A Convenient Large Scale Synthesis of 2,6-Dimethyl-4-(trimethylstannyl)pyridine

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Reaction of phosphorus oxychloride with 2,6-dimethylpyridine *N*-oxide hydrochloride (**1**) gave a mixture of 2-(chloromethyl)-6-methylpyridine (**2**) and 4-chloro-2,6-dimethylpyridine (**3**). Treatment of this mixture with triethylamine converted **2** to the quaternary salt **4** which was separated by water extraction leaving **3** which was subsequently reacted with trimethylstannyl sodium to yield 2,6-dimethyl-4-(trimethylstannyl)pyridine (**6**).

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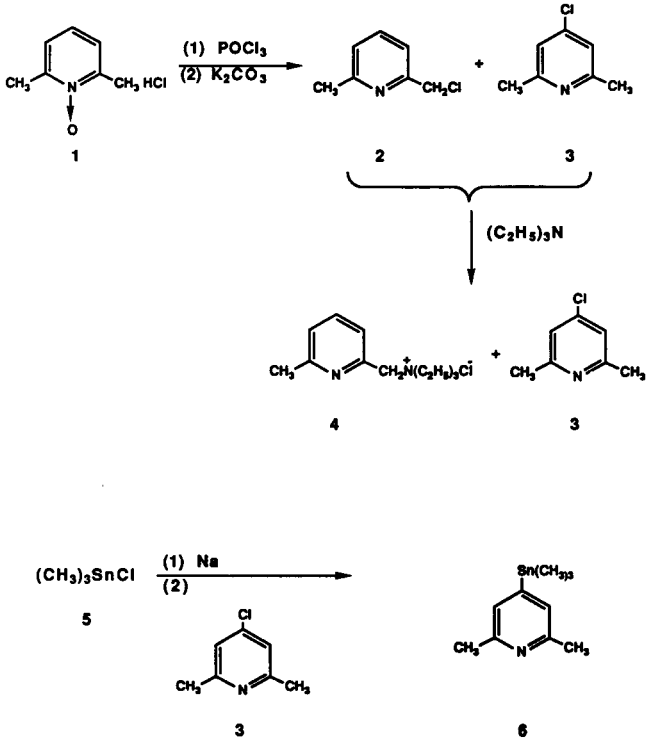
2,6-Dimethyl-4-(trimethylstannyl)pyridine (**6**) was needed in multigram quantities for the synthesis of a series of 7-(2,6-dimethyl-4-pyridinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids [2] which are very potent antibacterial agents [3]. Its preparation has been reported [4] in a general synthetic procedure which involves the condensation of trimethylstannyl sodium with 4-chloro-2,6-dimethylpyridine. We found this process to be unsuitable for a large scale synthesis for the following reasons. First, this procedure uses a 50% excess of sodium which makes it necessary to filter the unreacted sodium before the reaction with 4-chloro-2,6-dimethylpyridine (**3**). This is cumbersome as well as hazardous. Second, the difficulty in preparing large quantities of **3** by the published procedure [5,6] which involves the reaction between phosphorus oxychloride and 2,6-dimethylpyridine *N*-oxide. This reaction suffers from two disadvantages: (a) phosphorus oxychloride reacts violently [6] with 2,6-dimethylpyridine *N*-oxide making this reaction unsafe when run in large scale and (b) this reaction produces a mixture of 2-(chloromethyl)-6-methylpyridine (**2**) and **3** approximately in the ratio of 1:3. Recovery of pure **3** by fractional distillation [6] is not very effective because of the closeness of their boiling points.

Scheme



We have overcome these difficulties by making the following modifications. The need to filter unreacted sodium was eliminated by reducing the amount of excess sodium from 50 to 7%. 2,6-Dimethylpyridine *N*-oxide was replaced by 2,6-dimethylpyridine *N*-oxide hydrochloride (**1**) which reacts with phosphorus oxychloride only on heating. The marked difference in reactivity of 2,6-dimethylpyridine *N*-oxide and its salt **1** with phosphorus oxychloride is the result of a decrease in nucleophilicity of oxygen due to protonation. The separation of the mixture of **2** and **3** was accomplished by chemical means by exploiting the difference in the reactivity of the chloro group of the two compounds. Treatment of the mixture with triethylamine converted the more reactive **2** to quarternary salt **4** which was extracted with water leaving behind essentially pure **3** (61%).

Trimethylstannyl sodium prepared *in situ* from trimethyltin chloride and sodium was reacted with **3** to afford **6** in 73% yield.

EXPERIMENTAL

2,6-Dimethylpyridine *N*-oxide, trimethyltin chloride and 30% sodium/toluene dispersion were obtained from commercial sources. The ^{1}H nmr spectra were recorded on a Varian HA-100 spectometer in deuterated chloroform using tetramethylsilane as an internal standard.

2,6-Dimethylpyridine *N*-oxide Hydrochloride (**1**).

To stirred 6*N* hydrochloric acid (500 ml) cooled in an ice bath was added 2,6-dimethylpyridine *N*-oxide (320 g, 2.6 moles) over a period of 15 minutes. The resulting solution was concentrated to dryness under vacuum. The residue was digested with 2-propanol, filtered and dried to yield 310 g (93%) of a tan solid, mp 217-219° (lit mp 219.5° [7]).

4-Chloro-2,6-dimethylpyridine (**3**).

To mechanically stirred phosphorus oxychloride (400 ml) was added **1** (270 g, 1.69 moles). The resulting mixture was heated under reflux for 8 hours. After cooling to room temperature, most of the unreacted phosphorus oxychloride was removed *in vacuo* and the residual dark oil was poured slowly into a vigorously stirred slurry of aqueous potassium carbonate (414 g) and ice over a period of 1 hour. The reaction mixture was kept cold and basic by adding more ice and solid potassium carbonate during the addition. After the reaction mixture had come to room temperature, the oily product was extracted with chloroform (2 x 500 ml). The chloroform extract was treated with charcoal and then concentrated on a rotary evaporator below 50° to give 245 g of a dark liquid (mixture of **2** and **3**).

A solution of the above mentioned mixture (245 g), triethylamine (105 ml), and ethanol (400 ml) was heated under reflux for 24 hours. The unreacted triethylamine and ethanol were distilled off at atmospheric pressure leaving a residual mixture which was partitioned between ether (500 ml) and water (400 ml). The ether extract was dried (magnesium sulfate) and concentrated on a steam bath to give 148 g of a yellow liquid which was distilled at 71-73°/15 mm (lit bp 83-90°/40 mm [5], lit bp 87.5-88°/41 mm [6]) to afford 136 g (57%) of **3**; ^{1}H nmr δ 6.98 (s, 2H, 3-H, 5-H), 2.48 ppm (s, 6H, 2 x CH_3).

N,N,N-Triethyl-6-methyl-2-pyridinemethanaminium Chloride Monohydrate (**4**).

The aqueous layer from above was treated with charcoal and then concentrated to dryness. The light brown solid residue was recrystallized from ethanol-ether to afford 58.9 g (13%) of tan crystals of **4**, mp 103-104°; ^{1}H nmr: δ 7.8-7.22 (m, 3H, aromatic), 4.85 (s, 2H, —CH_2-N-), 3.6 (q, 6H, 3 x -N-CH_2CH$_3$), 2.7 [s (br), 2H, H_2O], 2.55 (s, 3H, -CH_3), 1.48 ppm (t, 9H, 3 x -NCH$_2$CH_3).

Anal. Calcd. for $C_{13}H_{23}ClN_2 \cdot H_2O$: C, 59.87; H, 9.66; N, 10.74. Found: C, 59.86; H, 9.52; N, 10.71.

2,6-Dimethyl-4-(trimethylstannyl)pyridine (**6**).

To mechanically stirred dimethoxyethane (500 ml) was added 30% sodium/toluene dispersion (100 g, 1.3 mmoles) under nitrogen at 0°. The resulting slurry was treated with a solution of trimethyltin chloride (121 g, 0.61 mole) in dimethoxyethane (100 ml) at 0-5° over 1.5 hours. The reaction mixture was further stirred at this temperature for 2.5 hours and then **3** (52 g, 0.39 mole) was added dropwise over a period of 45 minutes while the temperature was maintained below 5°. The resulting slurry was stirred at 0-5° for 1.5 hours more and then allowed to warm to room temperature. The insoluble inorganic material was removed by filtration through a supercel pad and the filtrate was concentrated on a rotary evaporator to give 94 g of a yellow oil which was distilled at 118-120°/15 mm (lit 109-112°/11 mm [4]) to yield 72 g (73%) of **6**; ^{1}H nmr: δ 7.1 (s, 2H, 3-H, 5-H), 2.55 (s, 6H, 2 x CH_3), 0.33 ppm [s, 9H, Sn$(CH_3)_3$].

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