Syntheses of Five Potential Heterocyclic Amine Food Mutagens

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The syntheses of the potential heterocyclic amine food mutagens, 3,5,7-trimethyl-2-aminoimidazo-[4,5-*b*]pyridine, 1,4,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine, 1,6,7-trimethyl-2-aminoimidazo[4,5-*c*]-pyridine, 3,4,6-trimethyl-2-aminoimidazo[4,5-*c*]pyridine, and 1,4,6-trimethyl-7-aminoimidazo[4,5-*c*]-pyridine are described.

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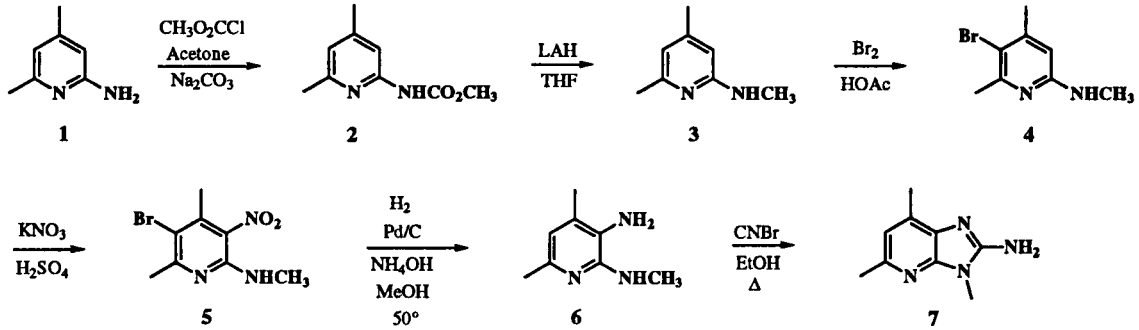
Our dietary intake not only provides us with required nutrients but also plays an important role in the causation, modulation, and prevention of cancer [1,2]. Heterocyclic amines are endogenous chemicals that constitute a significant health hazard. These compounds are the reaction products of cooking, heat processing, and pyrolysis of creatinine, sugars, and amino acids, which are present in protein-rich foods [3-6]. Studies of heterocyclic amines in cooked foods and human urine have shown that humans are continuously exposed to low levels of these compounds in the diet [1,7]. While the levels of these amines are probably not sufficient to produce cancer by themselves, a linear relationship between DNA adduct levels and a wide range of doses of these compounds has been demonstrated in animals [7]. The work suggests that even very low doses of heterocyclic amines form DNA adducts and thus may be implicated in the development of human cancer under conditions in which many other mutagens, carcinogens, tumor promoters, and factors stimulating cancer progression exist [1,7]. In addition, dietary intake of these amines in childhood and adolescence poses greater risk, because of the increased sensitivity to injury of developing tissues [1,8].

To assess the risk that consumption of these mutagens poses to humans, it is essential to isolate, identify, and synthesize these compounds. Although some of the heterocyclic amines have been identified and synthesized, one that contributes 10-15% of the total mutagenic activity of fried meat samples [9-11] has only been identified by mass spectra to have a molecular weight of 176 [9,11]. From the available data, the mutagenic compound was determined to be one of the twelve isomers of trimethyl-2-aminoimidazo-pyridine [9]. To investigate the biological risk associated with ingesting this unidentified compound, we have previously synthesized two of the possible isomers, 1,5,6-trimethyl-2-aminoimidazo[4,5-*b*]pyridine and 3,5,6-trimethyl-2-aminoimidazo[4,5-*b*]pyridine [12], and we now report the synthesis of five other possible isomers – 3,5,7-trimethyl-2-aminoimidazo[4,5-*b*]pyridine (**7**), 1,4,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**17**), 1,6,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**27**), 3,4,6-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**34**), and 1,4,6-trimethyl-7-aminoimidazo[4,5-*c*]pyridine (**41**) – so that they can be compared and tested against the unknown mutagen [13]. The syntheses of these five compounds have not previously been reported in the literature.

The synthesis of the potential food mutagen 3,5,7-trimethyl-2-aminoimidazo[4,5-*b*]pyridine (**7**) was completed as outlined in Scheme I. Treatment of commercially available 2-amino-4,6-dimethylpyridine (**1**) with methyl chloroformate gave the methyl carbamate **2** in high yield (94%). The carbamate **2** was reduced with lithium aluminum hydride to give 4,6-dimethyl-2-methylamino-pyridine **3**, also in high yield (94%). When the amine **3** was nitrated, the nitration occurred at the 5-position, and therefore the amine **3** was brominated at the 5-position to give 5-bromo-4,6-dimethyl-2-methylaminopyridine (**4**), which was then nitrated with potassium nitrate in sulfuric acid to give the nitro compound **5** in 78% yield. Catalytic reduction of **5** by using hydrogen with 10% palladium on

Scheme I

Synthesis of 3,5,7-Trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**7**)



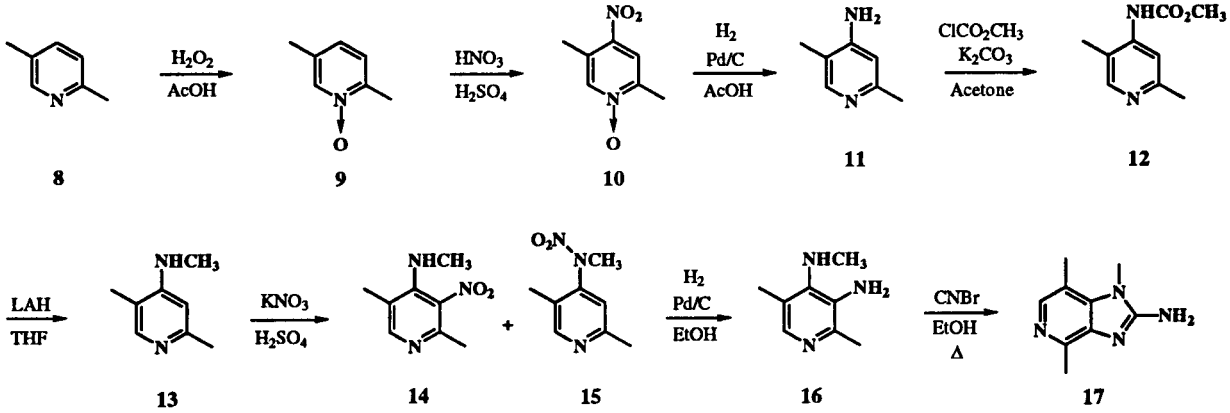
carbon as the catalyst in ammonium hydroxide and methanol at 50° yielded 3-amino-2-methylamino-4,6-dimethylpyridine (**6**), which was immediately used in the ring cyclization reaction with cyanogen bromide in ethanol in a bomb at 120° to give the desired final product **7**.

The synthesis of another potential food mutagen, 1,4,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**17**), was completed as shown in Scheme II. Treatment of commercially available 2,5-dimethylpyridine (**8**) with hydrogen peroxide in acetic acid gave a quantitative yield of 2,5-dimethylpyridine *N*-oxide (**9**). The *N*-oxide **9** was nitrated to provide 2,5-dimethyl-4-nitropyridine *N*-oxide (**10**) in moderate yield (43%). Reduction of the nitro compound **10** with 10% palladium on carbon with hydrogen at 50 psi and a reaction temperature of 60° gave 4-amino-2,5-dimethylpyridine **11** in high yield (97%). Treatment of the amine **11** with methyl chloroformate provided the carbamate **12** in moderate yield (50%). Reduction of the carbamate **11** with lithium aluminum hydride produced 2,5-dimethyl-4-methylaminopyridine (**13**) in high yield (90%). Nitration of **13** to give the nitro derivative **14** proceeded in very low yield (<5%) because of decomposition of the product **14** back to starting material **13** during workup. It was determined that to avoid cleavage of the nitro group, the reaction mixture must be poured into a very large volume of ice-water and the *p*H quickly adjusted to basic conditions by using a saturated solution of potassium hydroxide. It was further found that these difficulties could be overcome by modifying the nitration procedure by using potassium nitrate in concentrated sulfuric acid, which forms 2,5-dimethyl-4-methylamino-3-nitropyridine (**14**) and 2,5-dimethyl-*N*-nitro-*N*-methyl-4-aminopyridine (**15**), respectively, in a 4:1 ratio.

The formation of nitroamine compounds is known to occur with aromatic amines [14]. When the nitration reaction was done with fuming nitric acid instead of potassium nitrate, the formation of the nitroamine **15** was not observed. Mechanistically, it is thought that what appears to be direct nitration at higher acidities is instead an *N*-nitration followed by a fast rearrangement [14]. *N*-Nitro aromatic amines usually rearrange on treatment with acids to give *ortho*- and *para*-nitro products, with the *ortho* compound predominating. When **15** was treated with hydrochloric acid, no decrease in nitrosoamine **15** or increase in nitro compound **14** was observed.

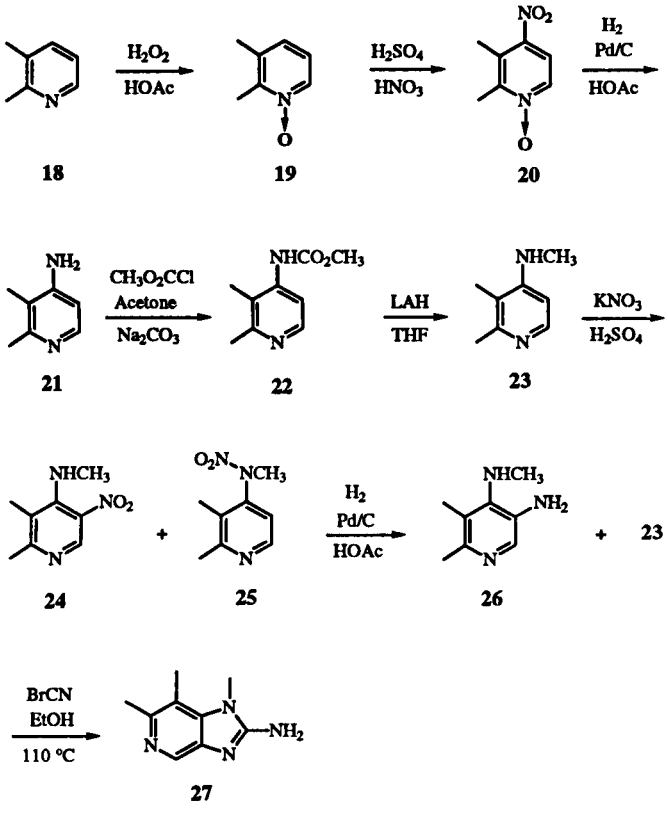
The two nitro compounds **14** and **15** are not readily separable, so the mixture was reduced to obtain 3-amino-2,5-dimethyl-4-methylaminopyridine (**16**) and 2,5-dimethyl-4-methylaminopyridine (**13**). Because these two products **16** and **13** are also somewhat inseparable and unstable, the mixture was carried on to the next reaction. Treatment of the mixture of **16** and **13** with cyanogen bromide in ethanol at 110° in a Teflon-lined bomb gave a low yield (14%) of 1,6,7-trimethyl-2-aminoimidazo[4,5-*c*]-pyridine (**16**) from **13**.

Scheme II
Synthesis of 1,4,7-trimethyl-2-aminoimidazo[4,5-c]pyridine (17)



The synthesis of another heterocyclic amine, 1,6,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**27**), was accomplished as shown in Scheme III. Treatment of commercially available 2,3-dimethylpyridine (**18**) with hydrogen peroxide in acetic acid forms the *N*-oxide **19** in high yield (83%). Nitration of 2,3-dimethylpyridine *N*-oxide (**19**) by using nitric acid in sulfuric acid results in the nitro derivative **20**. Reduction of 2,3-dimethyl-4-nitropyridine *N*-oxide (**20**) by using hydrogen with 10% palladium on carbon as the catalyst at 60° in glacial acetic acid gives 4-amino-2,3-dimethylpyridine (**21**) in high yield (94%). Treatment of **21** with methyl chloroformate forms 2,3-dimethyl-4-methoxycarbonylaminopyridine (**22**), which is then reduced with lithium aluminum hydride to yield 2,3-dimethyl-4-methylaminopyridine (**23**). The nitration of **23** to provide 2,3-dimethyl-4-methylamino-5-nitropyridine (**24**) was tried a number of ways. The classic nitration reaction conditions using nitric acid and sulfuric acid gave a low yield (18%),

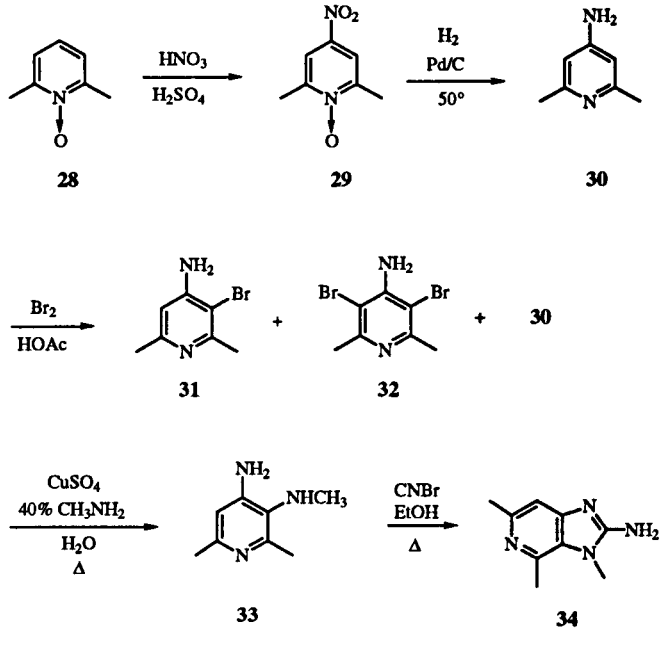
Scheme III
Synthesis of 1,6,7-Trimethyl-2-aminoimidazo[4,5-*c*]pyridine (27)



because under the reaction workup conditions the product **24** decomposed back to the starting material **23**. These difficulties were again overcome by using potassium nitrate in concentrated sulfuric acid, which formed 2,3-dimethyl-4-methylamino-5-nitropyridine (**24**) and 2,3-dimethyl-*N*-nitro-*N*-methyl-4-aminopyridine (**25**), respectively, in a 3:1 ratio. The two nitro compounds **24** and **25** are not readily separable, so the mixture was reduced to obtain 3-amino-5,6-dimethyl-4-methylaminopyridine (**26**) and 2,3-dimethyl-4-methylaminopyridine (**23**). Because these two products **26** and **23** are also somewhat inseparable and unstable, the mixture was carried on to the next reaction. Treatment of the mixture of **26** and **23** with cyanogen bromide in ethanol at 110° in a Teflon-lined bomb gave a low yield (1%) of 1,6,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**27**) from **23**. Purification of the final product **27** was attempted in a variety of ways, including chromatography (silica gel, reverse phase silica gel, alumina), trituration, and extraction. The material **27** was obtained in 80% purity. To increase the purity to acceptable levels, we tried to derivatize the amine function of **27**, purify the compound, and then deblock the compound back to the desired product **27**. This approach did not work. The final product **27** was ultimately purified by preparative recycling reverse phase high performance liquid chromatography (hplc) on a C_{18} column using water containing a trace amount of triethylamine and methanol as the solvent.

The synthesis of the potential food mutagen 3,4,6-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**34**) is shown in Scheme IV. In this synthesis, commercially available 2,6-dimethylpyridine *N*-oxide (**28**) is nitrated using standard conditions with a mixture of nitric and sulfuric acids to give **29** in good yield (84%). Reduction of the nitro compound **29** with hydrogen by using 10% palladium on carbon as the catalyst at 50° provides a high yield (97%) of 4-amino-2,6-dimethylpyridine (**30**). This reduction was also tried with iron and acetic acid; however, it was much more difficult to work up and purify. We also synthesized 4-amino-2,6-dimethylpyridine (**30**) directly from available 2,6-dimethylpyridine by using sodium amide and employing the Chichibabin reaction; however, the yield was only 5%. Bromination of the amine **30** gave a mixture of product **31**, dibromo compound **32**, and starting material **30** in a ratio of 61:18:22. The mixture was separated by taking the crude

Scheme IV
Synthesis of 3,4,6-Trimethyl-2-aminoimidazo[4,5-*c*]pyridine (34)



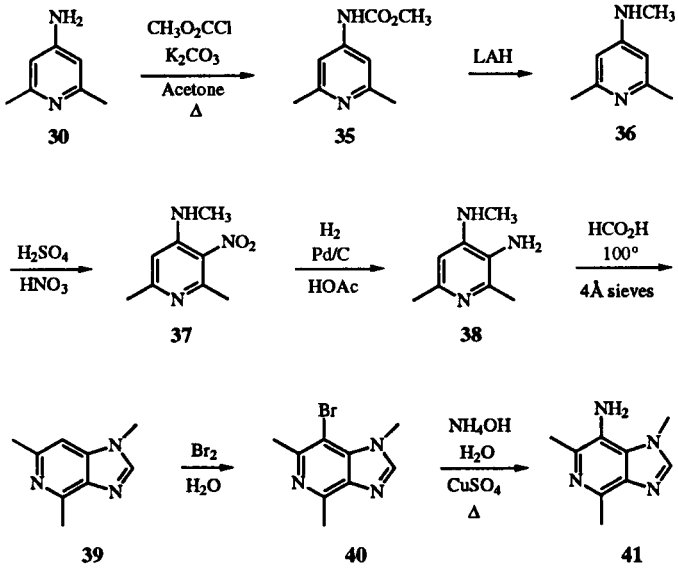
material into a large volume of hot hexane and filtering off the starting material **30**. The desired product **31** was then crystallized from the hexane, and the dibromo compound **32** remained in solution. The bromo compound **31** was heated at 200° in a stainless steel bomb for 3 hours with 40% aqueous methylamine solution and copper sulfate to give the diamino compound **33**. The nmr spectrum of the crude reaction mixture showed about 70% product. This product **33** was not isolated, because of its instability, but

was taken on to the next step, which was heating **33** with cyanogen bromide in ethanol. The product **34** was isolated by first treating the crude material with one equivalent of sodium hydroxide solution and then extracting with a large volume of chloroform, drying (sodium sulfate), and filtering. Most of the salts were removed using this method. Final purification was achieved by first triturating with large volumes of ethyl ether and finally triturating with small volumes of isopropanol. The product **34** retained small amounts of isopropanol, which were removed by retrituration with ethyl ether. The overall yield of final product **34** from bromo compound **31** was 9%.

The synthesis of another heterocyclic amine, 1,4,6-trimethyl-7-aminoimidazo[4,5-*c*]pyridine (**41**), is outlined in Scheme V. The starting material for the synthesis uses the common intermediate 4-amino-2,6-dimethylpyridine (**30**), whose preparation is shown in Scheme IV. Attempts to formylate the amine **30** with acetic formic anhydride [15], which had been successful with another aminopyridine compound [12], failed to give any product. The amine **30** was successfully formylated using methyl chloroformate, which gave the product, 2,6-dimethyl-4-methoxycarbonylaminopyridine (**35**), and starting material **30** in a 2:3 ratio. It was determined that the workup conditions used for similar reactions, which called for quenching with sodium hydroxide solution, had resulted in decomposition of the carbamate **35**. It was further determined that the product **35** is thermally unstable and should not be heated above 40°. Using modified conditions not requiring base, a quantitative yield of product **35** was obtained. Reduction of **35** with lithium aluminum hydride gave 2,6-dimethyl-4-methylaminopyridine (**36**) in high yield (98%). Nitration of **36** using standard nitric acid conditions provided a low yield (16%) of 2,6-dimethyl-4-methylamino-3-nitropyridine (**37**). Reduction of **37** in glacial acetic acid with hydrogen, using 10% palladium on carbon as the catalyst, was quantitative and gave 3-amino-2,6-dimethyl-4-methylaminopyridine (**38**).

Various attempts to form the imidazo ring by using cyanogen bromide or thiopseudourea ester [12] and thus synthesize 1,4,6-trimethyl-2-aminoimidazo[4,5-*c*]pyridine failed to produce any product. Cyclization of the diamine **38** was accomplished in near quantitative yield at 100° by using formic acid dried with molecular sieves to produce 1,4,6-trimethylimidazo[4,5-*c*]pyridine (**39**). When this reaction was done using formic acid that had been dried over molecular sieves, but the reaction mixture did not contain molecular sieves, the reaction did not work. The heterocycle **39** was cleanly brominated in good yield (70%) by using bromine in water. It was anticipated that the bromination would occur on the 2-position, and only after the final product **41** was synthesized did it become clear by nmr studies that bromination had taken place at the 7-position. Attempts to aminate the bromo compound **40** with commercial grade concentrated ammonia at 200° failed. Addition of copper sulfate catalyst gave a low yield of product **41**. When 47% ammonia/water (prepared by adding ammonia gas to water at 0°) was used and the reaction was run overnight at 185-200° in a bomb, a 42% yield of product **41** was obtained. Comparison of the nmr data from the other trimethyl-2-aminoimidazopyrimidine derivatives that have been synthesized, plus nuclear Overhauser enhancement (NOE) studies of this material **41**, made it clear that bromination and amination had occurred on the 7-position. The final products of these syntheses are undergoing biological evaluation.

Scheme V
Synthesis of 1,4,6-Trimethyl-7-aminoimidazo[4,5-*c*]pyridine (41)



EXPERIMENTAL

Melting points (uncorrected) were obtained using a Thomas-Hoover melting point apparatus. The ir spectra were recorded on a Perkin Elmer 1310 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 br, 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 Desert Analytics, Tucson, AZ.

Since 3,5,7-trimethyl-2-aminoimidazo[4,5-*b*]pyridine (**7**), 1,4,7-trimethylimidazo[4,5-*c*]pyridine (**16**), 1,6,7-trimethylimidazo[4,5-*c*]pyridine (**27**), 3,4,6-trimethyl-2-aminoimidazo-[4,5-*c*]pyridine (**34**), and 1,4,6-trimethyl-7-aminoimidazo-[4,5-*c*]pyridine (**41**) are potential **carcinogens** and **mutagens**, direct contact should be avoided.

4,6-Dimethyl-2-methoxycarbonylaminopyridine (**2**).

To a stirring suspension of 10.0 g (82.0 mmoles) of 2-amino-4,6-dimethylpyridine (**1**) and 52.1 g (492 mmoles) of sodium carbonate in 75 ml of dry acetone under argon was added dropwise 31.0 g (25.3 ml, 328 mmoles) of methyl chloroformate in 25 ml of acetone at 0°. The mixture was stirred at room temperature overnight, filtered, and concentrated under high vacuum. The residue was dissolved in chloroform, washed with water, dried (sodium sulfate), filtered, and concentrated to afford 13.9 g (94%) of a white solid **2**, mp 114-116°; ^{1}H nmr (deuteriochloroform): δ 2.33 (s, 3H), 2.42 (s, 3H), 3.79 (s, 3H), 6.71 (s, 1H), 7.65 (s, 1H), 8.12 (br s, 1H); ^{13}C nmr (deuteriochloroform): 21.2, 23.5, 52.1, 109.9 , 119.5, 149.9, 151.3, 154.0, 156.5; ir (potassium bromide): 3190, 2990, 1731, 1572, 1448, 1243, 1102, 1020, 844, 767 cm^{-1}; uv (methanol): λ_{max} 276 nm (ε 6,383); 232 (10,692), 202 (16,789); ms: (70 eV, electron impact) m/z (relative intensity) 180 (87, molecular ion), 149 (93), 122 (100), 106 (61), 94 (33), 79 (30), 65 (24), 53 (56), 39 (41), 27 (25); hrms Calcd. for $C_9H_{12}N_2O_2$: 180.0899. Found: 180.0899.

4,6-Dimethyl-2-methylaminopyridine (**3**).

To a stirring suspension of 22.9 g (603 mmoles) of lithium aluminum hydride in 300 ml of anhydrous tetrahydrofuran under argon at 0° was added dropwise 13.6 g (75.4 mmoles) of 4,6-dimethyl-2-methoxycarbonylaminopyridine (**2**) in 200 ml of anhydrous tetrahydrofuran. The mixture was refluxed for 1 hour and then cooled to 0°, after which 200 ml of 50% water/50% tetrahydrofuran was added dropwise. The mixture was filtered through Celite, concentrated to a small volume, extracted into chloroform (3 × 100 ml), dried (sodium sulfate), filtered, and evaporated to give 9.69 g (94%) of an oil **3** that solidified upon standing, mp 41-43°; ^{1}H nmr (deuteriochloroform): δ 2.21 (s, 3H), 2.33 (s, 3H), 2.87 (d, 3H, J = 5.3 Hz), 4.54 (br s, 1H), 6.01 (s, 1H), 6.31 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 21.1, 24.1, 29.3, 102.5, 113.6, 148.8, 156.5, 159.8; ir (potassium bromide): 3248, 1608, 1578, 1472, 1408, 1226, 803 cm^{-1}; uv (methanol): λ_{max} 305 nm (ε 5,066), 246 (6,200); ms: (70 eV, electron impact) m/z (relative intensity) 136 (63, molecular ion), 107 (100), 94 (25), 79 (32), 65 (23), 53 (38), 39 (57), 28 (41), 15 (31); hrms Calcd. for $C_8H_{12}N_2$: 136.1000. Found: 136.1000.

5-Bromo-4,6-dimethyl-2-methylaminopyridine (**4**).

To a stirring solution of 250 mg (1.84 mmoles) of 4,6-dimethyl-2-methylaminopyridine (**3**) in 2 ml of glacial acetic acid under argon was added dropwise a solution of 294 mg (1.84 mmoles) of bromine in 1 ml of glacial acetic acid. After 1 hour the mixture was poured into 25 ml of water, neutralized with sodium bicarbonate, extracted into chloroform (3 × 50 ml), dried (sodium sulfate), filtered, and concentrated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate/80% hexanes to afford 195 mg (49%) of a white solid **4**, mp 83-84°; ^{1}H nmr (deuteriochloroform): δ 2.31 (s, 3H), 2.50 (s, 3H), 2.86 (d, 3H, J = 5.3 Hz) 4.46 (br s, 1H), 6.12 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 23.5, 25.3, 29.3, 104.8, 111.0, 148.3, 155.2, 157.8; ir (potassium bromide): 3272, 1596, 1566, 1514, 1455, 1396, 1243, 1214, 1014, 820 cm^{-1}; uv (methanol): λ_{max} 312 nm (ε 4,685), 251 (12,015); ms: (70 eV, electron impact) m/z (relative intensity) 214 (100, molecular ion), 187 (76), 172 (17), 133 (18), 119 (34), 106 (85), 94 (42), 77 (54), 65 (40), 51 (76), 39 (71), 28 (56), 15 (63).

Anal. Calcd. for $C_8H_{11}N_2Br$•0.05 H_2O: C, 44.49; H, 5.18; N, 12.97. Found: C, 44.86; H, 5.09; N, 12.58.

5-Bromo-4,6-dimethyl-2-methylamino-3-nitropyridine (**5**).

In 20 ml of concentrated sulfuric acid at 0° was dissolved 2.84 g (13.1 mmoles) of 5-bromo-4,6-dimethyl-2-methylaminopyridine (**4**). To the solution was added 1.46 g (14.4 mmoles) of potassium nitrate, and the mixture was stirred at 0° for 1 hour and at room temperature for 2 hours. The mixture was poured onto 300 g ice, neutralized with sodium bicarbonate, extracted into ethyl acetate (3 × 300 ml), dried (sodium sulfate), filtered, and concentrated. Chromatography on silica gel eluting with 3% ethyl acetate/97% hexanes afforded 2.68 g (78%) of a bright orange solid **5**, mp 118-119°; ^{1}H nmr (deuteriochloroform): δ 2.56 (s, 3H), 2.61 (s, 3H), 3.06 (d, 3H, J = 4.9 Hz), 7.00 (br s, 1H); ^{13}C nmr (deuteriochloroform): δ 21.5, 27.0, 28.3, 29.7, 111.1, 144.3, 150.4, 161.3; ir (potassium bromide): 3413, 1590, 1525, 1490, 1420, 1373, 1243, 850 cm^{-1}; uv (methanol): λ_{max} 243 nm (ε 14,767); ms: (70 eV, electron impact) m/z (relative intensity) 259 (71, molecular ion), 242 (77), 227 (30), 214 (26), 199 (16), 187 (100), 172 (16), 159 (25), 133 (33), 119 (34), 106 (36), 92 (35), 78 (72), 65 (66), 51 (67), 39 (76), 30 (68), 15 (55).

Anal. Calcd. for $C_8H_{10}N_3O_2Br$: C, 36.94; H, 3.88; N, 16.16. Found: C, 37.05; H, 3.83; N, 15.86.

3-Amino-4,6-dimethyl-2-methylaminopyridine (**6**).

A sample of 500 mg (1.92 mmoles) of 5-bromo-4,6-dimethyl-2-methylamino-3-nitropyridine (**5**) was combined with 50 mg of 10% palladium on carbon and 2 ml of ammonium hydroxide in 10 ml of methanol and hydrogenated at 50 psi of hydrogen and 50° overnight. The cooled mixture was filtered through Celite and concentrated under high vacuum to afford a light brown residue, which was used without further purification. ^{1}H nmr (deuteriochloroform): δ 2.02 (s, 3H), 2.42 (s, 3H), 3.19 (s, 3H), 6.01 (s, 1H).

3,5,7-Trimethyl-2-aminoimidazo[4,5-*b*]pyridine (**7**).

The crude 3-amino-4,6-dimethyl-2-methylaminopyridine (**6**) was combined with 610 mg (5.70 mmoles) of cyanogen bromide in 10 ml of ethanol and heated in a Teflon-lined bomb at 120° for 18 hours. To the cooled mixture was added 1 ml of 8 *M* sodium hydroxide solution. The mixture was evaporated to dryness, adsorbed onto a small amount of Baker octadecylsilyl (C_{18}) packing material, placed on top of a small column of the same packing material, and eluted with 40% methanol/1% ammonium hydroxide/59% water and concentrated to dryness under high vacuum. The residue was then suspended in a small amount of methanol, filtered through Celite, and further purified by preparative reversed phase hplc eluting with the above solvent system to afford 125 mg (37% from **5**) of a white solid, mp >300°; ^{1}H nmr (dimethyl-d_6 sulfate): δ 2.34 (s, 3H), 2.43 (s, 3H), 3.49 (s, 3H), 6.58 (br s, 2H), 6.69 (s, 1H); ^{13}C nmr (dimethyl-d_6 sulfate): δ 15.6, 23.4, 27.0, 117.1, 131.1, 132.4, 145.7, 146.9, 154.6; ir (potassium bromide): 3331, 1649, 1549, 1490, 1390, 1255, 1085 cm^{-1}; uv (95% ethanol): λ_{max} 297 nm (ε 22,763), 253 (9,890), 205 (45,454); ms: (70 eV, electron impact) m/z (relative intensity) 176 (100, molecular ion), 161 (27), 148 (22), 134 (10), 119 (11), 92 (13), 65 (18), 39 (22), 28 (18), 15 (17); hrms Calcd. for $C_9H_{12}N_4$: 176.106. Found: 176.1054.

2,5-Dimethylpyridine *N*-Oxide (**9**).

To 20 ml of glacial acetic acid was added 10.0 g (0.09 mole) of 2,5-dimethylpyridine (**8**) followed by 25 ml of 30% hydrogen peroxide solution. The mixture was stirred at 90° for 18 hours and then evaporated to a volume of approximately 25 ml. The

concentrated solution was neutralized with solid sodium carbonate, extracted with chloroform (3 × 100 ml), washed with water, dried (sodium sulfate), and concentrated to yield 12.6 g (99%) of a yellow oil **9**; ^{1}H nmr (deuteriochloroform): δ 2.29 (s, 3H), 2.49 (s, 3H), 7.00 (d, 1H, J = 7.9 Hz), 7.14 (d, 1H, J = 7.9 Hz), 8.14 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 17.2, 17.8, 125.8, 126.8, 133.9, 139.1, 145.9; ir (neat): 3378, 1651, 1514, 1455, 1372, 1266, 1222, 1165, 1125, 1003, 821 cm^{-1}; uv (95% ethanol): λ_{max} 261 nm (ε 10,155), 217 (19,417); ms: (70 eV, electron impact) m/z (relative intensity) 123 (75, molecular ion), 106 (100), 79 (55), 63 (13), 51 (18), 39 (30), 26 (17), 18 (8); hrms Calcd. for C_7H_9NO: 123.0684. Found: 123.0684.

2,5-Dimethyl-4-nitropyridine *N*-Oxide (**10**).

To 75 ml of concentrated sulfuric acid at 0° was added dropwise 10.5 g (0.08 mole) of 2,5-dimethylpyridine *N*-oxide (**9**). After 5.6 ml (0.13 mole) of fuming nitric acid was added to the mixture, it was heated at 90° for 6 hours. The mixture was cooled, poured onto 500 g of ice, and neutralized with 120 ml of 50% sodium hydroxide solution, which turned the mixture brown. The solution was extracted with chloroform (4 × 250 ml), dried (sodium sulfate), filtered, and evaporated. The crude solid was purified by flash column chromatography on silica gel eluting with 5% methanol/95% chloroform to give 6.2 g (43%) of a yellow solid **10**, mp 154-156°, ^{1}H nmr (deuteriochloroform): δ 2.52 (s, 3H), 2.58 (s, 3H), 8.02 (s, 1H), 8.19 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 17.3, 17.7, 121.7, 129.8, 141.6, 142.5, 148.0; ir (potassium bromide): 3056, 1617, 1560, 1506, 1459, 1302, 1260, 1061, 861, 651 cm^{-1}; uv (95% ethanol): λ_{max} 372 nm (ε 9709), 239 (7345), 200 (20,254); ms: (70 eV electron impact) m/z (relative intensity) 168 (100, molecular ion), 151 (35), 121 (15), 104 (30), 91 (12), 77 (65), 65 (19), 51 (32), 39 (52), 29 (21), 18 (16); hrms Calcd. for $C_7H_8N_2O_3$: 168.0534. Found: 168.0534.

4-Amino-2,5-dimethylpyridine (**11**).

To 3.92 g (23.3 mmoles) of 2,5-dimethyl-4-nitropyridine *N*-oxide (**10**) in 50 ml of glacial acetic acid was added 300 mg of 10% palladium on carbon. The mixture was hydrogenated at 50 psi of hydrogen and 60° for 18 hours. The cooled solution was concentrated under reduced pressure to a thick syrup, combined with 50 ml of water, and then neutralized with solid sodium carbonate. The solution was extracted with chloroform (3 × 100 ml), dried (sodium sulfate), and concentrated to provide 2.58 g of product **11**. The aqueous phase was continuously extracted with chloroform for 18 hours to afford an additional 210 mg of product **10** for a total yield of 2.79 g (97%), mp 144-145°; ^{1}H nmr (deuteriochloroform): δ 2.07 (s, 3H), 2.38 (s, 3H), 4.06 (br s, 2H), 6.38 (s, 1H), 7.99 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 13.6, 23.9, 108.2, 114.3, 149.7, 151.4, 156.7; ir (potassium bromide): 3453, 3338, 3208, 1641, 1609, 1565, 1507, 1462, 1258, 1010 cm^{-1}; uv (95% ethanol): λ_{max} 266 nm (ε 7774), 247 (7987), 201 (20,670); ms: (70 eV, electron impact) m/z (relative intensity) 122 (100, molecular ion), 94 (30), 80 (20), 39 (17), 27 (12), 18 (23); hrms Calcd. for $C_7H_{10}N_2$: 122.0843. Found: 122.0846.

2,5-Dimethyl-4-methoxycarbonylaminopyridine (**12**).

To a stirring solution of 2.34 g (0.019 mole) of 4-amino-2,5-dimethylpyridine (**11**) and 12.2 g (114 mmoles) of sodium carbonate in 100 ml of dry acetone under argon at 0° was added 7.26 g (93.7 mmoles) of methyl chloroformate in 25 ml of dry acetone. After stirring at room temperature for 2 hours, the mixture was filtered and rinsed with acetone. From evaporation of the solvent, a yellow solid was obtained that was shown by nmr to be the biscarbamate. The solid was dissolved in 100 ml of acetone and combined with 25 ml of water and 822 mg of sodium bicarbonate. After stirring for 18 hours at room temperature, the mixture was concentrated to a volume of 30 ml and then continuously extracted for 18 hours with chloroform. Evaporation of the solvent yielded 1.73 g (50%) of desired product **12**, mp 132-134°; ^{1}H nmr (deuteriochloroform): δ 2.17 (s, 3H), 2.51 (s, 3H), 3.82 (s, 3H), 6.58 (br s, 1H), 7.87 (s, 1H), 8.19 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 13.9, 24.5, 52.7, 111.5, 116.7, 143.6, 150.1, 153.3, 157.9; ir (potassium bromide): 2928, 1738, 1582, 1526, 1439, 1289, 1244, 1069, 1007, 770 cm^{-1}; uv (95% ethanol): λ_{max} 273 nm (ε 2633), 238 (11,992), 204 (31,352); ms: (70 eV, electron impact) m/z (relative intensity) 180 (94, molecular ion), 148 (60), 121 (100), 94 (22), 77 (17), 59 (21), 52 (10), 39 (32), 27 (17), 18 (42); hrms Calcd. for $C_9H_{12}N_2O_2$: 180.0899. Found: 180.0898.

2,5-Dimethyl-4-methylaminopyridine (**13**).

To a stirred solution of 2.06 g (54.12 mmoles) of lithium aluminum hydride in 110 ml of anhydrous tetrahydrofuran under argon at 0° was added dropwise a solution of 1.62 g (9.02 mmoles) of 2,5-dimethyl-4-methoxycarbonylaminopyridine (**12**) dissolved in 65 ml of anhydrous tetrahydrofuran. The solution was refluxed for 1 hours, cooled to 0°, quenched with 30 ml of 50% water/50% tetrahydrofuran added dropwise, and then filtered through Celite. The filtrate was evaporated to a volume of 50 ml, extracted with chloroform (3 × 100 ml), washed with water, dried (sodium sulfate), filtered, and evaporated to give 1.01 g (90%) of a yellow solid **13**, mp 104-109°; ^{1}H nmr (deuteriochloroform): δ 2.02 (s, 3H), 2.43 (s, 3H), 2.89 (d, 3H, J = 5.0 Hz), 4.07 (br s, 1H), 6.30 (s, 1H), 7.91 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 13.6, 24.5, 29.6, 103.0, 113.9, 148.4, 152.9, 157.2; ir (potassium bromide): 3217, 1609, 1573, 1328, 1297, 1249, 1121, 1072, 1000, 936, 831 cm^{-1}; uv (95% ethanol): λ_{max} 272 nm (ε 13,493), 254 (13,012), 202 (22,590); ms: (70 eV, electron impact) m/z (relative intensity) 136 (100, molecular ion), 121 (67), 106 (12), 94 (22), 77 (13), 66 (7), 53 (8), 39 (18), 27 (9); hrms Calcd. for $C_8H_{12}N_2$: 136.1000. Found: 136.1001.

2,5-Dimethyl-4-methylamino-3-nitropyridine (**14**).

To 100 mg (0.735 mmoles) of 2,5-dimethyl-4-methylaminopyridine (**13**) dissolved in 2 ml of concentrated sulfuric acid at room temperature and then cooled to 0° was added 35 µl (0.809 mmoles) of fuming nitric acid. The mixture was allowed to warm to room temperature and stir for 3 hours. The reaction mixture was poured over 11 g of ice and neutralized with solid sodium carbonate. The mixture was extracted with chloroform (3 × 60 ml), dried (sodium sulfate), filtered, and evaporated. The residue was purified by preparative tlc using an Analtech Tapered Uniplate eluting with 5% methanol/95% chloroform to yield 5 mg (5%) of desired product **14**; ^{1}H nmr (deuteriochloroform): δ 2.18 (s, 3H), 2.46 (s, 3H), 2.93 (d, 3H, J = 5.6 Hz), 4.77 (br s, 1H), 7.98 (s, 1H).

Alternative Synthesis of 2,5-Dimethyl-4-methylamino-3-nitropyridine (**14**).

In 10 ml of concentrated sulfuric acid at 0° was dissolved 768 mg (5.65 mmoles) of 2,5-dimethyl-4-methylaminopyridine (**13**) followed by 798 mg (7.91 mmoles) of potassium nitrate. The mixture was stirred at room temperature for 18 hours, poured onto 100 g of ice, neutralized with solid sodium bicarbonate,

extracted into chloroform (3 × 100 ml), dried (sodium sulfate), and evaporated to afford 220 mg of a 4:1 mixture of 2,5-dimethyl-4-methylamino-3-nitropyridine **14** and 2,5-dimethyl-*N*-nitroso-*N*-methyl-4-aminopyridine (**15**).

3-Amino-2,5-dimethyl-4-methylaminopyridine (**16**).

To 220 mg of a crude sample of 2,5-dimethyl-4-methylamino-3-nitropyridine (**14**) containing 2,5-dimethyl-*N*-nitro-*N*-methyl-4-aminopyridine (**15**) and dissolved in 20 ml of ethanol was added 50 mg of 10% palladium on carbon, and the mixture was hydrogenated at 50 psi for 18 hours. The mixture was filtered through a pad of Celite and concentrated to give 190 mg of crude product (**16**) and 2,5-dimethyl-4-methylaminopyridine (**13**), which was used in the next step without further purification; ^{1}H nmr (deuteriochloroform): δ 2.22 (s, 3H), 2.40 (s, 3H), 2.87 (s, 3H), 7.70 (s, 1H).

1,4,7-Trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**17**).

The crude 190 mg of 3-amino-2,5-dimethyl-4-methylaminopyridine (**16**) and 2,5-dimethyl-4-methylaminopyridine (**13**) (4:1 ratio) was dissolved in 6 ml of ethanol, combined with 500 mg of cyanogen bromide, and heated in a bomb at 120° for 18 hours. To the cooled mixture was added 1 ml of 8 *M* sodium hydroxide solution. The reaction mixture was then concentrated and chromatographed over C_{18} reverse phase silica gel eluting with 40% methanol/50% water/10% ammonium hydroxide and triturated with methanol (2 × 2 ml) to afford 25 mg (14%) of a pure white solid (**17**), mp >300°; ^{1}H nmr (deuteriomethanol) δ 2.56 (s, 3H), 2.59 (s, 3H), 3.79 (s, 3H), 7.70 (s,1H); ^{13}C nmr (deuteriomethanol) δ 18.5, 19.9, 31.3, 115.0, 138.0, 139.5, 140.7, 144.2, 157.5; ir (potassium bromide): 3413, 3224, 3072, 1672, 1607, 1555, 1460, 1402, 1290, 1220, 1096 cm^{-1}; uv (95% ethanol): λ_{max} 295 nm (ε 5720), 232 (45,466); ms: (70 eV, electron impact) m/z (relative intensity) 176 (100, molecular ion), 161 (50), 148 (13), 134 (17), 119 (10), 107 (12), 92 (10), 80 (11), 66 (15), 52 (16), 39 (22), 28 (25), 15 (19); hrms Calcd. for $C_9H_{12}N_4$: 176.1062. Found: 176.1059.

2,3-Dimethylpyridine *N*-Oxide (**19**).

To 50 ml of glacial acetic acid was added 29.7 g (278 mmoles) of 2,3-dimethylpyridine (**18**) and 70 ml of 30% hydrogen peroxide. After heating at 90° for 18 hours, the mixture was cooled to 0° and 100 ml of water was added. To the cooled mixture was added solid sodium carbonate until a basic *p*H was achieved. The mixture was then extracted with chloroform (4 × 250 ml), dried (sodium sulfate), filtered, and concentrated to a light yellow solid that was then triturated with warm hexane to yield 28.7 g (83%) of pure product **19**, mp 94-95°; ^{1}H nmr (deuteriochloroform): δ 2.24 (s, 3H), 2.40 (s, 3H), 6.96 (m, 2H), 8.05 (d, 1H, J = 5.8 Hz); ^{13}C nmr (deuteriochloroform): δ 14.8, 20.5, 123.0, 128.0, 136.0, 138.2, 149.4; ir (potassium bromide): 3408, 1524, 1490, 1426, 1248, 1099, 1076, 794, 700 cm^{-1}; uv (95% ethanol): λ_{max} 261 nm (ε 12,222), 215 (23,968); ms: (70 eV, electron impact) m/z (relative intensity) 123 (100, molecular ion), 106 (74), 79 (18), 65 (10).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.90; H, 7.36; N, 11.24.

2,3-Dimethyl-4-nitropyridine *N*-Oxide (**20**).

To a stirring solution of 5.00 g (41.0 mmoles) of 2,3-dimethylpyridine *N*-oxide (**19**) in 15 ml of concentrated sulfuric acid at 0° was added 3.4 ml (61 mmoles) of concentrated nitric acid. The mixture was heated at 100° for 5 hours and then cooled to 0°. To the cooled mixture was added 100 g of ice followed by solid sodium carbonate added slowly until a *p*H of 10 was reached. The mixture was extracted with chloroform (3 × 100 ml), dried (sodium sulfate), filtered, and evaporated. The crude material was flash chromatographed on silica gel eluting with 5% methanol/95% chloroform to afford 5.33 g (78%) of a light yellow solid **20**, mp 91-92°; ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H), 2.59 (s, 3H), 7.72 (d, 1H, J = 7.4 Hz), 8.21 (d, 1H, J = 7.4 Hz); ^{13}C nmr (deuteriochloroform): δ 15.49, 17.04, 119.25, 130.90, 138.43, 145.42, 151.94; ir (potassium bromide): 3433, 3119, 1573, 1522, 1349, 1281, 1208, 1027, 842, 699, 624 cm^{-1}; uv (95% ethanol): λ_{max} 313 nm (ε 7,876), 242 (7,433), 203 (14,778); ms: (70 eV, electron impact) m/z (relative intensity) 168 (100, molecular ion), 151 (27), 123 (20), 104 (15), 93 (28), 77 (42), 65 (57), 51 (53).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.00; H, 4.84; N, 16.58.

4-Amino-2,3-dimethylpyridine (**21**).

To 50 ml of glacial acetic acid was added 4.83 g (28.7 mmoles) of 2,3-dimethyl-4-nitropyridine *N*-oxide (**20**) and 0.05 g of 10% palladium on carbon. The mixture was hydrogenated at 50 psi of hydrogen and 60° for 12 hours. The cooled solution was filtered through Celite and the filtrate evaporated to dryness. The residue was taken up in 200 ml of chloroform and washed with 40 ml of sodium carbonate solution. The aqueous phase was back-extracted with chloroform (2 × 200 ml) and the combined organic phases were dried (sodium sulfate), filtered, and concentrated to yield 3.30 g (94%) of a white solid **21**, mp 130-131°; ^{1}H nmr (deuteriochloroform): δ 2.06 (s, 3H), 2.46 (s, 3H), 4.10 (br s, 2H), 6.40 (d, 1H, J = 5.5 Hz), 7.98 (d, 1H, J = 5.5 Hz); ^{13}C nmr (deuteriochloroform): δ 13.0, 24.0, 109.0, 115.6, 147.5, 152.0, 157.6; ir (potassium bromide): 3443, 3346, 3198, 1642, 1588, 1483, 1435, 1334, 1278, 1127, 839 cm^{-1}; uv (95% ethanol): λ_{max} 267 nm (ε 32,631), 202 (71,902); ms: (70 eV, electron impact) m/z (relative intensity) 122 (100, molecular ion), 107 (7), 94 (14), 80 (37), 53 (13), 42 (9), 28 (11).

Anal. Calcd. for $C_7H_{10}N_2$•0.1 H_2O: C, 67.82; H, 8.29; N, 22.60. Found: C, 68.02; H, 7.95; N, 22.53.

2,3-Dimethyl-4-methoxycarbonylaminopyridine (**22**).

To a stirring suspension of 3.06 g (25.1 mmoles) of 4-amino-2,3-dimethylpyridine (**21**) and 15.9 g (150 mmoles) of sodium carbonate at 0° in 25 ml of dry acetone under argon was added dropwise 7.75 ml (100 mmoles) of methyl chloroformate. The mixture was stirred at room temperature for 3 hour and then evaporated *in vacuo* at 40°. The residue was suspended in 200 ml of chloroform, filtered, washed with water, dried (sodium sulfate), filtered, and concentrated to provide 3.38 g (60% yield) of a yellow solid **22**, mp 177-178°; ^{1}H nmr (deuteriochloroform): δ 2.16 (s, 3H), 2.53 (s, 3H), 6.69 (br s, 1H), 7.82 (d, 1H), 8.26 (d, 1H); ^{13}C nmr (deuteriochloroform): δ 13.5, 24.4, 53.6, 112.6, 119.5, 144.3, 148.0, 154.6, 158.3; ir (potassium bromide): 3449, 3150, 2923, 1738, 1601, 1540, 1434, 1412, 1306, 1228, 1097, 1042, 845, 775 cm^{-1}; uv (95% ethanol): λ_{max} 263 nm (ε 131), 238 (7,423), 203 (21,615); ms: (70 eV, electron impact) m/z (relative intensity) 180 (87, molecular ion), 148 (35), 121 (100), 106 (10), 94 (13), 79 (8), 65 (8), 53 (18), 39 (16), 27 (12), 15 (28); hrms Calcd. for $C_9H_{12}N_2O_2$: 180.0899. Found: 180.0897.

2,3-Dimethyl-4-methylaminopyridine (**23**).

To a stirring suspension of 4.28 g (113 mmoles) of lithium aluminum hydride in 100 ml of anhydrous tetrahydrofuran under argon at 0° was added 3.38 g (15.0 mmoles) of 2,3-dimethyl-4-methoxycarbonylaminopyridine (**22**) in 50 ml of dry tetrahydrofuran. After the reaction mixture had stirred at room temperature for 18 hours, 50 ml of 50% water/50% tetrahydrofuran was added dropwise followed by 15 ml of 15% sodium hydroxide solution. The mixture was filtered through Celite and concentrated to a volume of 20 ml, which was combined with 20 ml of water and then extracted with chloroform (3 × 100 ml), dried (sodium sulfate), filtered, and evaporated to yield 1.59 g (62%) of an orange solid **23**, mp 164-167° dec; ^{1}H nmr (deuteriochloroform): δ 2.03 (s, 3H), 2.46 (s, 3H), 2.89 (s, 3H), 6.36 (d, 1H, J = 5.6 Hz), 8.09 (d, 1H, J = 5.6 Hz); ^{13}C nmr (deuteriochloroform): δ 12.8, 24.0, 31.0, 103.6, 114.9, 148.0, 153.6, 156.0; ir (potassium bromide): 3236, 2985, 2933, 1624, 1436, 1162, 1087, 980 cm^{-1}; uv (95% ethanol): λ_{max} 334 nm (ε 1020), 271 (8316), 254 (8826); ms: (70 eV, electron impact) m/z (relative intensity) 136 (100, molecular ion), 121 (73), 107 (33), 94 (26), 80 (12), 65 (15), 52 (13), 39 (22), 28 (10); hrms Calcd. for $C_8H_{12}N_2$: 136.1000. Found: 136.1000.

2,3-Dimethyl-4-methylamino-5-nitropyridine (**24**).

To 4 ml of concentrated sulfuric acid at 0° was added 200 mg (1.54 mmoles) of 2,3-dimethyl-4-methylaminopyridine (**23**) followed by 0.11 ml of fuming nitric acid. The reaction mixture was heated at 110° for 3 hours, cooled to room temperature, poured onto 15 g of ice, and adjusted to *p*H 10 with solid sodium carbonate. The mixture was extracted with chloroform (3 × 50 ml), dried (sodium sulfate), filtered, and evaporated. The residue was purified by preparative tlc on an Analtech Tapered Uniplate eluting with 4% methanol/96% chloroform to give 50 mg (18%) of an orange solid (**24**); ^{1}H nmr (deuteriochloroform): δ 2.32 (s, 3H), 2.50 (s, 3H), 3.14 (d, 3H, J = 5.6 Hz), 7.64 (br s, 1H), 8.94 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 17.4, 24.9, 35.6, 119.4, 133.2, 146.3, 152.5, 163.2; ir (potassium bromide): 3447, 3247, 1597, 1503, 1458, 1356, 1243, 1162, 816 cm^{-1}; uv (95% ethanol): λ_{max} 372 nm (ε 4603), 247 (18,253), 199 (21,269); ms: (70 eV, electron impact) m/z (relative intensity) 181 (87, molecular ion), 163 (37), 148 (18), 134 (54) 119 (23), 106 (100), 93 (31), 79 (57), 65 (83), 52 (43), 39 (63), 28 (29); hrms Calcd. for $C_8H_{11}N_3O_2$: 181.0851. Found: 181.0848.

5-Amino-2,3-dimethyl-4-methylaminopyridine (**26**).

To a solution of 500 mg (3.85 mmoles) of 2,3-dimethyl-4-methylaminopyridine (**23**) in 10 ml of concentrated sulfuric acid at 0° was added 483 mg (4.78 mmoles) of potassium nitrate. The mixture was stirred at room temperature for 24 hours, poured onto 20 g of ice, neutralized with sodium bicarbonate, extracted with chloroform (3 × 100 ml), dried (sodium sulfate), filtered, and evaporated. The residue was dissolved in chloroform and filtered through a pad of silica gel eluting with 5% methanol/95% chloroform to yield 340 mg of a mixture consisting of **24** and **25** in a 3:1 ratio. This crude solid was dissolved in 25 ml of absolute ethanol, combined with 40 mg of 10% palladium on carbon, and hydrogenated at room temperature and 50 psi of hydrogen for 18 hours to give a mixture of **26** and **23**. The solution was filtered through Celite, concentrated, and immediately used to synthesize 1,6,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**27**), ^{1}H nmr (deuteriochloroform): δ 2.16 (s, 3H), 2.40 (s, 3H), 2.83 (s, 3H), 3.28 (br s, 1H), 3.41 (br s, 2H), 7.80 (s, 1H).

1,6,7-Trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**27**).

To the crude mixture of 5-amino-2,3-dimethyl-4-methylaminopyridine (**26**) and 2,3-dimethyl-4-methylaminopyridine (**23**) was added 10 ml of absolute ethanol and 311 mg (2.96 mmoles) of cyanogen bromide. The solution was heated in a Teflon-lined bomb at 110° for 18 hours. To the cooled solution was added 3 drops of 8 *M* sodium hydroxide solution to give a *p*H of 9. The mixture was concentrated to dryness *in vacuo* and triturated with 100 ml of hot chloroform, which was then concentrated to a dark solid. The solid was triturated with ethyl ether (1 × 3 ml) and then isopropanol (4 × 1.5 ml) and finally chromatographed on a C_{18} reverse phase silica gel column eluting with 50% methanol/40% water/10% concentrated ammonium hydroxide to yield 30 mg (5%) of an 80% pure solid **27**.

Alternative Synthesis of 1,6,7-Trimethyl-2-aminoimidazo-[4,5-*c*]pyridine (**27**).

To a solution of 1.00 g (7.35 mmoles) of 2,3-dimethyl-4-methylamino-5-nitropyridine (**24**) in 15 ml of concentrated sulfuric acid at 0° was added 1.04 g (10.29 mmoles) of potassium nitrate. The mixture was stirred at room temperature for 3 days, poured onto 150 g of ice, neutralized with solid sodium bicarbonate, extracted with chloroform (3 × 200 ml), dried (sodium sulfate), filtered, and concentrated. The residue was passed through a pad of silica gel eluting with 5% methanol/95% chloroform and evaporated. The dry material was dissolved in 50 ml of absolute ethanol, combined with 100 mg of 10% palladium on carbon, and hydrogenated for 2 hours at 50 psi of hydrogen. The mixture was filtered through a pad of Celite, concentrated, dissolved in 4 ml of ethanol, combined with 311 mg of cyanogen bromide, and heated in a Teflon-lined bomb at 110° overnight. To the cooled mixture was added 3 drops of 8 *M* sodium hydroxide solution to reach a *p*H of 9. The mixture was concentrated to dryness, dissolved in 100 ml of hot chloroform, filtered, and concentrated to a dark solid, which was triturated with ethyl ether (1 × 3 ml) and 2-propanol (4 × 1.5 ml) and chromatographed over C_{18} reverse phase silica gel eluting with 50% methanol/40% water/10% ammonium hydroxide. The residue was further purified by preparatory hplc on C_{18} reverse phase silica gel eluting with 85% methanol/15% triethylamine solution (0.5% in water) to give 11 mg (0.85%) of a white solid **27**, mp 283-285° dec; ^{1}H nmr (deuteriomethanol) δ 2.49 (s, 3H), 2.56 (s, 3H), 3.78 (s, 3H), 8.09 (s, 1H); ^{13}C nmr (deuteriomethanol) δ 13.2, 21.5, 32.0, 114.7, 133.2, 139.0, 140.8, 148.0, 158.4; ir (potassium bromide): 3430, 1655, 1560, 1459, 1439, 1332, 1291, 1240, 1079, 802 cm^{-1}; uv (95% ethanol): λ_{max} 297 nm (ε 4,323), 267 (3,796), 234 (47,105); ms: (70 eV, electron impact) m/z (relative intensity) 176 (100, molecular ion), 161 (23), 148 (17), 134 (8), 119 (7), 107 (21), 92 (8), 90 (8), 66 (15), 53 (16), 42 (23), 27 (18), 15 (13); hrms Calcd. for $C_9H_{12}N_4$: 176.1062. Found: 176.1054.

2,6-Dimethyl-4-nitropyridine *N*-Oxide (**29**).

A solution of 35 g (0.28 mole) of 2,6-dimethylpyridine *N*-oxide (**28**) in 80 ml of concentrated sulfuric acid was treated with 22 ml of concentrated nitric acid and then heated to 125-130° for 3 hours. The reaction mixture was poured over ice and then treated with approximately 350 g solid sodium carbonate to adjust the *p*H to 10. The product was extracted with chloroform (4 × 1 l), dried (sodium carbonate), filtered, and evaporated to leave 40 g (84%) of pure product **29**, mp 150-152°; ^{1}H nmr (deuteriochloroform): δ 2.58 (s, 6H), 8.03 (s, 2H); ^{13}C nmr (deuteriochloroform): δ 18.5, 117.9, 140.7, 150.3; ir (potassium

bromide): 3447, 3076, 2958, 1615, 1522, 1462, 1342, 1280, 1107, 944, 910, 749 cm^{-1}; uv (methanol): λ_{max} 329 nm (ε 10,950) 238 (7,470); ms: (70 eV, electron impact) m/z (relative intensity) 168 (100, molecular ion), 151 (18), 122 (10), 104 (30), 91 (8), 77 (27), 63 (45).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.15; H, 4.89; N, 16.46.

4-Amino-2,6-dimethylpyridine (30).

A solution of 15.6 g (92.5 mmoles) of 2,6-dimethyl-4-nitropyridine *N*-oxide (29) in 80 ml of glacial acetic acid was treated with 410 mg of 10% palladium on carbon. The mixture was hydrogenated at 45 psi of hydrogen and 50° for 19 hours, then filtered through Celite and the filter pad rinsed with chloroform. The filtrate was adjusted to *p*H 12 with 250 ml of 6 *N* sodium hydroxide solution. The product was extracted with chloroform (3 × 250 ml), dried (sodium sulfate), filtered, and evaporated to give 11.0 g (97%) of pure product **30**, mp 192-193°; ^1H nmr (deuteriochloroform): δ 2.38 (s, 6H), 3.98 (br s, 2H), 6.24 (s, 2H); ^{13}C nmr (deuteriochloroform): δ 24.4, 106.3, 153.4, 158.3; ir (potassium bromide): 3328, 3087, 2921, 1614, 1570, 1458, 1346, 1214, 1175, 991, 846 cm^{-1}; uv (methanol): λ_{max} 262 nm (ε 12,980), 251 (11,690), 211 (17,260); ms: (70 eV, electron impact) m/z (relative intensity) 122 (100, molecular ion), 107 (7), 94 (14), 80 (13), 53 (12).

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.67; H, 8.19; N, 22.92.

Alternative Synthesis of 4-Amino-2,6-dimethylpyridine (30).

A suspension of 15.3 g (0.20 mole) of sodium amide (50% toluene dispersion) and 17.5 g (0.16 mole) of 2,6-dimethylpyridine under argon was heated to 130° for 1 hour. Additional sodium amide (15.3 g, 0.20 mole) was added, and the mixture was heated at 140-150° overnight. The sample was cooled in an ice bath and treated with 300 ml of cold 10% sodium hydroxide solution. The mixture was then extracted with dichloromethane (2 × 250 ml), dried (sodium sulfate), filtered, and evaporated to leave 13.7 g of crude material. Distillation (bp 100-130° at 0.3 mm of Hg) of the material gave 7.5 g, which was further purified by trituration with hexane to give 1.0 g (5%) of pure product **30**.

4-Amino-3-bromo-2,6-dimethylpyridine (31).

A solution of 15.4 g (0.13 mole) of 4-amino-2,6-dimethylpyridine (**30**) in 30 ml of glacial acetic acid was slowly treated with a solution of 20.1 g (0.13 mole) of bromine dissolved in 15 ml of glacial acetic acid over 20 minutes with cooling. The mixture became a solid mass and was allowed to stand at room temperature for 1 hour. After cooling in an ice bath, the solid was treated with 300 ml of cold 20% sodium hydroxide solution and extracted with dichloromethane (3 × 250 ml). The extract was dried (sodium sulfate), filtered, and evaporated to give 25 g of material. The proton nmr spectrum revealed a mixture of product **31**, starting material **30**, and dibrominated compound **32** in a ratio of 61:17:22. The mixture was separated by swirling with 700 ml of hot hexane, which left the starting material **30** as a solid. The product crystallized out of the hexane solution on standing to give 12.7 g, while the dibrominated material **32** remained in solution. The yield of product **31** was 60% based on recovered starting material **30**, mp 97-98°; ^1H nmr (deuteriochloroform): δ 2.35 (s, 3H), 2.56 (s, 3H), 4.49 (br s, 2H), 6.34 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 23.8, 25.3, 105.1, 107.1, 150.4, 156.1, 156.7; ir (potassium bromide): 3408, 3310, 3203, 3125, 1633, 1592, 1546, 1426, 1198, 1029, 846 cm^{-1}; uv (methanol): λ_{max} 247 nm (ε 10,740), 210 (30,860); ms: (70 eV, electron impact) m/z (relative intensity) 200/202 (62, molecular ion), 121 (33), 106 (9), 94 (36), 80 (28), 66 (29), 52 (82), 42 (100).

Anal. Calcd. for $C_7H_9BrN_2$: C, 41.81; H, 4.51; N, 13.93. Found: C, 41.44; H, 4.88; N, 13.77.

4-Amino-2,6-dimethyl-3-methylaminopyridine (33).

A suspension of 1.60 g (7.96 mmoles) of 4-amino-3-bromo-2,6-dimethylpyridine (**31**) and 105 mg (0.42 mmoles) of copper sulfate in 10 ml of 40% methylamine in water was sealed under argon in a stainless steel bomb and then heated to 195-200° for 3 hours. The bomb was cooled (-20°), opened, and the contents treated with 5 ml of 3.2 *M* sodium hydroxide solution. The mixture was extracted with dichloromethane (5 × 50 ml), dried (sodium sulfate), filtered, and evaporated to give 1.4 g of crude product (**33**), which was used in the next step without further purification; ^1H nmr (deuteriochloroform): δ 2.34 (s, 3H), 2.42 (s, 3H), 2.63 (s, 3H), 3.99 (br s, 1H), 4.24 (br s, 2H), 6.34 (s, 1H).

3,4,6-Trimethyl-2-aminoimidazo[4,5-*c*]pyridine (34).

To 1.4 g of crude 4-amino-2,6-dimethyl-3-methylaminopyridine (**33**) in 3 ml of absolute ethanol in a Teflon-lined bomb was added 844 mg (7.97 mmoles) of cyanogen bromide. The resulting solution was purged with argon for 10 minutes, and then the bomb was sealed. The bomb was heated at 125-130° for 4 hours. After cooling (0°), the bomb was opened and the reaction solution treated with 318 mg (7.95 mmoles) of sodium hydroxide dissolved in 1 ml of water. Evaporation of the mixture and drying by azeotroping from absolute ethanol *in vacuo* left 1.5 g of crude product. The product was triturated with hot ethyl ether (2 × 25 ml) and hot isopropanol (4 × 1 ml) to give 134 mg of pure product (**34**). The overall yield from **31** was 9%, mp 295° dec; ^1H nmr (deuteriomethanol) δ 2.43 (s, 3H), 2.73 (s, 3H), 3.72 (s, 3H), 6.87 (s, 1H); ^{13}C nmr (deuteriomethanol) δ 21.1, 24.5, 32.6, 109.9, 131.2, 140.1, 151.3, 151.8, 160.5; ir (potassium bromide): 3511, 3323, 3080, 2781, 1675, 1560, 1479, 1175, 1112 cm^{-1}; uv (95% ethanol): λ_{max} 284 nm (ε 8,660), 259 (8,660), 218 (39,600); hrms Calcd. for $C_9H_{12}N_4$: 176.1062. Found: 176.1056.

2,6-Dimethyl-4-methoxycarbonylaminopyridine (35).

A suspension of 6.00 g (49.1 mmoles) of 4-amino-2,6-dimethylpyridine (**30**) in 120 ml of dry acetone at 0° under argon was treated with 54.4 g (0.394 mole) of potassium carbonate and 18.6 g (0.197 mole) of methyl chloroformate. The mixture was stirred at room temperature for 5 hours. The acetone was evaporated and the residue extracted into chloroform (4 × 250 ml). The organic extracts were washed with 50 ml of water, dried (sodium sulfate), filtered, and evaporated to give 8.85 g (100%) of product **35**, mp 78-85° dec; ^1H nmr (deuteriochloroform): δ 2.48 (s, 6H), 3.79 (s, 3H), 6.78 (br s, 1H), 7.02 (s, 2H); ^{13}C nmr (deuteriochloroform): δ 24.5, 52.6, 109.1, 145.8, 153.4, 158.9; ir (potassium bromide): 3496, 3411, 2927, 1716, 1606, 1551, 1443, 1275, 1238, 1096 cm^{-1}; uv (methanol): λ_{max} 244 nm (ε 9,465); ms: (70 eV, electron impact) m/z (relative intensity) 180 (69, molecular ion), 148 (100), 135 (9), 121 (10), 106 (17), 94 (23), 80 (13), 65 (36); hrms Calcd. for $C_9H_{12}N_2O_2$: 180.0898. Found: 180.0891.

2,6-Dimethyl-4-methylaminopyridine (**36**).

A solution of 8.85 g (49.1 mmoles) of 2,6-dimethyl-4-methoxycarbonylaminopyridine (**35**) in 500 ml of dry tetrahydrofuran under argon at 0° was treated with 8.20 g (0.216 mole) of lithium aluminum hydride. The reaction mixture was refluxed for 30 minutes. After the suspension was cooled to 0°, a solution of 130 ml of tetrahydrofuran and water (1:1) was added very slowly, followed by 25 ml of a 15% sodium hydroxide solution. The resulting suspension was filtered and the tetrahydrofuran evaporated. The mixture was extracted into chloroform (3 × 200 ml), dried (sodium sulfate), and filtered. Evaporation of the extract afforded 6.56 g (98%) of pure product **36**, mp 138-148° dec; ^{1}H nmr (deuteriochloroform): δ 2.39 (s, 6H), 2.83 (d, 3H, J = 5.2 Hz), 4.11 (br s, 1H), 6.15 (s, 2H); ir (potassium bromide): 3222, 3142, 3045, 2978, 1615, 1531, 1478, 1446, 1385, 1350, 1215, 1198, 985 cm^{-1}; uv (methanol): λ_{max} 271 nm (ε 13,550), 225 (4,197); ms: (70 eV, electron impact) m/z (relative intensity) 136 (100, molecular ion), 121 (9), 107 (15), 94 (18), 80 (8), 65 (21); hrms Calcd. for $C_8H_{12}N_2$: 136.1000. Found: 136.1001.

2,6-Dimethyl-4-methylamino-3-nitropyridine (**37**).

A suspension of 6.44 g (47.3 mmoles) of 2,6-dimethyl-4-methylaminopyridine (**36**) in 15 ml of concentrated sulfuric acid at 0° was treated with 3.7 ml (59.2 mmoles) of concentrated nitric acid. The reaction mixture was carefully heated, with internal temperature monitoring. When the heating bath temperature reached 75°, the internal temperature rose instantly to 170°. The total heating time was approximately 5 minutes. After the mixture was cooled with an ice bath, 175 ml of ice-water was added. The reaction mixture was neutralized by careful addition of 35 g of solid sodium carbonate. The resulting mixture was extracted into chloroform (4 × 250 ml). The organic phases were dried (sodium sulfate), filtered, and evaporated to obtain 4.96 g of crude product **37**. Chromatography of this material on silica gel eluting with chloroform and finally 1% methanol/99% chloroform provided 1.26 g (15%) of pure product **37**, mp 103-104°; ^{1}H nmr (deuteriochloroform): δ 2.45 (s, 3H), 2.70 (s, 3H), 2.97 (d, 3H, J = 5.1 Hz), 6.42 (s, 1H), 7.42 (br s, 1H); ^{13}C nmr (deuteriochloroform): δ 25.92, 26.60, 30.71, 131.72, 150.75, 157.49, 161.39; ir (potassium bromide): 3382, 2945, 1607, 1550, 1513, 1441, 1368, 1240, 1087, 1033, 845 cm^{-1}; uv (95% ethanol): λ_{max} 371 nm (ε 5,480), 278 (7,140), 242 (23,860); ms: (70 eV, electron impact) m/z (relative intensity) 181 (100, molecular ion), 164 (22), 135 (26), 120 (18), 106 (44), 93 (22), 79 (26), 65 (39).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.83; H, 6.03; N, 23.26.

3-Amino-2,6-dimethyl-4-methylaminopyridine (**38**).

A solution of 1.53 g (8.44 mmoles) of 2,6-dimethyl-4-methylamino-3-nitropyridine (**37**) in 100 ml of 95% ethanol was treated with 200 mg of 10% palladium on carbon and 50 psi of hydrogen for 18 hours at room temperature. The mixture was filtered and evaporated to obtain 1.28 g (100%) of pure product **38**, mp 78-85° dec; ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 3H), 2.43 (s, 3H), 2.89 (d, 3H, J = 5.2 Hz), 3.06 (br s, 2H), 4.59 (br s, 1H), 6.27 (s, 1H); ir (potassium bromide): 3364, 3245, 2980, 2917, 1593, 1520, 1452, 1354, 1282, 1251, 1207 cm^{-1}; uv (95% ethanol): λ_{max} 298 nm (ε 6,700), 259 (4,620), 219 (17,770); ms: (70 eV, electron impact) m/z (relative intensity) 151 (100, molecular ion), 136 (29), 122 (11), 109 (26); hrms Calcd. for $C_8H_{13}N_3$: 151.1109. Found: 151.1110.

1,4,6-Trimethylimidazo[4,5-*c*]pyridine (**39**).

A suspension of 115 mg (0.761 mmoles) of 3-amino-2,6-dimethyl-4-methylaminopyridine (**38**), 115 mg of 4-Å molecular sieves, and 1 ml of dry formic acid (molecular sieves) was refluxed under argon for 18 hours. The formic acid was evaporated *in vacuo* at 90° and the residue taken into 500 ml of hot chloroform. The solution was filtered to remove sieve dust and evaporated to yield 159 mg (100%) of product **39**, mp 123-124°; ^{1}H nmr (deuteriomethanol) δ 2.67 (s, 3H), 2.82 (s, 3H), 3.90 (s, 3H), 7.48 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 19.7, 24.7, 30.9, 101.5, 137.7, 139.7, 143.2, 150.4, 150.9; ir (potassium bromide): 3384, 3056, 2992, 2920, 1616, 1589, 1505, 1451, 1333, 1247, 1055, 828 cm^{-1}; uv (methanol): λ_{max} 276 nm (ε 4,496), 268 (5,297), 255 (5,762), 208 (40,210); ms: (70 eV, electron impact) m/z (relative intensity) 161 (100, molecular ion), 146 (19), 133 (5), 119 (8), 92 (6), 65 (6), 52 (6), 42 (14); hrms Calcd. for $C_9H_{11}N_3$: 161.0952. Found: 161.0950.

7-Bromo-1,4,6-trimethylimidazo[4,5-*c*]pyridine (**40**).

A suspension of 129 mg (0.800 mmoles) of 1,4,6-trimethylimidazo[4,5-*c*]pyridine (**39**) in 1 ml of water was cooled with an ice bath and treated slowly with 10 ml of 0.21 *M* bromine in water (2.1 mmoles) and the resulting mixture was stirred at room temperature for 4 hours. The mixture was then treated with 1 ml of saturated sodium bicarbonate solution and 2 ml of 10% sodium sulfite solution. The suspension was extracted with chloroform and the organic extracts dried (sodium sulfate) and evaporated to give 180 mg of crude product **40**. This was purified by chromatography on silica gel eluting with 5% methanol/95% chloroform to yield 110 mg (57%) of pure product **40**, mp 142-144°; ^{1}H nmr (deuteriochloroform): δ 2.74 (s, 3H), 2.80 (s, 3H), 4.13 (s, 3H), 7.76 (s, 1H); uv (methanol): λ_{max} 262 nm (ε 7,083), 213 (36,140); ms: (70 eV, electron impact) m/z (relative intensity) 239/241 (100, molecular ion), 224 (12), 160 (62), 145 (13), 133 (17), 119 (21); hrms Calcd. for $C_9H_{10}B_rN_3$: 239.0058. Found: 239.0057.

1,4,6-Trimethyl-7-aminoimidazo[4,5-*c*]pyridine (**41**).

A suspension of 55 mg (0.23 mmole) of 7-bromo-1,4,6-trimethylimidazo[4,5-*c*]pyridine (**40**) and 10 mg (0.04 mmole) of copper sulfate pentahydrate in 3 ml of 47% ammonia in water at 0° was sealed in an ampule and then heated at 185-200° overnight. After cooling, the ampule was opened and the contents treated with 140 mg (1.01 mmoles) of potassium carbonate and 1 g of silica gel. The water and ammonia were evaporated *in vacuo* and the absorbed material placed on a pad of 2 g of silica gel and eluted with 100 ml of 30% methanol/70% chloroform. The eluent was evaporated and the residue extracted with warm 5% methanol/95% chloroform (2 × 100 ml). Evaporation of the solution gave 47 mg of crude product **41**, which was purified by preparative tlc using an Analtech Tapered Uniplate eluting with 89% chloroform/9% methanol/2% trimethylamine. The region R_f= 0.4-0.6 was scraped and eluted with 5% methanol/95% chloroform. Evaporation gave 17 mg (42%) of pure product **41**, mp 240-250° dec; ^{1}H nmr (deuteriomethanol) δ 2.50 (s, 3H), 2.69 (s, 3H), 4.19 (s, 3H), 8.14 (s, 1H); ^{13}C nmr (deuteriomethanol) δ 16.9, 17.4, 34.2, 129.0, 132.1, 132.9, 139.8, 140.1, 148.2; ms: (70 eV, electron impact) m/z (relative intensity) 176 (M^+, 100), 161 (24), 148 (9), 134 (14); uv (95% ethanol): λ_{max} 218 nm (ε 18,300), 229 (16,100), 284 (4500), 315 (8,000); hrms Calcd. for $C_9H_{12}N_4$: 176.1062. Found: 176.1056.

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[13] The isomers, 3,5,7-trimethyl-2-aminoimidazo[4,5-*b*]pyridine (**7**), 1,4,7-trimethylimidazo[4,5-*c*]pyridine (**17**), 1,6,7-trimethyl-2-aminoimidazo[4,5-*c*]pyridine (**27**), 3,4,6-trimethyl-2-aminoimidazo-[4,5-*c*]pyridine (**34**), and 1,4,6-trimethyl-7-aminoimidazo[4,5-*c*]pyridine (**41**), are presently available as reference materials from Dr. Harold Seifried, National Cancer Institute, Chemical and Physical Carcinogenesis Branch, 6130 Executive Boulevard, EPN/700, Bethesda, MD 20892.

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