Synthesis of Two Potential Heterocyclic Amine Food Mutagens

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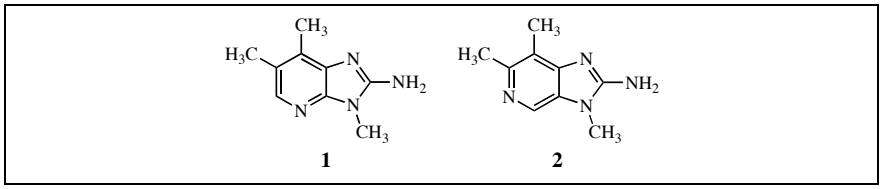
Received February 1, 2007



The syntheses of two potential food mutagens formed during cooking, 2-amino-3,6,7-trimethyl-3*H*-imidazo[4,5-*b*]pyridine (**1**) and 2-amino-3,6,7-trimethyl-3*H*-imidazo[4,5-*c*]pyridine (**2**), are described.

J. Heterocyclic Chem., **45**, 661 (2008).

INTRODUCTION

Several lines of evidence indicate that cooking conditions and dietary habits can contribute to human cancer risk through the ingestion of food mutagens. Our diet is a complex mixture that provides nutritional sustenance but may also be important in the causation, modulation, and prevention of cancer. Heterocyclic amines are formed in a temperature- and time-dependant manner during cooking from creatine or creatinine, certain free amino acids and sugars *via* the Maillard reaction, which are present in uncooked meat and fish muscle [1,2,3]. Heterocyclic amines have the general structure of two or three rings with an exocyclic amino group attached to one of the rings. Recent studies have shown an association with consumption of well-done meats and the risk of prostate cancer [4], pancreatic cancer [5], breast cancer [6], and colorectal cancers or adenomas [7-9]. While the amount of heterocyclic amines consumed in ordinary life is low and perhaps not sufficient to explain the incidence of human cancer the coexistence of many other mutagens/carcinogens of either autobiotic or xenobiotic type and the possibility that these amines induce genomic instability and heighten sensitivity to tumor promoters suggest minimizing exposure is prudent [10].

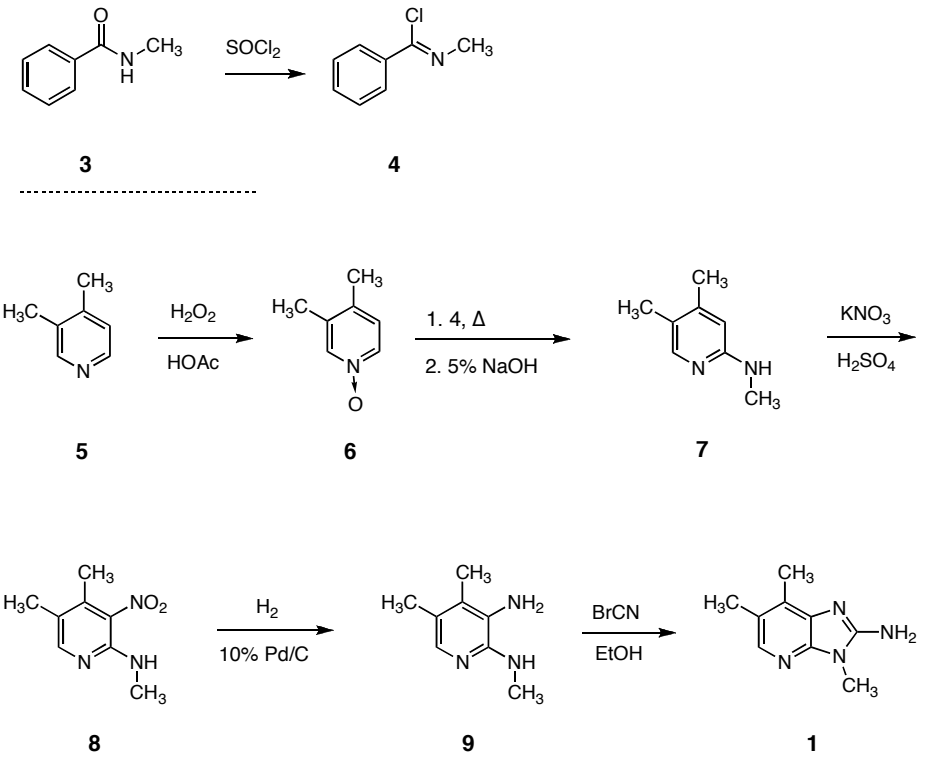
To understand the risk consuming heterocyclic amines poses to humans it is critical to isolate, identify, and synthesize these compounds. Although some of these compounds have been identified and synthesized, one that contributes 10-15% of total mutagenic activity of a fried meat sample [11-15] has only been identified by mass spectrometry to have a molecular weight of 176 [11,13,14]. From the available preliminary data, the mutagenic compound has been determined to be one of the twelve isomers of 2-amino-trimethylimidazopyridine (TMIP) [11,14]. To investigate the biological risk associated with ingesting this unidentified compound, we have previously synthesized eight of the possible isomers: 2-amino-1,5,6-trimethyl-3*H*-imidazo[4,5-*b*]pyridine; 2-amino-3,5,6-trimethyl-3*H*-imidazo[4,5-*b*]pyridine [16]; 2-amino-3,5,7-trimethyl-3*H*-imidazo[4,5-*b*]pyridine; 2-amino-1,4,7-trimethyl-3*H*-imidazo[4,5-*c*]pyridine; 2-amino-1,6,7-trimethyl-3*H*-imidazo[4,5-*c*]pyridine; 2-amino-3,4,6-trimethyl-3*H*-imidazo[4,5-*c*]pyridine [17], 2-amino-1,4,6-trimethyl-3*H*-imidazo[4,5-*c*]pyridine and 2-amino-1,5,7-trimethyl-3*H*-imidazo[4,5-*b*]pyridine [18]. We now report the syntheses of two other possible isomers-2-amino-3,6,7-trimethyl-3*H*-imidazo[4,5-*b*]pyridine (**1**) and 2-amino-3,6,7-trimethyl-3*H*-imidazo[4,5-*c*]pyridine (**2**)—so that they can be compared and tested against the unknown mutagen. The syntheses of the two compounds have not previously been reported in the literature.

RESULTS AND DISCUSSION

The initial successful synthesis 2-amino-3,6,7-trimethyl-3*H*-imidazo[4,5-*b*]pyridine (**1**) is shown in Scheme I. Commercially available 3,4-dimethylpyridine (**5**) was treated with 30% hydrogen peroxide to form 3,4-dimethylpyridine *N*-oxide (**6**). To form the 2-amino functionality we attempted to nitrate **6** using potassium nitrate in sulfuric acid without success. We also tried to brominate **6** without success. We then treated **5** with sodium amide in a Chichibabin reaction and obtained a 4:1 mixture of 2-amino-4,5-dimethylpyridine (**10**) and 2-amino-4,5-dimethylpyridine (**11**) in 36% yield as shown in Scheme II. The amines **10** and **11** were difficult to separate so the mixture was treated with potassium nitrate in acid, followed by silica gel chromatography to give 7% of 2-amino-4,5-dimethyl-3-nitropyridine (**12**).

In an effort to prepare **1** more efficiently we developed the synthesis shown in Scheme I. The *N*-oxide **6** was methylaminated using the reagent **4** to give 4,5-dimethyl-2-(methylamino)pyridine (**7**) in 40% yield. The amine **7** was nitrated to form 4,5-dimethyl-2-(methylamino)-3-nitropyridine (**8**) in 47% yield. The nitro group of **8** was quantitatively reduced to form the diamine **9**, which was

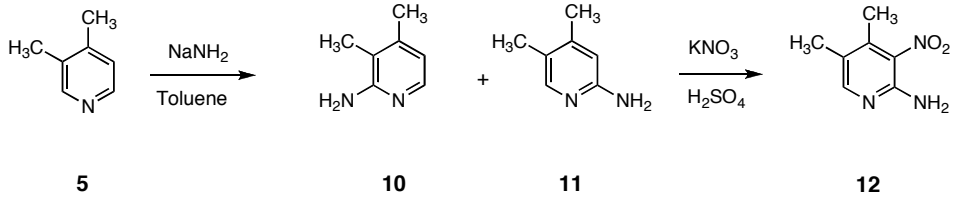
Scheme I



then cyclized using cyanogen bromide to give the desired final product **1**.

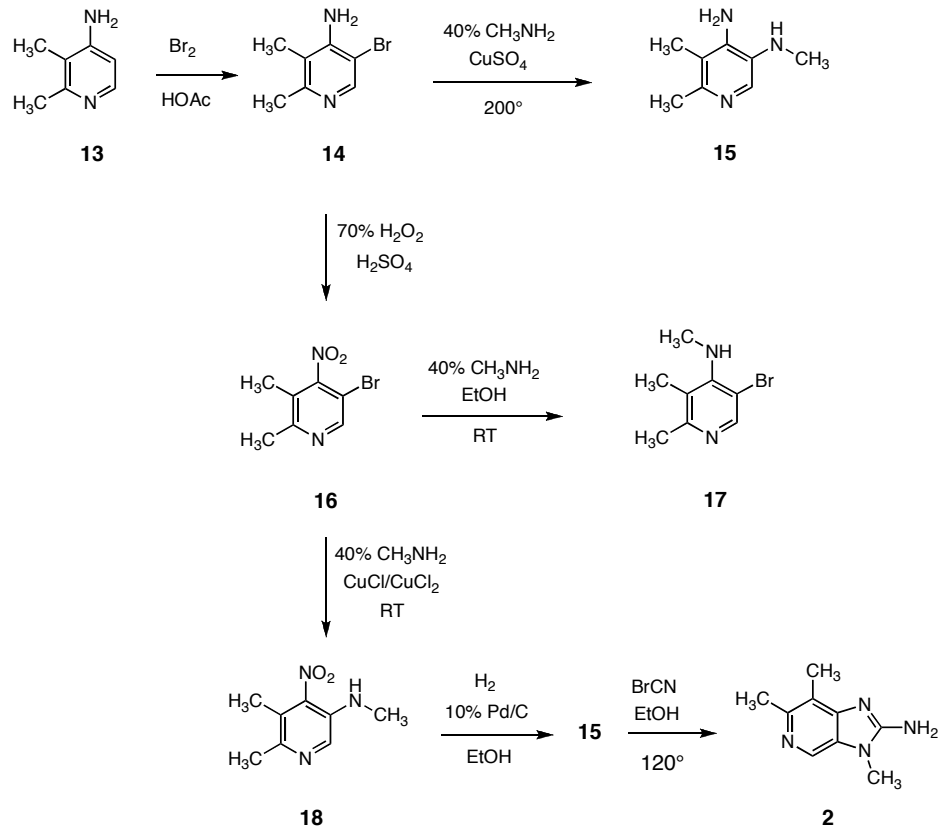
The synthesis of 2-amino-3,6,7-trimethyl-3*H*-imidazo-[4,5-*c*]pyridine (**2**) is shown in Scheme III. Bromination of 4-amino-2,3-dimethylpyridine (**13**), whose synthesis we have previously published [17] gave 4-amino-3-bromo-5,6-dimethylpyridine (**14**) in 59% yield. The bromo compound **14** was treated with 40% aqueous methyl amine and copper sulfate at 200° in a stainless steel bomb to form the diamine **15** in 10% yield, which was pure only after extensive chromatography. The reaction was not suitable to be able to prepare enough material to complete the synthesis. Treatment of **14** with 70% hydrogen peroxide in sulfuric acid provided 3-bromo-5,6-dimethyl-4-nitropyridine (**16**) in 32% yield. At room temperature treatment of **16** with aqueous methylamine resulted in displacement of the nitro group with methylamine to give 3-bromo-5,6-dimethyl-4-(methylamino)pyridine (**17**). By varying the reactions conditions, it was experimentally determined that by using 2 equivalents of copper (I) chloride and 0.1 equivalents of copper (II) chloride at room temperature, the correct product **18** was formed in 35% yield. Reduction of the nitro group of **18** gave the desired diamine **15** in quantitative yield. Ring closure of **15** using cyanogen bromide in ethanol at 120° in a bomb resulted in formation of 2-amino-3,6,7-trimethyl-3*H*-imidazo-[4,5-*c*]pyridine (**2**).

Scheme II



In conclusion, two potential heterocyclic amine food mutagens were synthesized for biological evaluation using an approach that is applicable to the preparation of similar heterocyclic compounds.

Scheme III



EXPERIMENTAL

Melting points (uncorrected) were obtained using a Thomas-Hoover melting point apparatus. The ir spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer, the uv spectra on a Varian DMS-90 spectrometer, and the nmr spectra on a Varian Gemini 300 MHz spectrometer. All chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. The nmr multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and b, broad. Column chromatography was done using E. Merck silica gel 40 (70-230 mesh, ASTM). All solvents were dried over 3Å molecular sieves, except tetrahydrofuran, which was dried by refluxing over sodium with benzophenone ketyl as an indicator. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA.

*Since 2-amino-3,6,7-trimethyl-3H-imidazo[4,5-b]pyridine (**1**) and 2-amino-3,6,7-trimethyl-3H-imidazo[4,5-c]pyridine (**2**) are potential carcinogens and mutagens, direct contact should be avoided.*

***N*-Methylbenzimidoyl chloride (4).** A solution of 10.0 g (74 mmoles) of *N*-methylbenzamide (**3**) in 10.6 g (89 mmoles) of thionyl chloride was heated at reflux for 2 hours under argon. The mixture was vacuum distilled at 65° and 0.3 mm Hg to give 9.21 g (81%) of product (**4**); ^{1}H nmr (deuteriochloroform) δ 3.48 (s, 3H), 7.39 (m, 3H), 7.97 (m, 2H).

3,4-Dimethylpyridine *N*-Oxide (6). A mixture of 5.00 g (46.7 mmoles) of 3,4-dimethylpyridine (**5**) in 12 mL of 30% hydrogen peroxide and 10 mL of glacial acetic acid was heated at 90° for 18 hours. The excess acetic acid was removed under high vacuum, and the solution was neutralized with sodium carbonate, extracted with 3 x 50 mL of chloroform, dried (sodium sulfate), filtered, and concentrated to give 4.15 g (72%) of a white solid (**6**); ^{1}H nmr (deuteriochloroform) δ 2.22 (s, 3H), 2.26 (s, 3H), 7.03 (d, 1H, J = 6.39 Hz), 7.99 (d, 1H, J = 6.39 Hz), 8.04 (s, 1H).

4,5-Dimethyl-2-(methylamino)pyridine (7). To 3.56 g (23.3 mmoles) of *N*-methylbenzimidoyl chloride (**4**) and 3,4-dimethylpyridine-*N*-oxide (**6**) was added 25 mL of trichloroethylene and the solution was heated at reflux under argon for 12 hours. The solution was cooled to room temperature, filtered and concentrated under vacuum. To the residue was added 50 mL of 5% sodium hydroxide solution. The solution was brought to reflux for 1 hour then steam distilled to afford 822 mg of a 2:1 mixture of product (**7**) and 3,4-lutidine (**5**). This material was combined with the distillation pot, extracted into chloroform, dried (sodium sulfate) and evaporated. Vacuum distillation at 0.3 mm Hg gave 1.53 g (48%) of a 2:1 mixture of product (**7**) and 3,4-lutidine (**5**), which was used in the next step without further purification; ^{1}H nmr (deuteriochloroform) δ 2.09 (s, 3H), 2.17 (s, 3H), 2.88 (d, 3H, J = 5.31 Hz), 4.32 (br s, 1H), 6.21 (s, 1H), 7.81 (s, 1H).

4,5-Dimethyl-2-(methylamino)-3-nitropyridine (8). To 1.53 g of crude 4,5-dimethyl-2-(methylamino)pyridine (**7**) dissolved in 10 mL of concentrated sulfuric acid was added 1.36 g (13.5 mmoles) of potassium nitrate in portions. The mixture was

allowed to stir for 16 hours at room temperature, then diluted with 35 mL of water, neutralized with 10% sodium carbonate solution and extracted into chloroform (3 x 150 mL), dried (sodium sulfate) and evaporated. Silica gel chromatography eluting with 10% ethyl acetate/90% hexanes gave 817 mg (40%) of desired product (**8**); ^{1}H nmr (deuteriochloroform) δ 2.17 (s, 3H), 2.34 (s, 3H), 3.03 (d, 3H, J = 4.86 Hz), 6.69 (br s, 1H), 8.06 (s, 1H); ^{13}C nmr (deuteriochloroform) 16.25, 16.68, 28.40, 121.31, 143.34, 151.33, 152.21, 152.40.

3-Amino-4,5-dimethyl-2-(methylamino)pyridine (9). A solution of 620 mg (3.4 mmoles) of 4,5-dimethyl-2-(methylamino)-3-nitropyridine (**8**) in 150 mL of ethanol was hydrogenated for 2 hours at 50 psi in the presence of 62 mg of 10% palladium on carbon at room temperature. The reaction mixture was filtered through Celite, washing cake with ethanol and then evaporating to give 514 mg (100%) of product (**9**); ^{1}H nmr (deuteriochloroform) δ 2.05 (s, 3H), 2.12 (s, 3H), 2.95 (s, 3H), 3.65 (br s, 3H), 7.56 (s, 1H).

2-Amino-3,6,7-trimethyl-3*H*-imidazo[4,5-*b*]pyridine (1). To 514 mg (3.4 mmoles) of 3-amino-4,5-dimethyl-2-(methylamino)pyridine (**9**) dissolved in 6 mL of ethanol was added 1.09 g (10.3 mmoles) of cyanogen bromide. The mixture was heated for 12 hours in a Teflon-lined bomb submerged in an oil bath set to 120°. The cooled material was passed through a plug of C18 reverse phase silica gel eluting with 50 mL of 5% aqueous ammonia, followed by 150 mL of water, then 100 mL of methanol. The concentrated methanol eluent was then purified on a preparative HPLC C18 reverse phase silica gel column eluting with 40:60:0.5 methanol:water:triethylamine to give 127 mg (21%) of desired final product (**1**); melting range 220-280° (dec); ^{1}H nmr (deuteriodimethylsulfoxide) δ 2.20 (s, 3H), 2.28 (s, 3H), 3.45 (s, 3H), 6.62 (br s, 2H), 7.64 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide)) δ 12.45, 15.83, 26.84, 124.30, 129.77, 134.70, 137.74, 145.98, 155.28; ir (potassium bromide) 3264, 3051, 1668, 1615, 1551, 1488, 1400, 1353, 1238, 1173, 1127, 1023 cm^{-1}; uv (95% ethanol) λ_{max} 296 nm (ε 13,784), 256 (6,284), 208 (22,745); ms (70 eV, electron impact) m/z (relative intensity) 176 (100, molecular ion), 161 (30), 148 (17), 134 (6), 107 (7), 92 (6), 80 (7), 65 (26), 53 (25), 42 (37); hrms: Calcd. for $C_9H_{12}N_4$: 176.1062. Found: 176.1065.

2-Amino-3,4-dimethylpyridine (10) and 2-Amino-4,5-dimethylpyridine (11). To 30.0 g (280 mmoles) of 3,4-dimethylpyridine (**5**) was added 42.0 g (560 mmoles) of 50% sodium amide in anhydrous toluene. The reaction mixture was heated at 180° for 24 hours under argon. To the cooled mixture was added 100 mL of water dropwise. After evolution of gas ceased, the mixture was extracted with ethyl acetate (3 x 150 mL), dried (sodium sulfate), filtered, and concentrated. The black oil was vacuum distilled at 0.6 mm of mercury to afford 12.30 g (36%) of a 4:1 mixture of 2-amino-3,4-dimethylpyridine (**10**) and 2-amino-4,5-dimethylpyridine (**11**); ^{1}H nmr (deuteriochloroform) δ 2.09 (s, 3H), 2.15 (s, 3H), 4.26 (br s, 2H), 6.32 (s, 1H), 7.78 (s, 1H).

2-Amino-4,5-dimethyl-3-nitropyridine (12). A 1.9:1 mixture of 2-amino-3,4-dimethylpyridine (**10**) and 2-amino-4,5-dimethylpyridine (**11**) (965 mg, 7.91 mmoles) was dissolved in 3 mL of concentrated sulfuric acid and treated with 799 mg of potassium nitrate (7.91 mmoles). The mixture was stirred at room temperature for 3 hours and at 100° for 1 hour. After cooling, the mixture was poured onto 30 g of ice, neutralized with sodium bicarbonate, extracted into ethyl acetate (3 × 75 mL), dried (sodium sulfate), filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 5% methanol/95% chloroform to afford 100 mg (7%) of a yellow solid (**12**); ^{1}H nmr (deuteriochloroform) δ 2.14 (s, 3H), 2.52 (s, 3H), 5.02 (br s, 2H), 8.68 (s, 1H).

4-Amino-3-bromo-5,6-dimethylpyridine (14). A solution of 2.85 g (23.3 mmoles) of 4-amino-2,3-dimethylpyridine (**13**) in 7 mL of glacial acetic acid under argon was cooled with a water bath at room temperature while being treated slowly with a solution of 2.4 mL (46.6 mmoles) of bromine in 2 mL of glacial acetic acid. The resulting solution was stirred at room temperature overnight. The mixture was cooled with an ice bath, treated with 56 mL of 5 *N* sodium hydroxide solution and extracted with dichloromethane (5 × 50 mL). The organic phases were washed with 50 mL of 0.5 *N* sodium thiosulfate solution and 50 mL of water, dried (sodium sulfate), and filtered. Evaporation of the solvent left 4.89 g of crude product, which was absorbed onto 30 g of silica gel and Soxhlet extracted overnight into chloroform. Evaporation of the solvent gave 2.77 g (59%) of product (**14**); ^{1}H nmr (deuteriochloroform) δ 2.13 (s, 3H), 2.44 (s, 3H), 4.53 (br s, 2H), 8.19 (s, 1H).

4-Amino-5,6-dimethyl-3-(methylamino)pyridine (15). In a sealed stainless steel bomb under argon, a suspension of 1.66 g of crude (90% pure, 7.43 mmoles) 4-amino-5-bromo-2,3-dimethylpyridine (**14**) and 102 mg (0.41 mmoles) of copper sulfate pentahydrate in 10 mL of 40% methylamine solution was heated to 195-200° for 3 hours. The reaction bomb was cooled to 0°, opened, and the contents treated with 50 mL of ice-cold 10% sodium hydroxide solution. The mixture was extracted with chloroform (3 × 50 mL), dried (sodium sulfate), and filtered. Evaporation of the solvent left 1.19 g of crude material, which was Kugelrohr distilled to give 158 mg (10%) of 70% pure product (**15**); bp 95-105° at 2 mm of mercury; ^{1}H nmr (deuteriochloroform) δ 1.96 (s, 3H), 2.30 (s, 3H), 3.37 (s, 3H), 4.70-4.90 (m, 3H), 7.93 (s, 1H).

3-Bromo-5,6-dimethyl-4-nitropyridine (16). A suspension of 6.5 g (32.3 mmoles) of 4-amino-3-bromo-5,6-dimethylpyridine (**14**) in 25 mL of concentrated sulfuric acid was heated to 90°. To the reaction was added 6.6 g (194 mmoles) of 70% hydrogen peroxide solution dropwise over 30 minutes. The mixture was cooled, diluted with 100 mL of water, then neutralized with 10% sodium carbonate solution, extracted into chloroform, dried (sodium sulfate), filtered, and evaporated. Silica gel chromatography eluting with 20% ethyl acetate/80% hexanes gave 2.4 g (32%) of product (**16**) as a yellow solid; ^{1}H nmr (deuteriochloroform) δ 2.24 (s, 3H), 2.55 (s, 3H), 8.56 (s, 1H); ^{13}C nmr (deuteriochloroform) δ 14.02, 22.85, 106.94, 123.71, 149.47, 159.26; ms (DCI) mz (relative intensity) 233/231 (100, molecular ion, H^+), 219/217 (10), 203/201 (15), 153 (15), 123 (8).

3-Bromo-5,6-dimethyl-4-(methylamino)pyridine (17). To 207 mg (0.89 mmoles) of 3-bromo-5,6-dimethyl-4-nitropyridine (**16**) and 6 mL of 40% aqueous methylamine was added 2 mL of ethanol and the reaction mixture was heated to 70° for 1 hour. The reaction mixture was cooled, then extracted into 25 mL of chloroform, dried (sodium sulfate), filtered, and evaporated to give 185 mg (97%) of product (**17**); ^{1}H nmr (deuteriochloroform) δ 2.22 (s, 3H), 2.39 (s, 3H), 2.95 (d, 3H, J = 4.41 Hz), 4.23 (br s, 1H), 8.19 (s, 1H); ^{13}C nmr (deuteriochloroform) δ 15.62, 22.96, 34.80, 110.12, 120.48, 147.59, 152.60, 157.20.

5,6-Dimethyl-3-(methylamino)-4-nitropyridine (18). A solution of 2.90 g (29.3 mmoles) of copper(I) chloride and 200 mg (1.47 mmoles) of copper(II) chloride in 50 mL of 40%

aqueous ammonia solution was added to a solution of 3.4 g (14.7 mmoles) of 3-bromo-5,6-dimethyl-4-nitropyridine (**16**) in 15 mL of ethanol. The resulting solution was allowed to stir for 24 hours at room temperature, then extracted into chloroform (2 x 20 mL), dried (sodium sulfate), filtered, and evaporated. Silica gel chromatography eluting with 5% methanol/95% chloroform gave 935 mg (35%) of product (**18**) as a yellow solid; ^{1}H nmr (deuteriochloroform) δ 2.28 (s, 3H), 2.48 (s, 3H), 2.96 (d, 3H, J = 5.19 Hz), 5.13 (br s, 1H), 8.07 (s, 1H); ms (70 eV, electron impact) m/z (relative intensity) 181 (75, molecular ion, H^+), 164 (20), 146 (12), 135 (8), 119 (15), 106 (25), 93 (20), 79 (40), 65 (75), 52 (70), 42 (100);

2-Amino-3,6,7-trimethyl-3*H*-imidazo[4,5-*c*]pyridine (2). A solution of 307 mg (1.7 mmoles) of 5,6-dimethyl-3-(methyl-amino)-4-nitropyridine (**18**) in 30 mL of ethanol was hydrogenated for 18 hours at 50 psi of hydrogen in the presence of 30 mg of 10% palladium on carbon at room temperature. The reaction mixture was filtered through Celite, rinsing the cake with ethanol, then concentrated. Added to the resulting material dissolved in 6 mL of ethanol was 540 mg (5.1 mmoles) of cyanogen bromide. The mixture was heated for 12 hours in a Teflon-lined bomb submerged in an oil bath set to 120°. The resulting material was applied to a plug of C18 reverse phase silica gel and eluted with 50 mL of 10% aqueous ammonia solution, followed by 100 mL of water, then 100 mL of methanol. The methanol eluent was concentrated and then triturated with isopropanol (3 x 3 mL) to give 66 mg (22%) of desired product (**2**) as a light brown solid; mp >300° (dec); ^{1}H nmr (deuteriomethanol) δ 2.40 (s, 3H), 2.53 (s, 3H), 3.61 (s, 3H), 8.15 (s, 1H); ^{13}C nmr (deuteriomethanol) δ 11.76, 19.26, 29.03, 117.30, 121.18, 131.02, 144.27, 151.06, 159.21; ir (potassium bromide) 3107, 1661, 1549, 1478, 1443, 1261, 1167, 1114, 761 cm^{-1}; uv (95% ethanol) λ_{max} 265 nm (ε 8,273), 215 (32,820); ms (70 eV, electron impact) m/z (relative intensity) 176 (100, molecular ion), 161 (37), 134 (7), 107 (12), 93 (17), 80 (72), 66 (17), 53 (21), 42 (40); hmrs Calcd. for $C_9H_{12}N_4$; 176.1062. Found: 176.1067.

Acknowledgment. This work was supported by the National Cancer Institute under Contract No. N01-CB-67257 and Grant No. PO1-CA55861. We would also like to thank Mr. M. G. Knize, Lawrence Livermore National Laboratory, Biomedical Sciences Division, University of California, for his assistance.

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