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

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

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\text{CH}_3\text{OOC} \quad \text{CH}_3\text{COCOOCH}_3
\]

(II)

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

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

The second synthetical path starts with the Guasschi reaction of acetaldehyde with cyanocacetamide 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 Lukes and Kuthan 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 Palecek and Kuthan.

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. Yield 1.0 g (87%), m.p. 84—86°C (lit.2 m.p. 84—85°C). NMR (CDCl₃) τ 6.08 (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. Yield 360 mg (33%). UV (ethanol) λmax 241 (inf.), 359 nm (lit.3 λmax 242 (inf.), 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 1.9 g (70%), m.p. 82—83°C (lit.4 m.p. 76—79°C; after sublimation m.p. 85—86°C). NMR (CDCl₃) τ 1.02 (2H), τ 7.16 (3H).

Dimethyl 4-methylpyridine-3,5-dicarboxylate (I). 10 g of 3,5-dicarboxylic acid (VII) was kept 12 h in 200 ml of 75% H₂SO₄ 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 5.8 g (90%), m.p. 98—99°C (lit.4 m.p. 99—100°C).


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