4-(3-Nitrophenyl)-2-picoline

Anica Markovac, Ambalal R. Patel, Maurice P. LaMontagne and Arthur B. Ash*

Ash Stevens Inc., 5861 John C. Lodge Freeway, Detroit, Michigan 48202

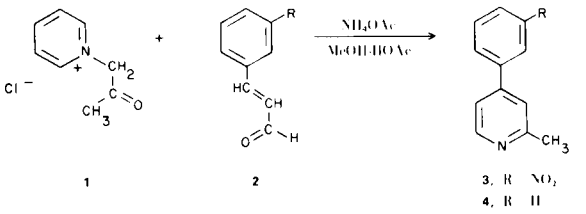
Received September 27, 1976

The preparation of 4-(3-nitrophenyl)-2-picoline (**3**) was accomplished in one step by the Zecher-Krohnke ring-closure reaction. Compound **3** is the starting material for 2-formyl-4-(3-aminophenyl)pyridine thiosemicarbazone (4-APPT), a promising antineoplastic agent.

J. Heterocyclic Chem., **14**, 147 (1977).

2-Formyl-4-(3-aminophenyl)pyridine thiosemicarbazone (4-APPT) has been shown by Agrawal and coworkers to possess significant antineoplastic activity in mice (1,2). They note also that 4-APPT serves as a potent inhibitor of ribonucleoside diphosphate reductase with increased *in vivo* resistance to enzymatic degradation (1,2). To permit further evaluation of the clinical potential of the drug, a larger quantity was prepared recently in this laboratory. This synthesis utilized the practical, well-developed six-step synthesis reported by Agrawal, *et al.*, (1) starting with 4-(3-nitrophenyl)-2-picoline (**3**). Their improved preparation of the latter compound, however, was based on the methylation of commerically-available 4-phenylpyridine to obtain the intermediate, 4-phenyl-2-picoline (**4**) (63%), which was nitrated to yield a mixture of the *o*-, *m*- and *p*-nitrophenyl isomers (**2**). These were separated utilizing solubility differences between the hydrochloride or nitrate salts; the required *meta* isomer, compound **3**, was isolated in 27% yield. This Note describes an improved procedure useful for the preparation of large quantities of compounds **3** and **4** with primary emphasis on **3** as starting material for 4-APPT.

The new route utilized the Zecher-Krohnke ring-closure reaction between a *N*-pyridinium salt prepared from an α-haloketone, an α,β-unsaturated ketone and ammonium acetate (3). This versatile reaction has been extensively developed over the years in this laboratory to acquire variously-substituted pyridines in a one-step reaction (4). For the present work, 1-(acetylmethyl)pyridinium chloride (**1**) was prepared in 70% yield by treating chloroacetone with pyridine (**5**). To explore the feasibility of the ring-closure reaction utilizing an α,β-unsaturated aldehyde, the pyridinium salt was condensed with cinnamaldehyde and ammonium acetate in methanol solvent to give 4-phenyl-2-picoline (**4**) in 50% yield (Scheme I). Cinnamaldehyde was replaced with 3-nitrocinnamaldehyde (6) and condensed with the pyridinium salt and ammonium acetate in methanol-acetic acid (9:1, v/v) to give 4-(3-nitrophenyl)-2-picoline (**3**) in 35-40% yields. Some 245 g. of **3** was prepared in this manner. To our best knowledge, these are the first examples in which an α,β-unsaturated aldehyde was employed in the Zecher-Krohnke reaction.



EXPERIMENTAL

Melting points were taken in open capillaries using a Thomas-Hoover apparatus and are uncorrected.

1-(Acetylmethyl)pyridinium Chloride (**1**).

Chloroacetone (461.5 g., 5 moles) was dissolved in acetonitrile (930 ml.) and pyridine (474 g., 6 moles) was added with swirling. The reaction mixture was heated to 40-45° for 15 minutes (steam bath). Ether (725 ml.) was added to the cooled mixture which was allowed to stand at room temperature overnight. The resulting solid was collected, washed with ether (1 l.) and dried at 75°/0.4 mm for 4 hours to give the title pyridinium salt, 603 g. (70%), m.p. 202-204° (lit. (5) m.p. 201° dec.).

3-Nitrocinnamaldehyde (**2**).

The procedure of F. Kinkeline (6) was used with modifications. Water (30 l.) containing sodium hydroxide (60 g.) was added to a solution of 3-nitrobenzaldehyde (750 g.) in ethanol (15 l.) in a 30-gallon polyethylene tank. To this solution was added a cold (5°) solution of acetaldehyde (264 g.) in ethanol (225 ml.) with vigorous stirring (important) over 10 minutes. The product started to precipitate near the end of the addition and the mixture was then stirred slowly for 1 hour. The crude product was collected by filtration and washed with water (4 l.). A second identical run was carried out simultaneously.

The combined wet product from both runs was dissolved in chloroform (8 l.). The water was separated and extracted with chloroform (1 l.). The combined chloroform extract was washed with water (2 l.), decolorized and evaporated. The solid residue was dissolved in hot chloroform (1.5 l.) to which boiling methanol (580 ml.) was added. The solution, after cooling, was allowed to stand over the weekend. The precipitated product was collected by filtration and washed successively with chloroform-methanol (1:1, v/v, 800 ml.) and with petroleum ether (30-60°, 600 ml.). After drying, there was obtained 3-nitrocinnamaldehyde **2**, 519 g., m.p. 114-116° (lit. (6) m.p. 116°). The filtrate was diluted with methanol and cooled to yield a second crop, 112 g., m.p. 112-114°, overall yield, 631 g. (31%).

4-(3-Nitrophenyl)-2-picoline (**3**).

The above pyridinium salt (1.026 kg., 6 moles) was added to methanol (5.4 l.), followed by ammonium acetate (1.8 kg., 23.3 moles) and acetic acid (600 ml.). The mixture was warmed to 40° with stirring. 3-Nitrocinnamaldehyde (531 g., 3 moles) was added to the warm mixture which was refluxed for 8 hours with stirring. The reaction mixture was cooled to 35-40°, refrigerated overnight and filtered. The resulting solid product was washed with water (1.2 l.) and dried at 65°/0.3 mm to constant weight to give the title 2-picoline as a first crop, 224 g. (35%), m.p. 154-155° (lit. (2) m.p. 155-156°). Concentration of the filtrate gave additional impure material, 65 g., m.p. 150-153°, which was recrystallized from ethanol to give a second crop, 21 g. (3%), m.p. 153-155°. The nmr spectrum was in agreement with data reported by Agrawal, *et al.*, (2).

4-Phenyl-2-picoline (**4**).

A mixture of cinnamaldehyde (2.6 g., 0.02 mole), the above pyridinium salt (4 g.) and ammonium acetate (7 g.) in methanol (60 ml.) was refluxed for 18 hours. The solvent was evaporated, the residue was suspended in water and the suspension was extracted with ether. The extract was dried (potassium carbonate) and evaporated. The residue was distilled to give the title compound, 1.75 g. (50%), as an oil, b.p. 100-102°/0.2 mm (lit. (1) 102-103°/0.2 mm).

Anal. Calcd. for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.17; H, 6.54; N, 8.25.

A picrate salt was prepared, m.p. 220-224°.

Anal. Calcd. for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.54; N, 14.07. Found: C, 54.30; H, 3.58; N, 14.22.

Acknowledgment.

This work was supported by Contract No. NO1-CM-57012 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare. The advice and encouragement of the Project Officer, Dr. Robert R. Engle, is greatly appreciated.

REFERENCES AND NOTES

(1) K. C. Agrawal, A. J. Lin, B. A. Booth, J. R. Wheaton and A. C. Sartorelli, *J. Med. Chem.*, **17**, 631 (1974).

(2) K. C. Agrawal, B. A. Booth, S. M. DeNuzzo and A. C. Sartorelli, *ibid.*, **18**, 368 (1975).

(3) W. Zecher and F. Krohnke, *Chem. Ber.*, **94**, 690 and 698 (1961); F. Krohnke and W. Zecher, *Angew. Chem. Int. Ed. Engl.*, **1**, 626 (1962).

(4) M. P. LaMontagne, A. Markovac and M. S. Ao, *J. Med. Chem.*, **16**, 1040 (1973), and the preceding papers in the series.

(5) F. Krohnke, *Ber.*, **66**, 607 (1933).

(6) F. Kinkeline, *ibid.*, **18**, 483 (1885).