

Tetraethyl 4-(3-Nitrophenyl)-2,3,5,6-pyridinetetracarboxylate

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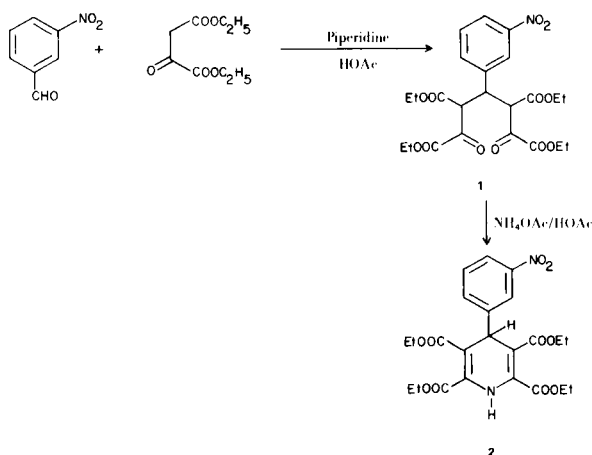
Received March 5, 1976

Reaction of 3-nitrobenzaldehyde with diethyl oxalacetate in the presence of piperidine acetate and then ammonium acetate/acetic acid gave a moderate yield of tetraethyl 1,4-dihydro-4-(3-nitrophenyl)-2,3,5,6-pyridinetetracarboxylate. This was oxidized with nitric acid to tetraethyl 4-(3-nitrophenyl)-2,3,5,6-pyridinetetracarboxylate which was hydrolyzed and decarboxylated to give 4-(3-nitrophenyl)pyridine.

J. Heterocyclic Chem., **13**, 927 (1976).

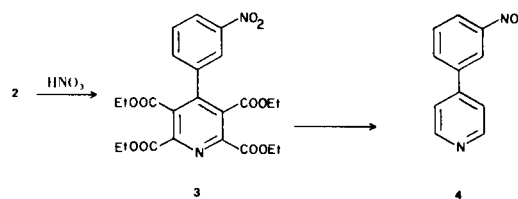
Recently we described two methods for converting an aromatic aldehyde into a 4-arylpyridine (1). This note describes a third method for the same transformation.

The Hantzsch pyridine synthesis (2) usually gives pyridines substituted with alkyl or aryl groups in the 2- and 6-positions and alkoxy-carbonyl, acyl or cyano groups in the 3- and 5-positions. We have found that if diethyl oxalacetate is condensed with 3-nitrobenzaldehyde in the presence of piperidine acetate and the resulting crude diketone **1** then treated with ammonium acetate in acetic acid, the dihydropyridine **2** can be obtained in fair yield.



Attempts to obtain **2** by direct combination of *m*-nitrobenzaldehyde, diethyl oxalacetate and ammonium acetate were unsatisfactory (2a).

Oxidation of **2** with dilute nitric acid gave an excellent yield of **3** which was hydrolyzed and decarboxylated to give **4**, an intermediate in the synthesis of antibacterial pyridylquinolones (3).



EXPERIMENTAL (4)

Diethyl Oxalacetate.

The commercial sodium derivative of diethyloxalacetate (97%, 280 g., 1.29 moles) was suspended in 300 ml. of water with vigorous stirring. A solution of 110 ml. of hydrochloric acid in 310 ml. of water was added and stirring continued for 5 minutes. After addition of dichloromethane and stirring for 10 minutes, the layers were separated and the dichloromethane layer dried over magnesium sulfate. Evaporation of the dichloromethane *in vacuo* gave 200 g. (90.3%) of crude orange oil which was used without purification in the next step.

Tetraethyl 1,4-Dihydro-4-(3-nitrophenyl)-2,3,5,6-pyridinetetracarboxylate (**2**).

A mixture of crude diethyl oxalacetate (207.5 g., 1.1 moles) 3-nitrobenzaldehyde (83.2 g., 0.55 mole) and 1 l. of ethanol was stirred vigorously until most of the aldehyde had dissolved. A solution of 25 ml. of piperidine and 40 ml. of acetic acid in 100 ml. of ethanol was added after which the temperature rose from 25° to 34° and the solution became dark. After standing overnight, the solution was heated to 50° for 1 hour.

To one-half of the above solution was added a warm solution of ammonium acetate (85 g., 1.1 moles) in 400 ml. of acetic acid. The solution was heated to boiling in an open flask, allowing the ethanol to evaporate. The solution was concentrated to a dark oil, made basic with dilute ammonium hydroxide, extracted (dichloromethane), the dichloromethane layer washed successively with 10% potassium carbonate, 5% sodium bisulfate, water, then dried (magnesium sulfate), charcoaled and evaporated. The residue was taken up in 600 ml. of ether, a small amount of insoluble material

was filtered off and the filtrate evaporated to an oil. On stirring with a little ethanol, the product crystallized to give 65.7 g. of product. Evaporation of the filtrate and trituration of the residue with 2-propanol gave another 13.6 g. of product, m.p. 112-124° (58.7%). Recrystallization (methanol) gave material m.p. 121-124°.

Anal. Calcd. for $C_{23}H_{26}N_2O_{10}$: C, 56.32; H, 5.34; N, 5.71. Found: C, 56.11; H, 5.19; N, 6.19.

Tetraethyl 4-(3-Nitrophenyl)-2,3,5,6-pyridinetetracarboxylate (**3**).

A solution of 4.0 ml. of 70% nitric acid in 12.0 ml. of water was heated to 60°. Finely powdered **2** (4.21 g., 0.0084 mole) was added all at once with stirring. Heating was continued at 60° for 1 hour. The solution was poured on ice, extracted (dichloromethane), the extract dried (magnesium sulfate) and evaporated to give an oil which crystallized. Recrystallization (methanol) gave 4.0 g. (97.6%) of product, m.p. 117-119°.

Anal. Calcd. for $C_{23}H_{24}N_2O_{10}$: C, 56.56; H, 4.95; N, 5.74. Found: C, 56.18; H, 5.00; N, 5.70.

4-(3-Nitrophenyl)pyridine (**4**).

A solution of 5.6 g. of potassium hydroxide in 50 ml. of water was added to a solution of the tetraester **3** in 50 ml. of warm ethanol, refluxed for 2 hours and acidified with dilute hydrochloric acid. The tan solid was collected, washed with water and then

acetone. The crude tetraacid (6.44 g., 83.5%) was suspended in 100 ml. Dowtherm® and heated to 200° with stirring until gas evolution ceased. The solution was cooled, extracted twice with dilute hydrochloric acid, the extracts washed with ether and the hydrochloric acid solution basified with ammonium hydroxide. Extraction with dichloromethane and evaporation of the dried (magnesium sulfate) extract gave a tan solid which was recrystallized from 2-propanol to give 0.8 g. (23.3%) of product, m.p. 111-112°. Lit. (5) m.p. 109-110°.

REFERENCES AND NOTES

- (1) P. M. Carabateas and Gordon L. Williams, *J. Heterocyclic Chem.*, **11**, 819 (1974).
- (2) E. Klingsberg, Ed., "Pyridine and its Derivatives," Interscience Publishers, Part I, p. 500-502; After this work was completed, the preparation in 5.27% yield of 4-phenyl-2,3,5,6-tetracarbethoxy-1,4-dihydropyridine was reported: B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi and E. Macko, *J. Med. Chem.*, **17**, 956 (1974).
- (3) U. S. Patent 3,753,993; *Chem. Abstr.*, **78**, P 84280n (1973).
- (4) Melting points were taken in capillaries and are corrected. All compounds had compatible ms, nmr and/or ir spectra.
- (5) D. J. W. Bullock, *J. Chem. Soc.*, 5311 (1965).