Thermal Cyclization of 4-Azido-3-nitropyridines to Furoxanes [1]

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4-Chloro-3-nitro-2-pyridines **3** and **10**, obtained from 4-hydroxy-2-pyridones **1** and **8** after nitration and chlorination, gave with sodium azide 4-azido-3-nitropyridines **4** and **11**, which cyclized on thermolysis to furoxans **6** and **12**. Desoxygenation of the furoxan **6** with triphenylphosphane gave the furazan **7**. Thermal decomposition conditions of the azide **4** and the desoxygenation reaction of **6** to **7** were studied by differential scanning calorimetry (DSC).

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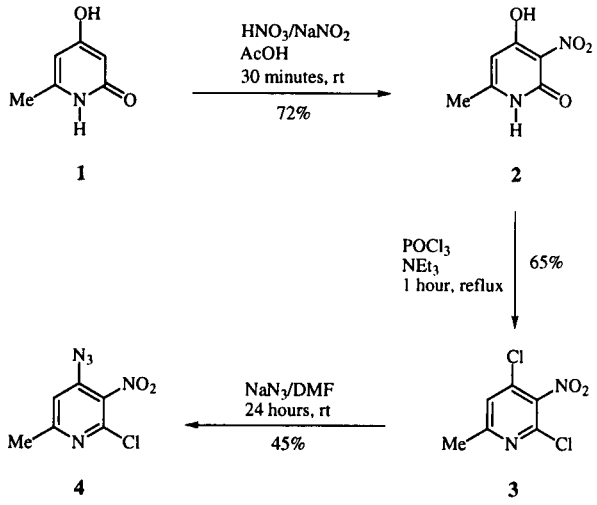
Recently we reported that 4-azidopyridines with *ortho*-acyl substituents gave on thermolysis the corresponding isoxazolo derivatives [1]. In the present work we extended this reaction type to azidopyridines having an *ortho*-nitro group as heteroacyl substituent giving as ring closure product furoxans [2]. A further point of interest was to study the thermal cyclization of *ortho*-acyl azidoarenes by means of differential scanning calorimetry (DSC), a method which we found very suitable for the determination of thermal reaction conditions [3], besides safety aspects, another fact which is important in synthetic azide chemistry.

The reaction sequence to 4-azido-3-nitropyridine **4** started from 4-hydroxy-6-methylpyridin-2(1*H*)-one **1**, which was obtained from commercially available 4-hydroxy-6-methylpyran-2(1*H*)-one by reaction with concentrated ammonia. The pyridone **1** was nitrated to 4-hydroxy-6-methyl-3-nitropyridin-2(1*H*)-one (**2**) by reaction of nitric acid in acetic acid at room temperature in the presence of sodium nitrite [5], a method which is superior to the reported nitration method of similar structures using nitric acid in boiling acetic acid [4]. Chlorination of **2** with phosphoryl chloride or phosphoryl chloride/phosphorous pentachloride similar to earlier results [6] gave only poor yields of impure chlorination products. The addition of triethylamine to the phosphoryl chloride reagent, however, accelerated the reaction speed and afforded 2,4-dichloro-3-nitropyridine (**3**) after 1 hour in good yields. However, it was not possible to exchange regioselectively either the 2-oxo- or 4-hydroxy function.

The reaction of 2,4-dichloro-3-nitropyridine **3** with sodium azide in dimethylformamide gave at room temperature in moderate yields the 4-azido-2-chloropyridine **4**. This compound was found to be highly reactive; attempts to use slightly higher temperatures (about 40-60 °C) in order to obtain shorter reaction times afforded a mixture of two main products and a large number of by-products. Recently we reported that dichloroquinolines can be transformed regioselectively into 2- and 4-azidoquinolines depending on the reaction conditions [7]. Attempts

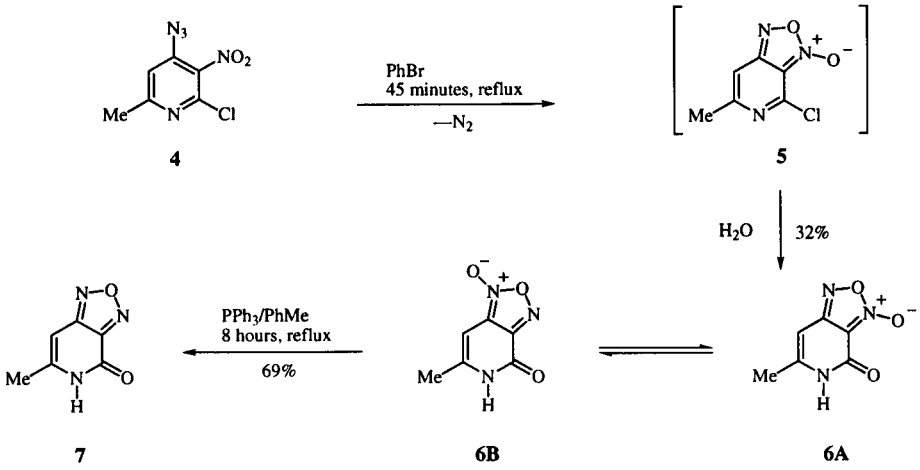
Scheme 1



to obtain 2-azido-4-chloro-6-methyl-3-nitropyridine in a similar manner, however, failed.

To investigate the thermal properties and to plan the thermal cyclization of the azide **4**, the calorimetric decomposition was studied by differential scanning calorimetry. A DSC diagram reveals that after the melting point (110 °C) at about 115 °C a small exothermic reaction takes place (-75 mcal/mg) which is followed by a subsequent exothermic reaction at about 160 °C (-117 mcal/mg), and then decomposition can be observed starting at about 180 °C. In the preparative scale, we heated azidopyridine **4** in refluxing bromobenzene at 156 °C, which resulted in the formation of a brown precipitate. After workup, however, the obtained compound was found to be the oxadiazolopyridone **6**, the hydrolyzation product of the expected 4-chloro derivative **5**. The tlc comparison of **6** with the crude brown precipitate obtained immediately after the cyclization revealed that this intermediate (probably **5**) was not identical with the later isolated oxadiazolopyridone **6**; however, efforts to isolate pure 4-chloro derivative **5** were fruitless. The tlc of **6** showed a pure homogeneous product, but in the ^{1}H nmr a pair of signals of the proton at C-7 and the NH were observed. These results can be explained

Scheme 2



4 5 7 6B 6A

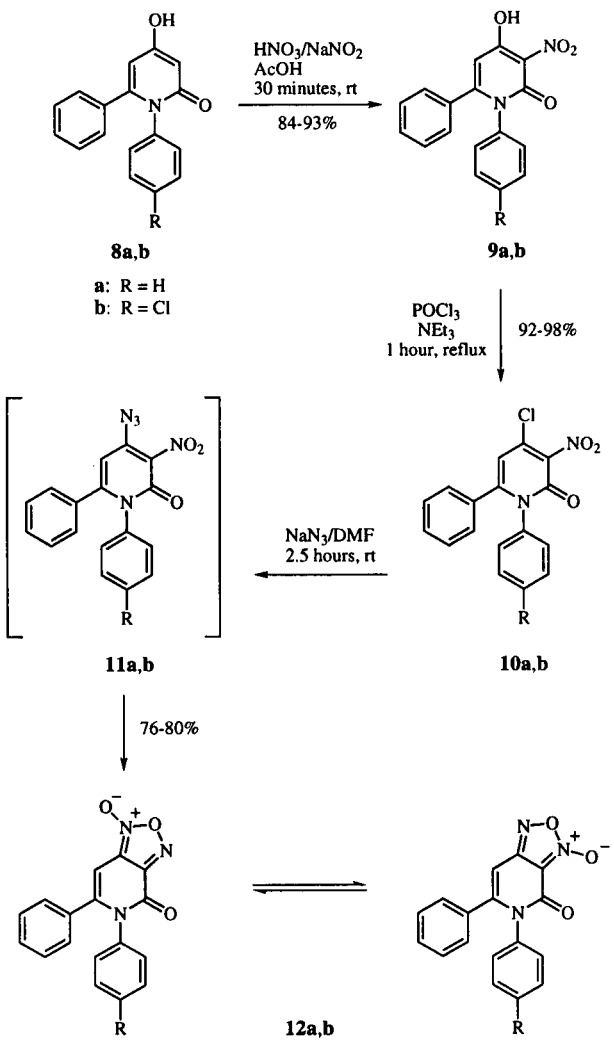
by a mixture of two isomeric forms, **6A** and **6B**, as described in earlier reports on benzofuroxans [8]. Calorimetric measurements of **6**, however, were not sensitive enough to show signals deriving from the transformation of the isomers.

Deoxygenation of oxadiazole-*N*-oxides is known to give the corresponding oxadiazoles; as the reagent, in many cases, triphenylphosphane was used at temperatures between 50-100 °C [12]. The conversion of *N*-oxide **6** with triphenylphosphane to the corresponding oxadiazole **7** was found by calorimetric studies to take place after the melting area of triphenylphosphane (70-75 °C) starting at 90-110 °C. The preparative experiment afforded an oily product, which was separated chromatographically to give the furazan **7** in good yields.

The nitration of 1,6-diaryl-4-hydroxypyridones **8** to 4-hydroxy-3-nitropyridones **9** was performed similarly to the reaction of **1** to **2**. Chlorination of 4-hydroxypyridones **9** with triethylamine as basic catalyst gave a single product in contrast to some findings we obtained in earlier investigations [9], and the structure of it was unequivocally assigned to the 4-chloro-2-pyridone **10** according to the ir spectra, which showed carboxamide signals at 1670-1690 cm^{-1}, whereas isomer 2-chloro-4-pyridones are known to possess carbonyl signals below 1600 cm^{-1} [10].

When the chloropyridones **10** were reacted with sodium azide in dimethylformamide, already at room temperature spontaneous cyclization took place to give the oxadiazolopyridones **12** in good yields. It was not possible to isolate the intermediate azides **11** at lower temperatures. In this case, mixtures of **10**, **11** and **12** were always obtained, which could not be separated. In the nmr spectra of **12** again a pair of signals of the single hydrogen at C-7 was visible because of the two isomers of **12**. Attempts to

Scheme 3



8a,b (a: R = H; b: R = Cl) 9a,b 11a,b 10a,b 12a,b

deoxygenate the *N*-oxide **12** to a furazan similar to **7** was unsuccessful because only a mixture of compounds was obtained.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes. Infrared spectra were taken in potassium bromide pellets on a Perkin-Elmer 298 or a Galaxy Series FTIR 7000 spectrophotometer; the ^{1}H nmr spectra were recorded on a Varian Gemini 200 or a Bruker AM 360 instrument. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent for nmr was deuterio dimethyl sulfoxide unless otherwise stated. Elemental analyses were performed on a C, H, N Fisons elemental analyzer, Mod. EA 1108 and are within ±0.4 of the theoretical percentages. Differential scanning calorimetry data were obtained on a Rheometric Scientific DSC-Plus instrument with the DSC software V5.42. The DSC plots were recorded between 25-500 °C, with a heating rate of 2-10 °C/minute, and 1-3 mg of the compound in sealed aluminium crucibles (11 bar).

Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel F-254 (MERCK) plates using uv light (254 and 366 nm) for detection.

4-Hydroxy-6-methylpyridin-2(1*H*)-one (**1**).

A solution of 4-hydroxy-6-methylpyran-2(1*H*)-one (51.4 g, 0.40 mole) in 25% ammonium hydroxide solution (58 ml) was heated to 100 °C, which caused foaming of the reaction mixture. After a short time the reaction product **1** began to precipitate. The mixture was kept for 6 hours at 100 °C, then water (30 ml) was added to the hot solution and the mixture cooled to room temperature. The precipitate was filtered by suction and dried. The product obtained was pure enough for further reactions without further purification; the yield was 40.6 g (80%), colorless prisms, mp 325-328 °C, lit. mp 330 °C [11].

4-Hydroxy-6-methyl-3-nitropyridin-2(1*H*)-one (**2**).

To a suspension of the hydroxypyridone **1** (15.0 g, 0.12 mole) in glacial acetic acid (225 ml), concentrated nitric acid (22.5 ml) was added. To start the reaction, sodium nitrite (0.6 g, 8.7 mmoles) was added and the mixture stirred for 30 minutes at room temperature. From the dark brown solution, orange-brown crystals were formed. The mixture was poured onto ice/water and the solid was filtered by suction after 1 hour standing to yield 14.6 g (72%) yellowish prisms, mp >360 °C (ethanol); ir: = 3200-2700 br, 1670 s (C=O), 1620 s cm^{-1}; ^{1}H nmr: δ 2.20 (t, *J* = 8 Hz, CH_3), 5.85 (s, 1 ArH).

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.33; H, 3.64; N, 16.52.

2,4-Dichloro-6-methyl-3-nitropyridine (**3**).

A solution of the nitropyridone **2** (5.0 g, 29.4 mmoles) in phosphoryl chloride (100 ml) and triethylamine (4.3 ml) was heated under reflux for 1 hour. After cooling the mixture was poured under stirring onto ice/water (500 ml) and stirred further until the brown oil was changed to a grey-white solid. The mixture was then brought to *p*H 6 with concentrated sodium hydroxide solution and filtered by suction after 12 hours standing; the yield was 3.9 g (64%), colorless prisms, mp 74 °C (methanol/water); ir: 3080 w, 1570 m, 1555 s cm^{-1}; ^{1}H nmr: δ 2.55 (s, CH_3), 7.92 (s, 1 ArH).

Anal. Calcd. for $C_6H_4Cl_2N_2O_2$: C, 34.81; H, 1.95; N, 13.53; Cl, 34.25. Found: C, 34.96; H, 1.96; N, 13.62; Cl, 33.85.

4-Azido-2-chloro-6-methyl-3-nitropyridine (**4**).

A suspension of the dichloropyridine **3** (3.0 g, 14 mmoles) and sodium azide (1.3 g, 20.3 mmoles) in dimethylformamide (50 ml) was stirred at room temperature for 24 hours. Then the mixture was poured onto ice/water (150 ml) and the solid filtered by suction; the yield was 1.4 g (45%), brownish microprisms, mp 110.0-112.4 °C (acetone/water); calorimetric data for thermolysis: mp onset 107 °C, mp peak maximum 110 °C, reaction onset temperature 110 °C, peak maximum 114 °C, ΔH = -75 mcal/mg, second reaction onset temperature 154 °C, peak maximum 160 °C, ΔH = -117 mcal/mg, decomposition onset 176 °C, peak maximum 181 °C; ir: 2160 s (N_3), 2140 (s, N_3), 1600 s, 1560 s cm^{-1}.

Anal. Calcd. for $C_6H_4ClN_5O_2$: C, 33.74; H, 1.89; N, 32.79. Found: C, 33.50; H, 2.01; N, 32.84.

6-Methyl-4-oxo-4,5-dihydro-1,2,5-oxadiazolo[3,4-*c*]pyridin-3-oxide (**6**).

A suspension of the azidopyridine **4** in bromobenzene (15 ml) was heated under reflux for 45 minutes. The solvent was removed under reduced pressure and the residual oil triturated with cyclohexane. After standing for several days yellow crystals were formed which were filtered by suction. The yield was 0.5 g (32%), yellow crystals, mp 219-220 °C (toluene); ir: 3200-2900 br, 1700 s (C=O), 1635 s (C=O), 1600 sh cm^{-1}; ^{1}H nmr: δ 2.13 (s, CH_3), 6.13 and 6.30 (s, H at C-7 of each isomer), 11.34 and 11.70 (s, NH of each isomer).

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.12; H, 3.02; N, 25.14. Found: C, 43.11; H, 3.20; N, 25.07.

6-Methyl-1,2,5-oxadiazolo[3,4-*c*]pyridin-4(5*H*)-one (**7**).

A suspension of the oxadiazolo[3,4-*c*]pyridin-3-oxide **6** (1.9 g, 11.4 mmoles) and triphenylphosphane (3.58 g, 13.6 mmoles) in toluene (30 ml) was heated under reflux for 8 hours. Then the solvent was removed under reduced pressure. The resulting oil was purified by dry-flash chromatography on silica gel with toluene-hexane (1:1) as eluent. The yield was 1.2 g (69%), yellow oil; calorimetric data: reaction/decomposition starting at 122 °C, peak maximum 164 °C, decomposition/reaction starting at 210 °C, peak maximum 294 °C, ΔH = -126 mcal/mg; ir: 3400-2900 m, br, 1710 s, 1660 s, 1580 s; ^{1}H nmr: δ 2.2 (s, CH_3), 6.30 (s, H at C-7), 11.65 (s, NH).

A satisfactory elemental analysis was not obtained because of easy decomposition.

4-Hydroxy-1,6-diphenylpyridin-2(1*H*)-one (**8a**).

A solution of 3-acetyl-4-hydroxy-1,6-diphenylpyridin-2(1*H*)-one [1] (41.8 g, 0.42 mole) in 90% sulfuric acid (60 ml) was heated for 15 minutes to 140 °C. The mixture was poured onto ice (1.2 l) and after standing for 2 hours filtered by suction and washed thoroughly with water. The yield was 34.2 g (95%), color-

less prisms, mp 295-296 °C (ethanol); ir: 1650 m (C=O), 1610 m, 1540 s cm^{-1}; ^1H nmr: δ 5.80 (d, J = 1.5 Hz, 5-H), 6.00 (d, J = 7 Hz, 3-H), 7.15-7.45 (m, 10 ArH), 10.95 (s, OH).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.83; H, 4.76; N, 5.47.

1-(4-Chlorophenyl)-4-hydroxy-6-phenylpyridin-2(1*H*)-one (**8b**).

This compound was obtained from 3-acetyl-1-(4-chlorophenyl)-4-hydroxy-6-phenylpyridin-2(1*H*)-one [1] (1.77 g, 5.2 mmoles) and sulfuric acid (10 ml) according to the method described for **8a**. The yield was 1.5 g (97%), yellowish prisms, mp 300-302 °C (dec.) (methanol); ir: 1650 m (C=O), 1610 m, 1540 s cm^{-1}; ^1H nmr: δ 5.75 (d, J = 1.5 Hz, 5-H), 5.95 (d, J = 7 Hz, 3-H), 7.10-7.40 (m, 9 ArH), 10.9 (s, OH).

Anal. Calcd. for $C_{17}H_{12}ClNO_2$: C, 68.58; H, 4.06; N, 4.70. Found: C, 68.59; H, 4.19; N, 4.60.

4-Hydroxy-3-nitro-1,6-diphenylpyridin-2(1*H*)-one (**9a**).

To a suspension of 4-hydroxypyridone **8a** (8.0 g, 11.4 mmoles) in acetic acid (20 ml), was added concentrated nitric acid (2.1 ml), which caused partial dissolution of the solid. To start the reaction, sodium nitrite (0.06 g, 0.9 mmole) was added which caused complete dissolution of the solid. The mixture was stirred at room temperature for 30 minutes. In this period a yellow solid began to precipitate. The mixture was poured onto ice/water (75 ml) and the precipitate was filtered by suction after standing for 1 hour. The yield was 9.95 g (84%), yellow prisms, mp 221-222 °C (ethanol); ir: 3080-2740 w, 2670-2520 w, 1630 m (C=O), 1590 s cm^{-1}; ^1H nmr: δ 6.20 (s, 5-H), 7.0-7.35 (m, 10 ArH).

Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.32; H, 4.10; N, 9.06.

1-(4-Chlorophenyl)-4-hydroxy-3-nitro-6-phenylpyridin-2(1*H*)-one (**9b**).

This compound was obtained from 4-hydroxypyridone **8b** (1.27 g, 4.3 mmoles) according to the procedure described for **9a**. The yield was 1.37 g (93%), yellow prisms, mp 88-90 °C (ethanol); ir: 3200-2780 w, br, 1680 s (C=O), 1650 m, 1610 s, 1550 s cm^{-1}; ^1H nmr: δ 6.10 (s, 5-H), 7.20-7.40 (m, 9 ArH).

Anal. Calcd. for $C_{17}H_{11}ClN_2O_4$: C, 59.58; H, 3.23; N, 8.17. Found: C, 59.26; H, 3.45; N, 7.84.

4-Chloro-3-nitro-1,6-diphenylpyridin-2(1*H*)-one (**10a**).

A solution of 3-nitropyridone **9a** (1.55 g, 5 mmoles) in phosphoryl chloride (30 ml) and dry triethylamine (2 ml) was heated under reflux for 1 hour. After cooling the mixture was poured onto crushed ice (100 g) and after warming to room temperature filtered by suction. The yield was 1.60 g (98%), yellow-brown prisms, mp 188 °C (toluene/hexane); ir: 1810 w, 1670 s (C=O), 1600 w, 1570 w cm^{-1}; ^1H nmr: δ 6.40 (s, 5-H), 7.05-7.35 (m, 10 ArH).

Anal. Calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.68; H, 3.62; N, 8.34.

4-Chloro-1-(4-chlorophenyl)-3-nitro-6-phenylpyridin-2(1*H*)-one (**10b**).

This compound was obtained from 3-nitropyridone **9b** (1.07 g, 3.1 mmoles) in phosphoryl chloride (20 ml) and triethylamine (1 ml) according to the procedure described for **10a**. The yield was 1.03 g (92%), brownish microprisms, mp 209 °C (dec.) (toluene/hexane); ir: 1690 w, sh, 1660 s (C=O), 1630 w, sh cm^{-1}; ^1H nmr: δ 6.85 (s, 5-H), 7.25-7.35 (m, 5 ArH), 7.40-7.50 (m, 4 ArH).

Anal. Calcd. for $C_{17}H_{10}Cl_2N_2O_3$: C, 56.53; H, 2.79; N, 7.76. Found: C, 56.50; H, 3.04; N, 7.67.

4-Oxo-5,6-diphenyl-1,2,5-oxadiazolo[3,4-*c*]pyridin-3-oxide (**12a**).

A suspension of the 4-chloropyridone **10a** (2.87 g, 9.1 mmoles) and sodium azide (1.3 g, 20 mmoles) in dimethylformamide (30 ml) was stirred for 2.5 hours at room temperature. During this time a slow gas evolution could be observed. When the gas evolution had stopped, the mixture was poured onto 150 ml ice/water and the precipitate filtered by suction. The yield was 2.25 g (80%), yellow-brown prisms, mp 174-175 °C (ethanol); ir: 3080 w, 3060 w, 1700 s (C=O), 1630 s, 1620 sh cm^{-1}; ^1H nmr: δ 6.15 and 6.45 (s, H at C-7 of each isomer), 7.25-7.40 (m, 5 ArH), 7.70-7.80 (m, 3 ArH), 8.05-8.15 (m, 3 ArH).

Anal. Calcd. for $C_{17}H_{11}N_3O_3$: C, 66.88; H, 3.63; N, 13.76. Found: C, 66.80; H 3.85; N, 13.68.

5-(4-Chlorophenyl)-4-oxo-6-phenyl-1,2,5-oxadiazolo[3,4-*c*]-pyridin-3-oxide (**12b**).

This compound was obtained from 4-chloropyridone **10b** (0.92 g, 2.5 mmoles) and sodium azide (0.65 g, 10 mmoles) in dimethylformamide (15 ml) according to the procedure described for **10a**. The yield was 0.64 g (76%), dark yellow brown prisms, mp 187-188 °C (cyclohexane); ir: 3100-3040 w, br, 1700 s (C=O), 1630 s, 1595 sh cm^{-1}.

Anal. Calcd. for $C_{17}H_{10}ClN_3O_3$: C, 60.10; H, 2.97; N, 12.37. Found: C, 60.42; H, 3.25; N, 12.13.

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