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# Spontaneous conversion of 2-azido-3-nitropyridines to pyridofuroxans

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ABSTRACT

Several pyridofuroxans were obtained by spontaneous $N_2$ elimination from the corresponding 2-azido-3-nitropyridines. In this particular case, the presence of nitrogen in the pyridine ring must facilitate a cyclic extrusion mechanism. The pyridofuroxans prepared in this study did not present tautomerism as evidenced by NMR.



Nitric oxide (NO) is a small, relatively unstable, and diatomic-free radical. It has become one of the most studied and fascinating entities in biological chemistry. This inorganic gas is synthesized by animals and humans. It plays a role, often as a biological messenger, in a wide range of physiological processes. Its expanding range of functions already includes neurotransmission, blood clotting, blood pressure control, and non-specific immune response to bacterial infections.[1,2]

Furoxans and benzofuroxans represent an important class of thiol-dependent NO donors.[3] There have been several comprehensive reviews regarding their chemistry.[4–6] A wide range of biological activity has been claimed for benzofuroxan and derivatives.[6–10] Some are depressants of the central nervous system, muscle relaxants, and anticonvulsants. Others present nematocidal, antimicrobial, fungicidal, herbicidal, and algicidal properties. Nitrobenzofuroxans, pyridofuroxans, and fused benzofuroxans have been found to inhibit nucleic acid and protein synthesis in leukemia and other forms of cancer cells.

In organic synthesis, benzofuroxans have been used as intermediates in the preparation of several pharmaceutical compounds such as benzimidazole-3-oxides.[6] They react very easily with carbonyl compounds in basic media to give quinoxaline-1,4-dioxides with interesting biological properties (antibacterial, antiviral, antifungal, antihelmintic, and insecticidal).[10–13]

Benzofuroxans have been prepared by oxidation of *o*-quinone dioxime or *o*-nitroanilines with alkaline hypochlorite. They have also been prepared by photolysis or thermolysis of *o*-nitrophenylazides. However, the latter method has been reported to give better yields.[14–18] Another report has described a one-pot synthesis of benzofuroxans from *o*-chloronitrobenzenes, involving nucleophilic displacement of chlorine by azide followed by in situ cyclization under solid-phase-transfer catalysis conditions.[19]

To induce thermal cyclization, *o*-nitrophenylazide is usually refluxed in acetic acid or toluene for several hours.[17] This process could in principle occur through a singlet nitrene mechanism or through an electrocyclic process in which nitrogen is extruded and the new heterocycle is partly formed at the transition state.[20–22] In fact, computational studies[23] support earlier assertions based on experiments that the pyrolysis produces benzofuroxan by a concerted one-step mechanism.[24] However, in a recent ultrafast study on the photochemistry of 2-azidonitrobenzene the presence of a singlet nitrene intermediate was demonstrated.[25]

Commercially available 2-amino-3-nitropyridines **1a–c** were attempt to be converted to the corresponding 2-azido-3-nitropyridines **2a–c** by the previously reported procedure with minor modifications (Scheme 1).[17,32] However, IR characterization of the corresponding products indicated no azide to be present. Furthermore, the pyridofuroxans **3a–c** characteristic IR bands were observed in the crystalline products.[26] Two strong bands at 1650–1600 $cm^{-1}$ (stretching of polar exocyclic NO bond), one strong band at 1550–1500 $cm^{-1}$ (Stretching of C=N bond), another strong band at 1100–1050 $cm^{-1}$ (symmetric stretching of polar endocyclic NO bond), and a rather weak band at 850–800 $cm^{-1}$ (antisymmetric stretching of polar endocyclic NO bond). Further NMR and MS analysis confirmed these results.[27–29]

This transformation, in which an intermediate *o*-nitrophenylazide spontaneously decomposes at ambient temperature to give benzofuroxan has been previously reported only for 3,5-diamino-2,4,6-trinitroazidobenzene.[30] It was assumed that intramolecular

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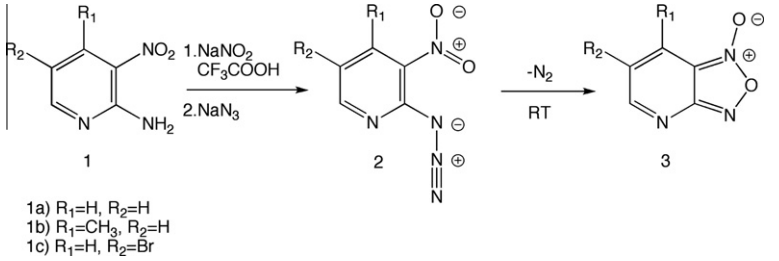
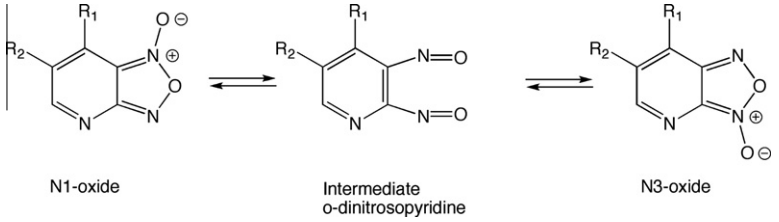



**Scheme 1.**




**Scheme 2.**

hydrogen bonding (between the neighboring amino and nitro groups) enforced high degree of coplanarity between the nitro group and the benzene ring, thus facilitating $N_2$ elimination (Scheme 1).

The pyridofuroxans **3a–c** described here were isolated as single crystalline products. There was no evidence for the existence of more than one isomer. In a previous study, a valence tautomerization has been proposed for these type of compounds (Scheme 2).[31] The rearrangement involves oxygen migration between N1 and N3 and the isomerization occurs via an *o*-dinitrosopyridine intermediate. NMR analysis of the compounds prepared **3a–c** indicated the N1-oxide as the only isomer present. In fact, it has been reported that this isomer is favored in a pyridofuroxan crystalline solid at ambient temperature.[31] It has been demonstrated that the N1-oxide isomer is favored due to electronic repulsion between the lone pairs of oxygen (N–O) and nitrogen in the pyridine ring.[5] Furthermore, steric and electronic effects due to nitrogen on pyridofuroxans have been previously studied.[5] Energetically favorable charge delocalization can also contribute to the position of this equilibrium.[5]

In conclusion, 2-azido-3-nitropyridines **2a–c** decompose spontaneously to give the corresponding pyridofuroxans **3a–c**. Therefore, the pyridine ring must facilitate the cyclic transition state for the concerted one-step mechanism.

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27. *4-Pyridofuroxan*, **3a**. Yellow solid; yield 40%; mp 182 °C. $^1$H NMR (MeOD, ppm): 8.52 (1H, dd, aromatic $H_{ortho}$, $J_{ortho}$ = 7.81 Hz, $J_{meta}$ = 1.95 Hz), 6.50 (1H, t, aromatic $H_{meta}$, $J_{ortho}$ = 6.52 Hz), 7.82 (1H, dd, aromatic $H_{para}$). IR (cm$^{-1}$): 3109 (C–H), 1650 and 1590 (two peaks, exocyclic NO bond), 1550–1500 (two peaks, C=C and C=N), 1080 (endocyclic NO bond), 850 (weak peak, N–O furoxan). Exact mass for $C_5H_3N_3O_2$: 137.0225 amu, observed: 137.0220 amu.
28. *7-Methyl-4-pyridofuroxan*, **3b**. Pale brown solid; yield 60%; mp 212–214 °C. $^1$H NMR (MeOD, ppm): 2.17 (3H, s, $CH_3$), 7.38 (1H, d, aromatic $H_{ortho}$, $J_{ortho}$ = 6.64 Hz), 6.25 (1H, d, aromatic $H_{meta}$). IR (cm$^{-1}$): 3104 and 2983 (C–H), 1660–1610 (two peaks, exocyclic NO bond), 1520–1500 (two peaks, C=C and C=N), 1100 (endocyclic NO bond), 855 (weak peak, N–O furoxan). Exact mass for $C_6H_5N_3O_2$: 151.0381 amu, observed: 151.0380 amu.
29. *6-Bromo-4-pyridofuroxan*, **3c**. Yellow solid; yield 73%; mp 208–210 °C. $^1$H NMR (MeOD, ppm): 8.40 (1H, d, aromatic $H_{ortho}$, $J_{meta}$ = 2.73 Hz), 7.85 (1H, d, aromatic $H_{para}$). IR (cm$^{-1}$): 3056 (C–H), 1720 and 1650 (two peaks, exocyclic NO bond), 1570–1520 (two peaks, C=C and C=N), 1204 (C–Br), 1080 (endocyclic NO bond), 840 (weak peak, N–O furoxan). Exact mass for $C_5H_2BrN_3O_2$: 151.0381 amu, observed: 151.0380 amu.
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32. *Experimental procedure*: the corresponding 2-amino-3-nitropyridine (6 mmol) derivative **1** was dissolved in 5 mL of trifluoroacetic acid. The solution was cooled to 15 °C and kept at this temperature throughout the reactions. An aqueous solution (2 M) of sodium nitrite was slowly added (32 mmol). The reaction mixture was stirred for 30 min. An aqueous solution of sodium azide (32 mmol, 2 M) was added dropwise. The resulting mixture was allowed to warm to room temperature for one more hour. The white precipitate produced was filtered, washed with water, and dried to give the corresponding pyridofuroxan **3**.