Novel synthesis of 3-monosubstituted furoxans

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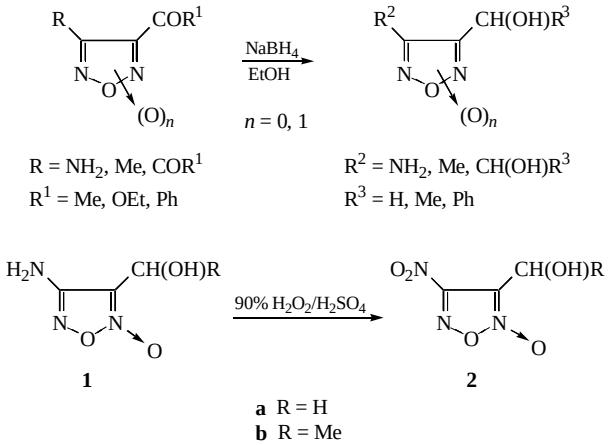
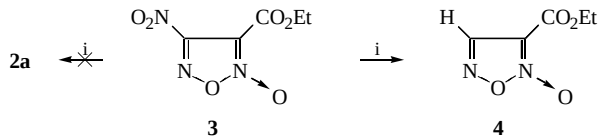
The nitro group in 3-substituted 4-nitrofuroxans (4-nitro-1,2,5-oxadiazol 2-oxides) can be replaced by the hydride ion under the action of $NaBH_4$ in EtOH, and this reaction is convenient for the preparation of 3-monosubstituted furoxans.

Recently,[1] we have proposed a general preparative synthesis of -hydroxyalkyl(benzyl)furoxan and -furazan derivatives based on the reduction of acyl and ethoxycarbonyl substituents in these heterocycles with $NaBH_4$ in EtOH. Acyl, methyl and amino groups were second substituents in the compounds studied. The reaction was completed within 10–30 min at 10–15 °C. The 4-amino groups in 4-amino-3-(-hydroxymethyl- and ethyl)-furoxans **1a**,**b** were oxidised to nitro groups to form corresponding 4-nitro-3-(-hydroxymethyl- and ethyl)furoxans **2a**,**b** (Scheme 1).



Scheme 1

In this work, we attempted to obtain nitroalcohol **2a** by the reduction of a furoxan derivative containing a nitro group, 3-ethoxycarbonyl-4-nitrofuroxan **3**,[2] using the same reducting agent. Compound **3** was found to react with $NaBH_4$ in EtOH under milder conditions (–10 °C, ~1 min); however, previously unknown 3-ethoxycarbonylfuroxan **4** was isolated (yield 51%) instead of expected **2a** (Scheme 2). These conditions seem to be favourable to the nucleophilic substitution of the hydride ion for the nitro group in compound **3**. It is likely that the ethoxycarbonyl group cannot be reduced to the hydroxymethyl group under mild conditions. The chemical shift of the hydrogen atom at C(4) in the ^{1}H NMR spectrum of compound **4** is 8.2 ppm, and the chemical shift of the C(4) atom in the ^{13}C NMR spectrum is 148.5 ppm. These values are consistent with the data published for the parent furoxan[3] and 3-phenylfuroxan.[4] The mass spectrum exhibits a peak of the molecular ion.



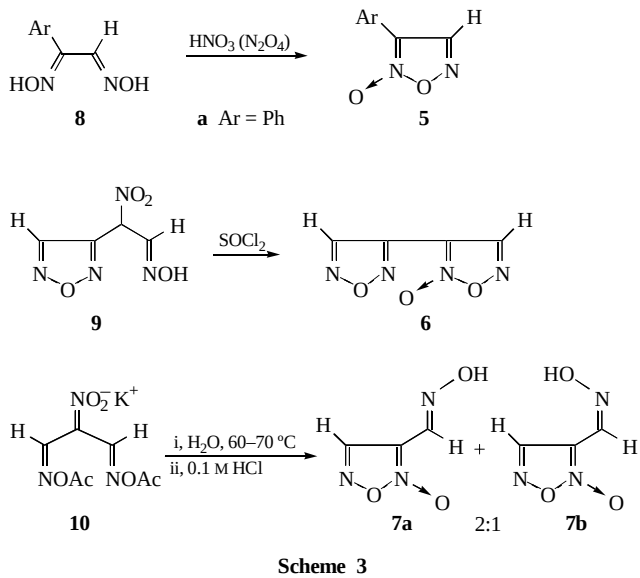
Scheme 2 *Reagents and conditions*: $NaBH_4$ (2 mol), EtOH, –10 °C, 1 min, then HCl/H_2O.

The reactions of nitroaromatic compounds with $NaBH_4$ can proceed *via* various pathways depending upon the reaction conditions and the type of substitution in the ring. For instance, azobenzenes, azoxybenzenes and anilines can be obtained by this reaction.[5] Nitroaromatic compounds with electron-accepting substituents are reduced by $NaBH_4$ to cyclohexene derivatives[6] or form stable Meisenheimer complexes with hydride.[7] The nucleophilic substitution of the hydride ion for the nitro group in aromatic compounds under the action of $NaBH_4$ was also described. However, this reaction requires the presence of bulky substituents adjacent to the nitro group to prevent its conjugation with the ring and the presence of electron-withdrawing groups to activate the ring towards the hydride ion attack.[8] In the oxadiazole series, this reaction was observed for the first time, and it could not be predicted in advance. Though the oxadiazole ring possesses a very high electron-withdrawing effect,[9] only one substituent is adjacent to the nitro group in compound **3**. Moreover, the nitro groups in both the 4- and 3-positions of the furoxan cycle are almost coplanar with the ring (16° in 3-methyl-4-nitrofuroxan[10] and 11° in 3-nitro-4-phenylfuroxan[11]).

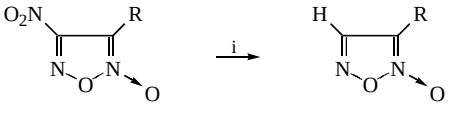
3-Monosubstituted furoxans in contrast to 4-monosubstituted ones are not easily accessible compounds. Only few examples of such structures have been described: 3-arylfuroxans **5** and 3-furazanylfuroxans **6** and isomeric furoxan-3-aldoximes **7a**,**b**. These compounds were prepared by different methods. 3-Arylfuroxans **5** were synthesised by oxidation of the -forms of corresponding monoarylglyoximes **8**.[12-15] 3-Furazanylfuroxan **6** was obtained by dehydration of -(furazanyl)nitrooxime **9**.[16] Furoxan-3-aldoximes **7a**,**b** were synthesised as a mixture of isomers by transformation of a diacetyl derivative of nitromalonaldehyde **10**[17] (Scheme 3). In this connection, the replacement of the nitro group by the hydride ion in 3-R-4-nitrofuroxans can be useful for the preparation of 3-monosubstituted furoxans.

To estimate the application field of this reaction, we studied the interaction of 3-alkyl-4-nitrofuroxans **11a**,**b** and 3-phenyl-4-nitrofuroxan **12** with $NaBH_4$ in EtOH. The following expected 3-monosubstituted furoxans were isolated in high yields in all cases: 3-methyl- and 3-ethylfuroxans **13a**,**b** (which were unknown previously) and 3-phenylfuroxan **5a** (Scheme 4).†

Thus, the interaction of 3-substituted 4-nitrofuroxans with $NaBH_4$ in EtOH is a new, general and convenient method for



Scheme 3



11 **13**
12 R = Ph **5a** R = Ph
a R = Me
b R = Et

Scheme 4 *Reagents and conditions*: i, $NaBH_4$ (2 mol), EtOH.

the synthesis of hitherto hardly accessible 3-monosubstituted furoxans, and the result of this reaction is independent of the second substituent (alkyl, aryl or alkoxycarbonyl).

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† All new compounds had satisfactory elemental analysis data, and their structures were confirmed by IR and NMR spectroscopy and mass spectrometry. IR spectra were recorded in KBr pellets. ^1H, ^{13}C and ^{15}N NMR spectra (300, 75.5 and 30.4 MHz, respectively) were measured in $CDCl_3$, internal standard $SiMe_4$ for ^1H and ^{13}C and external standard $MeNO_2$ for ^{15}N.

Preparation of 3-monosubstituted furoxans (general procedure). A solution of $NaBH_4$ (5 mmol) in 50 ml of anhydrous ethanol was added to a solution of nitrofuroxan (2.5 mmol) at –10 °C, and the reaction mixture was stirred at corresponding temperatures (compound **3**: –10 °C, 1 min; compounds **11a**,**b**: 20 °C, 5–6 min; compound **12**: 5–10 °C, 10 min). Next, the reaction system was cooled, 12 mmol of conc. HCl was added, EtOH was evaporated and 3-monosubstituted furoxans were purified by column chromatography on SiO_2 ($CHCl_3$–hexane eluent).

3-Ethoxycarbonylfuroxan **4**: yield 53%, high-boiling liquid, R_f 0.62 ($CHCl_3$). ^1H NMR, δ: 1.20 (t, 3H, Me, ^3J 7.7 Hz), 4.17 (q, 2H, CH_2, ^3J 7.7 Hz), 8.20 (s, 1H, CH). ^{13}C NMR ([$^2H_6$]acetone) δ: 14.45 (q, Me, ^1J 137 Hz), 83.47 (t, CH_2, ^1J 147 Hz), 109.18 (C-3 in furoxan ring, ^2J 10.8 Hz), 148.05 (d, C-4 in furoxan ring, ^1J 205 Hz), 158.80 (C=O). IR (ν/cm^{-1}): 1395, 1417, 1438, 1523, 1623 (furoxan ring), 1732, 1760 (CO), 2857, 2925, 2995 (CH in Et), 3145 (CH in furoxan ring). MS, *m*/*z*: 158 (M^+).

Phenylfuroxan **5a**: yield 89%, mp 107–108 °C (lit.,[10] 108–109 °C).

3-Methylfuroxan **13a**: yield 74%, bp 63–64 °C (2 Torr), R_f 0.2 ($CHCl_3$–heptane, 1:4). ^1H NMR, δ: 2.18 (s, 3H, Me), 8.55 (s, 1H, CH). ^{13}C NMR, δ: 8.16 (dq, Me, ^1J 132 Hz, ^3J 6.0 Hz), 113.45 (m, C-3 in furoxan ring, ^2J 6.0 Hz), 148.25 (dt, C-4 in furoxan ring, ^1J 200 Hz, ^3J 3.2 Hz). ^{15}N NMR, δ: –22.95 (N-2, $^3J_{CH–N-2}$ 4.0 Hz), –2.77 (N-5, ^2J 11.8 Hz). IR (ν/cm^{-1}): 1380, 1495, 1620 (furoxan ring), 2930 (CH in Me), 3140 (CH in furoxan ring). MS, *m*/*z*: 100 (M^+).

3-Ethylfuroxan **13b**: yield 49%, bp 86–87 °C (2 Torr), R_f 0.29 ($CHCl_3$–CCl_4, 1:1). ^1H NMR, δ: 1.27 (t, 3H, Me, ^3J 8.1 Hz), 2.54 (q, 2H, CH_2, ^3J 8.1 Hz), 8.14 (s, 1H, CH). ^{13}C NMR, δ: 10.49 (q, Me, ^1J 121 Hz), 16.38 (t, CH_2, ^1J 141 Hz), 116.7 (m, C-3 in furoxan ring, ^2J 11.4 Hz), 145.16 (d, C-4 in furoxan ring, ^1J 182.7 Hz). ^{15}N NMR, δ: –23.19 (m, N-2, $^3J_{CH–N-2}$ 1.7 Hz), –1.56 (d, N-5, ^2J 12.1 Hz). IR (ν/cm^{-1}): 1410, 1445, 1470, 1500, 1625 (furoxan ring), 2900, 2960, 2990 (CH in Et), 3135 (CH in furoxan ring). MS, *m*/*z*: 114 (M^+).

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