The Schmidt Rearrangement of Methyl Furoxanyl Ketones and Furoxancarboxylic Acids: a New Synthetic Route to Aminofuroxans

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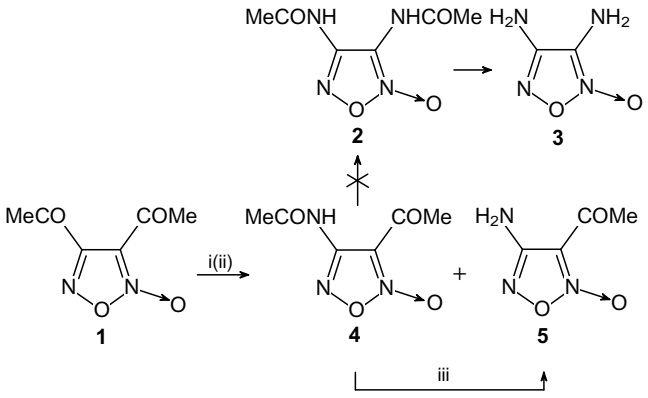
The Schmidt rearrangement of methyl furoxanyl ketones and furoxancarboxylic acids has been carried out for the first time, exemplified by 3,4-diacetylfuroxan and 4-carboxy-3-(ethoxycarbonyl)furoxan, and this reaction has been shown to be a convenient method for the preparation of aminofuroxans.

The most generally used method for the preparation of amino(aryl)furoxans is the oxidation of *anti*-forms of *C*-arylaminoglyoximes.[1–3] However, some aminoglyoximes with non-aromatic substituents (Me, NH_2, NHAlk, H) exist only in *trans*-forms and are not capable of yielding aminofuroxans by oxidation.[4,5] Most probably, the *trans*-position of the oxime groups is favoured by intramolecular hydrogen bonds. A few isolated examples of the synthesis of aminofuroxans by other reactions are known,[6,7] but these methods are not general. An alternative approach to the preparation of aminofuroxans could be sextet rearrangement at the nitrogen atom (Schmidt, Curtius, Hofmann, Lossen rearrangements) of the corresponding furoxan derivatives. Only one paper is known to deal with the Curtius reaction in the furoxan series,[8] rearrangement of the isomeric 3(4)-azidocarbonyl-4(3)-methylfuroxans affording isomeric alkoxycarbonylamino derivatives but not amines.

In the present paper the possibility of preparing aminofuroxans by the Schmidt rearrangement of methyl furoxanyl ketones and furoxancarboxylic acids as exemplified by 3,4-diacetylfuroxan **1** and 4-carboxy-3-(ethoxycarbonyl)furoxan **16** has been studied. The interaction of aryl methyl ketones with HN_3 in the presence of acidic catalysts is known to give a mixture of the corresponding *N*-aryl- and *N*-methylamides in the ratio 95:5.[9] In the case of methyl furoxanyl ketones one would expect to obtain *N*-(acethylamino)furoxans as the main products of the reaction.

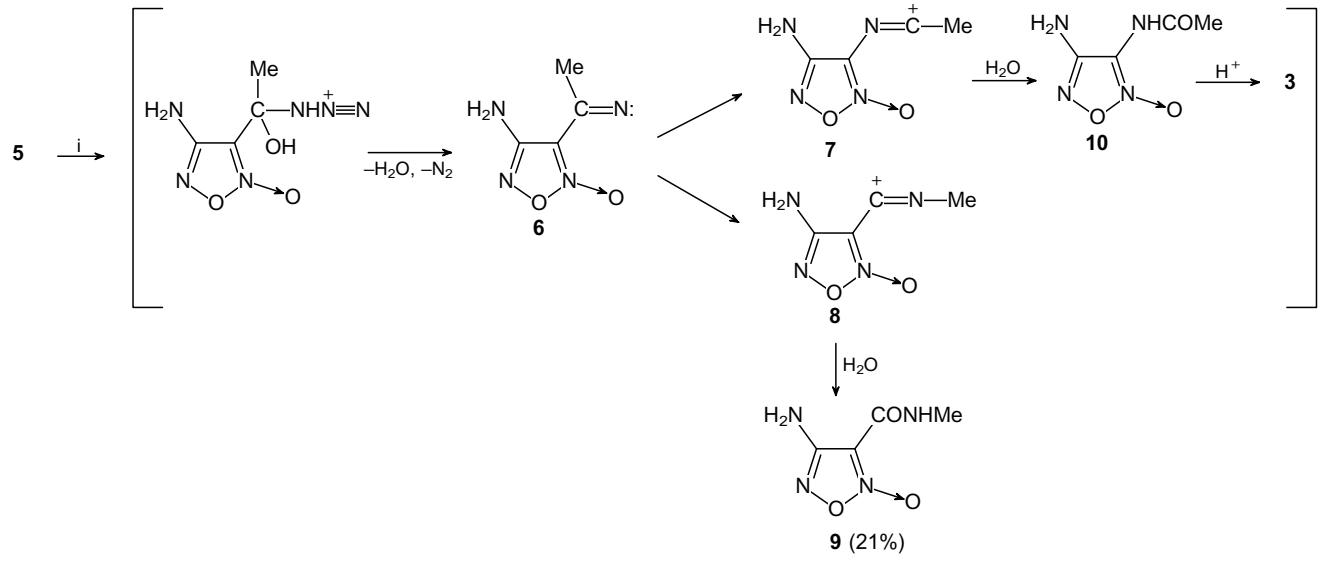
We studied the behaviour of 3,4-diacetylfuroxan **1** in the Schmidt reaction with the aim of preparing 3,4-bis(acetylamino)furoxan **2** – a derivative of the as yet unknown 3,4-diaminofuroxan **3**. Only one of the two MeCO groups reacted, even with an excess of HN_3 in $CHCl_3$ (or CH_2Cl_2) in the presence of H_2SO_4. A mixture of 3-acetyl-4-(acetylamino)-furoxan **4** and the product of its hydrolysis – 3-acetyl-4-aminofuroxan **5** – was obtained. Later, a method was developed with which to hydrolyse the amide **4** to the amine **5** directly in the mixture (Scheme 1).



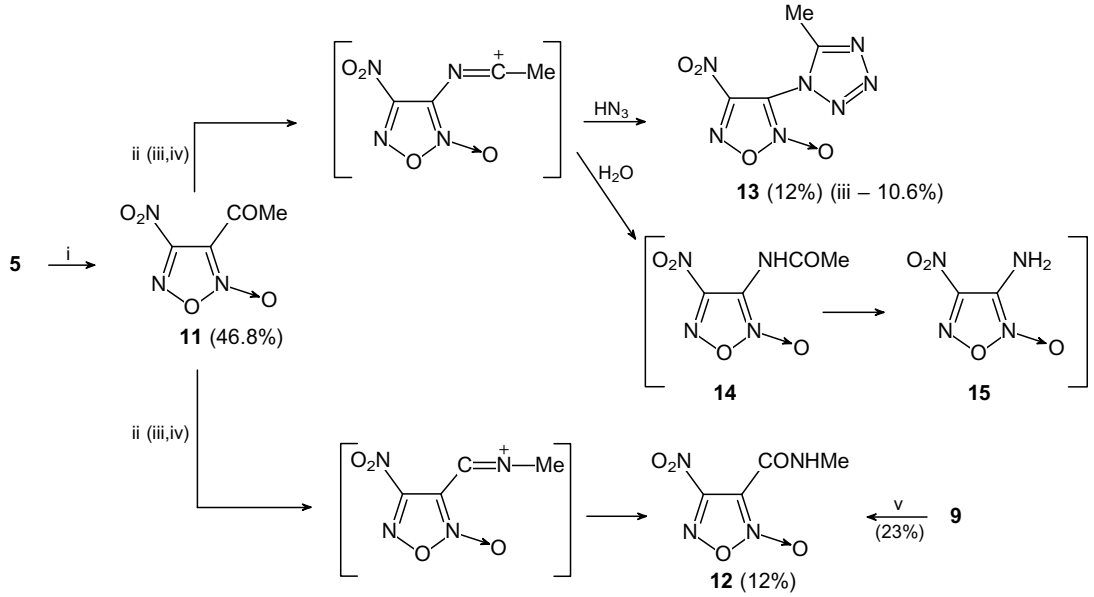
Scheme 1 *Reagents and conditions:* i, NaN_3 (2.2 mol), conc. H_2SO_4 (10 mol), CH_2Cl_2, 0–3 °C, 3 h; ii, HN_3 (7–10% solution in $CHCl_3$) (1.1 or 2.2 mol), 0–5 °C, 1.5–2 h; iii, 1% solution of H_2SO_4 in aqueous MeOH, 20 °C, 4 h.

The position of the MeCO group in compound **5** was established by ^{13}C NMR spectroscopy – the C-3 furoxan ring signal had a spin-spin coupling constant $^3J_{^{13}C-^1H} = 2.5$ Hz with the methyl protons. Additional confirmation of the structure of compound **5** is provided by its oxidation to 3-acetyl-4-nitrofuroxan **11**. The NO_2 group in compound **11** was shown by ^{13}C NMR spectroscopy to be connected with the C-4 atom of the furoxan ring – the signal of this atom shows quadrupolic broadening owing to spin-spin coupling ^{13}C-$^{14}N(NO_2)$. This broadening disappears in a triple resonanse experiment ^{13}C-{^1H,^{14}N}.

The 3-MeCO group in compound **5** does not undergo the Schmidt rearrangement under the conditions studied. The reaction proceeded on decreasing the acidity of the reaction mixture with polyphosphoric acid (PPA) as catalyst. As a result only the second possible product of the Schmidt rearrangement – the *N*-methylamide of 4-aminofuroxan-3-



Scheme 2 *Reagents and conditions:* i, NaN_3 (2 mol), PPA, 20 °C, 48 h.

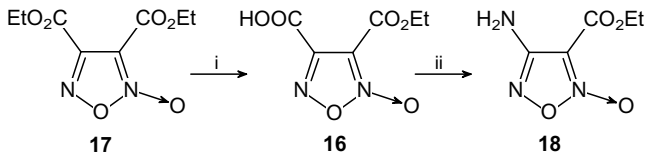


Scheme 3 *Reagents and conditions:* i, H_2O_2 (90%) (5 mol), $(CF_3CO)_2O$ (6 mol), CH_2Cl_2, 20 °C, 5 h; ii, NaN_3 (4 mol), H_2SO_4 (40 mol), CH_2Cl_2, 0 °C, 15 min; 20 °C, 15 h; iii, HN_3 (3.5 mol), H_2SO_4 (35 mol), CH_2Cl_2, 10 °C, 20 min; 20 °C, 3.5 h; iv, NaN_3 (4 mol), PPA, 20 °C, 24 h; v. H_2O_2 (6 mol), $(CF_3CO)_2O$, 20 °C, 2.5 h.

carboxylic acid **9** – was isolated under these conditions, although compound **5** was completely consumed. According to well-known data on the Schmidt reaction mechanism[10] the possible transformation routes for compound **5** under the conditions studied are presented in Scheme 2. Two imino-carbonium ions **7** and **8** may be formed due to migration of the furoxanyl or methyl entity, respectively, to the electron-deficient nitrogen atom of intermediate **6**. Amide **9** is obtained by hydration of ion **8**. Hydration of ion **7** should yield amide **10**, a derivative of diaminofuroxan **3**. The absence of any other products in the reaction mixture except **9** points indirectly to the low stability of **10** and **3**. The stability of amide **9** under the reaction conditions was shown by a separate experiment.

3-Acetyl-4-nitrofuroxan **11**, as well as **1** and **5**, was tested for the Schmidt rearrangement. Compound **11** interacted with HN_3 in the presence of both H_2SO_4 and PPA, but the expected products of 3-MeCO group rearrangement, **14** and **15**, were not obtained in both cases. A mixture of the *N*-methylamide of 4-nitrofuroxan-3-carboxylic acid **12** and 5-methyl-1-(4-nitrofuroxan-3-yl)tetrazole **13** was isolated in the presence of H_2SO_4 in small yield, whereas only **13** was obtained in the presence of PPA. Nevertheless, formation of tetrazole **13** is indicative of the migration of the furoxanyl entity in the Schmidt reaction of the 3-acetylfuroxan derivative (Scheme 3). Compound **12** was also obtained by oxidation of the amine **9**. The small yields of compounds **12** and **13** and their stability under the reaction conditions, as shown by separate experiments, imply that compounds **14** and **15** – the possible products of the main direction of conversion of **11** – are unstable. Recently, the low stability of aminonitrofuroxan **15** was demonstrated.[11]

Carboxylic acids are known to undergo the Schmidt rearrangement with much more difficulty than ketones. The interaction of 4-carboxy-3-(ethoxycarbonyl)furoxan **16** with HN_3 as should be expected was only successful at a higher temperature, with a greater excess of HN_3 and at a greater acidity of the reaction medium (Scheme 4). The poor yield of the final product **18** (6.1%) is possibly due to hydrolysis of the compound **16** to furoxan dicarboxylic acid with its subsequent decarboxylation under the reaction conditions.



Scheme 4 *Reagents and condition:* i, conc. H_2SO_4, 20 °C, 12 h (*cf.* ref. 12); ii, HN_3,(5 mol: 2 mol and then 1 mol every 3 h), $CHCl_3$, 100% H_2SO_4, 40 °C, 12 h.†

† All new compounds synthesized had satisfactory elemental analysis data and their structures were confirmed by ^1H and ^{13}C NMR, IR and mass spectroscopic data. The mixtures of compounds **4, 5** and **12, 13** were separated using preparative TLC with SiO_2 (eluent: hexane–ethyl acetate). NMR spectroscopic data are indicated in δ (ppm); mass spectroscopic data in *m*/*z* (relative intensivity %); and IR spectroscopic data in ν/cm^{-1}.

4: M.p. 109–110 °C (CCl_4); ^1H NMR ($CDCl_3$): 2.25 (s, 3H, MeCON), 2.56 (s, 3H, MeCO), 8.1 (br. s, 1H, NH); IR (KBr): 850, 935, 955, 995, 1020, 1030, 1130, 1200, 1225, 1315, 1360, 1400, 1420, 1540, 1550, 1620 (fur. c.), 1680 (CONH), 1725 (COMe), 3375 (NH).

5 (63%): M.p. 144–145 °C (CCl_4); ^1H NMR ($[^2H_6]$acetone): 2.58 (s, 3H, Me), 6.13 (br. s, 2H, NH_2); ^{13}C NMR ($[^2H_6]$acetone): 29.2 (Me), 110.5 (C-3, $^3J_{^{13}C-^1H}$ 2.5 Hz), 157.5 (C-4), 190.1 (C=O); IR (KBr): 850, 950, 1000, 1200, 1340, 1370, 1415, 1500, 1630, 1680 (fur. c.), 1710 (C=O), 3325, 3340 (NH_2); MS: 143 (M^+, 96), 127 (4), 119 (22), 113 (100), 100 (25), 85 (14).

9: M.p. 193 °C (decomp.); ^1H NMR ($[^2H_6]$acetone): 2.85 (d, 3H, Me), 6.5 (br.s, 2H, NH_2), 8.4 (br.s, 1H, NHCO); ^{13}C NMR ($[^2H_6]$DMSO): 25.70 (Me), 104.55 (C-3 fur. c.), 156.27 (C-4 fur. c.), 157.18 (C=O); IR (KBr): 860, 970, 1030, 1190, 1350, 1420, 1550, 1560, 1575, 1635 (fur. c.), 1680 (C=O), 3240, 3325, 3390, 3450 (NH_2NH); MS: 158 (M^+, 9), 142 (9), 128 (86), 98 (12), 85 (51), 58 (100).

11: B.p. 72–74 °C (1 mmHg); ^1H NMR ($CDCl_3$): 2.63 (s, Me); ^{13}C NMR ($[^2H_6]$DMSO): 28.5 (Me), 108.8 (C-3 fur. c.), 158.0 (C-4 fur. c.), 186.8 (C=O); IR (NaCl, liquid): 800, 960, 1025, 1170, 1290, 1350 and 1520 (NO_2), 1640 (fur. c.), 1730 (C=O), 2940 (CH).

12: M.p. 105–105.5 °C; ^1H NMR ($[^2H_6]$DMSO): 2.92 (d, 3H, Me, ^2J 4.5 Hz), 4.30 (q, 1H, NH, ^2J 4.5 Hz); IR (KBr): 760, 780, 850, 1000, 1055, 1085, 1160, 1240, 1355 and 1500 (NO_2), 1640 (fur. c.), 1670 (C=O), 2820, 2875, 2920, 3000 (CH), 3115, 3295 (NH).

13: M.p. 90–92 °C (decomp.); ^1H NMR ($CDCl_3$): 2.54 (s, 3H, Me); ^{13}C NMR ($CDCl_3$): 8.97 (Me), 108.17 (C-3 fur. c.), 156.0 (C-4 fur. c.), 184.65 (C-5 tetr.c.); IR (KBr): 755, 800, 950, 965, 985, 1015, 1060, 1100, 1160, 1295, 1310 and 1500 (NO_2), 1410, 1445, 1560, 1585, 1655 (fur. c.), 2810, 2860, 2940, 2985, 3015; MS: 213 (M^+).

18: M.p. 125–126 °C (CCl_4); ^1H NMR ($CDCl_3$): 1.52 (t, 3H, Me), 4.53 (q, 2H, CH_2), 5.1 (br. s, 2H, NH_2); ^{13}C NMR ($[^2H_6]$DMSO): 14.03 (Me), 62.60 (CH_2), 103.40 (C-3 fur. c.), 156.58, 157.25 (C-4 fur. c., C=O); IR (KBr): 860, 870, 1000, 1020, 1160, 1350, 1410, 1530, 1620 (fur. c.), 1720 (C=O), 3330, 3455 (NH_2); MS: 173 (M^+), 143, 115.

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Received: Moscow, 1st December 1994
Cambridge, 31st January 1995; Com. 4/07390H