) in $CHCl_3$ (10 ml) and the mixture was stirred for 3 h at 20 °C. The reaction mixture was poured into hexane (50 ml), filtered, cooled and the precipitate deposited was collected by filtration. Yield 0.27 g, 87%, mp 146–147 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, 3H, Me, J 7.0 Hz), 1.9 (dd, 1H, 9′-H, J 9.7 Hz, J 2.9 Hz), 3.54 (m, 1H, 9-H), 3.71 (dt, 1H, CH_2Me, J 16.1 Hz, J 7.3 Hz), 4.11 (dt, 1H, CH_2Me, J 15.8 Hz, J 7.7 Hz), 4.34 (dd, 1H, 4-H, J 12.4 Hz, J 6.1 Hz), 5.69 (dd, 1H, 1-H, J 7.2 Hz, J 3.6 Hz).

contains some impurities. Nevertheless, it was possible to fully assign all signals of H and C atoms and to conclude that the product represents the only isomer (**4**) indicated in Scheme 3. Such reactivity is reminiscent to that of 4-nitrobenzodifuroxan (NBDF)[14] whose superelectrophilic nature was proved by reactions with dienes, ethyl vinyl ether and neutral C-nucleophiles (indoles). It should be noted that in case of NBDF the corresponding adduct with 5-methoxyindole had *trans* configuration which was established by X-ray analysis.[14] At the same time, benzofuroxans annelated with isoxazole[3] and pyridine[2] rings did not form similar adducts with indoles.

In conclusion, 5-nitro[1,2,5]thiadiazolo[3,4-*e*]benzofuroxan was synthesized and its pericyclic and nitroolefinic reactivity was examined. The results obtained show that compounds **1a/1b** behave as superelectrophile (undergo the Diels–Alder reactions and give adduct with very poorly nucleophilic 5-methoxyindole). The adducts with 2,3-dimethylbutadiene, ethyl vinyl ether and 5-methoxyindole can be considered as complex hybrid molecules containing two or three biologically important units. Combination of NO-donor furoxan and other pharmacophoric fragments (thiadiazole, oxazine, indole) may lead to several types of activity, which is useful for creation of potent pharmaceutically interesting compounds.

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^{13}C NMR ($CDCl_3$) δ: 14.75 (C^{12}), 29.76 (C^4), 32.92 (C^9), 66.13 (C^{11}), 103.49 (C^{10}), 110.33 (C^{3a}), 116.97 (C^5), 144.92 (C^{8a}), 146.18 (C^{8b}), 149.35 (C^{5a}). IR (KBr, ν/cm^{-1}): 1596 and 1641 (C=N→O). MS (ESI), *m*/*z*: 312.0406 (calc. for $C_{10}H_9N_6O_5S$, *m*/*z*: 312.0397, $[M + H]^+$).

†† *4-(5-Methoxy-1*H*-indol-3-yl)-5-nitro-4,5-dihydro[1,2,5]thiadiazolo[3,4-e][2,1,3]benzoxadiazole 3-oxide* **4**. 5-Methoxyindole (74 mg, 0.5 mmol) was added to a solution of compounds **1a/1b** (0.12 g, 0.5 mmol) in ethyl acetate (10 ml) and the mixture was stirred for 3 h at 20 °C. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (10 ml) and poured into hexane (60 ml). The solid was filtered and dried to give compound **4**. Yield 0.181 g, 93%, mp 115–116 °C (decomp.). ^{1}H NMR (CD_3CN) δ: 3.81 (s, 3H, OMe), 5.68 (d, 1H, 4-H, *J* 3.2 Hz), 6.50 (d, 1H, 5-H, *J* 3.2 Hz), 6.81 (d, 1H, 9-H, *J* 2.6 Hz), 6.88 (dd, 1H, 13-H, *J* 8.1 Hz, *J* 1.6 Hz), 7.11 (s, 1H, 11-H), 7.34 (d, 1H, 14-H, *J* 8.3 Hz), 9.32 (br. s, 1H, NH). ^{13}C NMR (CD_3CN) δ: 35.06 (C^4), 56.23 (OMe), 84.20 (C^5), 100.51 (C^{11}), 106.08 (C^{10}), 112.25 (C^{3a}), 113.89 (C^{14}), 114.81 (C^{13}), 125.57 (C^9), 126.45 (C^{10a}), 132.46 (C^{14a}), 147.30 (C^{8a}), 148.43 (C^{5a}), 154.05 (C^{8b}), 155.56 (C^{12}). IR (KBr, ν/cm^{-1}): 1352 and 1563 (NO_2), 1643 (C=N→O).

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