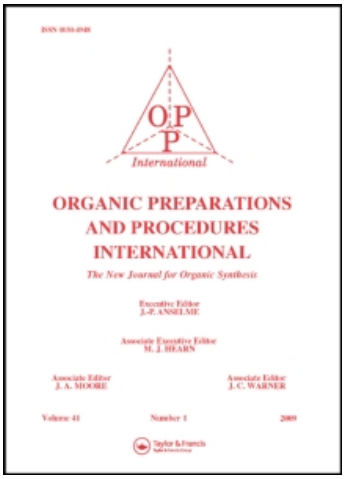


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

4-CARBOMETHOXYNICOTINIC ACID

B. S. Moore[a]; R. W. McLaughlin[a]; F. J. Urban[a]; G. R. Young[a]
[a] Central Research Division, Process Research and Development, Pfizer Inc, Groton, CT

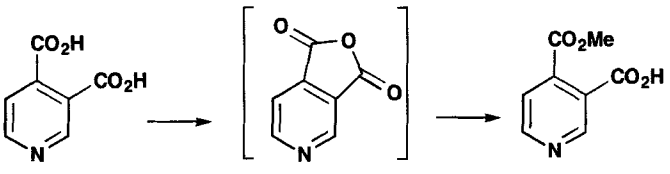
To cite this Article Moore, B. S. , McLaughlin, R. W. , Urban, F. J. and Young, G. R.(1996) '4-CARBOMETHOXYNICOTINIC ACID', Organic Preparations and Procedures International, 28: 3, 360 — 361
To link to this Article: DOI: 10.1080/00304949609356545
URL: http://dx.doi.org/10.1080/00304949609356545

4-CARBOMETHOXYNICOTINIC ACID

Submitted by B. S. Moore, R. W. McLaughlin, F. J. Urban* and G. R. Young
(01/02/96)

Pfizer Inc, Central Research Division
Process Research and Development
Eastern Point Rd., Groton, CT 06340

4-Carbomethoxynicotinic acid (**3**) has been described as an intermediate for the preparation of several alkaloid natural products[1] as well as quinuclidines.[2] The synthesis of monoester **3** depended upon the regioselective opening of anhydride **2** with methanol or sodium methoxide in either neat methanol or in the presence of a cosolvent such as methylene chloride or tetrahydrofuran at temperatures between –78° to reflux.[3] In all these reports, anhydride **2** was prepared from 3, 4-pyridinedicarboxylic acid (**1**) by refluxing with an excess of acetic anhydride and isolated as a low melting solid after vacuum distillation. This paper describes an efficient preparation of monoester **3** which avoids the isolation of anhydride **2** and is suitable for large scale synthesis.



1 **2** **3**

The conversion of diacid **1** to anhydride **2** was carried out with three equivalents of acetic anhydride and one equivalent of triethylamine in methyl acetate at reflux for 2 hours. Considerably more acetic anhydride was needed to drive the reaction to completion without triethylamine and the solvent was chosen to avoid possible transesterification and to keep the mixture as a solution. After anhydride formation was complete, the solution was added slowly to methanol at –10° with stirring under nitrogen. The methanol solution was warmed to 30° at which point an exotherm was noted which was possibly the methanolysis of the excess acetic anhydride. The volatiles were removed *in vacuo* and the residual oil was dissolved in water. The pH was adjusted to 1.2 to precipitate monoester **3** in 66% yield and >98% purity. The aqueous filtrate was treated with sodium hydroxide to hydrolyze the isomeric ester and starting diacid was precipitated at pH 0.5 in 22% yield.

The experimental procedure for laboratory scale has been carried out on 100 kilograms of diacid **1** without modification and provided monoester **3** in the same yield and purity.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on a Brucker WM 300 (300 MHz) spectrometer in dimethylsulfoxide-d_6.

4-Carbomethoxynicotinic Acid.- 3,4-Pyridinedicarboxylic acid (**1**, 33.4 g, 20 mmoles) was suspended in methyl acetate (330 mL) under nitrogen and stirred while triethylamine (20.24 g, 20 mmoles) was added in one portion; this resulted in an exotherm of a few degrees. Acetic anhydride (61.3 g, 60 mmoles) was added to this suspension in a slow stream and the mixture was heated to reflux for 2 hrs. The solution was cooled to room temperature and added dropwise to methanol (400 mL) at –10° over 20 minutes. The reaction was held at this temperature for 30 minutes, then warmed to 30° at which point there was a slight exotherm to 35°. The volatiles were removed *in vacuo* and the residual oil was dissolved in water (360 mL). The pH at this point was 2.9. The aqueous solution was stirred at room temperature while 6N HCl (34 mL) was added dropwise until a steady pH of 1.2 was reached. The thick slurry was stirred in an ice water bath for 30 minutes and the solid was collected, washed with cold water, and dried *in vacuo* to provide 23.7 g, 66% of **3**, mp. 171–172°, lit.[3b] 171–172°. ^{1}H NMR: δ 9.03 (s, 1), 8.88 (d, 1), 7.63 (d, 1), 3.83 (s, 3). ^{13}C NMR δ 167.3, 166.5, 155.9, 153.6, 150.6, 140.8, 122.1, 53.3.

For recovery of starting diacid **1**, the filtrate and wash from the isolation of **3** were stirred while sodium hydroxide pellets (32 g, 0.8 mole) were added to bring the pH to 11.2. The solution was heated to 90° and held at that temperature for 30 minutes. The aqueous solution was cooled to room temperature, and the pH adjusted to 0.5 with conc. HCl. The resulting slurry was stirred at 5° for one hour, and the solid collected, washed with water, and dried *in vacuo*. The yield of recovered 3,4-pyridine dicarboxylic acid **1** was 7.3 g (22%). The material was of suitable purity for reuse in the monoester preparation.

REFERENCES

1. D. M. Ketcha and G. W. Gribble, *J. Org. Chem.*, **50**, 5451 (1985); I. Praly-Deprez; C. Rivalle; C. Huel; J. Belehradek; C. Paoletti and E. Bisagni, *J. Chem. Soc., Perkin Trans. I*, 3165 (**1991**); J. C. Bottaro and G. A. Berchtold, *J. Org. Chem.*, **45**, 1176 (1980)

2. R. J. Snow and L. J. Street, *Tetrahedron Lett.*, **30**, 5795 (1989); R. J. Snow; R. Baker; R. H. Herbert; I. J. Hunt; K. J. Merchant and J. Saunders, *J. Chem. Soc., Perkin Trans. I*, 409 (**1991**)

3. a) W. R. Ashcroft; M. G. Beal and J. A. Joule, *ibid.*, 3012 (**1981**); b) L. Thunus and M. Dejardin-Duchene, *J. Pharm. Belg.*, **24**, 3 (1969); c) A. Kirpal, *Monatsh. Chem.*, **23**, 929 (1902).

****