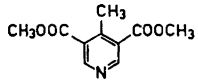
On the Preparation of Dimethyl 4-Methylpyridine-3,5-dicarboxylate*

MAURI LOUNASMAA**

Department of Chemistry, University of Oulu, Oulu, Finland

In connection with a synthetical problem dimethyl 4-methylpyridine-3,5-dicarboxylate (I) [1] was needed.



(I)

For that purpose, the convenience of two different synthetical paths was investigated.

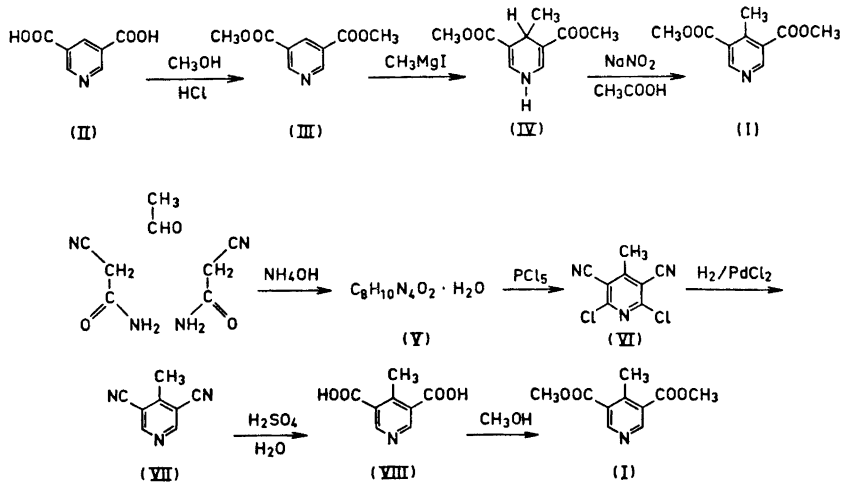
The first one starts from 3,5-pyridinedicarboxylic acid (II), which, after esterification to (III),[2] was treated with a solution of methylmagnesium iodide in ether. The obtained dimethyl 4-methyl-1,4-dihydropyridine-3,5-dicarboxylate (IV) [3] was then oxidized to the desired dimethyl 4-methylpyridine-3,5-dicarboxylate (I).

The second synthetical path starts with the Guareschi reaction of acetaldehyde with cyanoacetamide in the presence of ammonia. From the salt monohydrate (V) thus formed, the 2,6-dichloro-3,5-dicyano-4-methylpyridine (VI) was obtained by treatment with phosphorus pentachloride. Hydrogenolysis, followed by hydrolysis and esterification then gave the product (I) *via* (VII) and (VIII).

The second reaction scheme is similar to that described by Lukeš and Kuthan [4] for the preparation of diethyl 4-methylpyridine-3,5-dicarboxylate. However, as our yields generally were quite low, several experimental modifications, of which the most successful are described in the experimental part, were tried.

Of the two methods, it seems to us that the first one is the method of choice for small-scale preparations. However, if product (I) is needed in larger quantities, the second method seems to be more convenient.

An attractive alternative to the described procedures for the preparation of dimethyl 4-methylpyridine-3,5-dicarboxylate (I) has recently been published by Paleček and Kuthan.[5]



* This work was mainly carried out during a visit at Indiana University, Department of Chemistry, Bloomington, Indiana 47401, USA, and supported by *Public Health Service*, U.S. Department of Health, Education, and Welfare (Grant GM-11571).

** Present address: Institut de Chimie des Substances Naturelles, 91-Gif-sur-Yvette, France.

Experimental. Dimethyl pyridine-3,5-dicarboxylate (III). The product was prepared from 1.0 g of 3,5-pyridinedicarboxylic acid (II) (Matheson Coleman & Bell) by the method described by Thunus and Dejardin-Duchêne.[2] Yield 1.0 g (87 %), m.p. 84–85°C (lit.[6] m.p. 84–85°C). NMR ($CDCl_3$) τ 0.68 (2H) (d) (J 2 cps), τ 1.18 (1H) (t) (J 2 cps), τ 6.02 (6H)(s).

Dimethyl 4-methyl-1,4-dihydropyridine-3,5-dicarboxylate (IV). This product was prepared from 1.0 g of dimethyl pyridine-3,5-dicarboxylate (III) by the method described by Paleček *et al.*[3] Yield 360 mg (33 %). UV (ethanol) λ_{max}. 241 (infl.), 359 nm (lit.[3] λ_{max} 242 (infl.), 360 nm).

Dimethyl 4-methylpyridine-3,5-dicarboxylate (I). To a magnetically stirred solution of 360 mg of dimethyl 4-methyl-1,4-dihydropyridine-3,5-dicarboxylate (IV) in 3 ml of glacial acetic acid at 20°C was added 350 mg of sodium nitrite in small portions. After *ca.* 4 h, water was added and the mixture extracted with ether. The ether extracts were washed with water, dried over sodium sulfate, and evaporated under vacuum. The product was purified by column chromatography (silica gel/chloroform). Yield 260 mg (74 %). m.p. 97–99°C (lit.[1] m.p. 99–100°C). The NMR spectrum was identical with that described by Wenkert *et al.*[1]

2,6-Dichloro-3,5-dicyano-4-methylpyridine (VI). 23 ml of acetaldehyde was added during 1/2 h to an efficiently cooled (5°C) and very vigorously stirred suspension of 58.5 g of cyanoacetamide (Aldrich) in a mixture of 10 ml of 25 % ammonia and 300 ml of water. The temperature rose during the addition to about 10°C and a clear solution resulted. The stirring was continued and after 10 min a white precipitate started to separate. After 24 h stirring, the reaction mixture was filtered. The precipitate was very carefully washed with ice-water and then dried at 110–115°C. The salt monohydrate (V) and 110 g of phosphorus pentachloride were carefully mixed and heated in a round-bottom flask. The temperature was raised to 120°C with an oil-bath. After a 2 h reaction time, when the whole mixture was a dark brown liquid, the mixture was cooled and slowly poured into 300 g of ice-water with vigorous, manual stirring. The precipitate was separated by filtration, washed very carefully with ice-water, dried, and extracted several times with chloroform. The chloroform extracts were washed with water, dried over sodium sulfate and evaporated under vacuum. The brown crystals (19 g) were extracted with hexane in a Soxhlet apparatus. The precipitate was separated from the hot hexane. Yield 10.4 g (14 %), m.p. 153–155°C (lit.[4] m.p. 154–155°C).

3,5-Dicyano-4-methylpyridine (VII). 4 g of 2,6-dichloro-3,5-dicyano-4-methylpyridine (VI) was hydrogenated in the presence of 600 mg of $PdCl_2$ and 5 g of potassium acetate in 100 ml of ethanol/benzene (1/1). After 680 ml of hydrogen had been introduced, the reaction mixture was filtered, the solvent evaporated under vacuum and the residue extracted with benzene. The benzene was evaporated under vacuum and the crude product purified by column chromatography (silica gel/chloroform). Yield 1.9 g (70 %), m.p. 82–83°C (lit.[4] m.p. 76–79°C; after sublimation m.p. 85–86°C). NMR ($CDCl_3$) τ 1.02 (2H), τ 7.16 (3H).

Dimethyl 4-methylpyridine-3,5-dicarboxylate (I). 10 g of 3,5-dicyano-4-methylpyridine (VII) was kept 12 h in 200 ml of 75 % H_2SO_4 under nitrogen at 130°C. The solution was cooled to about 65°C, 400 ml of methanol was added, and the heating was continued for 4 h. The solution was cooled, sodium bicarbonate added, and the mixture filtered. The filtrate was evaporated to dryness under vacuum, and 400 g of ice-water added. After the solution was saturated with potassium carbonate, it was extracted several times with ether. The precipitate was dissolved in a minimum quantity of water and the solution saturated with potassium carbonate and extracted several times with ether. The combined ether fractions from both treatments were dried over potassium carbonate and evaporated under vacuum. Yield 8.8 g (60 %), m.p. 96–98°C (lit.[1] m.p. 99–100°C).

1. Wenkert, E., Haglid, F. and Mueller, S. L. *J. Org. Chem.* **34** (1969) 247.
2. Thunus, L. and Dejardin-Duchêne, M. *J. Pharm. Belg.* **1969** 3.
3. Paleček, J., Ptáčková, L. and Kuthan, J. *Collect. Czech. Chem. Commun.* **34** (1969) 427.
4. Lukeš, R. and Kuthan, J. *Collect. Czech. Chem. Commun.* **25** (1960) 2173.
5. Paleček, J. and Kuthan, J. *Collect. Czech. Chem. Commun.* **34** (1969) 3336.
6. Kuthan, J. and Paleček, J. *Collect. Czech. Chem. Commun.* **31** (1966) 2618.

Received February 8, 1971.