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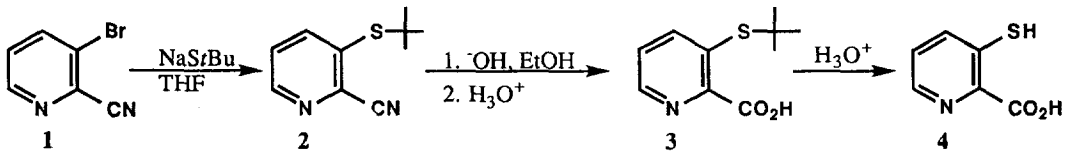
A Convenient Preparation of 3-Mercaptopicolinic Acid

Kevin A. Memoli
Chemical Sciences, Wyeth-Ayerst Research, CN 8000, Princeton N.J. 08543-8000

Abstract: A procedure for the convenient preparation of 3-mercaptopicolinic acid from readily available starting materials is described.

3-Mercaptopicolinic acid (**4**) is a potent inhibitor of gluconeogenesis[1] and was required in bulk for use as a reference in some of our discovery programs. However, the existing methods were found to be inconvenient for the preparation of large quantities of material due to low overall yields and or the use of noxious reagents.[2-4] Therefore, a procedure which was amenable to the preparation of bulk quantities was desirable and is described herein. The approach is similar to that previously used by Blank et al.[5] to prepare analogs of **4**, but differs significantly in the use of the *t*-butyl moiety as the protecting group.



1 **2** **3** **4**

3-Bromo-2-cyanopyridine(**1**) is readily obtained from commercially available 3-bromopyridine.[6] Several attempts were made to utilize the available 3-hydroxypicolinic acid, but to no avail. Nevertheless, the bromonitrile served well, reacting smoothly with sodium *t*-butylthiolate in refluxing THF to afford the 3-*t*-butylthio-2-cyanopyridine (**2**) in high yield.

All attempts to directly convert **2** to **4** via acid hydrolysis failed, necessitating a sequential approach. Hydrolysis of the nitrile with concentrated NaOH proceeded well, providing 3-*t*-butylthio-2-carboxypyridine (**3**) in high yield, and offered a good opportunity to remove non-acidic impurities. It is worthy of note that the compound is amphoteric, thus requiring strict control of the reaction conditions to avoid loss of product. It is imperative that the ammonia gas evolved during the hydrolysis be completely removed. Failure to do so will result in incomplete neutralization with concomitant loss of product in the aqueous layer.

The final step is likewise straightforward and proceeds smoothly. However, there are several characteristics of the final product that make manipulation somewhat problematic. First of all, the thiol is susceptible to oxidation, especially in basic solution. Therefore, an acid labile protecting group was used. Also, again the compound is amphoteric and exact quantities of reagents must be used to avoid over or under neutralization.

Experimental: NaH (60%, 1.64 g, 41.0 mmol) was suspended in 150 mL of dry THF under N_2. To this suspension was added 4.6 mL of *t*-butylthiol (3.7 g, 41.0 mmol) and the resulting mixture was heated at 50 °C for 1 h or until H_2 evolution ceased. To the white suspension was added 5.0 g of **1** and the reaction was refluxed for 1.5 h, TLC (1:1 Hex/EtOAc). The solvent was removed under vacuum and the resulting residue was lixiviated with 200 mL of CH_2Cl_2. This solution was filtered and the solvent removed under vacuum. The 3-thio-*t*-butylcyanopyridine (**2**) thus obtained was an amber oil weighing 5.4 g which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (1H, dd), 8.01 (1H, dd), 7.49 (1H, dd), 1.39 (9H, s).

NaOH (5.2 g, 130 mmol) was dissolved in 10 mL of 1:1 H_2O/EtOH. To this solution was added 2.5 g (13.0 mmol) of **2** obtained above and the mixture was refluxed for 1 h under N_2, TLC (5% MeOH/CH_2Cl_2), the apparatus being arranged so as to allow for a current of N_2 to be passed through to effect removal of the evolved NH_3. The reaction was then cooled, diluted with 50 mL of H_2O, washed with 2x25 mL of Et_2O and neutralized with 65.0 mL of 2.00 N HCl (130 mmol). It was then extracted with 3x50 mL of CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered and the solvent removed in vacuo. The 3-*t*-butylthiopicolinic acid (**3**) so obtained was a yellow crystalline solid weighing 2.3 g (85%). mp: 132-134 °C. ^1H NMR (400 MHz,$CDCl_3$) δ 8.51 (1H, broad), 8.11 (1H, d), 7.49 (1H, broad), 1.42 (9H, s).

A solution of **3** in 25.0 mL of 2.00 N HCl was refluxed under N_2 for 11 h. The reaction was monitored by NMR. The solvent was removed on a rotary evaporator at 50 °C under vacuum and the residue dried at 40 °C under high vacuum over P_2O_5 for 24 h. The hydrochloride salt thus obtained was a yellow crystalline solid weighing 1.9 g (91%), mp: 200 °C (dec.).

1.0 g (5.2 mmol) of the hydrochloride salt was added to 2.1 mL of 2.50 N NaOH. The mixture was stirred for 1 h then filtered and washed with 10 mL of COLD H_2O. The 3-mercaptopicolinic acid (**4**) so obtained was dried at 40 °C under high vacuum over silica gel overnight. The product was a golden-yellow solid weighing 600 mg (74%), which was analytically pure, mp: 185 °C(dec.), Lit.: 183.5 °C.[3]

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