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The Curtius Rearrangement of Azidocarbonylfuroxans: Some Peculiarities and the Synthesis of Aminofuroxans

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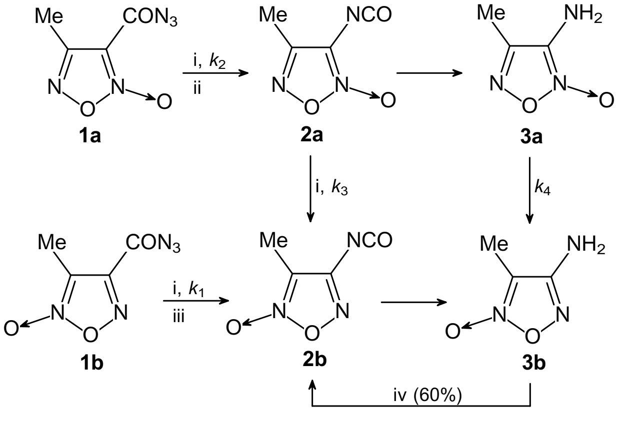
The kinetics of the Curtius rearrangement of the isomeric 3(4)-azidocarbonyl-4(3)-methylfuroxans has been studied; CON_3 group rearrangement was shown to proceed faster at the 3- *versus* the 4-position and to be favoured by an electron-withdrawing substituent at the second ring carbon atom; a series of previously inaccessible isomeric aminofuroxans has been synthesized.

Earlier[1] we studied the Schmidt rearrangement of some acetylfuroxans and furoxancarboxylic acids and showed that this reaction can be used as a method for the preparation of aminofuroxans, but some differences were found in the behaviour of the 3-MeCO and 4-MeCO groups. Unfortunately, the conditions of this reaction (heterogeneous system, conc. H_2SO_4) did not permit the estimation of these differences quantitatively by kinetic measurements. Moreover, an attempted synthesis of the unknown 3,4-diaminofuroxan **14** by the Schmidt reaction failed.



Scheme 1 *Reagents and conditions:* i, CCl_4, 70 °C, 10 h; ii, H_2O (2 mol), dioxane, 70 °C, 1 h; iii, H_2O (2 mol), dioxane, 100 °C, 40 min; iv, current of $COCl_2$, $MeCO_2Et$, 20 °C, 3 h.

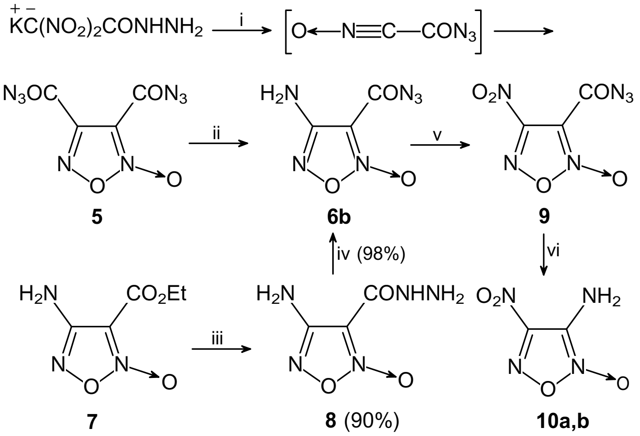
In the present communication we continue to study the synthesis of aminofuroxans by sextet rearrangement at the nitrogen atom of the corresponding furoxan derivatives using the Curtius rearrangement of azidocarbonylfuroxans. The conditions for this reaction (organic solvent, homogeneous medium) are more favourable for kinetic measurements.

Only one pair of isomeric azidocarbonylfuroxans – 3(4)-(azidocarbonyl)-4(3)-methylfuroxans **1a,b** has been described.[2] These compounds underwent the Curtius rearrangement in the presence of EtOH yielding isomeric urethanes. However, measurement of the reaction rate and isolation of the free amines **3a,b** were not carried out in this work. Later,[3] amine **3b** was obtained in the same laboratory by reduction of 3-methyl-4-nitrofuroxan in small yield. The synthesis of amine **3a** has not yet been described.

We studied the kinetics of rearrangement of compounds **1a,b** into 3(4)-isocyanato-4(3)-methylfuroxans **2a,b** by ^1H NMR spectroscopy. The reaction was carried out in an ampoule so as to record the ^1H NMR spectra at 70 ± 1 °C in CCl_4 (Scheme 1). The alternative formation of isocyanate **2b** was realized with amine **3b** and $COCl_2$. The structure of isocyanate **2a** was confirmed by spectroscopic data. As expected, the kinetics of the rearrangement of compounds **1a,b** into isocyanates **2a,b** are first-order. The values[†] of the rate constants $k_1 = (4.7 \pm 0.2) \times 10^{-5}\ s^{-1}$, $k_2 = (13.2 \pm 0.7) \times 10^{-5}\ s^{-1}$ and $k_3 = (13.2 \pm 0.7) \times 10^{-5}\ s^{-1}$ show that the 3-CON_3 group rearranges more rapidly than the 4-CON_3 group, and that 4-isocyanatofuroxan **2b** is thermodynamically preferable to 3-isocyanatofuroxan **2a**. The rearrangement conditions found allowed us to obtain amines **3a,b**. The reaction was carried out in aqueous dioxane. In order to accelerate the process the rearrangement of compound **1b** was performed at 100 °C, complete conversion being reached after 40 min. Milder conditions (70 °C, 1 h) were used for the preparation of 3-amino isomer **3a** because of its ability to isomerise into 4-amino isomer **3b**. Under these conditions only 37% of **1** reacted. (The pronouced tendency of 3-aminofuroxans to isomerise into 4-aminofuroxans is well-known[4]). The rate constant of this process was also measured [$k_4 = (4.4 \pm 0.2) \times 10^{-5}\ s^{-1}$]. Interestingly, no N,N'-bis(3-methylfuroxanyl)urea was formed during the preparation of amines **3a,b.** This is obviously caused by the strong electron-withdrawing effect of the furoxan ring. A similar situation was observed during the Curtius rearrangement of polynitroarylcarboxylic acid azides.[5]

[†] The coincidence of k_2 and k_3 in numerical values is purely fortuitous.

With the goal of possibly obtaining 3,4-diaminofuroxan **14** by the Curtius rearrangement, bis(azidocarbonyl)furoxan **5** was synthesized by the interaction of dinitroacetic acid hydrazide (potassium salt) **4** with N_2O_4, employing the generation of nitrile oxides from the salts of substituted dinitromethanes as elaborated in our earlier work.[6,7] The $CONHNH_2$ group transformed into the CON_3 group simultaneously with generation of a nitrile oxide fragment (Scheme 2). Compound **5** was found to undergo the Curtius rearrangement markedly faster than azidocarbonylfuroxans **1a,b**. The reaction was completed within just 10 min at 80 °C in aqueous dioxane. However, instead of the expected 3,4-diaminofuroxan **14** only the product **6b** was obtained because just one of the two CON_3 groups of **5** took part in the rearrangement. Aminocarboazide **6b** was also prepared from aminoester **7** (previously synthesized[1]) through aminocarbohydrazide **8** (Scheme 2).



Scheme 2 *Reagents and conditions:* i, N_2O_4 (2 mol), CCl_4, 0–5 °C, 20 min, 18–20 °C, 1 h; ii, H_2O–dioxane, 80 °C, 10 min; iii, $NH_2NH_2{\cdot}H_2O$ (3 mol), MeOH, 0 °C, 1 h; iv, $NaNO_2$ (2 mol), HCl/H_2O, 0 °C, 25 min; v, 80% H_2O_2 (50 mol), H_2SO_4, 20 °C, 1 h; vi, H_2O–dioxane, 80 °C, 15 min [ratio of 4-NH_2(**10b**):3-NH_2(**10a**) = 6:1].

The position of the NH_2 group in amine **6b** was established by ^{13}C NMR spectroscopic data. The C-3 furoxan ring signal has a spin-spin coupling constant with the protons of the NH_2 group $^{3}J = 3.8$ Hz. It was shown earlier[8] that in amino derivatives of 1,2,5-oxadiazoles $^{3}J_{^{13}C-^{1}H}$ (NH_2) for a ring carbon not connected with an NH_2 group is much greater than $^{2}J_{^{13}C-^{1}H}$ for C-NH_2. In some cases the latter coupling is completely absent (as in this case). 3-Azidocarbonyl-4-nitrofuroxan **9** was synthesized by oxidation of amine **6b**. Compound **9** undergoes the Curtius rearrangement as readily as compound **5** giving a mixture of isomeric 4(3)-amino-3(4)-nitrofuroxans **10a,b**, previously obtained by another method[9] (Scheme 2). It is evident that electron-withdrawing substituents accelerate this rearrangement.

The formation of the 4-amino isomer **6b** from compound **5** seems to be surprising. However, the rearrangement of compound **5** in the presence of MeOH confirmed the trends found for isomers **1a,b**. Short heating at 55 °C leads mainly to formation of 3-(methoxycarbonyl)amino derivative **11a**.[‡] A small increase in temperature (60 °C) yields a mixture of compound **11a** and its isomerisation product **11b**, the former predominating. A further increase in temperature and time of heating gives **12**, a product of isomerisation of both CON_3 groups (Scheme 3). It is obvious that the rearrangement of compound **5** at 80 °C (Scheme 2) gave firstly isomer **6a**, which further isomerized into isomer **6b** under the reaction conditions. Compound **6a** was isolated in a small yield only after decreasing the reaction temperature to 20 °C, a partial isomerisation of isomer **6a** into isomer **6b** being found even at this temperature (Scheme 3).

Amine **6b** rearranged successfully in the presence of EtOH giving the monoethoxycarbonyl derivative **13** of diaminofuroxan **14**. However, an attempt to obtain compound **14** by rearrangement of the amine **6b** in aqueous dioxane failed, although **6b** was consumed completely. An attempt at acidic hydrolysis of compound **13** into **14** at 20 °C also resulted in complete destruction (Scheme 3).[‡] This result combined with previous investigations[1] allows us to conclude that 3,4-diaminofuroxan **14** is an unstable compound.

[‡] All new compounds synthesized had satisfactory elemental analysis data and their structures were confirmed by ^{1}H, ^{13}C, $^{14/15}$N NMR, IR and mass spectroscopic data. Compounds **3a, 6a** and **11b** were isolated using preparative column chromatography with SiO_2. TCL was carried out using silufol UV-254.

3a (obtained in mixture with **3b**), yield 68% (on the basis of **1a** converted), m.p. 130.5–131.7 °C, R_f 0.22 ($CHCl_3$/EtOAc = 1:1), MS *m/z* 115 (M^+), λ_{max}/nm (MeOH) 215 (log ε 3.46), 295 (log ε 3.74); IR (KBr) ν/cm^{-1}: 3385, 3328, 3290 (NH), 1688 (NH), 1632, 1550, 1470 (ring), 1432 (CH), 1340, 1240 (C-NH), 2855 (CH); ^{1}H NMR ([$^{2}H_6$]DMSO, HMDS) δ 2.31 (s, 3H, Me), 5.83 (br.s, 2H, NH_2).

3b: yield 59%, m.p. 133.0–134.5 °C, R_f 0.37, MS *m/z* 115 (M^+), λ_{max}/nm: 247 (3.89); IR (KBr) ν/cm^{-1}: 3420, 3350, 3250, 3218 (NH), 1666, 1560 (NH), 1635, 1570, 1482, 1391 (ring), 1325, 1210 (C-NH), 2940 (CH); ^{1}H NMR ([$^{2}H_6$]DMSO, HMDS) δ 2.08 (s, 3H, Me), 6.18 (br.s, 2H, NH_2); ^{13}C NMR ([$^{2}H_6$]DMSO, TMS) δ 158.5 (C-4), 108.8 (C-3), 7.4 (Me).

5: yield 60%, colourless oil, n_D^{20} 1.5506, R_f 0.67 ($CHCl_3$), MS *m/z* 224 (M^+, 24%), 194 (78), 154 (12), 122 (75), 108 (100); λ_{max}/nm: 209, 244, 272; IR (NaCl, liquid), ν/cm^{-1}: 2180 (as N_3), 1720 (C=O), 1635, 1512, 1338 (ring), 1490 (s N_3); ^{13}C NMR ([$^{2}H_6$]acetone) δ 108.8 (C-3), 149.5 (C-4), 161.3 (C=O at C-3), 163.4 (C=O at C-4). **CAUTION!** This compound is very explosive and should be kept in solution.

6a: yield 3% (20% in mixture with **6b** by ^{1}H NMR), bright yellow solid, m.p. 108–109 °C, R_f 0.11 ($CHCl_3$), λ_{max}/nm: 211, 233, 242, 378; IR (KBr) ν/cm^{-1}: 3445, 3350, 3250 (NH), 2210, 2180, 2132 (as N_3), 1705 (C=O), 1664 (NH), 1596, 1530, 1378 (ring), 1450 (s N_3), 1275 (CN); ^{1}H NMR ([$^{2}H_6$]acetone) δ 5.63 (br.s, NH_2), ([$^{2}H_6$]DMSO) δ 6.30 (br.d, NH_2).

6b: yield 73%, pale yellow solid, m.p. 129–130 °C, R_f 0.25, λ_{max}/nm: 215, 243, 277; IR (KBr) ν/cm^{-1}: 3443, 3335 (NH), 2212, 2169 (as N_3), 1671 (C=O), 1603 (NH), 1612, 1521, 1370 (ring), 1432 (s N_3), 1220 (CN); ^{1}H NMR ([$^{2}H_6$]acetone) δ 6.13 (br.s, NH_2), ([$^{2}H_6$]DMSO) δ 6.48 (br.s, NH_2); ^{13}C NMR ([$^{2}H_6$]DMSO) δ 161.9 (C=O), 155.9 (C-4), 104.7 (C-3, $^{3}J_{^{13}C-^{1}H}$ 3.8 Hz).

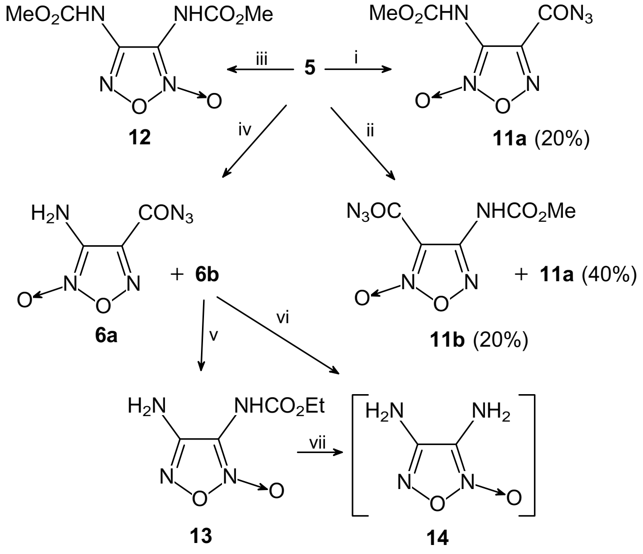
9: yield 68%, yellow solid, m.p. 27–28 °C, R_f 0.46 ($CHCl_3$), λ_{max}/nm: 214, 267; IR (CCl_4) ν/cm^{-1}: 2142, 2188 (as N_3), 1709 (C=O), 1628, 1510, 1362 (ring), 1578 (as NO_2), 1476 (s N_3), 1312 (s NO_2); ^{13}C NMR ([$^{2}H_6$]acetone, TMS) δ 156.5 (t, C-4, $J_{^{13}C-^{1}H}$ 13.0 Hz), 103.9 (C-3), 159.3 (C=O); ^{14}N NMR ([$^{2}H_6$]acetone, $MeNO_2$) δ −36.8 (NO_2), −131.5 (br.s, $N{=}N^+{=}N^-$), −149.5 ($N{=}N^+{=}N^-$).

11a: m.p. 102.5–104.5 °C (decomp.), R_f 0.08 ($CHCl_3$), λ_{max}/nm: 208, 220, 245, 303; IR (KBr) ν/cm^{-1}: 3328 br (NH), 2970 (CH), 2200, 2167 (as N_3) 1732, 1720, 1700 (C=O), 1650, 1560 (ring), 1490 (s N_3); ^{1}H NMR ($CDCl_3$, TMS) δ 3.83 (s, 3H, OMe), 7.02 (br.s, 1H, NH); ^{13}C NMR ([$^{2}H_6$]acetone, TMS) δ 115.3 (C-3), 148.9 (C-4), 154.0 (C=O at NH, $^{3}J_{^{13}C-^{1}H}$ 4.1 Hz), 164.0 (C=O at C-4), 53.9 (OMe); ^{15}N NMR ([$^{2}H_6$]acetone, $MeNO_2$) δ −307.0 (NH $^{1}J_{^{15}N-^{1}H}$ 96.7 Hz).

11b: m.p. 110–112 °C (decomp.), R_f 0.14, λ_{max}/nm: 215, 237, 258; IR (KBr) ν/cm^{-1}: 3372 (NH), 2980 (CH), 2122, 2183 (as N_3), 1772, 1674 (C=O), 1628, 1610, 1672, 1560, 1541, 1330 (ring), 1462 (s N_3); ^{1}H NMR ($CDCl_3$, TMS) δ 3.91 (s, 3H, OMe), 8.32 (br.s, 1H, NH); ^{13}C NMR ($CDCl_3$, TMS) δ 103.1 (C-3), 149.4 (C-4), 163.2 (C=O at ring), 150.8 (C=O at NH), 53.8 (OMe); ^{15}N NMR ($CDCl_3$) δ −288.3 (NH $^{1}J_{^{15}N-^{1}H}$ 95.2 Hz).

12: yield 43%, m.p. 113–115 °C, R_f 0.14 ($CHCl_3$/EtOAc = 4:1), λ_{max}/nm: 210, 261; IR (KBr) ν/cm^{-1}: 3279 (NH), 2972 (CH), 1778, 1747, 1718 (C=O), 1648, 1590 (ring), 1230 (CN); ^{1}H NMR ([$^{2}H_6$]DMSO, TMS) δ 3.69 (s, 3H, OMe, 3.73 (s, 3H, OMe), 9.69 (br.s, 1H, NH at C-3), 10.74 (br.s, 1H, NH at C-4); ^{13}C NMR ([$^{2}H_6$]DMSO, TMS) δ 111.3 (C-3), 150.5 (C-4), 153.5 (C=O at C-3), 152.6 (C=O at C-4), 53.1 (OMe), 53.0 (OMe).

13: yield 30%, m.p. 129–130 °C, R_f 0.24 (C_6H_6/MeOH = 20:1), MS *m/z* 188 (M^+, 25%), 158 (15), 130 (69), 128 (41), 100 (9); IR (KBr) ν/cm^{-1}: 3400, 3330, 3300 (NH), 3000 (CH), 1720 (C=O), 1650, 1550, 1490, 1475, 1385, 1190, 1160, 1035, 910, 880 (ring); ^{1}H NMR ([$^{2}H_6$]acetone) δ 1.18 (t, 3H, Me), 4.19 (q, 2H, CH_2), 5.62 (br.s, 2H, NH_2), 7.03 (s, 1H, NH); ^{13}C NMR ([$^{2}H_6$]DMSO) δ 156.3 (C=O), 153.5 (C-4), 109.6 (C-3), 62.0 (CH_2), 14.3 (Me).



Scheme 3 *Reagents and conditions:* i, CCl_4–MeOH, 55 °C, 10 min; ii, CCl_4–MeOH, 60 °C, 1 h; iii, CCl_4–$CHCl_3$–MeOH, reflux, 8 h; iv, CCl_4–H_2O, 20 °C, 3 days; v, toluene–EtOH, reflux, 3 h; vi, dioxane–H_2O, 100 °C, 2 h; vii, HCl (35%), 20 °C, 1 h.

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