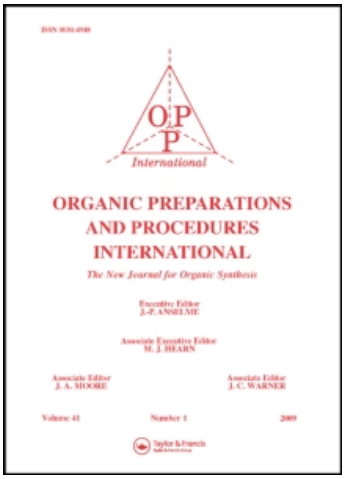

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A CONVENIENT SYNTHESIS OF 3-(2-METHYLPYRIDYL)ACETIC ACID METHYL ESTER, A PYRITHIAMINE INTERMEDIATE

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OPPI BRIEFS

A CONVENIENT SYNTHESIS OF 3-(2-METHYLPYRIDYL)ACETIC ACID METHYL ESTER, A PYRITHIAMINE INTERMEDIATE

Submitted by (09/07/93)

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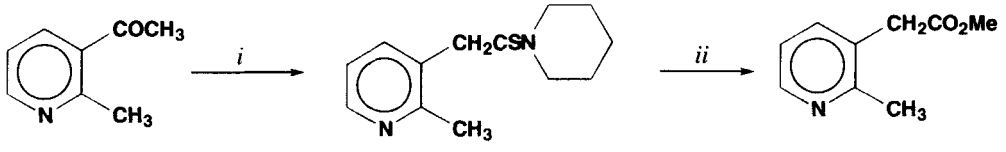
3-(2-Methylpyridyl)acetic acid methyl ester (**1**) is an important intermediate used by Dornow and Petsch[1] in preparing of pyrithiamine,[2] a pyridine analogue of thiamine (Vitamin B_1). Alkyl substituted 3-pyridylacetic acid esters of type **1** are difficult to prepare by conventional methods. An early synthesis of **1**[3] consisted in a high pressure Willgerodt reaction of 2-methyl-3-acetylpyridine (**2**) to 3-(2-methylpyridyl)acetic acid amide followed by methanolysis. A four-step synthesis of 3-(2-methylpyridyl)acetic acid ethyl ester from the commercially available ethyl 2-methylnicotinate has also been reported.[4,5] The ester **1** was also isolated together with two other components (yields not given) from the reaction product of 2-picoline-1-oxide with methyl phenylpropiolate when exposed to moist air.[6] We now report on the Willgerodt-Kindler reaction of 2-methyl-3-acetylpyridine (**2**) using high boiling morpholine in an open reflux equipment instead of pressure apparatus as a more convenient route to **1**.



2 **3** **1**

i) S, morpholine *ii*) H_2SO_4, MeOH

The readily available 2-methyl-3-acetylpyridine (**2**)[7] was treated with morpholine and sulfur under gentle reflux to give pure 2-methyl-3-pyridinethioacetic acid morpholide (**3**) in 64% yield. Small quantities of 3-(2-methylpyridyl)-2-oxothioacetic acid morpholide (**5**) could be isolated as a side-product. Treatment of **3** with ethanolic KOH solution under reflux for 72 hrs gave only 3-(2-methylpyridyl)acetic acid morpholide (**4**) in 83% yield instead of the corresponding pyridylacetic acid; a similar incomplete hydrolysis has also been reported in the case of 4-pyridinethioacetomorpholide.[8] Methanolysis of either the thioacetomorpholide **3** and the acetomorpholide **4** led to **1** in 85% and 96% yield respectively.

EXPERIMENTAL SECTION

Melting points are uncorrected. The IR spectra of $CHCl_3$ solutions were taken on a Bruker IFS 113v instrument; ^1H NMR spectra were obtained with a Bruker-Spectrospin WM 250 spectrometer using $CDCl_3$ solutions and TMS as an internal standard; MS (CI) spectra were acquired with a Jeol-D 300 spectrometer.

3-(2-Methylpyridyl)thioacetic Acid Morpholide (3).- A mixture of 2-methyl-3-acetylpyridine[7] **2** (5.41 g, 40 mmols), morpholine (3.5 mL, 40 mmol) and sulfur (1.28 g, 40 mmol) was gently refluxed with stirring for 8 hrs in an oil bath maintained at 120°C. The crude product was poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, evaporated to dryness and recrystallized from i-PrOH to provide 6.1g (64%) of **3** as white crystals, mp. 124-125°C. IR (cm^{-1}) 1462, 1277 (CS); ^1H NMR (ppm, Hz) 2.51 (s, 3H, CH_3), 3.54-4.43 (m, 8H, morpholine), 4.23 (s, 2H, CH_2), 7.15 (dd, 1H, H-5, J_{45} 7.6, J_{56} 4.8), 7.50 (dd, 1H, H-4, J_{45} 7.6, J_{46} 1.4), 8.42 (dd, 1H, H-6, J_{56} 4.8, J_{46} 1.4); MS (CI) 236 (M^+);

Anal. Calcd. for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.82; N, 11.85; S, 13.57
Found: C, 61.07; H, 7.00; N, 11.71; S, 13.58

The i-PrOH mother liquors yielded (preparative TLC, ether-methanol 9:1) small amounts (4%) of **3-(2-methylpyridyl)-2-oxothioacetic acid morpholide (5)** as yellow crystals, mp. 119-122°C (from i-Pr_2O). IR (cm^{-1}): 1672 (CO), 1462, 1275 (CS). ^1H NMR (ppm, Hz): δ 2.89 (s, 3H, CH_3), 3.66-4.34 (m, 8H, morpholine), 7.25 (dd, 1H, H-5, J_{45} 7.9, J_{56} 4.8), 8.00 (dd, 1H, H-4, J_{45} 7.9, J_{46} 1.7), 8.65 (dd, 1H, H-6, J_{56} 4.8, J_{46} 1.7); MS (CI) 250 (M^+);

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81
Found: C, 57.80; H, 5.65; N, 11.33; S, 12.98

3-(2-Methylpyridyl)acetic Acid Morpholide (4).- To a solution of **3** (1.88 g, 8 mmol) in ethanol (8 mL), was added powdered KOH (0.72 g, 12 mmol); the mixture was refluxed with stirring for 3 hrs. The solvent was removed *in vacuo*, and the residue partitioned between water and CH_2Cl_2. The organic layer washed with water and evaporated to provide 1.46 (83%) of **4** as white crystals, mp. 91-93°C (from CH_2Cl_2-i-Pr_2O). IR (cm^{-1}): 1644 (CO). ^1H NMR (ppm, Hz): δ 2.51 (s, 3H, CH_3), 3.45-3.68 (m, 8H, morpholine), 3.69 (s, 2H, CH_2), 7.15 (dd, 1H, H-5, J_{45} 7.7, J_{56} 4.9), 7.43 (dd, 1H, H-4, J_{45} 7.7, J_{46} <1), 8.42 (dd, 1H, H-6, J_{56} 4.9, J_{46} <1); MS (CI) 220 (M^+);

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72 . Found: C, 65.44; H, 7.27; N, 12.92

3-(2-Methylpyridyl)acetic Acid Methyl Ester (1).- A solution of 4 mmol of **3** or of **4** in methanol (0.8 mL) with conc.H_2SO_4 (0.8 mL) was heated at 100°C for 3 hrs. The solvent was removed *in vacuo* and the residue was dissolved in water, made alkaline with Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness to provide 85% and 96% yield of **1** respectively, bp. 126°/14 mm Hg, lit.[3] bp. 128°/14 mm Hg. IR (cm^{-1}): 1738 (CO_2CH_3); ^1H NMR (ppm, Hz): δ 2.54 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 7.12 (dd, 1H, H-5, J_{45} 7.6, J_{56} 4.8), 7.50 (dd, 1H, H-4, J_{45} 7.6, J_{46} 1.3), 8.42 (dd, 1H, H-6, J_{56} 4.8, J_{46} 1.3).

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CONVENIENT SYNTHESIS OF 2,3-DIHYDROXY-2-METHYLPROPANAMIDE *via* 2,3-EPOXY-2-METHYLPROPANAMIDE

Submitted by (11/03/93)

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In the course of an investigation of the photopolymerization of methacrylamide (**1**) in the presence of chromium in aqueous solution, unexpected results were obtained.[1] Even though the experimental conditions were similar to those used for acrylamide,[2] no polymerization occured; instead, only one product could be isolated.