# Two Methods for Conversion of an Aromatic Aldehyde to a 4-Arylpyridine. A Method for Preparation of 3-Alkyl-4-arylpyridines.

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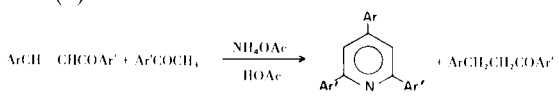
The need for 4-(3-nitrophenyl)pyridine and 3-methyl-4-(3-nitrophenyl)pyridine, intermediates in the synthesis of antibacterial pyridylquinolones (1), led us to examine a number of synthetic routes to these compounds from 3-nitrobenzaldehyde, two of which are reported here.

The first method is a modification of the pyridine synthesis of Weiss who has shown that 2,4,6-triarylpyridines can be synthesized in moderate yields by the following reaction (2).



We have found that when Ar′ = 2-furyl, compound **1**, Ar = (*m*-nitrophenyl), Ar′ = 2-furyl can be prepared and readily oxidized to 4-(*m*-nitrophenyl)-2,6-pyridinedicarboxylic acid **2** which can be decarboxylated to 4-(*m*-nitrophenyl)pyridine **3**, as shown in Fig. 1.

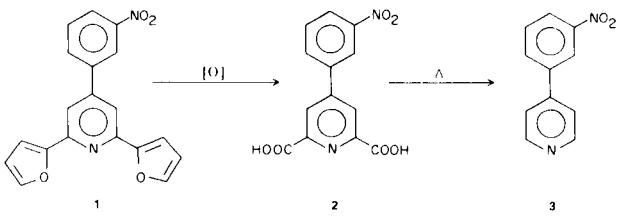


Figure 1

Introduction of a 3-alkyl substituent into a pyridine ring is usually a difficult task (3); a slight modification of the above scheme as shown in Fig. 2 allowed the facile preparation of **5**, 3-methyl-4-(*m*-nitrophenyl)pyridine. The 3-methyl group was supplied by using 2-propionyl furan as the second component. Presumably other alkyl substituents could be introduced by proper choice of the 2-acyl furan.

Oxidation of the furan rings could be carried out using ozone/hydrogen peroxide but dilute nitric acid was more convenient and gave higher yields. The dilute nitric acid used did not oxidize the 3-methyl group in **5** which probably would have been the case had more concentrated acid been used (5). A furan ring has also been oxidized to a carboxylic acid using potassium permanganate in acetone (4). Dicarboxylation was carried out by heating the diacids in Dowtherm®.

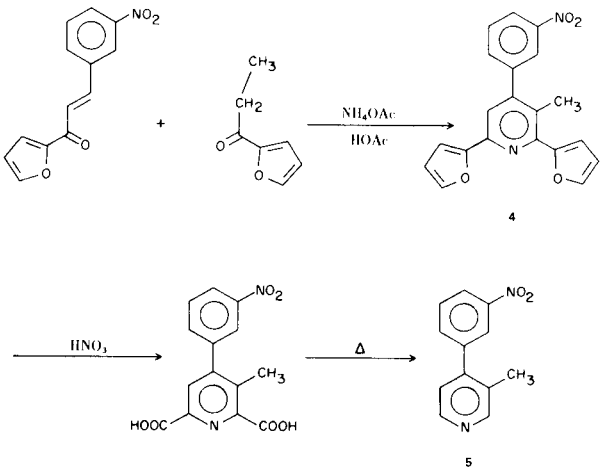


Figure 2

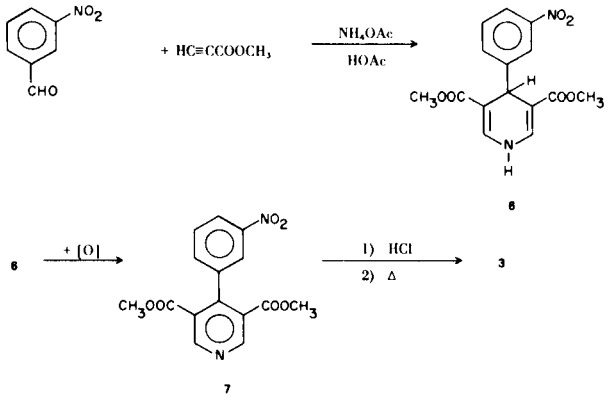


Figure 3

Unlike the Hantzsch pyridine synthesis (6) which gives pyridines substituted in the 2- and 6-positions by alkyl or aryl groups, the second method gives a 2,6-unsubstituted

pyridine. Reaction of 3-nitrobenzaldehyde with methyl propiolate and ammonium acetate gives **6** in fair yield as shown in Fig. 3.

Oxidation of **6** with dilute nitric acid gave **7**, which was hydrolyzed and decarboxylated to **3**.

## EXPERIMENTAL (7)

2-Propionylfuran.

A mixture of 33 ml. of propionic acid and 100 g. (0.476 mole) of trifluoroacetic anhydride was cooled to 15°. Furan, 23.4 g. (0.343 mole) was added dropwise with cooling at less than 25° during 15 minutes. The purple solution was allowed to stand at room temperature for 1 hour, poured on ice, basified with solid potassium carbonate, extracted 5 times (chloroform), dried (magnesium sulfate), concentrated and distilled. The product, 27.3 g. (64.3%), had b.p. 67-68°/8 mm, lit. (8) b.p. 78-80°/17 mm, m.p. 28-29°.

Larger runs (3.0 moles) were made by the procedure described (9) for 2-acetylfuran, using furan, propionic anhydride and phosphoric acid catalyst. Yields were 75-77%.

2,6-Di(2-furyl)-4-(*m*-nitrophenyl)pyridine.

A mixture of 24.3 g. (0.1 mole) of 1-(2-furyl)-3-(*m*-nitrophenyl)-propenone (10), 11.0 g. (0.1 mole) of 2-acetylfuran, 180 ml. of acetic acid and 50 g. of ammonium acetate was refluxed 1 hour with stirring, evaporated *in vacuo* to a brown semi-solid, treated with 200 ml. of water, extracted (dichloromethane), dried (magnesium sulfate) and evaporated to a black gum which rapidly crystallized. The solid was slurried with acetonitrile, collected and recrystallized (acetonitrile) to give 9.8 g. (59%) of yellow crystals m.p. 197-199°.

*Anal.* Calcd. for $C_{19}H_{12}N_2O_4$: C, 68.67; H, 3.64; N, 8.43. Found: C, 68.36; H, 3.61; N, 8.62.

2,6-Di(2-furyl)-3-methyl-4-(*m*-nitrophenyl)pyridine.

From 341.2 g. (1.403 moles) of 1-(2-furyl)-3-(*m*-nitrophenyl)-propenone (10), 174.1 g. (1.403 moles) of 2-propionylfuran, 2800 ml. of acetic acid and 1050 g. of ammonium acetate there was obtained by the above procedure 130.1 g. (53.6%) of yellow crystals, m.p. 199-201.5°.

*Anal.* Calcd. for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09; Found: C, 69.18; H, 4.03; N, 9.27.

3-Methyl-4-(*m*-nitrophenyl)pyridine.

A solution of 2 l. of concentrated nitric acid, 3 l. of water and 4.9 g. of ammonium metavanadate was prepared and divided into 5 equal portions. Each was heated to boiling and 24.5 g. of 2,6-di-(2-furyl)-3-methyl-4-(*m*-nitrophenyl)pyridine (98 g. total, 0.295 mole) was slowly added with vigorous stirring. The solution was boiled 15 minutes after addition was completed. The 5 batches were combined, evaporated *in vacuo* to give 60.1 g. (70.8%) of tan solid, m.p. 232-236° dec.

The crude diacid, (50 g., 0.173 mole) was added to 500 ml. of Dowtherm® and heated to 220° with stirring. Vigorous gas evolution occurred and an almost clear black solution occurred. After 15 minutes at 220°, the solution was cooled, filtered and the filtrate extracted four times with 200 ml. portions of 3*N* hydrochloric acid. The hydrochloric acid extract was washed with ether, which was discarded. After charcoaling, the acid extract was basified with ammonium hydroxide, extracted (dichloromethane) and the dichloromethane evaporated to a greenish oil which crystallized on cooling. Purification was effected by crystallization of the nitrate salt from water or by crystallization of the base from 2-propanol, m.p. 87-90°, 21.9 g. (59%).

*Anal.* Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.13; H, 4.72; N, 13.24.

4-(*m*-Nitrophenyl)pyridine.

Oxidation of 2,6-difuryl-4-(*m*-nitrophenyl)pyridine as described for the 3-methyl analog gave 76.8% of crude diacid, m.p. 264-270° dec.

Decarboxylation similarly gave 40.7% of 4-(*m*-nitrophenyl)-pyridine, m.p. 111-113°. Lit. (11) m.p. 109-110°.

Dimethyl 1,4-Dihydro-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

A mixture of *m*-nitrobenzaldehyde (15.1 g., 0.1 mole) of methyl propiolate (25.2 g., 0.3 mole) of ammonium acetate (15.4 g., 0.2 mole) and acetic acid (100 ml.) was refluxed 4 hours with stirring. The solution was concentrated *in vacuo* to a yellow solid which was taken up in chloroform (300 ml.) and washed twice with water. After drying (magnesium sulfate) the chloroform was evaporated to a yellow solid *in vacuo*. The solid was stirred with a little methanol, collected and dried *in vacuo* to give 18.0 g. (56.7%) of product m.p. 185-187°. Recrystallization acetonitrile gave m.p. 185-187°.

*Anal.* Calcd. for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.43; N, 8.50. Found: C, 56.44; H, 4.37; N, 8.94.

Dimethyl 4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

A mixture of nitric acid (60 ml., d = 1.42) and water (150 ml.) was heated to 65° with stirring. The dihydro compound was added in portions with stirring at 65-70°. Stirring was continued for 10 minutes at 70° after the addition was completed. After cooling, during which the nitrate salt crystallized, the mixture was basified (ammonium hydroxide), extracted 3 times (dichloromethane), the extract dried (magnesium sulfate) and evaporated to a yellow solid. Recrystallization (methanol) gave 17.4 g. (97.9%) of product, m.p. 114-116°.

Anal. Calcd. for C H N O : C, 56.97; H, 3.82; N, 8.86. Found: C, 56.90; H, 3.81; N, 8.91.

4-(*m*-Nitrophenyl)-3,5-pyridinedicarboxylic Acid and 4-(*m*-Nitrophenyl)pyridine.

A solution of dimethyl 4-(*m*-nitrophenyl)-3,5-pyridine dicarboxylate in 20 ml. of concentrated hydrochloric acid and 20 ml. of water was refluxed for 4 hours, evaporated *in vacuo* to 3.0 g. (92.7%) of off-white solid, m.p. 252-259° dec. The analytical sample (methanol/water) had m.p. 263-264°.

*Anal.* Calcd. for $C_{13}H_8N_2O_6$: C, 54.24; H, 2.82; N, 9.72. Found: C, 53.95; H, 2.97; N, 9.58.

The above solid (2.3 g., 0.0799 mole) was suspended in Dowtherm® (50 ml.) containing cuprous oxide (0.6 g.), stirred and boiled vigorously for 5 minutes. The mixture was cooled, diluted with 2 volumes of dichloromethane, filtered, the filtrate extracted 3 times with 3*N* hydrochloric acid, the extracts washed with dichloromethane and the dichloromethane discarded. The acid solution was basified (ammonium hydroxide) extracted (dichloromethane), the extract dried (magnesium sulfate) and evaporated to a solid. After recrystallization (isopropyl acetate), the product (1.1 g., 68.6%) had m.p. 111-112°. Lit. (11) m.p. 109-110°.

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