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*Mendeleev Commun.*, 2017, **27**, 448–450

Mendeleev Communications

# Bis[1,2,5]oxadiazolo[3,4-*c*:3′,4′-*e*]pyridazine 4,5-dioxide as a synthetic equivalent of 4,4′-dinitroso-3,3′-bifurazan

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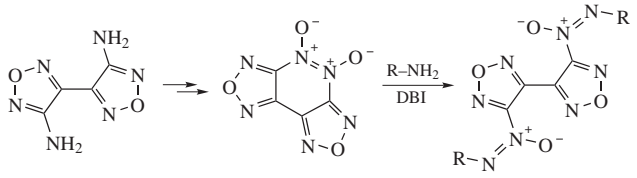
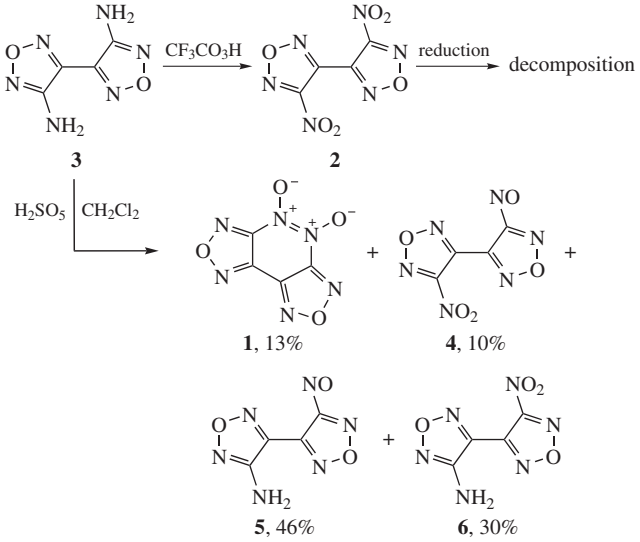
DOI: 10.1016/j.mencom.2017.09.005

**The novel heterocyclic system, bis[1,2,5]oxadiazolo[3,4-*c*:3′,4′-*e*]pyridazine 4,5-dioxide, was obtained along with other products in the course of oxidation of 3,3′-bi-1,2,5-oxadiazole-4,4′-diamine. This compound acts as a synthetic equivalent of 4,4′-dinitroso-3,3′-bifurazan affording bis-diazene oxide derivative in the Kovacic reaction.**




Nitric oxide (NO) donors represent a chemically diverse family of substances with a common molecular mechanism of action, the ability to release NO, a gaseous molecule with the properties of a radical, which is the final effector of vascular dilatation.[1] Nitric oxide helps to regulate a wide array of biological effects.[2] The NO-regulated biochemical and physiological events are important for cell function because NO is one of the main intracellular messengers as well as a neurotransmitter not only for the cardiovascular system, but also for central nervous system, host's immunity and response against tumor cells.[3,4] Numerous NO prodrugs (NO donors) release NO or NO-like species under physiological conditions either spontaneously or in the presence of thiols or other cofactors. There has been a recent focus on the therapeutic potential of hybrid drugs, *e.g.* compounds with the combination of two pharmacologically active substructures in a single molecule.[5,6] Among these classes of NO prodrugs, special interest is given to compounds containing one *N*-oxide group (1,2,5-oxadiazole 2-oxides, furoxans)[7–16] or even two *N*-oxide groups: pyrazole di-*N*-oxides,[17,18] diazetidine di-*N*,*N*′-oxides[19] and pyridazine di-*N*,*N*′-oxides.[20] The mechanism of biological activity of these derivatives is complex and may involve generation of nitric oxide and NO-like species. Apparently, their potency to produce NO is increased in the case of electron-withdrawing substitutions or fused rings.[21] Pyridazine di-*N*,*N*′-oxides fused with two heterocyclic rings were never investigated as potential NO donors. Herein we report the synthesis of bis[1,2,5]oxadiazolo[3,4-*c*:3′,4′-*e*]pyridazine 4,5-dioxide **1** and the study of its ring opening to 4,4′-dinitroso-3,3′-bifurazan with further synthesis of bis-diazene oxide derivatives by the Kovacic reaction. The tricycle **1** can be considered as potential useful NO-donor.

2,2′-Dinitro-1,1′-biaryl and 2,2′-dinitro-1,1′-bihetaryl are conventional precursors for the preparation of 4,5-dioxides of diareno-,[22–24] dipyrido-[25] and dithieno[2,3-*c*:3′,2′-*e*]pyridazines.[26] In our experiments, treatment of 4,4′-dinitro-3,3′-bi(1,2,5-oxadiazole) **2** with various reducing agents ($NaBH_4$, $N_2H_4$/Ni, Zn dust, $H_2$/Ni Raney) led to full decomposition of the bifurazan **2** with the formation of complex mixture from which no individual compounds could be isolated. Therefore, we have decided to use 3,3′-bi-1,2,5-oxadiazole-4,4′-diamine **3** as a starting material for the synthesis of the target **1** (Scheme 1). The oxidation of compound **3** with Caro's acid was investigated in detail.[†] Four




**Scheme 1**

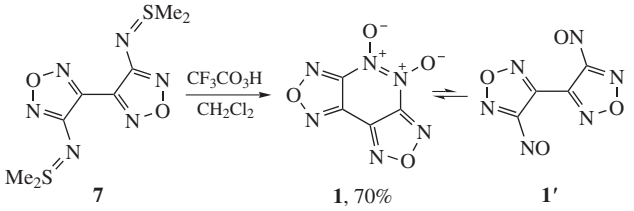
† *Oxidation of 3,3′-bi-1,2,5-oxadiazole-4,4′-diamine* **3**. Diamine **3** (1.0 g, 6 mmol) was added to a mixture of conc. $H_2O_2$ (85%, 2.4 ml, 82.0 mmol) and $H_2SO_4$ ($d$ = 1.83 g cm$^{-3}$, 2.8 ml, 50.0 mmol) in $CH_2Cl_2$ (40 ml) at 10–15 °C. The reaction mixture was stirred at this temperature for 2 h, poured into crushed ice (50 g), extracted with $CH_2Cl_2$ (2×20 ml). The combined extracts were washed with water, $NaHCO_3$ and brine, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was separated by column chromatography (Silica gel Merck 60, $CH_2Cl_2$). 4′-Nitro-3,3′-bi-1,2,5-oxadiazol-4-amine **6** was identical to the literature.[37]

*4-Nitro-4′-nitroso-3,3′-bi-1,2,5-oxadiazole* **4**. Light blue crystals, yield 130 mg (10%), mp 55–57 °C (decomp.), $R_f$ 0.88 ($CH_2Cl_2$). IR (KBr, $\nu$/cm$^{-1}$): 1580 (C=N), 1550, 1475, 1310, 1330, 1000, 930, 910, 825, 790. MS (EI, 70 eV), $m/z$ (%): 212 $[M]^+$ (10), 182 $[M-NO]^+$ (5), 152 $[M-2NO]^+$ (5).

main products were isolated, whose yields depended on the ratio between hydrogen peroxide and sulfuric acid and on the reaction temperature. The best overall yield was achieved when the reaction was carried out at low temperature (10–15 °C). The reaction mixture was subjected to column chromatography, and, among other products, di-*N*-oxide **1** was isolated in 13% yield. All our attempts to improve the latter were unsuccessful.

Curiously, two previously unknown nitroso derivatives **4** and **5** exhibited completely different stability. 4′-Nitroso-3,3′-bi-1,2,5-oxadiazol-4-amine **5**, a stable blue compound which can be stored in a freezer for months, was characterized by NMR, IR spectroscopy, mass spectrometry and elemental analysis. Blue low-melting (mp 55–57 °C) 4-nitro-4′-nitroso-3,3′-bi-1,2,5-oxadiazole **4** in $CH_2Cl_2$ solution at room temperature slowly underwent oxidation to afford 4,4′-dinitro-3,3′-bi-1,2,5-oxadiazole **2** which was identified by IR spectroscopy and mass spectrometry. Nitrosofurazans are rare compounds; to the best of our knowledge only four representatives are described,[27–30] whereas furazans containing two nitroso groups are not known.

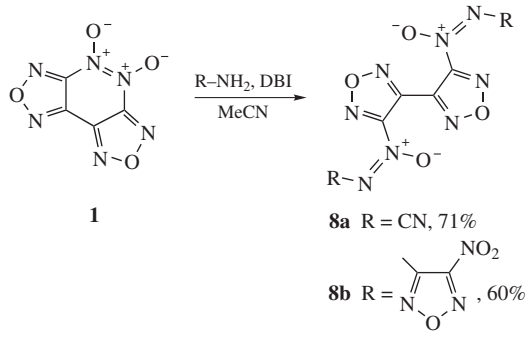
Bis[1,2,5]oxadiazolo[3,4-*c*:3′,4′-*e*]pyridazine 4,5-dioxide **1**, a light yellow solid, can be regarded as tautomer (‘an inner dimer’) of 4,4′-dinitroso-3,3′-bifurazan **1′**. To elaborate the rational way of its synthesis, the oxidation of bis-sulfilimine **7**, which can be readily prepared from compound **3**,[31] was investigated. *m*-Chloroperoxybenzoic acid (*m*CPBA) generally used in the oxidation of sulfilimines to nitroso heterocycles[32–34] did not react with bis-sulfilimine **7**, while Caro’s acid ($H_2SO_5$) oxidized it to 4,4′-dinitro derivative **2**. However, treatment of disulfilimine **7** with trifluoroperoxyacetic acid gave selectively the target di-*N*,*N′*-oxide **1** in high yield (Scheme 2).‡




**7** **1**, 70% **1′**

**Scheme 2**

Nitrosofurazans are known to react with amines and oxidizing agent (most often dibromoisocyanurate, DBI) to form azoxy derivatives (the Kovacic reaction).[28,35,36] Treatment of di-*N*,*N′*-oxide **1** with cyanamide or 4-nitro-1,2,5-oxadiazol-3-amine in the presence of DBI in MeCN led to bis-diazene oxide derivatives **8** in high yields (Scheme 3).§




**1** **8a** R = CN, 71%

**8b** R = , 60%

**Scheme 3**

In conclusion, a new pyridazine di-*N*,*N′*-oxide **1** fused with two electron-withdrawing furazan rings, which can be of interest as a nitric oxide donor, has been synthesized. For the first time the pyridazine di-*N*,*N′*-oxide moiety was recognized as dinitroso equivalent which can be regarded as the precursor of the corresponding bis-diazene oxides. The described procedure may serve as a one-pot method for introduction of two diazene oxide groups into heterocyclic ring.

This work was supported by the Russian Science Foundation (grant no. 14-50-00126).

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*4′-Nitroso-3,3′-bi-1,2,5-oxadiazol-4-amine* **5**. Light blue crystals, yield 500 mg (46%), mp 77–78 °C (decomp.), $R_f$ 0.51 ($CH_2Cl_2$). $^{13}$C NMR ($CDCl_3$) $\delta$: 135.4, 135.7, 158.9, 171.3. IR (KBr, $\nu$/cm$^{-1}$): 3460 ($NH_2$), 3330 ($NH_2$), 1620, 1600 (C=N), 1530, 1500, 1470, 1390, 1310, 1230, 1070, 990, 910, 880, 750. MS (EI, 70 eV), *m*/*z* (%): 182 [M]$^+$ (20), 152 [M – NO]$^+$ (6), 122 [M – 2NO]$^+$ (5). Found (%): C, 26.49; H, 0.95; N, 46.15. Calc. for $C_4H_2N_6O_3$ (%): C, 26.38; H, 1.11; N, 46.15.

*Bis[1,2,5]oxadiazolo[3,4-c:3′,4′-e]pyridazine 4,5-dioxide* **1**. Light yellow crystals, yield 150 mg (13%), mp 104–105 °C (decomp.), $R_f$ 0.30 ($CH_2Cl_2$). $^{13}$C NMR ($CDCl_3$): 135.3, 157.3. $^{14}$N NMR (21.7 MHz, $CDCl_3$) $\delta$: –87.7 (N→O). IR (KBr, $\nu$/cm$^{-1}$): 1585 (C=N), 1530, 1465, 1370, 1360, 1220, 1145, 1100, 1005, 925, 875. MS (EI, 70 eV), *m*/*z* (%): 196 [M]$^+$ (100), 180 [M – O]$^+$ (20), 164 [M – 2O]$^+$ (30), 136 (13), 124 (63), 84 (40). Found (%): C, 24.73; N, 42.91. Calc. for $C_4N_6O_4$ (%): C, 24.49; N, 42.86.

‡ *Synthesis of compound* **1** *from* N,N′*-(3,3′-bi-1,2,5-oxadiazole-4,4′-diyl)-bis(1,1-dimethyl-λ$^4$-sulfanimine)* **7**. Trifluoroacetic anhydride (6 ml, 42.0 mmol) and bis-sulfilimine **7** (0.86 g, 3 mmol) were added subsequently to a mixture of conc. $H_2O_2$ (85%, 1.2 ml, 41.0 mmol) and $CH_2Cl_2$ (20 ml) with stirring at 0–5 °C. The reaction mixture was kept at 0 °C for 2 h, poured into cooled saturated $NaHCO_3$ solution (60 ml) and stirred at this temperature for 1 h. The precipitate was filtered, washed with water and dried. Yield 410 mg (70%).

§ *Synthesis of bis-diazene oxides* **8**. Dibromoisocyanuric acid (1.15 g, 3.9 mmol) was added in portions to a solution of compound **1** (0.25 g, 1.3 mmol) and amine (3.9 mmol) in $CH_2Cl_2$ (20 ml) at room temperature. The reaction mixture was stirred for 1 h, filtered from isocyanuric acid and excess of DBI, and evaporated under reduced pressure. The residue was subjected to flash chromatography [Silica gel Merck 60, $CCl_4$–$CH_2Cl_2$ (5:1)].

*(1*E*,1′*E*)-1,1′-(3,3′-Bi-1,2,5-oxadiazole-4,4′-diyl)bis(2-cyanodiazene 1-oxide)* **8a**. Light yellow crystals, yield 250 mg (71%), mp 76–77 °C. $^{13}$C NMR ($CDCl_3$) $\delta$: 108.1 (C≡N), 137.2, 157.1. $^{14}$N NMR (21.7 MHz, $CD_2Cl_2$) $\delta$: –51.7 (N→O). IR (KBr, $\nu$/cm$^{-1}$): 2210 (C≡N), 1560 (C=N), 1500, 1430, 1405, 1300, 1210, 1090, 1060, 1010, 920, 910, 890, 870. MS (EI, 70 eV), *m*/*z* (%): 276 [M]$^+$ (60). Found (%): C, 25.98; N, 51.00. Calc. for $C_6N_{10}O_4$ (%): C, 26.10; N, 50.73.

*(1*E*,1′*E*)-1,1′-(3,3′-Bi-1,2,5-oxadiazole-4,4′-diyl)bis[2-(4-nitro-1,2,5-oxadiazol-3-yl)diazene 1-oxide]* **8b**. Light yellow crystals, yield 810 mg (60%), mp 97–99 °C. $^{13}$C NMR ($CDCl_3$): 139.3, 149.6, 157.6, 160.6. $^{14}$N NMR (21.7 MHz, $CD_2Cl_2$) $\delta$: –37.3 ($NO_2$), –66.1 (N→O). IR (KBr, $\nu$/cm$^{-1}$): 1560 (C=N), 1540, 1480, 1330, 1290, 1200, 1170, 1140, 1060, 1020, 990, 900, 820. MS (EI, 70 eV), *m*/*z* (%): 452 [M]$^+$ (100). Found (%): C, 21.17; N, 43.44. Calc. for $C_8N_{14}O_{10}$ (%): C, 21.25; N, 43.37.

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*Received: 9th January 2017; Com. 17/5143*