

A NOVEL SYNTHETIC SCHEME FOR 2-ETHYLTHIOISONICOTINAMIDE

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Abstract — 4-Picoline was converted to 4-cyanopyridine by ammoxidation in 98% yield. The latter was ethylated by radicals generated from silver nitrate catalyzed oxidative decarboxylation of propionic acid to form 2-ethyl-4-cyanopyridine, which was treated with ammonium sulfide to give 2-ethylthioisonicotinamide. A setup for laboratory ammoxidation was designed. Pyridine was alkylated with decarboxylating acetic, propionic, *n*-butanoic, isobutyric, and *n*-pentanoic acids to form the corresponding 2- and 4-alkylpyridines. 4-Cyanopyridine was also alkylated similarly to obtain 2-alkyl- and 2,6-dialkyl-4-cyanopyridines.

2-Ethylthioisonicotinamide is an important drug in the treatment of tuberculosis. Its synthesis depends heavily on the intermediacy of 2-ethyl-4-cyanopyridine which is prepared by a variety of lengthy schemes with low overall yields.¹⁻⁵ 2-Ethylthioisonicotinamide has now been synthesized in three steps from 4-picoline. These reactions independently have been known for some time, but their combination to form a novel synthetic scheme merits attention.

The first step was the fluidized-bed ammoxidation of 4-picoline. Ammoxidation was originally developed for the industrial production of acrylonitrile from propylene.⁶ Formation of 4-cyanopyridine by ammoxidation of 4-picoline was also described.⁷ While fluidized-bed ammoxidation can be carried out efficiently in the industry, its practice in the laboratory was difficult; a suitable apparatus design was not found in the literature. We have now established, however, a procedure with a home-made setup for the laboratory fluidized-bed ammoxidation of 4-picoline to

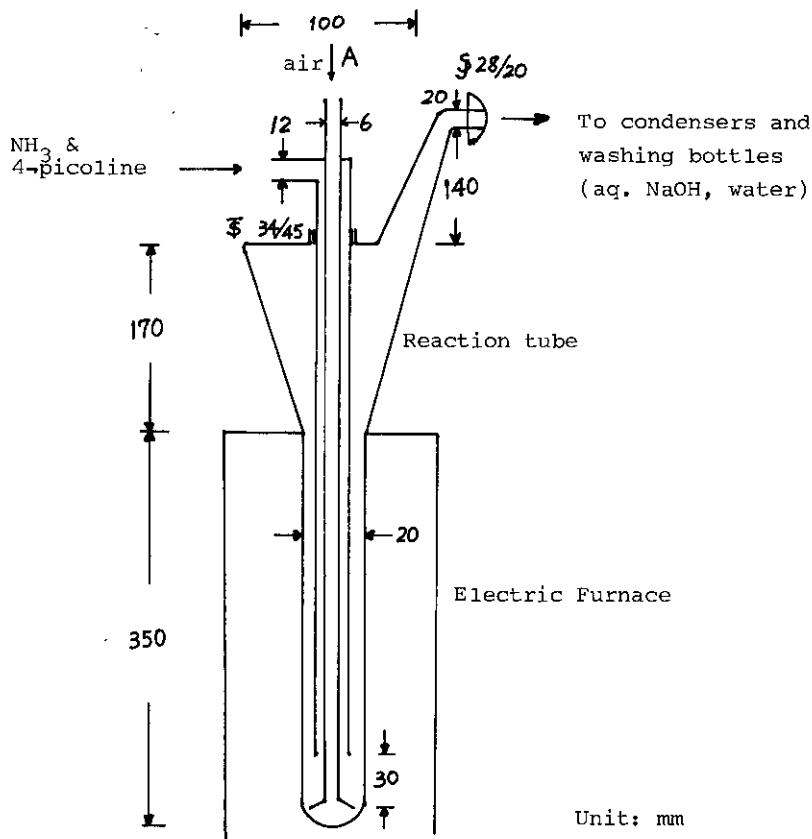
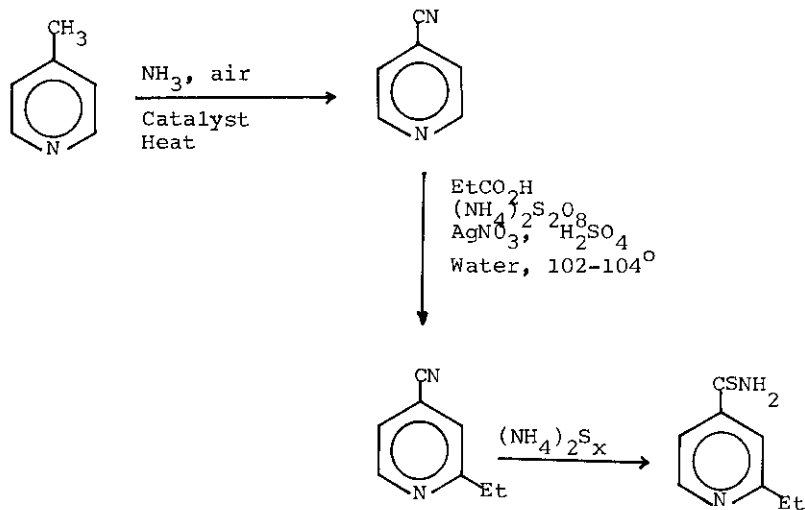


Fig. 1. Amoxidation Setup

form 4-cyanopyridine in 98% yield. (Fig. 1. The upper part of the reaction tube outside of the furnace was wrapped with asbestos. All ground glass joints were 24/40 unless otherwise indicated.) When the furnace was heated to 500°, Sohio 41 Catalyst powder (12 ml) was introduced through A and air was passed at 0.9-1.1 l/min for one hour to activate the catalyst. While the same air stream was passing, ammonia gas was introduced at 0.15-0.18 L/min and liquid 4-picoline at 0.31 ml (0.31 g)/min. Most of the catalyst powder was fluidized in the region 6-21 cm up from the bottom of the reaction tube. The temperature in this region was 488±12°. The operation continued for 30 min when delivery of ammonia and 4-picoline was stopped leaving only air to flow. After another 30 min the furnace was turned off and allowed to cool to room temperature when air stream was stopped. The amounts of reactants involved in this ammoxidation were: 4-picoline (9.3 g, 0.1 mole), ammonia (0.17-0.22 mole), and oxygen (0.22-0.27 mole). The product, 4-cyanopyridine (98% yield), had mp 81.5-82° after one sublimation (lit. 8, 82°). PMR and IR data were in agreement with the literature.^{9,10}

The second step was ethylation of 4-cyanopyridine with the ethyl radical generated by oxidative decarboxylation of propionic acid according to Minisci et al.¹¹ From an experiment at 102° involving 4-cyanopyridine (10.4 g, 0.1 mole), water (70 ml), conc. sulfuric acid (0.1 mole), silver nitrate (0.01 mole), propionic acid (0.5 mole), and ammonium peroxydisulfate (0.1 mole in 30 ml of water), there were obtained 5.7 g (54.8% recovery) of 4-cyanopyridine, bp 50° (4 mm Hg) and 5.8 g of a fraction, bp 55-98° (4 mm Hg). PMR spectrum showed that the latter was a mixture of 2-ethyl- and 2,6-diethyl-4-cyanopyridines in the ratio 4 to 1. The yields based on 4-cyanopyridine unrecovered were 74.4 and 18.6%, respectively. The mixture was distilled using a Podbielniak Series 3400 MINI-CAL Distillation Apparatus to give the pure components: 2-ethyl-4-cyanopyridine, bp 97-98° (17 mm Hg) (lit. 1, 97-99° at 15 mm Hg); 2,6-diethyl-4-cyanopyridine, bp 111° (17 mm Hg) (lit. 11, no data). Spectral data for 2-ethyl-4-cyanopyridine were as follows. PMR (δ, CDCl₃): 8.77 (1H, d, J 2.4 Hz, H-6 of the ring), 7.38 (2H, m, H-3 and H-5), 2.90 (2H, q, CH₂), 1.34 (3H, t, CH₃). IR (KBr): 3080 (C=C-H), 2200 (C≡N), 1600, 1555 (pyridine ring CH vibration), 1475, 1430 (CH₂), 1410, 1380 (CH₃), 845 cm⁻¹ (2 adjacent ring protons). In the final step, a mixture of 2-ethyl-4-cyanopyridine (2.00 g, 15.1 mmoles) and sodium laurylbenzenesulfonate (0.20 g, 1.0 mmole) was heated to 40-50°, to which was added 10 ml of a saturated ammonium sulfide solution (yellow) in 50 min. The reaction mixture was further stirred for 70 min and stored in a refrigerator with

Table I. Alkylation of Pyridine. Reactants, Products, Yields, and Boiling Points

| Alkyl Source ^a | | Bp, °C(mm Hg) | | | | | | |
|--|----------------------|----------------------|----------------------|-------------------|------|------------------------|------|--|
| RCOOH | Product ^b | % Yield ^c | % Yield ^d | Obs. ^e | | Lit. ^f | Ref. | |
| CH ₃ COOH | 2-Methyl | 22.1 | 33.9 | 39.5-40 | (21) | 128 -129 | 14 | |
| | 4-Methyl | 17.9 | 27.6 | 50 | (21) | 145 | 15 | |
| CH ₃ CH ₂ COOH | 2-Ethyl | 22.1 | 26.9 | 38.5-39 | (13) | 148 -150 | 16 | |
| | 4-Ethyl | 20.6 | 25.1 | 47 -47.5 | (13) | 169.6-170 ^g | 17 | |
| CH ₃ CH ₂ CH ₂ COOH | 2- <u>n</u> -Propyl | 33.2 | 36.6 | 51 | (13) | 166 -168 | 18 | |
| | 4- <u>n</u> -Propyl | 25.8 | 28.4 | 59.5-60 | (13) | 189 | 19 | |
| (CH ₃) ₂ CHCOOH | 2-Isopropyl | 23.3 | 25.3 | 47.5-48.5 | (16) | 159.8 ^h | 20 | |
| | 4-Isopropyl | 34.7 | 37.7 | 59 | (15) | 173 | 21 | |
| CH ₃ CH ₂ CH ₂ CH ₂ COOH | 2- <u>n</u> -Butyl | 28.5 | 31.0 | 66.5-67 | (15) | 191 -193 | 22 | |
| | 4- <u>n</u> -Butyl | 28.5 | 31.0 | 81 | (17) | 207 -209 | 19 | |

(a) Reactants: pyridine, 23.7 g, 0.3 mole; carboxylic acid, 0.5 mole; ammonium peroxydisulfate, 62.4 g, 0.3 mole; silver nitrate, 1.7 g, 0.01 mole.
Reaction temperature: 70-80°.

(b) 2- and 4-Alkylpyridines.

(c) Based on pyridine used.

(d) Based on pyridine unrecovered.

(e) Fractionation was performed on a Podbielniak Series 3400 MINI-CAL Distillation Apparatus.

(f) At 760 mm Hg unless otherwise indicated.

(g) At 750 mm Hg.

(h) At 753 mm Hg.

Table II. Alkylation of 4-Cyanopyridine.
 Reactants, Products, Yields, and Boiling Points

| Alkyl Source ^a | | | | Bp, °C(mm Hg) | | | |
|--|---------------------------------------|----------------------|----------------------|----------------------|-----------------------|------|--|
| RCOOH | Product ^b | % Yield ^c | % Yield ^d | Obs. ^e | Lit. | Ref. | |
| CH ₃ COOH | 2-Methyl | 28.1 | 81.4 | 93 (21) | 90-94(20) | 23 | |
| | 2,6-Dimethyl | 1.9 | 5.7 | 81.5-82 ^k | 81-82 ^k | 5 | |
| CH ₃ CH ₂ COOH | 2-Ethyl | 32.8 | 74.4 | 97-98(17) | 83-84(6.5) | 24 | |
| | 2,6-Diethyl ^g | 8.2 | 18.6 | 111 (17) | No data | 11 | |
| CH ₃ CH ₂ CH ₂ COOH | 2- <u>n</u> -Propyl | 27.5 | 47.5 | 106 (14) | 90-95(4) | 19 | |
| | 2,6-Di- <u>n</u> -propyl ^h | 5.5 | 9.5 | 98 (5) | New cpd. ^f | | |
| (CH ₃) ₂ CHCOOH | 2-Isopropyl | 37.5 | 71.3 | 96 (13) | Nondistillable | 24 | |
| | 2,6-Diisopropyl | 12.5 | 23.8 | 110 (13) | No data ^f | 13 | |
| CH ₃ CH ₂ CH ₂ CH ₂ COOH | 2- <u>n</u> -Butyl ⁱ | 23.8 | 48.6 | 90-94(4) | No data | 25 | |
| | 2,6-Di- <u>n</u> -butyl ^j | 1.2 | 2.4 | 117 (4) | New cpd. | | |

(a) Reactants: 4-Cyanopyridine, 10.4 g, 0.1 mole; carboxylic acid, 0.5 mole; ammonium peroxydisulfate, 22.8 g, 0.1 mole; silver nitrate, 1.7 g, 0.01 mole. Reaction temperature: 100-102°.

(b) Mono- and di-alkyl-4-cyanopyridines.

(c) Based on 4-cyanopyridine used.

(d) Based on 4-cyanopyridine unrecovered.

(e) Fractionation was performed on a Podbielniak Series 3400 MINI-CAL Distillation Apparatus.

(f) Chem. Abstr., 1972, 77, 48278 p erroneously quoted these compounds to have been described in Ref. 11.

Elemental analysis found(calcd.):

(g) C, 75.05(74.97); H, 7.52(7.55); N, 17.60(17.48). M⁺ 160.

(h) C, 76.56(76.55); H, 8.42(8.57). M⁺ 188.

(i) C, 76.15(75.92); H, 6.89(6.37). M⁺ 160.

(j) C, 77.93(77.78); H, 9.13(9.32). M⁺ 216.

(k) mp

methanol(100 ml) added to precipitate sulfur, which was filtered off. The filtrate was concentrated to 5 ml and stored in a refrigerator to effect crystallization of 2-ethylthioisonicotinamide, which was recrystallized from methanol to give 2.44 g(quantitative yield), mp 164-164.5^o(lit. 1, 164^o). PMR(DMSO-d₆): 10.20, 9.80(1H, each s, CSNH₂), 8.53(1H, d, \underline{J} 2.6 Hz, H-6), 7.52(2H, m, H-3 and H-5), 2.79(2H, q, CH₂), 1.24(3H, t, CH₃). IR(KBr): 3250(NH₂), 2980(C=C-H), 1600, 1550(pyridine ring CH), 1420(C=S), 1400(CH₃), 845 cm⁻¹(2 adjacent ring protons). Elemental analysis:

Calcd. for C₈H₁₀N₂S: C, 57.80; H, 6.06; N, 16.85; S, 19.29.

Found: C, 58.10; H, 6.13; N, 16.60; S, 19.49.

Of the numerous methods for alkylation of the pyridine ring,¹² the method of Minisci^{11,13} appeared attractive for preparation of 2-ethyl-4-cyanopyridine, since the procedure is simple using inexpensive and readily available reagents. Accordingly, a study on the alkylation of pyridine and 4-cyanopyridine by this method was undertaken.

Alkylation of pyridine herein reported was carried out by this method for the first time in this study except ethylation¹³(Table I). The PMR data of these alkylpyridines were in agreement with the structures and the literature where available; data for the 2-isopropyl and the last two products in Table I could not be found in the literature. 2-Isopropylpyridine as an example: 8.44(1H, dd, \underline{J} 4.4 and 1.5 Hz, H-6), 7.42(1H, m, H-4), 7.02(2H, m, H-3, H-5), 3.00(1H, septet, CH), 1.24(6H, d, 2 Me).

4-Cyanopyridine was alkylated in a similar manner(Table II). The alkylations using n-butanoic and n-pentanoic acids have not been reported previously. 2,6-Di-n-propyl- and 2,6-di-n-butyl-4-cyanopyridines are new compounds. 2,6-Diethyl-,¹¹ 2-isopropyl-,²⁴ 2,6-diisopropyl-,¹³ and 2-n-butyl-4-cyanopyridines²⁵ were described in the literature without boiling points and elemental analysis. These missing data are now reported in Table II. PMR data for all the alkyl-4-cyanopyridines agree with the structures. These data were not found in the literature except for 2-isopropyl- and 2,6-diisopropyl-4-cyanopyridines.¹³ For 2-n-Butyl-4-cyanopyridine as an example: 8.64(1H, dd, \underline{J} 10 and 2 Hz, H-6), 7.40(2H, m, H-3, H-5), 1.72(2H, m, CH₂), 1.38(2H, quintet, CH₂), 2.87(2H, t, CH₂), 0.94(3H, t, Me).

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