New approaches to the preparation of azoxyfuroxans

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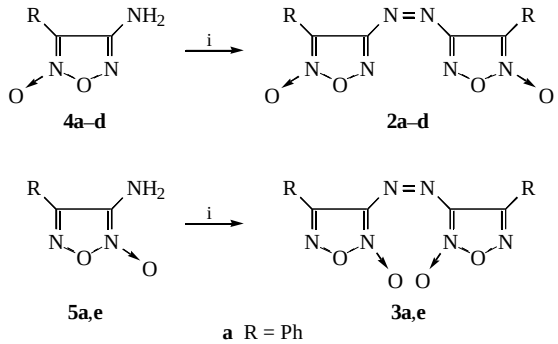
A new convenient method for the synthesis of 4,4′-azoxyfuroxans by reductive condensation of 4-nitrofuroxans (4-nitro-1,2,5-oxadiazole 2-oxides) has been developed; the title compounds can also be synthesised by oxidation of 4-amino- and 4,4′-azofuroxans, and a general method for the synthesis of isomeric azofuroxans is suggested.

The first representatives of azoxyfuroxans (4,4′-azoxy-3,3′-diphenyl- and -3,3′-dimethylfuroxans **1a**,**b**) were synthesised by the oxidation of 4-trioctylphosphinimino-3-phenyl(methyl)furoxans under the action of MCPBA.[1] However, this method is inconvenient, because the latter needs to be specially prepared. However, azoxy derivatives of the aromatic and heteroaromatic series exhibit various biological activities (antibacterial, anticancer, antituberculous, and nematocidal).[2] Therefore, it was reasonable to search for new, more convenient approaches to the preparation of azoxyfuroxans with various substituents.

The synthesis of aromatic azoxy derivatives is normally based on the transformation of amino-, azo-, or nitro-substituted derivatives using various oxidising or reducing agents. Until recently, it has been impossible to perform similar reactions in the furoxan series, because the corresponding starting furoxan derivatives were lacking. We have recently developed convenient methods for the synthesis of amino- and nitrofuroxans.[3–7] In this work, we studied the possibility of preparing azoxyfuroxans **1**† by the oxidative condensation of aminofuroxans, by oxidation of azofuroxans, and by reductive condensation of nitrofuroxans. It seemed probable that the first two reactions would be efficient, since similar transformations with amino- and azo-furazans proceed successfully.[8,9] The possibility of reductive condensation of nitrofuroxans seemed less probable, because of the sensitivity of the furoxan ring towards reducing agents.[10]

The oxidation of 4- and 3-aminofuroxans **4** and **5** by $KMnO_4$ in the presence of HCl (Scheme 1) was used to obtain the starting isomeric 4,4′- and 3,3′-azofuroxans **2** and **3**.‡ The synthesis of compounds **2** and **3** is of independent interest, because only a few representatives of these structures are described in the literature.[11,12] This reaction was established to apply to both 4- and 3-aminofuroxans **4** and **5** and to be almost independent of the second substituent in the aminofuroxan.

The possibility of direct oxidation of aminofuroxans to azoxyfuroxans was studied using 4-aminofuroxans **4** only, since it is known[11] that 3-aminofuroxans **5** give a mixture of compounds by the action of oxidants of the peroxide type, which are those usually used for these transformations in the furazan series.[8]



Scheme 1 *Reagents and conditions*: i, $KMnO_4$ (1.5–2 mol), $HCl/H_2O/CH_2Cl_2$, 20 °C, then HOOC–COOH.

A mixture of hydrogen peroxide and H_2SO_4 was used as the oxidant. The studies showed that electron-withdrawing substituents in position 3 of the furoxan ring (for example, CON_3, compound **4f**) prevent the formation of azoxy derivatives. The oxidation

† *4,4′-Azoxy-3,3′-diphenylfuroxan* **1a**: yield 52%, mp 190–192 °C (MeOH), (lit.,[1] 190–192 °C).

4,4′-Azoxy-3,3′-dimethylfuroxan **1b**: yield 58%, mp 187–189 °C ($CHCl_3$), (lit.,[1] 187–189 °C).

4,4′-Azoxy-3,3′-dihydroxymethylfuroxan **1g**: yield 27%, mp 103–104 °C, R_f 0.45 ($CHCl_3$:PriOH, 9:1). ^{1}H NMR ($CDCl_3$) δ: 4.75 (d, 2H, CH_2), 4.96 (d, 2H, CH_2), 5.05 d (1H, OH), 5.07 d (1H, OH). ^{13}C NMR ($CDCl_3$) δ: 54.04 and 54.72 (CH_2), 111.42 and 111.59 (C-3 in furoxan ring), 156.12 and 159.48 (C-4 in furoxan ring). ^{14}N NMR ($CDCl_3$, internal standard $MeNO_2$) δ: –68.0 [N=N(O)]. IR (ν/cm^{-1}): 1315 [N=N(O)], 1600 (furoxan ring), 2800, 2920 (CH), 3320 (OH).

4,4′-Azoxy-3,3′-diethylfuroxan **1h**: yield 49%, mp 129–130 °C ($CHCl_3$), R_f 0.47 (hexane:CH_2Cl_2, 1:2). ^{1}H NMR ($CDCl_3$) δ: 1.21 and 1.24 (t, Me), 2.63 and 2.96 (q, CH_2). IR (ν/cm^{-1}): 1185 [N=N(O)], 1536, 1650 (furoxan ring). MS, *m*/*z*: 270 (M^+).

4,4′-Azoxy-3,3′-bis(2-methoxyethyl)furoxan **1i**: yield 17%, mp 72.5–73 °C, R_f 0.11 (benzene:EtOAc, 20:1). ^{1}H NMR ($CDCl_3$) δ: 2.99 and 3.27 (t, CH_2), 3.28 and 3.29 (s, Me), 3.70 and 3.77 (t, CH_2O). ^{13}C NMR ($CDCl_3$) δ: 24.33 and 25.22 (Me), 58.76 ($2CH_2$), 67.81 and 68.12 (CH_2O), 110.77 and 110.94 (C-3 in furoxan ring), 156.90 and 160.18 (C-4 in furoxan ring). IR (ν/cm^{-1}): 1323 [N=N(O)], 1630 (furoxan ring); MS, *m*/*z*: 330 (M^+).

‡ *4,4′-Azo-3,3′-diphenylfuroxan* **2a**: yield 96%, mp 160–162 °C, R_f 0.45 (CCl_4:$CHCl_3$, 1:1). ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.5 (m, 3H, *m*- and *p*-CH in Ar), 7.65 (m, 2H, *o*-CH in Ar). IR (ν/cm^{-1}): 1330, 1465, 1610 (furoxan ring). UV (EtOH, λ_{max}/nm): 227, 270. MS, *m*/*z*: 350 (M^+).

4,4′-Azo-3,3′-dimethylfuroxan **2b**: yield 96%, mp 156–158 °C, R_f 0.4 ($CHCl_3$:CH_2Cl_2, 1:1). ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, Me). IR (ν/cm^{-1}): 1400, 1540, 1655 (furoxan ring). UV (EtOH, λ_{max}/nm): 263, 352. MS, *m*/*z*: 226 (M^+).

4,4′-Azo-3,3′-diethoxycarbonylfuroxan **2c**: yield 68%, mp 128–129 °C, R_f 0.51 ($CHCl_3$). ^{1}H NMR ([$^2H_6$]acetone) δ: 1.26 (t, Me, ^3J 7.2 Hz), 4.40 (q, CH_2, ^3J 7.2 Hz). ^{13}C NMR ([$^2H_6$]acetone) δ: 14.17 (Me), 64.39 (CH_2), 103.82 (C-3 in furoxan ring), 155.89 (C-4 in furoxan ring), 162.29 (C=O). IR (ν/cm^{-1}): 1620, 1630 (furoxan ring), 1720 (C=O), 2960 (CH);

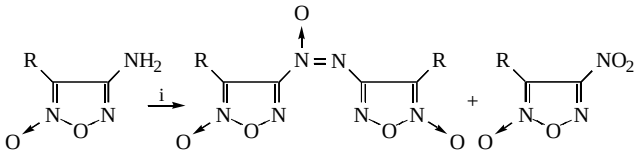
3,3′-Diacetyl-4,4′-azofuroxan **2d**: yield 22.5%, mp 123–125 °C, R_f 0.64 (benzene:methanol, 10:0.3). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.63 (s). IR (ν/cm^{-1}): 1330, 1370, 1500, 1630 (furoxan ring), 1650 (CO), 2940 (CH). UV (EtOH, λ_{max}/nm): 261, 342. MS, *m*/*z*: 282 (M^+).

4,4′-Azo-3,3′-bis(2-methoxyethyl)furoxan **2i**: yield 7%, mp 89.5–91 °C, R_f 0.18 (benzene:EtOAc, 20:1). ^{1}H NMR ($CDCl_3$) δ: 3.46 (t, CH_2), 3.63 (s, Me), 4.02 (t, CH_2O). ^{13}C NMR ($CDCl_3$) δ: 25.24 (CH_2), 58.54 (Me), 66.31 (CH_2O), 107.72 (C-3 in furoxan ring), 165.3 (C-4 in furoxan ring). IR (ν/cm^{-1}): 1118, 1622 (furoxan ring), 2840, 2870, 2915, 2950, 3000 (CH). MS, *m*/*z*: 314 (M^+).

3,3′-Azo-4,4′-diphenylfuroxan **3a**: yield 96%, mp 196–197 °C, R_f 0.65 (hexane:ethylacetate, 3:1). ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.65 (m, 3H, *m*- and *p*-CH), 8.05 (m, 2H, *o*-CH). IR (ν/cm^{-1}): 1335, 1475, 1570 (furoxan ring). UV (EtOH, λ_{max}/nm): 216, 252, 349. MS, *m*/*z*: 350 (M^+).

3,3′-Azo-4,4′-dibenzoylfuroxan **3e**: yield 67%, mp 143–144 °C, R_f 0.57 (acetone). ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.42 (m, 2H, *m*-H in Ar), 7.7 (m, 1H, *p*-H in Ar), 7.9 (m, 2H, *o*-H in Ar). ^{13}C NMR ([$^2H_6$]DMSO) δ: 124.0 (C-3 in furoxan ring), 128.5, 129.2, 130.1, 132.8 (Ar), 148.5 (C-4 in furoxan ring), 167.3 (C=O). IR (ν/cm^{-1}): 1325, 1390, 1460, 1500, 1600, 1630 (furoxan ring), 1680, 1700 (C=O). UV (EtOH, λ_{max}/nm): 263, 293, 380.

3-Hydroxymethyl-4-nitrofuroxan **6g**: yield 16%, oil, IR and NMR spectral data are identical with those of **6g** in ref. 17.



4b,**f**,**g**
b R = Me
f R = CON_3
g R = CH_2OH

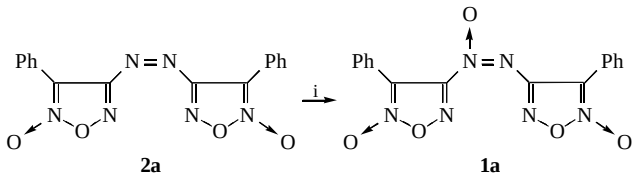
1b 33%
1f 0%
1g 27%

6b 12%
6f 65%
6g 16%

Scheme 2 *Reagents and conditions*: i. H_2O_2 (85%) (2.5 mol)/conc. H_2SO_4, 20 °C, 30 min, then 30 °C, 30 min and 65 °C, 30 min.

was carried out using hydrogen peroxide of different concentrations. With dilute hydrogen peroxide, the starting compound **4f** is unchanged, while an increase in the concentration of hydrogen peroxide leads to the formation of 4-nitrofuroxan **6f**. The oxidation of 4-aminofuroxans with electron-donating substituents **4b**,**g** gives a mixture of azoxy derivatives **1b**,**g** (predominantly) and nitrofuroxans **6b**,**g** (Scheme 2).

A peroxide type oxidant (peracetic acid) was also used for the oxidation of isomeric azofuroxans **2** and **3**. The isomeric diphenylazofuroxans **2a** and **3a** were studied. It was found that only 4,4′-azo-3,3′-diphenylfuroxan **2a** formed an azoxy derivative **1a** (Scheme 3). The isomer **3a** was not affected by the oxidant. Evidently, this transformation is sterically hindered by the *N*-oxide groups.

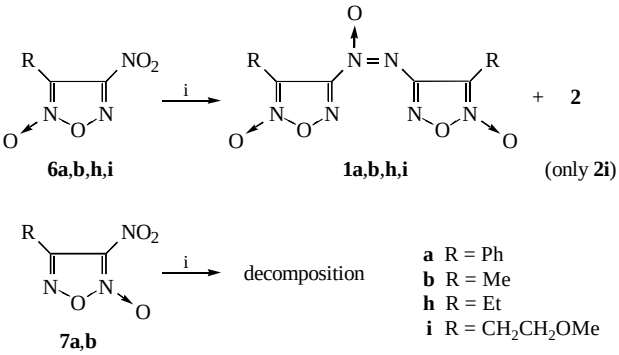


2a **1a**

Scheme 3 *Reagents and conditions*: i, 30% H_2O_2 (24 mol), AcOH (170 mol), Ac_2O (110 mol), 80–90 °C, 7 h, then reflux with addition of H_2O_2 until colourless.

An appropriate reducing agent should be chosen for the synthesis of compounds **1** by the reductive condensation of 4-nitrofuroxans. Various reagents (aldehydes, hydrazines, Mg and Zn metals, and Sn^{II} salts) are used in the aromatic series for this purpose.[13] The reactions are usually carried out in an alkaline medium, but the reactions of compounds with electron-withdrawing substituents are performed in neutral or weakly acidic media. Since the furoxan ring possesses a strong electron-withdrawing effect,[14] we used zinc dust in acetic acid for the transformation of 4-nitrofuroxans into 4,4′-azoxyfuroxans. Although this reagent can reduce the furoxan ring,[15,16] it can be expected that, due to an increase in the reactivity of the nitro group under the action of the ring, its transformation will occur rapidly under very mild conditions, and the ring itself be untouched.

First, the reaction was studied using 4-nitro-3-methylfuroxan **6b**. It was carried out at low temperature with a small excess of the reducing agent. The reaction afforded a mixture of the expected 4,4′-azoxy-3,3′-dimethylfuroxan **1b** (predominantly) and its azo analogue **2b**. The mixture was separated by column chromatography on SiO_2. The reduction of the azoxy fragment in compound **1b** is the most probable reason for the production of **2b**. To prevent this process and to obtain almost pure **1b**, a 1:1 acetic acid–water mixture was used as the solvent. In this mixture the starting nitrofuroxan **6b** is only slightly soluble, and the azoxy compound **1b** is virtually insoluble. It precipitates and does not react further. The other azoxyfuroxans were synthesised under similar conditions in high yields (Scheme 4).§ In all cases, the AcOH:H_2O ratio was selected according to the solubility of the starting and final compounds. Pure azoxyfuroxans **1** were obtained after recrystallisation from appropriate solvents. Only in the case of 3-methoxyethyl-4-nitrofuroxan **6i**, the formation of the azo derivative was not avoided. Clearly, the $MeOCH_2CH_2$ group increases the solubility of **1i** in the AcOH/H_2O mixture, resulting in its partial reduction to **2i**. 3-Nitrofuroxans **7a**,**b** (4-methyl-3-nitro- and 3-nitro-4-phenylfuroxans were studied) do not form the expected 3,3′-azoxy derivatives with zinc dust in AcOH; they decompose under the reaction conditions.



6a,**b**,**h**,**i** **1a**,**b**,**h**,**i** (only **2i**)

7a,**b**

decomposition

a R = Ph
b R = Me
h R = Et
i R = CH_2CH_2OMe

Scheme 4 *Reagents and conditions*: i, Zn dust (1.5–2.5 mol), AcOH/H_2O.

Thus, the reductive condensation of 4-nitrofuroxans **6** is a new and convenient method for the preparation of 4,4′-azoxyfuroxans **1**. It is noteworthy that nitrofurazans (methyl- and phenylnitrofurazans were studied) do not form azoxy derivatives under the action of the Zn/AcOH mixture. This reaction is specific for 4-nitrofuroxans only.

All new compounds had satisfactory elemental analysis data and their structures were confirmed by IR, NMR and mass spectroscopy.†,‡

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§ *Synthesis of 4,4′-azoxyfuroxans* **1** *by reductive condensation of 4-nitrofuroxans* **6** *(general procedure)*. 4-Nitrofuroxan (10 mmol) was added to a mixture of AcOH/water (**6a**, 20:15 ml and 15 ml of MeOH; **6b**, 15:15 ml; **6h**, 15:30 ml; **6i**, 10:15 ml). The reaction mixture was cooled to 0–2 °C and Zn dust (1.5–2.5 mmol) was added at this temperature over 2–4 h. The mixture was then warmed to 20 °C and stirred at this temperature for 1 h; the product obtained was filtered off and crystallised.

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