New version of mononuclear heterocyclic rearrangement

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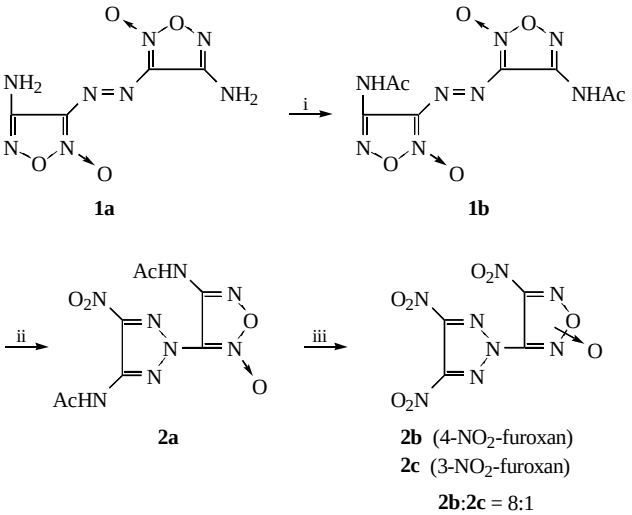
Thermal recyclization of the 3-diazenofuroxanyl unit to form the 4-nitro-1,2,3-triazole fragment has been found in noncondensed 1,2,5-oxadiazol 2-oxide derivatives (3,3′-azofuroxans) with acetamido substituents in the 4,4′-positions.

Recently,[1] we have developed a general preparative methods for the synthesis of azo- and azoxyfuroxans. This work is devoted to the study of their reactivity. It has been found unexpectedly that 4,4′-bis(acetamido)-3,3′-azofuroxan **1b** upon heating gives a new compound with the same molecular formula. According to the ^{1}H and ^{13}C NMR spectroscopic data, this compound contains two different acetamido groups. The ^{13}C NMR spectrum contains four downfield signals (117.68, 144.73, 148.02 and 150.14 ppm), two of which (117.68 and one of the downfield signals at 148.02 or 150.14 ppm) are most likely assigned to the furoxan ring.[2] Two other signals can be assigned to another aromatic heterocycle. In addition, a signal of the nitro group (–26.0 ppm) appeared in the ^{14}N NMR spectrum. Therefore, a molecule of the new compound contains two aromatic heterocycles (one of which is the furoxan ring), two different acetamido groups and one nitro group.

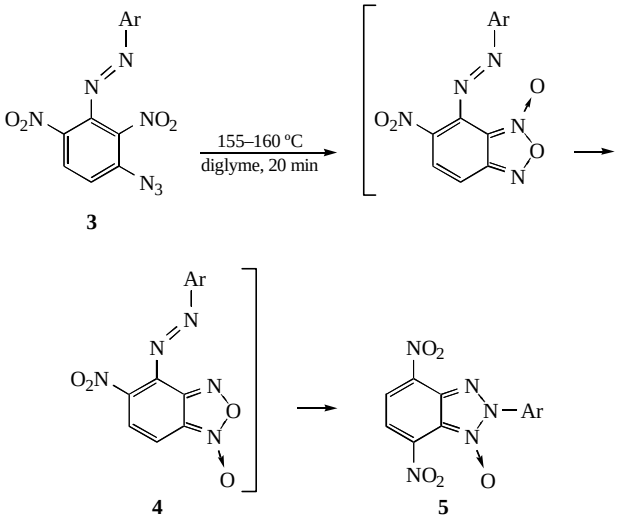
To obtain a simpler spectral pattern, the acetamido groups in the new compound were oxidized to nitro groups by a mixture of conc. H_2O_2 and conc. H_2SO_4. This reaction afforded a mixture of two new compounds in the 8:1 ratio, which were separated by chromatography on SiO_2. According to the ^{14}N NMR data, the prevailing compound contained three nitro groups, two of which had equal chemical shifts (–37.0 ppm), and the third nitro group had a chemical shift of –39.0 ppm. The ^{13}C NMR spectrum exhibited only three signals at 124.48, 145.41 and 147.98 ppm, two of which were broadened and appeared as triplets due to spin–spin coupling with atoms of the ^{14}N nitro groups. This shape of the signals is typical of C–NO_2 fragments. The presence of the C–NO_2 fragments was confirmed by narrowing of these signals in the ^{13}C NMR spectrum after decoupling of ^{14}N in both of the nitro groups. The ratio of the integral intensities showed that the carbon atom with a chemical shift of 124.48 ppm is bound to a nitro group, and two other nitro groups are linked to the carbon atoms with chemical shifts of 147.98 ppm. Obviously, the compound obtained contained two equivalent C–NO_2 fragments, which are a part of a heteroaromatic ring. Two other signals in the ^{13}C NMR spectrum belong to the furoxan ring.



Scheme 1 *Reagents and conditions*: i, Ac_2O (20 mol), H_2SO_4 (cat. amount), 30 °C, 10 min; ii, AcOH:Ac_2O = 4:1, 50 °C, 3 h; iii, conc. H_2O_2/conc. H_2SO_4, 22–24 °C, 40 min.

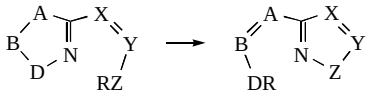
The comparison of the elemental analysis and NMR data suggests that the structure of this compound is 4-nitro-3-(4,5-dinitro-1,2,3-triazol-2-yl)furoxan **2b**. The ^{15}N NMR spectrum confirmed the presence of the triazole ring (two equivalent signals with the chemical shifts of 36.31 ppm and a signal with the chemical shift of 162.75 ppm; these data agree with the data published for ^{15}N spectra of 2-substituted 1,2,3-triazoles[3]). The second compound is its isomer **2c**. (It is known that the furoxan ring is prone to tautomerism,[4] especially when two electron-withdrawing substituents are present). Thus, the primary product obtained by heating of azofuroxan **1b** is the product of its thermal rearrangement, *viz.*, 4-acetamido-3-(5-acetamido-4-nitro-1,2,3-triazol-2-yl)furoxan **2a**. Starting diazenofuroxan **1b** was synthesised by the acetylation of 4,4′-diamino-3,3′-azofuroxan **1a** with acetic anhydride in the presence of a catalytic amount of conc. H_2SO_4 (Scheme 1).

Two rearrangements resulting in the 1,2,3-triazole ring are known in the furoxan series. The first rearrangement is the formation of 1,2,3-triazol 1-oxide derivatives under the action of amide anions on benzofuroxans[5] or of primary aliphatic amines on 4-amino-3-nitrofuroxans.[6] This transformation is probably initiated by the nucleophilic attack of an amide anion or amine on the N(5) atom of the furoxan ring.

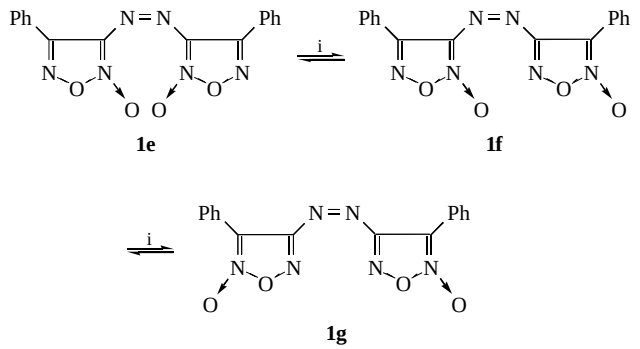


Scheme 2

The second rearrangement (a version of the Boulton–Katritzky rearrangement[7]) is the recyclization of 4-aryldiazeno-5-nitrobenzofuroxan **4** to 2-aryl-4,7-dinitrobenzo-1,2,3-triazole **5**. Starting benzofuroxan **4** was not isolated but appeared as an intermediate product upon heating of 2,6-dinitro-3-azidoaryldiazenobenzene **3**. In this case, the reaction also starts from the nucleophilic



Scheme 3

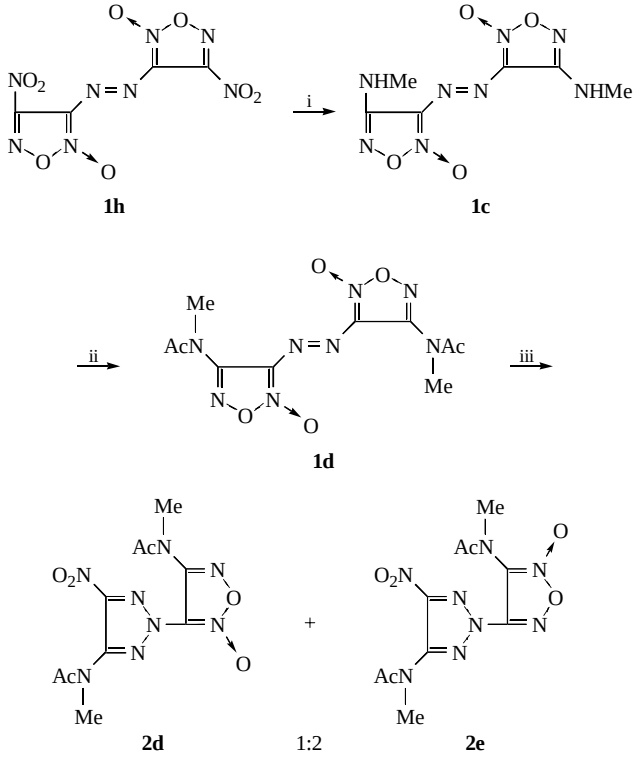


Scheme 4 *Reagents and conditions*: i, AcOH, 110 °C, 10 h.

attack of a diazene unit on the N(5) atom of the furoxan ring (Scheme 2).

The rearrangement found is formally similar to the latter case, but it occurs with the noncondensed furoxan system. Moreover, several mononuclear heterocyclic rearrangements are known,[8] which correspond to the general Scheme 3. However, the rearrangement under consideration can be presented by none of these schemes, because, first, azofuroxans, in particular, **1a** and its dinitro analogue **1h**, are planar systems with the *trans* arrangement of furoxan rings with respect to the azo group[9] and hence it is difficult to imagine the nucleophilic attack of the diazene unit on the N(5) atom in compound **1b**. Second, the isomerisation of the furoxan ring as the first stage of the reaction should be ruled out, because the acetamido and nitro groups in compound **2a** are bound to two different carbon atoms of the triazole ring.

To obtain additional information on this reaction, we used other 3,3′-azofuroxans with various substituents in the 4,4′-positions, namely, 4,4′-diamino-, 4,4′-bis(dimethylamino)-, 4,4′-bis(*N*-methylacetamido)- and 4,4′-diphenyl-azofuroxans **1a**,**c**–**e**, respectively. We found that amino derivatives **1a**,**c** remained unchanged upon heating at 100 °C for 2 h. Heating of diphenyl derivative **1e** at 110 °C for 10 h resulted in the formation of a mixture of the starting compound **1e** and products of isomerisation of one and two furoxan rings **1f** and **1g**, respectively (Scheme 4).



Scheme 5 *Reagents and conditions*: i, $CHCl_3$:Et_2O = 3:1, $MeNH_2$ (in gas phase), 20 °C, 40 min; ii, Ac_2O (2 mol), H_2SO_4 (cat. amount), 20 °C, 30 min; iii, AcOH (or EtOAc, dioxane), 80–100 °C, 1.5–2 h.

Only bis(acetamido) derivative **1d** undergoes the aforementioned rearrangement to form a mixture of isomeric triazolylfuroxans **2d** and **2e** in the 1:2 ratio. The starting azofuroxan **1c** was synthesised by nucleophilic substitution for the nitro groups in 3,3′-azo-4,4′-dinitrofuroxan **1h**, and **1d** was obtained by the acetylation of **1c** (Scheme 5).†

Thus, it was established that the presence of 4,4′-acetamido groups in the starting 3,3′-azofuroxan **1** is the key condition for this rearrangement. Based on this fact, we can suggest a hypothetical scheme of this reaction, which includes two successive rearrangements. The first rearrangement is the transformation of one of the acetamidofuroxan fragments in compound **1** into the 1,2,4-oxadiazole unit with the cleavage of the O(1)–N(5) bond of the furoxan ring and the release of a nitromethylene fragment (intermediate **6**). The second rearrangement is the transformation of compound **6** into **2**.

† All new compounds exhibited satisfactory elemental analysis data and their structures were confirmed by IR, NMR and mass spectroscopy. *Spectroscopic data*: ^{1}H NMR (300 MHz), ^{13}C NMR (75.47 MHz), standard TMS; ^{14}N and ^{15}N NMR (21.6 MHz), internal standard $MeNO_2$.

3,3′-Azo-4,4′-bis(acetamido)furoxan **1b**: yield 93%, mp 196–198 °C, R_f 0.49 ($CHCl_3$:Pr^iOH, 9:1). ^{1}H NMR (CF_3COOD) δ: 2.3 (s, 3H, Me), 11.1 (br. s, NH). IR (ν/cm^{-1}): 1595 (furoxan ring), 1695 (C=O), 3233 (NH). MS, *m*/*z*: 312 (M^+).

3,3′-Azo-4,4′-bis(methylamino)furoxan **1c**: yield 75%, mp 201–203 °C, R_f 0.32 (benzene:EtOAc, 9:1). ^{1}H NMR ([$^2H_6$]acetone) δ: 3.0 (d, Me). IR (ν/cm^{-1}): 1516, 1604 (furoxan ring), 2865, 2940 (CH), 3433 (NH). MS, *m*/*z*: 256 (M^+).

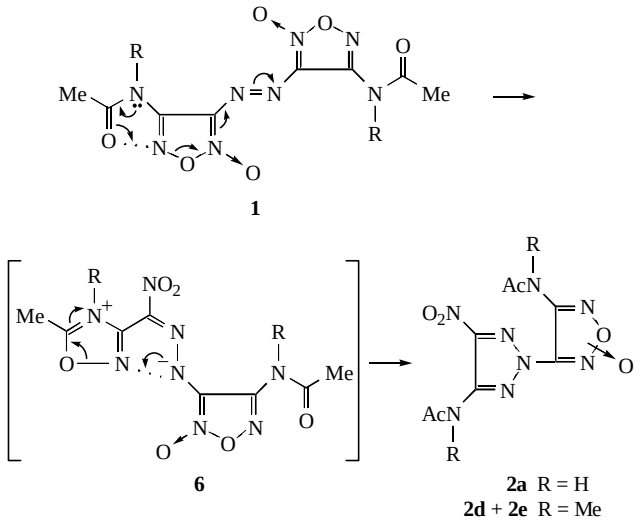
3,3′-Azo-4,4′-bis(N-methylacetamido)furoxan **1d**: yield 91%, mp 125–126.5 °C, R_f 0.20 (benzene:EtOAc, 3:1). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.12 (s, MeCO), 3.40 (s, NMe). ^{13}C NMR ([$^2H_6$]DMSO) δ: 21.35 (*Me*CO, ^1J 146.3 Hz), 35.34 (NMe, ^1J 145.5 Hz), 126.66 (C-3 in furoxan ring), 149.68 (C-4 in furoxan ring), 170.28 (C=O).

4-Acetamido-3-(5-acetamido-4-nitro-1,2,3-triazol-2-yl)furoxan **2a**. A suspension of **1b** (1.0 g, 3.2 mmol) in AcOH (40 ml) and Ac_2O (5 ml) was heated at 48–50 °C for 3 h. The reaction mixture was evaporated to 5 ml and cooled, and the precipitate was filtered off. Yield 65%, mp 141–143 °C, R_f 0.21 ($CHCl_3$:Pr^iOH, 9:1). ^{1}H NMR (CF_3COOD) δ: 2.21 (s), 2.36 (s, 6H, 2MeCO), 11.43 (br. s, 2H, 2NH). ^{13}C NMR (CF_3COOD) δ: 29.19 and 29.94 (2Me), 117.68 (C-3 in furoxan ring), 144.74 (C-4 in triazole ring), 146.02 (C-5 in triazole ring), 150.14 (C-4 in furoxan ring), 178.04, 178.81 (C=O). ^{14}N NMR (CH_3COOD) δ: –26.6 (NO_2). IR (ν/cm^{-1}): 1333, 1580 (NO_2), 1640 (furoxan ring), 1708 (C=O), 2995, 3050 (CH), 3235 (NH).

4-Nitro-3-(4,5-dinitro-1,2,3-triazol-2-yl)furoxan **2b**: yield 22%, mp 94.5–95 °C ($CHCl_3$, decomp.), R_f 0.51 (benzene). ^{13}C NMR ($CDCl_3$) δ: 113.6 (C-3 in furoxan ring), 146.3 (C-4 and C-5 in triazole ring), 154.8 (C-4 in furoxan ring). ^{14}N NMR ($CDCl_3$) δ: –37.0 (2NO_2 of triazole ring), –39.0 (NO_2 of furoxan ring). ^{15}N NMR ($CDCl_3$) δ: 6.75 (N-2 in furoxan ring), 21.11 (N-5 in furoxan ring), 36.41 (N-1 and N-3 in triazole ring), 38.77 (NO_2 of triazole ring), 40.05 (NO_2 of furoxan ring), 162.75 (N-2 in triazole ring). IR (ν/cm^{-1}): 1320, 1332, 1570 (NO_2), 1685 (furoxan ring). MS, *m*/*z*: 288 (M^+).

3-Nitro-4-(4,5-dinitro-1,2,3-triazol-2-yl)furoxan **2c**: yield 3%, oil. ^{13}C NMR ($CDCl_3$) δ: 124.48 (C-3 in furoxan ring, $^1J_{^{13}C-^{14}N}$ 21.3 Hz), 145.41 (C-4 in furoxan ring), 147.96 (C-4 and C-5 in triazole ring). ^{14}N NMR ($CDCl_3$) δ: –37 ($\Delta\nu_{1/2}$ 16 Hz, NO_2 of triazole ring), –43 ($\Delta\nu_{1/2}$ 3.0 Hz, NO_2 of furoxan ring). MS, *m*/*z*: 288 (M^+).

The mixture of *4(3)-(N-methylacetamido)-3(4)-(4-nitro-5-N-methylacetamido-1,2,3-triazol-2-yl)furoxans* **2d** and **2e** (2:1): total yield 38%, oil. **2d**: ^{1}H NMR ([$^2H_6$]acetone) δ: 2.26 (s, 3H, MeCO of triazole ring), 2.30 (s, 3H, MeCO of furoxan ring), 3.48 (s, 3H, NMe of triazole ring), 3.55 (s, 3H, NMe of furoxan ring). ^{13}C NMR ([$^2H_6$]acetone) δ: 21.23 (*Me*CO of furoxan ring, ^1J 141.6 Hz), 21.90 (*Me*CO of triazole ring), 31.10 (NMe of furoxan ring), 35.44 (NMe of triazole ring, ^1J 142.3 Hz), 115.15 (C-3 in furoxan ring), 145.2 (*C*–NAc of triazole ring), 148.34 (C–NO_2 in triazole ring), 150.42 (C-4 in furoxan ring), 171.16 (CO in triazole ring), 172.73 (CO in furoxan ring). ^{14}N NMR ([$^2H_6$]acetone) δ: –28.0 (NO_2, $\Delta\nu_{1/2}$ 77 Hz). **2e**: ^{1}H NMR ([$^2H_6$]acetone) δ: 2.05 (s, 3H, MeCO of furoxan ring), 2.20 (s, 3H, MeCO of triazole ring), 3.20 (s, 3H, NMe of furoxan ring), 3.35 (s, 3H, NMe of triazole ring). ^{13}C NMR ([$^2H_6$]acetone) δ: 21.53 (*Me*CO of furoxan ring, ^1J 129.3 Hz), 22.03 (*Me*CO of triazole ring, ^1J 142.3 Hz), 30.34 (NMe of furoxan ring, ^1J 137.2 Hz), 35.34 (NMe of triazole ring, ^1J 143.3 Hz), 115.94 (C-3 in furoxan ring, ^3J 3.0 Hz), 145.2 (*C*–NAc in triazole ring), 148.56 (C–NO_2 in triazole ring), 150.07 (C-4 in furoxan ring), 170.26 (CO in furoxan ring), 171.16 (CO in triazole ring).



1

6

2a R = H
2d + **2e** R = Me

Scheme 6

The scheme suggested is consistent with the known methods of synthesis and the reactivity of 1,2,4-oxadiazoles, for example, the preparation of 1,2,4-oxadiazoles by thermal cyclization of a benzamidine derivative.[10] Moreover, the thermal cleavage of the O(1)–N(2) bond under the action of nucleophiles to form a new heterocycle, in particular, 1,2,3-triazole,[11–13] is the typical reaction of 1,2,4-oxadiazoles, including intramolecular reactions. In addition, it is noteworthy that both rearrangements in Scheme 6 agree with the general scheme (Scheme 3) of mononuclear heterocyclic rearrangements.

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