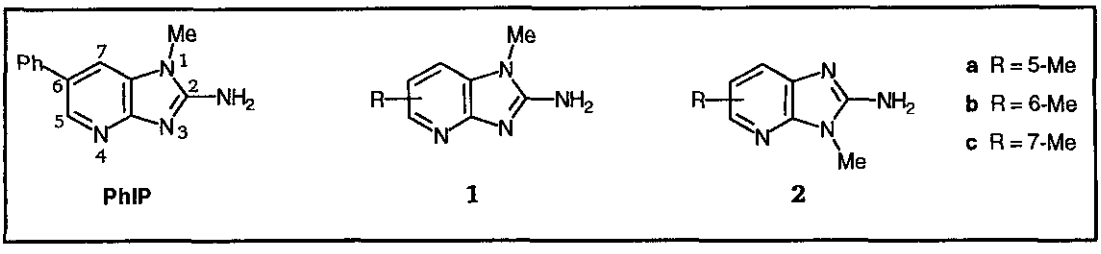
SYNTHESIS OF THE MUTAGENIC 2-AMINO-1,6-DIMETHYL-IMIDAZO[4,5-*b*]PYRIDINE (1,6-DMIP) AND FIVE OF ITS ISOMERS

Stefan Lindström, Tania Ahmad, and Spiros Grivas*

Department of Chemistry, Swedish University of Agricultural Sciences, P.O. Box 7015, S-750 07 Uppsala, Sweden

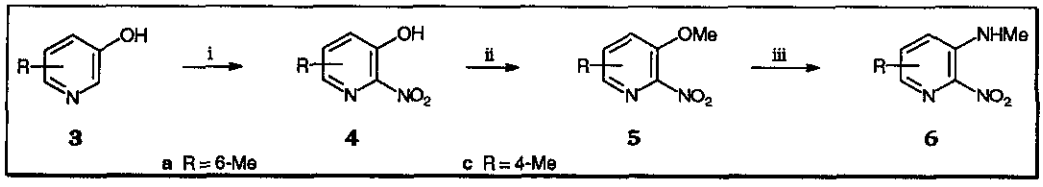
Abstract — Synthetic routes to 2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine and its 1,5-, 1,7-, 3,5-, 3,6- and 3,7-dimethyl isomers from methyl derivatives of 3-hydroxy- or 2-amino-pyridine and 2-chloronicotinic acid are described.

Pyridine and imidazopyridine derivatives show various biological activities: analgesic, sedative, antiinflammatory, herbicidal, etc., and thus are widely used in the pharmaceutical and agrochemical industry.[1] 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (**PhIP**) belongs to a group of genotoxic heterocyclic amines (**HA**) to which we are continuously exposed since they are present in diesel-exhaust particles, in rain water, in soil, in cigarette smoke condensate, and in cooked foods.[2] A great deal of effort has been devoted to developing analytical methods for the detection and efficient extraction of these environmental pollutants from complex mixtures.[3] Synthetic samples of the **HA** are required for reference purposes in analytical studies, for animal experiments, for biological assays, and often for their unequivocal identifications. For instance, the identity of **PhIP** could not be determined unambiguously by spectroscopic methods because of the limited amount available. Thus, **PhIP** and its much less mutagenic 3-methyl isomer were synthesized and compared with the sample isolated.[4] Similarly, the 6-methyl analogue of **PhIP** (2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine, **1,6-DMIP**) (**1b**) was suspected to be among the mutagenic **HA** found in cooked foods.[5] Its structure was later confirmed by comparison with a synthetic sample.[6] As part of a programme dealing with the synthesis of the **HA**,[7-9] with studies on their binding to biomolecules as well as their structure–activity relationships,[10] we now wish to report the synthesis of the six dimethyl 2-aminoimidazopyridines (**1**) and (**2**).



RESULTS AND DISCUSSION

The mutagenicty of the **HA** shows great variation depending on the number and positions of the methyl groups.[10,11] Therefore, in contrast to previously reported syntheses of **HA**,[12] we employed synthetic routes that yield the desired DMIP isomers free from any methyl isomers. Substituted pyridines are synthesized from acyclic synthons[13,14] or, more commonly, by modification of commercially available pyridine derivatives. In analogy with our recent work on the synthesis of 6-aryl(methylamino)nitropyridines,[9] key intermediates in our present synthetic routes were the six stable (methylamino)nitropicolines (**6**) and (**14**). These were obtained from commercially available or previously described methyl derivatives of 3-hydroxy- or 2-amino-pyridine as outlined in Schemes 1–3.

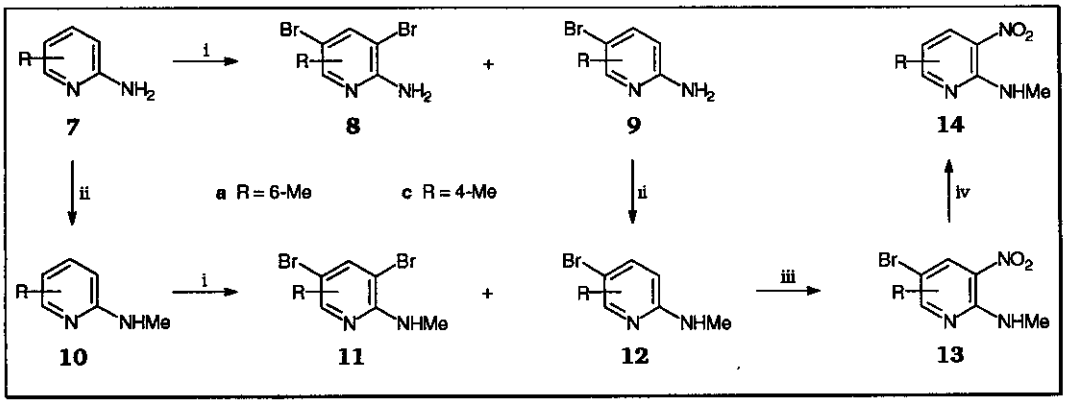


Scheme 1 *Reagents and conditions:* i, fuming HNO_3, conc. H_2SO_4, 0–20°C, 2 h; ii, MeI, K_2CO_3, Me_2CO, reflux or pressure bomb, overnight; iii, 40% aq. $MeNH_2$, 70°C, overnight

Pyridines (**3a**) and (**3c**)[15] (Scheme 1) were readily nitrated at room temperature to yield **4a**[16] and **4c**.[16] Subsequent methylation to **5a**[17] and **5c** was accomplished by treatment with methyl iodide and potassium carbonate in acetone. The methylation of **4c** required more drastic conditions compared to **4a**. Treatment of **5** with methylamine afforded the two desired nitroamines (**6**) readily. The overall isolated yield from **3** was 42% for **6a** and 15% for **6c**. The steps in the sequence **4c** → **5c** → **6c** proceeded in considerably lower yields than **4a** → **5a** → **6a**, probably because of crowding at positions 3 and 4.

Bromination of pyridine (**7a**) (Scheme 2) yielded the 3,5-dibromo derivative (**8a**)[18] in 5% yield and the desired **9a**[18] in 78% yield. Monomethylation of **9a** by treatment with 1-hydroxymethylbenzotriazole ($BtCH_2OH$) followed by $NaBH_4$ reduction[19] afforded **12a** in 67% isolated yield. Alternatively, **12a** was obtained in 79% yield, together with a small amount of the dibromo derivative (**11a**) (8% yield), from the bromination of **10a**, which was obtained in 74% yield by methylation of **7a**. The two routes leading to **12a** were more or less equally convenient and efficient. Subsequent nitration of **12a** afforded **13a** which was debrominated with Pd(0)/sodium formate in DMF[20] to the key intermediate (**14a**).[23] The overall isolated yield from **12a** to **14a** was 28%. Position 5 was first blocked with bromine and position 3 then nitrated (**12** → **13**), since nitration of the 2-aminopyridines would lead mainly to the undesired 5-substituted derivatives.[21]

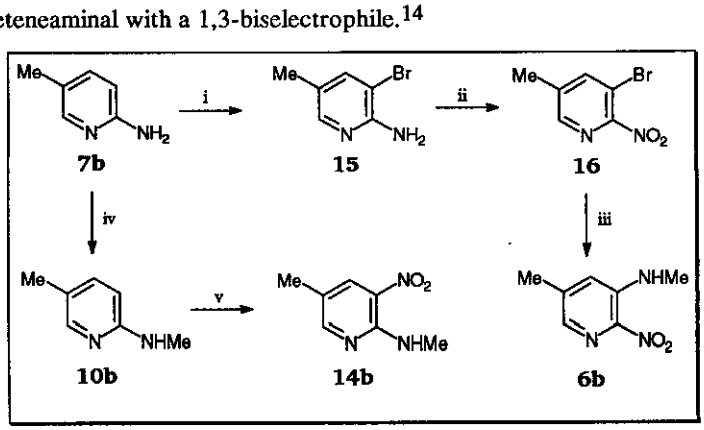
In a similar manner, **9c**[18] was methylated to **12c**, which could also be obtained by bromination of **10c**.[19] However, the route *via* **9c** proceeded in 29% overall yield compared to that *via* **10c**, which proceeded in 45% yield from **7c**. Subsequent nitration to **13c** and debromination[20] gave the desired **14c**.[22]



Scheme 2 *Reagents and conditions:* i, Br_2, AcOH, 20°C, 1 h; ii, a) $BtCH_2OH$, EtOH, 20°C, 5 h; b) $NaBH_4$, THF, reflux, 8 h; iii, fuming HNO_3, conc. H_2SO_4, 0–20°C, 1 h; iv, $(PPh_3)_4Pd$, HCO_2Na, DMF, 100°C, 7 h

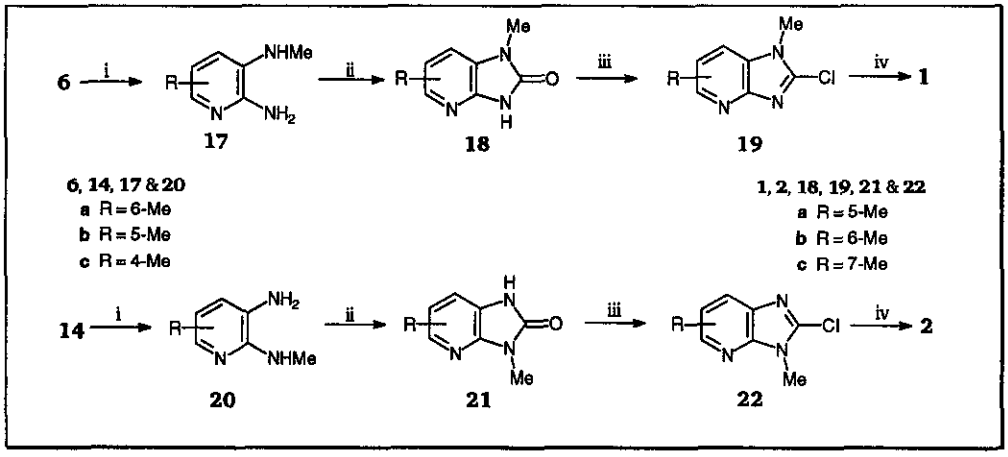
In an alternative and convenient way, 2-chloro-4-methyl-3-nitropyridine was treated with methylamine to afford **14c** in 83% yield. The picolines (**13**) are potential intermediates for the synthesis of the 5- and 7-Me derivatives of **PhIP** *via* Pd(0)-catalysed phenylation, as we recently described.[9]

Bromination of commercially available **7b** to **15**[18] (Scheme 3) followed by oxidation of **15** with H_2SO_5 afforded **16** in 30% overall yield from **7b**. Treatment of **16** with methylamine afforded the desired **6b** in 73% yield. The isomeric **14b**[24] was obtained by nitration of **10b** which in turn was obtained by methylating[19] **7b**. The overall isolated yield of **14b** from **7b** was 50%. Compounds (**14a**),[23] (**14b**)[24] and (**14c**)[22] have each been prepared *via* a multistep sequence, the last step of which was treatment of the appropriate methyl derivative of 2-chloro-3-nitropyridine with methylamine. Picoline (**14a**) has also been synthesized by condensation of a nitroketeneaminal with a 1,3-biselectrophile.[14]



Scheme 3 *Reagents and conditions:* i, Br_2, AcOH, 20°C, 1 h; ii, fuming H_2SO_4, 30% H_2O_2, 8–20°C, 60 h; iii, 40% aq. $MeNH_2$, 70°C, 4 h; iv, a) $BtCH_2OH$, EtOH, 20°C, 5 h; b) $NaBH_4$, THF, reflux, 8 h; v, fuming HNO_3, conc. H_2SO_4, 0–20°C, 1 h

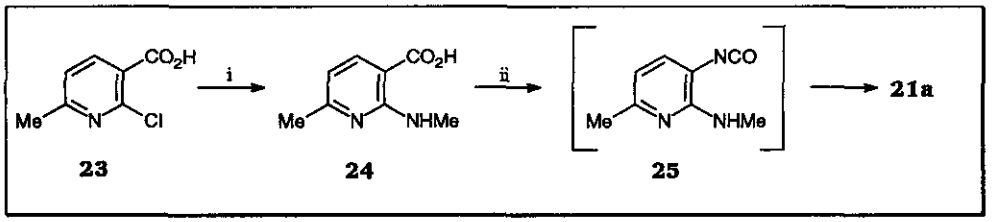
The six (methylamino)nitropicolines (**6**) and (**14**) were reduced to the corresponding air-sensitive **17** and **20** (Scheme 4). In contrast to related imidazo-quinolines,[7] -isoquinolines[7] and -quinoxalines,[8] the straightforward ring-closure of *ortho*-diaminopyridines with cyanogen bromide to imidazopyridines is a low-yield reaction,[4,9] yielding several products. **PhIP**[4] and **1,6-DMIP** (**1b**)[6] have been obtained in low yields by treating the appropriate diamines with BrCN (pressure bomb, 175°C). We repeated this reaction and obtained **1c** from the crude **17c** in less than 10% yields. In view of these discouraging results, an alternative pathway was employed and the remaining five crude diamines were condensed with urea to afford the corresponding hydantoins (**18**) and (**21**) in 40–60% yields. These were then chlorinated with PCl_5 in $POCl_3$ to yield **19** and **22** (35–70%). The 2-chloro compounds were finally treated with ammonia in a Teflon-lined pressure bomb to afford the corresponding DMIP isomers (**1a**), (**1b**) and (**2a–c**) in 35–70% isolated yields. The route *via* the apparently unknown **18**, **19**, **21** and **22**, in which the 2-oxo and 2-chloro substituents are available for transformation into other useful functionalities, has been employed for the synthesis of other 2-aminoimidazopyridines including **PhIP**.[25]



Scheme 4 *Reagents and conditions:* i, H_2, Raney Ni, MeOH, 20°C, 1 h; ii, $(NH_2)_2CO$, 135°C, 6 h; iii, PCl_5, $POCl_3$, reflux, 2–5 h; iv, 25% NH_4OH, pressure bomb, 100°C, overnight

An entirely different and convenient approach to the hydantoins (**21**) is exemplified by the synthesis of **21a** as shown in Scheme 5. Treatment of the commercially available monohydrate of **23** with methylamine afforded **24** in 60% yield. One-pot rearrangement of **24** to the isocyanate **25** by DPPA $[(PhO_2)P(O)N_3]$[26] followed by *in situ* ring-closure yielded **21a** in 65% isolated yield.

Preliminary mutagenic activity results (Ames test) showed that all six DMIP isomers had much lower activity than **PhIP**, and that **1,6-DMIP** was most potent among the title compounds.[27]



Scheme 5 *Reagents and conditions:* i, 33% ethanolic $MeNH_2$, pressure bomb, 120°C, 6 h; ii, DPPA, Et_3N, dioxane, reflux, overnight

EXPERIMENTAL

1-Hydroxymethylbenzotriazole ($BtCH_2OH$)[28] and compounds (**3c**,[15] **9a**,[18] **9c**,[18] **10a**,[29] **10c**,[19] and **15**[18]) were obtained according to, or in close analogy with, the cited references. 1-Chloro-4-methyl-3-nitropyridine and compounds (**3a**, **7a–c**) and the monohydrate of **23** were obtained commercially (Aldrich). The yields have not been optimized. All organic solvents were either freshly distilled or of p. a. quality and the ethanol was 95%. Solvent mixtures are defined by volume ratios (v/v). Petroleum refers to petroleum ether, bp 60–70°C. Flash liquid chromatography (fc) was performed on silica gel (230–400 mesh ASTM, Merck). All reactions and purifications were monitored by tlc with uv detection on aluminium sheets coated with silica gel 60 F_{254} (Merck). All evaporations were performed under reduced pressure at 40°C. Comparisons with authentic samples were made by means of tlc and ^1H nmr spectroscopy. Melting points (uncorrected) were determined on a Mettler FP5 or FP62 instrument. The ^1H nmr spectra were obtained on a Varian VXR-400 spectrometer at 25°C, and referenced to the solvent ($CHCl_3$ 7.26, MeOD 3.31 or Me_2SO 2.49 ppm). Coupling constants *J* are given in Hz and without sign. The mass spectra were obtained on a Finnigan 4021 instrument with direct insertion, 70 eV electron impact ionisation, and an ion source temperature of 200°C. Ions containing isotopes ^{81}Br and ^{37}Cl are not listed.

Preparations according to Scheme 1.

6-Methyl-2-nitro-3-pyridinol (**4a**). Compound (**3a**) was nitrated as described below for **4c** to yield **4a** (86%), identical with a commercial sample.

4-Methyl-2-nitro-3-pyridinol (**4c**). Compound (**3c**)[15] (5.4 g, 49.5 mmol) was dissolved in cold conc. sulfuric acid (65 ml) and cooled with ice–water. To the solution was added fuming nitric acid (2.2 ml, 97 mmol). After 2 h at 20°C (tlc: $CHCl_3$–MeOH, 50:1), the pH was adjusted to 3–4 (40% aq. NaOH), and the precipitate was recrystallized (ethanol) to yield **4c** (4.5 g, 59%), mp 86–88°C (lit.,[30] 83–85°C).

3-Methoxy-6-methyl-2-nitropyridine (**5a**). Compound (**4a**) (3 g, 19.5 mmol) in acetone (30 ml) was refluxed overnight (tlc: $CHCl_3$–MeOH, 100:1) with potassium carbonate (2.9 g, 20.8 mmol) and methyl iodide (2.9 g, 20.2 mmol). The reaction mixture was worked up as described for **5c**, and recrystallization (ethanol) of the evaporation residue yielded **5a** (2.2 g, 67%), mp 87–89°C (lit.,[17] 88–89°C).

3-Methoxy-4-methyl-2-nitropyridine (**5c**). Compound (**4c**) (1.4 g, 9.1 mmol) was heated at 100°C in a Teflon-lined pressure bomb with methyl iodide (2.7 g, 18.8 mmol) and potassium carbonate (2.7 g, 19.3 mmol) in acetone (30 ml) for 8 h (tlc: $CHCl_3$–MeOH, 100:1). The acetone was evaporated and the residue was dissolved in water and extracted with chloroform. Recrystallization (ethanol) of the evaporation residue yielded **5c** (0.73 g, 48%), mp 26–28°C. *Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.0; H, 4.8; N, 16.7. Found: C, 49.6; H, 4.7; N, 16.3. Ms, *m/z* (% rel. int.): 168 (12, M^+), 122 (60), 92 (100). ^{1}H Nmr ($CDCl_3$): δ 2.44 (4-Me, s), 3.93 (O-Me, s), 7.39 (5-H, d, *J* 4.7), 8.13 (6-H, d, *J* 4.7).

6-Methyl-3-methylamino-2-nitropyridine (**6a**). Compound (**5a**) was treated as described below for **6c** to yield **6a** (73%), mp 108–109°C. *Anal.* Calcd for $C_7H_9N_3O_2$: C, 50.3; H, 5.4; N, 25.1. Found: C, 50.4; H, 5.6; N, 25.3. Ms, *m/z* (% rel. int.) 167 (71, M^+), 137 (4), 121 (100). ^{1}H Nmr ($CDCl_3$): δ 2.52 (6-Me, s), 3.03 (N-Me, s), 7.27 (4-H, d, *J* 8.5), 7.35 (5-H, d, *J* 8.5), 7.7 (N-H, br s).

4-Methyl-3-methylamino-2-nitropyridine (**6c**). Compound (**5c**) (0.1 g, 0.59 mmol) was heated at 70°C with 40% aq. methylamine (4 ml, 53 mmol) overnight (tlc: $CHCl_3$–MeOH, 100:1). The mixture was extracted with chloroform, and recrystallization (ethanol–water) of the evaporation residue yielded **6c** (53 mg, 53%), mp 88–89°C. *Anal.* Calcd for $C_7H_9N_3O_2$: C, 50.3; H, 5.4; N, 25.1. Found: C, 50.3; H, 5.3; N, 25.3. Ms, *m/z* (% rel. int.): 167 (18, M^+), 121 (44), 92 (100). ^{1}H Nmr ($CDCl_3$): δ 2.49 (4-Me, s), 3.04 (N-Me, d, *J* 5.8), 7.24 (5-H, d, *J* 3.9), 7.86 (6-H, d, *J* 3.9).

Preparations according to Scheme 2.

3,5-Dibromo-6-methyl-2-methylaminopyridine (**11a**). Pyridine (**11a**) was precipitated by adjusting the pH of the filtrate obtained after filtration of **12a** to 6–7 (40% aq. NaOH). Recrystallization (ethanol) yielded **11a** (8%), mp 46–48°C. *Anal.* Calcd for $C_7H_8N_2Br_2$: C, 30.2; H, 2.9; N, 10.1. Found: C, 29.9; H, 2.9; N, 10.0. Ms, *m/z* (% rel. int.): 280 (100, M^+), 252 (78), 170 (27).^{1}H Nmr ($CDCl_3$): δ 2.48 (6-Me, s), 2.99 (N-Me, d, *J* 4.9), 4.9 (N-H, br s), 7.65 (4-H, s).

3,5-Dibromo-4-methyl-2-methylaminopyridine (**11c**). Pyridine (**11c**) was precipitated by adjusting the pH of the filtrate obtained after filtration of **12c** to 6–7 (40% aq. NaOH). Recrystallization (ethanol) yielded **11c** (15%), mp 88–89°C *Anal.* Calcd for $C_7H_8N_2Br_2$: C, 30.2; H, 2.9; N, 10.1. Found: C, 29.9; H, 2.9; N, 10.1. Ms, *m/z* (% rel. int.): 280 (83, M^+), 252 (100), 170 (50). ^{1}H Nmr ($CDCl_3$): δ 2.49 (4-Me, s), 2.99 (N-Me, d, *J* 4.9), 5.1 (N-H, br s), 8.11 (6-H, s).

5-Bromo-6-methyl-2-methylaminopyridine (**12a**). *Method A.* Reduction of *1-(6-methyl-2-pyridylamino-methyl)benzotriazole*[31] as described[19] afforded **10a**[29] in 78% yield. This was brominated as described below for **12c** to yield **12a** (79%), mp 64–65°C. *Anal.* Calcd for $C_7H_9N_2Br$: C, 42.0; H, 4.5; N, 14.0. Found: C, 42.4; H, 4.5; N, 13.8. Ms, *m/z* (% rel. int.): 200 (97, M^+), 185 (72), 172 (100). ^{1}H Nmr ($CDCl_3$): δ 2.47 (6-Me, s), 2.87 (N-Me, d, *J* 5.3), 4.6 (N-H, br s), 6.11 (3-H, d, *J* 8.7), 7.49 (4-H, d, *J* 8.7).

Method B. Treatment of **9a**[18] with $BtCH_2OH$ and subsequent reduction of the product as described below for **12c** afforded **12a** (67%), identical to that synthesized by method A.

5-Bromo-4-methyl-2-methylaminopyridine (**12c**). *Method A.* Compound (**10c**) (3.4 g, 27.8 mmol) was dissolved in acetic acid (5 ml). The solution was cooled to below 20°C and a solution of bromine (4.5 g, 27.9 mmol) in acetic acid (3 ml) was added dropwise. The reaction mixture was kept at 20°C for 1 h (tlc: $CHCl_3$–MeOH, 10:1). The mixture was poured on ice–water, the pH was adjusted to 3–4 (40% aq. NaOH), and the precipitate was recrystallized (ethanol) to yield **12c** (2.7 g, 48%), mp 81–82°C. *Anal.* Calcd for $C_7H_9N_2Br$: C, 42.0; H, 4.5; N, 14.0. Found: C, 41.7; H, 4.5; N, 13.9. Ms, *m/z* (% rel. int.): 200 (100, M^+), 185 (3), 172 (96). ^{1}H Nmr ($CDCl_3$): δ 2.29 (4-Me, s), 2.88 (N-Me, d, *J* 4.9), 4.5 (N-H, br s), 6.28 (3-H, s), 8.09 (6-H, s).

Method B. Compound (**9c**)[18] (5.5 g, 29.4 mmol) was refluxed with $BtCH_2OH$ (4.9 g, 32.9 mmol) in abs. ethanol (75 ml) for 30 min. The mixture was kept at 4°C overnight (tlc: $CHCl_3$–MeOH, 20:1). The product was treated with $NaBH_4$ as described[19] to yield **12c** in 72% yield, identical to that synthesized by method A.

5-Bromo-6-methyl-2-methylamino-3-nitropyridine (**13a**). Compound (**12a**) was nitrated as described below for **13c** to yield **13a** (78%), mp 137–138°C. *Anal.* Calcd for $C_7H_8N_3O_2Br$: C, 34.3; H, 3.3; N, 17.2. Found: C, 34.1; H, 3.1; N, 16.9. Ms, *m/z* (% rel. int.): 245 (36, M^+), 228 (61), 171 (100). ^{1}H Nmr ($CDCl_3$): δ 2.61 (6-Me, s), 3.15 (N-Me, d, *J* 4.9), 8.2 (N-H, br s), 8.48 (4-H, s).

5-Bromo-4-methyl-2-methylamino-3-nitropyridine (**13c**). Compound (**12c**) (1.4 g, 5.7 mmol) was dissolved in conc. sulfuric acid (6 ml) and cooled with ice–water. To the stirred solution was added fuming nitric acid (0.32 ml, 7.3 mmol). After 1 h at 20°C (tlc: $CHCl_3$–MeOH, 100:1) the reaction mixture was poured on ice-water, the pH was adjusted to 3–4 (25% aq. ammonia), and the precipitate was recrystallized (ethanol) to yield **13c** (1.2 g, 70%), mp 139–140°C. *Anal.* Calcd for $C_7H_8N_3O_2Br$: C, 34.3; H, 3.3; N, 17.2. Found: C, 34.2; H, 3.1; N, 16.9. Ms, *m/z* (% rel. int.): 245 (45, M^+), 228 (56), 171 (100). ^{1}H Nmr ($CDCl_3$): δ 2.54 (4-Me, s), 3.05 (N-Me, d, *J* 4.9), 6.9 (N-H, br s), 8.36 (6-H, s).

6-Methyl-2-methylamino-3-nitropyridine (**14a**). Compound (**13a**) was debrominated to **14a** (36%), mp 106–108°C (lit.,[23] 102°C) as described below for **14c**, Method A.

4-Methyl-2-methylamino-3-nitropyridine (**14c**). *Method A.* A mixture of compound (**13c**) (50 mg, 0.2 mmol), sodium formate (20.4 mg, 0.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.02 mmol) in dimethylformamide (0.4 ml) was kept at 100°C for 7 h under nitrogen atmosphere (tlc: $CHCl_3$–MeOH, 100:1). The cooled mixture was partitioned between chloroform and water. The evaporation residue from the organic phase was recrystallized (ethanol–water) to yield **14c** (11.7 mg, 34%), mp 87–88°C (lit.,[22] 84–85°C).

Method B. 2-Chloro-4-methyl-3-nitropyridine (0.5 g, 2.9 mmol) was refluxed with 40% aq. methylamine (10 ml, 134 mmol) for 30 min (tlc: $CHCl_3$–MeOH, 20:1). After addition of ethanol (3 ml), the mixture was kept at 4°C overnight. The precipitate was recrystallized (ethanol–water) to yield **14c** (0.4 g, 83%), identical to that synthesized by method A.

Preparations according to Scheme 3.

3-Bromo-5-methyl-2-nitropyridine (**16**). A solution of **15**[18] (5 g, 26.7 mmol) in conc. sulfuric acid (20 ml) was added dropwise to a cold mixture of fuming sulfuric acid (65% SO_3, 65 ml) and 30% hydrogen peroxide (30 ml, 0.3 mol) with external cooling (–5°C). The reaction mixture was kept at 8°C overnight and at 20°C for another 48 h (tlc: $CHCl_3$–MeOH, 20:1). The mixture, whose colour changed from green-yellowish to orange, was poured on ice–water, and the precipitate was recrystallized (ethanol–water) to yield **16** (2.2 g, 40%), mp 61–62°C. *Anal.* Calcd for $C_6H_5N_2O_2Br$: C, 33.3; H, 2.3; N, 13.0. Found: C, 33.1; H, 2.2; N, 12.8. Ms, *m/z* (% rel. int.): 216 (16, M^+), 186 (2), 170 (100). ^{1}H Nmr ($CDCl_3$): δ 2.46 (5-Me, s), 7.96 (4-H, dd, *J* 1.9 and 0.7), 8.27 (6-H, dd, *J* 1.9 and 0.7).

5-Methyl-3-methylamino-2-nitropyridine (**6b**). Compound (**16**) (3.1 g, 14.3 mmol) was heated at 70°C with 40% aq. methylamine (50 ml, 0.6 mol) for 4 h (tlc: $CHCl_3$–MeOH, 50:1). Ethanol (10 ml) was added, and the mixture was kept at 8°C overnight. The precipitate was recrystallized (water–ethanol) to yield **6b** (1.8 g, 73%), mp 125–126°C. *Anal.* Calcd for $C_7H_9N_3O_2$: C, 50.3; H, 5.4; N, 25.1. Found: C, 50.0; H, 5.4; N, 24.8. Ms, *m/z* (% rel. int.): 167 (51, M^+), 121 (63), 92 (100). ^{1}H Nmr ($CDCl_3$): δ 2.40 (5-Me, s), 3.02 (N-Me, d, *J* 5.1), 7.09 (4-H, d, *J* 1.7), 7.73 (6-H, d, *J* 1.7), 7.8 (N-H, br s).

5-Methyl-2-methylamino-3-nitropyridine (**14b**). Compound (**10b**)[32] (5.6 g, 45.8 mmol) was dissolved in conc. sulfuric acid (60 ml) and cooled in an ice–water bath. To the stirred solution was added fuming nitric acid (2.3 ml, 52.5 mmol). After 1 h at 20°C (tlc: $CHCl_3$–MeOH, 50:1), the reaction mixture was poured on ice, the pH was adjusted to 4–5 (25% aq. ammonia), and the precipitate was recrystallized (ethanol) to yield **14b** (4.9 g, 64%), mp 124–125°C (lit.,[24] 124–125°C).

Preparations according to Scheme 4.

General procedure for the preparation of compounds (**1a**, **1b**, and **2a–c**) (cf. reference 25).

A mixture of the appropriate 2-chloroimidazopyridine (0.1 g, 0.55 mmol), obtained as described below, and 25% aq. ammonia (6 ml, 80 mmol) was heated at 100°C in a Teflon-lined pressure bomb overnight. After cooling, the mixture was evaporated onto silica gel and purified by fc. The evaporation residue was crystallized (toluene–1-butanol) to yield the desired 2-aminoimidazopyridine.

*2-Amino-1,5-dimethylimidazo[4,5-*b*]pyridine* (**1a**) (fc: $CHCl_3$–MeOH; 3:1). Yield: 60%, mp 259–260°C. *Anal.* Calcd for $C_8H_{10}N_4$: C, 59.2; H, 6.2; N, 34.6. Found: C, 58.8; H, 6.4; N, 34.3. Ms, *m/z* (% rel. int.): 162 (100, M^+), 161 (65), 147 (20), 134 (15). ^{1}H Nmr (Me_2SO-d_6): δ 2.39 (5-Me, s), 3.46 (N-Me, s), 6.70 (6-H, d, *J* 7.8), 6.8 (NH_2, br s), 7.32 (7-H, d, *J* 7.8).

*2-Amino-1,6-dimethylimidazo[4,5-*b*]pyridine* (**1b**)[6] (fc: $CHCl_3$–MeOH, 7:1). Yield: 65%, mp 288–290°C. ^{1}H Nmr (Me_2SO-d_6): δ 2.28 (6-Me, s), 3.45 (N-Me, s), 6.7 (NH_2, br s), 7.24 (7-H, m), 7.77 (5-H, m).

2-Amino-1,7-dimethylimidazo[4,5-b]pyridine (**1c**). Compound (**6c**) was reduced as described below for compounds (**18**) and (**21**) and treated with cyanogen bromide in a Teflon-lined pressure bomb as described for **PhIP**[4] and **1b**.[6] Yield: 8 %, mp 270–272°C. *Anal.* Calcd for $C_8H_{10}N_4$: C, 59.2; H, 6.2; N, 34.6. Found: C, 59.0; H, 6.1; N, 34.4. Ms, *m/z* (% rel. int.): 162 (100, M^+), 161 (87), 147 (14), 134 (19). ^{1}H Nmr (CD_3OD): δ 2.69 (7-Me, s), 3.80 (N-Me, s), 7.86 (5-H, d, *J* 5.5), 6.84 (6-H, m).

2-Amino-3,5-dimethylimidazo[4,5-b]pyridine (**2a**) (fc: $CHCl_3$–MeOH, 9:1). Yield: 40%, mp 205–206°C. *Anal.* Calcd for $C_8H_{10}N_4$: C, 59.2; H, 6.2; N, 34.6. Found: C, 59.1; H, 6.2; N, 34.4. Ms, *m/z* (% rel. int.): 162 (100, M^+), 161 (68), 147 (9), 134 (26). ^{1}H Nmr ($CDCl_3$): δ 2.58 (5-Me, s), 3.64 (N-Me, s), 4.6 (NH_2, br s), 6.91 (6-H, d, *J* 7.9), 7.51 (7-H, d, *J* 7.9).

2-Amino-3,6-dimethylimidazo[4,5-b]pyridine (**2b**) (fc: $CHCl_3$–MeOH, 9:1). Yield: 65%, mp 184–185°C. *Anal.* Calcd for $C_8H_{10}N_4$: C, 59.2; H, 6.2; N, 34.6. Found: C, 59.4; H, 6.3; N, 35.0. Ms, *m/z* (% rel. int.): 162 (100, M^+), 161 (66), 147 (5), 134 (25). ^{1}H Nmr ($CDCl_3$): δ 2.39 (6-Me, s), 3.62 (N-Me, s), 4.9 (NH_2, br s), 7.43 (7-H, m), 7.89 (5-H, m).

2-Amino-3,7-dimethylimidazo[4,5-b]pyridine (**2c**) (fc: $CHCl_3$–MeOH, 9:1). Yield: 35%, mp 227°C (subl.). *Anal.* Calcd for $C_8H_{10}N_4$: C, 59.2; H, 6.2; N, 34.6. Found: C, 58.9; H, 6.2; N, 34.3. Ms, *m/z* (% rel. int.): 162 (100, M^+), 161 (66), 147 (5), 134 (25). ^{1}H Nmr (Me_2SO-d_6): δ 2.34 (7-Me, s), 3.47 (N-Me, s), 6.7 (NH_2, br s), 6.77 (6-H, d, *J* 5.0), 7.72 (5-H, d, *J* 5.0).

General procedure for the preparation of compounds (**18**) and (**21**) (cf. reference 25).
Raney nickel (1/2 teaspoonful) was added to a solution of the appropriate (methylamino)nitropicoline (0.3 g, 1.8 mmol) in methanol (5 ml). The mixture was hydrogenated under ambient conditions with vigorous stirring. After *ca.* 1 h, the completion of the reaction was indicated by tlc (MeCN). The catalyst was filtered off quickly by suction through Celite under a nitrogen atmosphere. Urea (0.4 g, 6.6 mmol) was added immediately to the filtrate containing the crude diamines (**17**) and (**20**). The solvent was evaporated and the reaction flask containing the residue was heated in an oil–bath at 135°C for 6 h (tlc: MeCN). The reaction mixture was then boiled with ethanol (75 ml) for 3 min and filtered hot by suction through Celite. The filtrate was evaporated onto silica gel. Fc (EtOAc–MeOH, 20:1) and recrystallization (ethanol–water) yielded the desired imidazopyridin-2-one.

1,5-Dimethylimidazo[4,5-b]pyridin-2-one (**18a**). Yield 60%, mp >300°C. *Anal.* Calcd for $C_8H_9N_3O$: C, 58.9; H, 5.6; N, 25.8. Found: C, 58.6; H, 5.6; N, 25.9. Ms, *m/z* (% rel. int.): 163 (100, M^+), 162 (34), 148 (9), 134 (29). ^{1}H Nmr (Me_2SO-d_6): δ 2.38 (5-Me, s), 3.25 (N-Me, s), 6.85 (6-H, dq, *J* 7.9 and 0.5), 7.28 (7-H, d, *J* 7.9), 11.3 (N-H, br s).

1,6-Dimethylimidazo[4,5-b]pyridin-2-one (**18b**). Yield 50%, mp 225°C (decomp.). *Anal.* Calcd for $C_8H_9N_3O$: C, 58.9; H, 5.6; N, 25.8. Found: C, 58.7; H, 5.6; N, 25.6. Ms, *m/z* (% rel. int.): 163 (100, M^+), 162 (40), 148 (4), 135 (6), 134 (58). ^{1}H Nmr ($CDCl_3$): δ 2.37 (6-Me, s), 3.40 (N-Me, s), 7.01 (7-H, m), 7.90 (5-H, m), 10.6 (N-H, br s).

3,5-Dimethylimidazo[4,5-b]pyridin-2-one (**21a**). Yield 40%, mp 199–200°C. *Anal.* Calcd for $C_8H_9N_3O$: C, 58.9; H, 5.6; N, 25.8. Found: C, 58.9; H, 5.6; N, 25.9. Ms, *m/z* (% rel. int.): 163 (100, M^+), 162 (23), 148 (5), 134 (71). ^1H Nmr ($CDCl_3$): δ 2.54 (5-Me, s), 3.50 (N-Me, s), 6.84 (6-H, d, *J* 7.8), 7.17 (7-H, d, *J* 7.8), 10.2 (N-H, br s).

3,6-Dimethylimidazo[4,5-b]pyridin-2-one (**21b**). Yield 46%, mp 182–183°C. *Anal.* Calcd for $C_8H_9N_3O$: C, 58.9; H, 5.6; N, 25.8. Found: C, 58.5; H, 5.5; N, 25.6. Ms, *m/z* (% rel. int.): 163 (100, M^+), 162 (32), 148 (3), 134 (70). ^1H Nmr ($CDCl_3$): δ 2.35 (6-Me, s), 3.50 (N-Me, s), 7.17 (7-H, d, *J* 1.0), 7.89 (5-H, d, *J* 1.0), 9.5 (N-H, br s).

3,7-Dimethylimidazo[4,5-b]pyridin-2-one (**21c**). Yield 50%, mp 256°C (decomp.). *Anal.* Calcd for $C_8H_9N_3O$: C, 58.9; H, 5.6; N, 25.8. Found: C, 58.0; H, 5.5; N, 25.2. Ms, *m/z* (% rel. int.): 163 (100, M^+), 162 (17), 148 (1) 134 (73). ^1H Nmr ($CDCl_3$): δ 2.42 (7-Me, s), 3.51 (N-Me, s), 6.84 (6-H, d, *J* 5.4), 7.97 (5-H, d, *J* 5.4), 10.3 (N-H, br s).

General procedure for the preparation of compounds (**19**) and (**22**) (cf. reference 25).
The appropriate imidazopyridin-2-one (0.1 g, 0.6 mmol) and phosphorus pentachloride (0.13 g, 0.6 mmol) was refluxed in phosphorus oxychloride (5 ml) for 2–5 h (tlc: MeCN). The residue obtained after distillation under reduced pressure was treated with ice. The mixture was then basified with 40% sodium hydroxide and extracted with ether. Fc and recrystallization (petroleum–$CHCl_3$) yielded the desired 2-chloroimidazopyridine.

2-Chloro-1,5-dimethylimidazo[4,5-b]pyridine (**19a**) (fc: $CHCl_3$–MeOH, 10:1). Yield: 60%, mp 188–189°C. *Anal.* Calcd for $C_8H_9N_3Cl$: C, 53.0; H, 4.5; N, 23.2. Found: C, 52.7; H, 4.3; N, 22.8. Ms, *m/z* (% rel. int.): 181 (100, M^+), 180 (11), 166 (47), 146 (7). ^1H Nmr ($CDCl_3$): δ 2.67 (5-Me, s), 3.79 (N-Me, s), 7.10 (6-H, d, *J* 8.2), 7.50 (7-H, d, *J* 8.2).

2-Chloro-1,6-dimethylimidazo[4,5-b]pyridine (**19b**) (fc: $CHCl_3$–MeOH, 30:1). Yield: 36%, mp 186–187°C. *Anal.* Calcd for $C_8H_9N_3Cl$: C, 53.0; H, 4.5; N, 23.2. Found: C, 52.8; H, 4.4; N, 23.0. Ms, *m/z* (% rel. int.): 181 (100, M^+), 180 (38), 166 (32), 146 (8). ^1H Nmr ($CDCl_3$): δ 2.49 (6-Me, m), 3.79 (N-Me, s), 7.42 (7-H, m), 8.38 (5-H, m).

2-Chloro-3,5-dimethylimidazo[4,5-b]pyridine (**22a**) (fc: $CHCl_3$). Yield: 35%, mp 103–104°C. *Anal.* Calcd for $C_8H_9N_3Cl$: C, 53.0; H, 4.5; N, 23.2. Found: C, 52.6; H, 4.3; N, 22.8. Ms, *m/z* (% rel. int.): 181 (100, M^+), 180 (60), 166 (13), 146 (46). ^1H Nmr ($CDCl_3$): δ 2.65 (5-Me, s), 3.84 (N-Me, s), 7.09 (6-H, d, *J* 8.1), 7.82 (7-H, d, *J* 8.1).

2-Chloro-3,6-dimethylimidazo[4,5-b]pyridine (**22b**) (fc: Petroleum–EtOAc, 3:1). Yield: 68%, mp 80–81 °C. *Anal.* Calcd for $C_8H_9N_3Cl$: C, 53.0; H, 4.5; N, 23.2. Found: C, 52.8; H, 4.5; N, 22.9. Ms, *m/z* (% rel. int.): 181 (100, M^+), 180 (87), 166 (17), 146 (65). ^1H Nmr ($CDCl_3$): δ 2.46 (6-Me, s), 3.84 (N-Me, s), 7.74 (7-H, m), 8.20 (5-H, m).

2-Chloro-3,7-dimethylimidazo[4,5-b]pyridine (**22c**) (fc: $CHCl_3$–MeOH, 150:1). Yield: 70%, mp 56–57°C. *Anal.* Calcd for $C_8H_9N_3Cl$: C, 53.0; H, 4.5; N, 23.2. Found: C, 52.8; H, 4.2; N, 22.9. Ms, *m/z* (% rel. int.): 181 (100, M^+), 180 (50), 166 (14), 146 (94). ^1H Nmr ($CDCl_3$): δ 2.63 (7-Me, d, *J* 0.6), 3.85 (N-Me, s), 7.04 (6-H, dd, *J* 4.9 and 0.6), 8.22 (5-H, d, *J* 4.9).

Preparations according to Scheme 5.

6-Methyl-2-methylamino-3-pyridinecarboxylic acid (**24**). A mixture of the monohydrate of **23** (1 g, 5.3 mmol) and 33% ethanolic methylamine (10 ml, 80 mmol) was heated at 120°C in a Teflon-lined pressure bomb for 6 h (tlc: $CHCl_3$–MeOH, 3:1). The mixture was evaporated, the residue was dissolved in water (15 ml) and the pH was adjusted to 4.5 (AcOH). Extraction with 1-butanol followed by fc ($CHCl_3$–MeOH, 3:1) of the evaporation residue gave crude **24**. This was dissolved in $CHCl_3$ with a minimum of ethanol and filtered. The clear solution was brought to boil and petroleum was added until precipitation started. Cooling yielded pure **24** (0.5 g, 60%), mp 190–191°C. *Anal.* Calcd for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1; N, 16.9. Found: C, 58.0; H, 6.3; N, 16.9. Ms, *m/z* (% rel. int.): 166 (54, M^+), 147 (7), 138 (7), 93 (100). ^1H Nmr (CD_3OD) : δ 2.44 (6-Me, s), 3.06 (N-Me, s), 6.50 (5-H, d, *J* 7.8), 8.14 (4-H, d, *J* 7.8).

3,5-Dimethylimidazo[4,5-b]pyridin-2-one (**21a**). A mixture of compound (**24**) (250 mg, 1.5 mmol), diphenyl phosphorazidate (540 mg, 1.9 mmol) and triethylamine (0.43 ml, 3 mmol) in dry 1,4-dioxane (10 ml) was refluxed under nitrogen atmosphere overnight (tlc: EtOAc–MeOH, 20:1). The mixture was evaporated and the residue was extracted with chloroform after addition of water (25 ml). Fc (EtOAc–MeOH, 30:1) followed by recrystallization ($CHCl_3$–petroleum) yielded **21a** (160 mg, 65%), identical to that described under **18b**.

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32. Obtained as colourless oil after methylation of **7b** as described[19] (79% yield). Ms, *m/z* (% rel. int.): 122 (81, M^+), 121 (46), 107 (4), 93 (100). ^{1}H Nmr ($CDCl_3$): δ 2.15 (5-Me, s), 2.87 (N-Me, d, *J* 3.4), 4.5 (N-H br s), 6.30 (4-H, d, *J* 8.5), 7.23 (3-H, dd, *J* 6.0 and 0.8), 7.89 (6-H, d, *J* 0.8).

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