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

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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. 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. 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. 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. 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. Its structure was later confirmed by comparison with a synthetic sample. As part of a programme dealing with the synthesis of the HA, with studies on their binding to biomolecules as well as their structure–activity relationships, we now wish to report the synthesis of the six dimethyl 2-aminoimidazopyridines (1) and (2).
RESULTS AND DISCUSSION

The mutagenicity of the HA shows great variation depending on the number and positions of the methyl groups.\textsuperscript{10,11} Therefore, in contrast to previously reported syntheses of HA,\textsuperscript{12} we employed synthetic routes that yield the desired DMIP isomers free from any methyl isomers. Substituted pyridines are synthesized from acyclic synthons\textsuperscript{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)nitropyrithenes,\textsuperscript{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](image)

Pyridines (3a) and (3c)\textsuperscript{15} (Scheme 1) were readily nitrated at room temperature to yield 4a\textsuperscript{16} and 4c.\textsuperscript{16} Subsequent methylation to 5a\textsuperscript{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)\textsuperscript{18} in 5% yield and the desired 9a\textsuperscript{18} in 78% yield. Monomethylation of 9a by treatment with 1-hydroxymethylbenzotriazole (BtCH\textsubscript{2}OH) followed by NaBH\textsubscript{4} reduction\textsuperscript{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\textsuperscript{20} to the key intermediate (14a).\textsuperscript{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.\textsuperscript{21}
In a similar manner, 9c\textsuperscript{18} was methylated to 12c, which could also be obtained by bromination of 10c\textsuperscript{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\textsuperscript{20} gave the desired 14c\textsuperscript{22}.

![Scheme 2](image)/i. Br\textsubscript{2}, AcOH, 20°C, 1 h; ii. a) BtCH\textsubscript{2}OH, EtOH, 20°C, 5 h; b) NaBH\textsubscript{4}, THF, reflux, 8 h; iii. fuming HNO\textsubscript{3}, conc. H\textsubscript{2}SO\textsubscript{4}, 0–20°C, 1 h; iv. (PPh\textsubscript{3})\textsubscript{2}Pd, HCO\textsubscript{2}Na, 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\textsuperscript{9}.

Bromination of commercially available 7b to 15\textsuperscript{18} (Scheme 3) followed by oxidation of 15 with H\textsubscript{2}SO\textsubscript{5} afforded 16 in 30% overall yield from 7b. Treatment of 16 with methylamine afforded the desired 6b in 73% yield. The isomeric 14b\textsuperscript{24} was obtained by nitration of 10b which in turn was obtained by methylation\textsuperscript{19} 7b. The overall isolated yield of 14b from 7b was 50%. Compounds (14a),\textsuperscript{23} (14b)\textsuperscript{24} and (14c)\textsuperscript{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.\textsuperscript{14}

![Scheme 3](image)/i. Br\textsubscript{2}, AcOH, 20°C, 1 h; ii. fuming H\textsubscript{2}SO\textsubscript{5}, 30% H\textsubscript{2}O\textsubscript{2}, 8–20°C, 60 h; iii. 40% aq. MeNH\textsubscript{2}, 70°C, 4 h; iv. a) BtCH\textsubscript{2}OH, EtOH, 20°C, 5 h; b) NaBH\textsubscript{4}, THF, reflux, 8 h; v. fuming HNO\textsubscript{3}, conc. H\textsubscript{2}SO\textsubscript{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,\textsuperscript{7} -isoquinolines\textsuperscript{7} and -quinoxalines,\textsuperscript{8} the straightforward ring-closure of ortho-diaminopyridines with cyanogen bromide to imidazopyridines is a low-yield reaction,\textsuperscript{4,9} yielding several products. PhIP\textsuperscript{4} and 1,6-DMIP (1b)\textsuperscript{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\textsubscript{5} in POCl\textsubscript{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.\textsuperscript{25}

![Scheme 4 Reagents and conditions:](image)

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\textsubscript{2})P(O)N\textsubscript{3}]\textsuperscript{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.\textsuperscript{27}
EXPERIMENTAL

1-Hydroxymethylbenzotriazole (BtCH₂OH)²⁸ and compounds (3c,¹⁵ 9a,¹⁸ 9c,¹⁸ 10a,²⁹ 10e,¹⁹ and 15¹⁸) 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 F₂₅₄ (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 VX400 spectrometer at 25°C, and referenced to the solvent (CHCl₃ 7.26, MeOD 3.31 or Me₂SO 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 ⁸¹Br and ³⁷Cl are not listed.

Preparations according to Scheme 1.

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

4-Methyl-2-nitro-3-pyridin-4-one (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: CHCl₃–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: CHCl₃–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: CHCl₃–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 262–28°C. Anal. Calcd for C₇H₈N₂O₃: 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). ¹H Nmr (CDCl₃): δ 2.44 (4-Me, s), 3.93 (3-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 C₇H₉N₃O₂: 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). ¹H Nmr (CDCl₃): δ 2.52 (6-Me, s), 3.03 (3-Me, s), 7.27 (4-H, d, J 8.5), 7.35 (5-H, d, J 8.5), 7.7 (N-H, brs).

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: CHCl₃–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 C₇H₉N₃O₂: 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 (M⁺), 92 (100). ¹H Nmr (CDCl₃): δ 2.49 (4-Me, s), 3.04 (3-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 C₇H₉N₂Br₂: 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). ¹H Nmr (CDCl₃): 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 C₇H₉N₂Br₂: 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). ¹H Nmr (CDCl₃): 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 C₇H₉N₂Br: 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). ¹H Nmr (CDCl₃): 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 BiCH₂OH 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: CHCl₃–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 C₇H₅N₂Br: 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). **¹H Nmr (CDCl₃):** 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) (5.5 g, 29.4 mmol) was refluxed with BtCH₂OH (4.9 g, 32.9 mmol) in abs. ethanol (75 ml) for 30 min. The mixture was kept at 4°C overnight (tlc: CHCl₃–MeOH, 20:1). The product was treated with NaBH₄ as described to yield 12c in 72% yield, identical to that synthesized by method A.

6-Methyl-2-methylamino-3-nitropyridine (14a). Compound (13a) was debrominated to 14a (36%), mp 106–108°C (lit., 23 84–85°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: CHCl₃–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: CHCl₃–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\(_7\)H\(_5\)N\(_2\)O\(_2\)Br: 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\(_3\)): \(\delta\) 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\(_7\)H\(_9\)N\(_3\)O\(_2\): 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\(_3\)): \(\delta\) 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-nitopyridine (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\(_8\)H\(_{10}\)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\(_2\)SO-d\(_6\)): \(\delta\) 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\(_2\)SO-d\(_6\)): \(\delta\) 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 and 1b.  

Yield: 8%, mp 270–272°C. Anal. Calcd for C_{8}H_{14}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_{3}OD): 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_{8}H_{14}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 (66), 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_{8}H_{14}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-dimethylimidazol[4,5-b]pyridine (2c) (fc: CHCl_{3}–MeOH, 9:1). Yield: 35%, mp 227°C (subl.). Anal. Calcd for C_{8}H_{14}N_{4}: C, 59.2; H, 6.2; N, 34.6. Found: C, 59.0; H, 6.2; N, 34.3. Ms, m/z (% rel. int.): 162 (100, M^+), 161 (66), 147 (5), 134 (25).  

^1^H Nmr (CD_{3}SO-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 7.9), 7.72 (5-H, d, J 7.9).

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_{8}H_{9}N_{3}O: 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_{2}SO-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_{8}H_{9}N_{3}O: 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 C₈H₉N₃O: 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 (CDCl₃): 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 C₈H₉N₃O: 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 (CDCl₃): 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 C₈H₉N₃O: 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 (CDCl₃): 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. Fe and recrystallization (petroleum–CHCl₃) yielded the desired 2-chloroimidazopyridine.

2-Chloro-1,5-dimethylimidazo[4,5-b]pyridine (19a) (fc: CHCl₃–MeOH, 10:1). Yield: 60%, mp 188–189°C. Anal. Calcd for C₈H₇N₃Cl: 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 (CDCl₃): 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: CHCl₃–MeOH, 30:1). Yield: 36%, mp 186–187°C. Anal. Calcd for C₈H₇N₃Cl: 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 (CDCl₃): δ 2.49 (5-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: CHCl₃). Yield: 35%, mp 103–104°C. Anal. Calcd for C₈H₇N₃Cl: 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 (CDCl₃): 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 C₈H₇N₃Cl: 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 (CDCl₃): δ 2.46 (5-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: CHCl₃–MeOH, 150:1). Yield: 70%, mp 56–57°C. Anal. Calcd for C₉H₉N₃Cl: 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 (CDCl₃): 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: CHCl₃–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 (CHCl₃–MeOH, 3:1) of the evaporation residue gave crude 24. This was dissolved in CHCl₃ 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 C₉H₁₀N₂O₂: 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 (CD₃OD): 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 (CHCl₃–petroleum) yielded 21a (160 mg, 65%), identical to that described under 18b.

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27. K. Wakabayashi, National Cancer Center, Tokyo (personal communication).
29. Obtained as colourless oil after methylation of 7a as described19 (77% yield). Ms, m/z (% rel. int.): 122 (88, M+), 121 (48), 107 (3), 93 (100). 1H NMR (CDCl3): δ 2.33 (6-Me, s), 2.83 (N-Me, d, J 3.1), 4.9 (N-H br s), 6.14 (3-H, d, J 8.3), 6.40 (5-H, d, J 7.3), 7.31 (4-H, m).
32. Obtained as colourless oil after methylation of 7b as described19 (79% yield). Ms, m/z (% rel. int.): 122 (81, M+), 121 (46), 107 (4), 93 (100). 1H NMR (CDCl3): 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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