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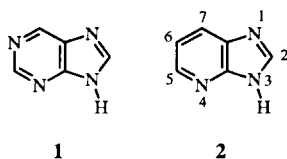
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The tetrakis(triphenylphosphine)palladium(0)-catalyzed coupling of benzenboronic acid with 2-chloro, 6-bromo and 6-bromo-2-chloro derivatives of 1- and 3-methylimidazo[4,5-*b*]pyridines to novel 2-phenyl-, 6-phenyl- and 2,6-diphenylimidazo[4,5-*b*]pyridines is described. The phenylation of imidazo[4,5-*b*]pyridines containing labile hydrogens was not successful.

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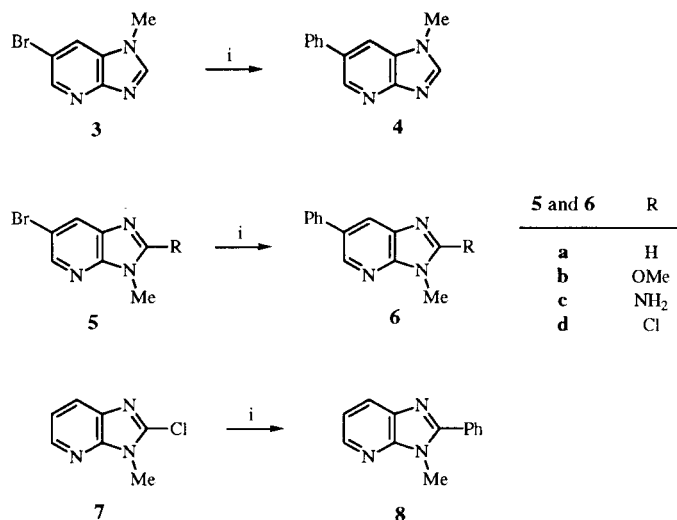
Introduction.

Analogues of purine (**1**), such as derivatives of imidazo[4,5-*b*]pyridine (**2**), have caused considerable attention because of their significant bioactivities [1]. Like purine and other compounds with unsubstituted imidazole nitrogens, **2** is an inseparable mixture of two tautomers. In general, this is well understood, and only one form is shown. Here, only the 3*H*-form of **2** and relevant derivatives are displayed. On the other hand, 1-alkyl derivatives of **2** may be readily separated from their 3-alkyl isomers. Isomers like **3** and **5a** (Scheme 1) must therefore be clearly distinguished. Certain amines related to **2** have been identified as potent environmental mutagens [2]. Recently, within a program aiming at syntheses of biologically active imidazoazaarenes [3], we employed the palladium(0)-catalyzed arylation of bromopyridines with areneneboronic acids [4].



Applications of transition metals in organic synthesis have assumed enormous proportions in the past few years [5]. Biaryls, higher oligomers and polymers, including heteroaryls, have been successfully formed by, *e.g.*, Pd- or Ni-catalyzed coupling reactions between (i) aryl halides, (ii) organometallics (Sn, Zn, *etc.*) and aryl halides, and (iii) organometallics and phenol derivatives (aryl triflates, methyl ethers, *O*-carbamates, *etc.*) [6]. The use of areneboronic acids and aryl halides is one of the preferred methods, since boronic acids are generally stable, tolerate a number of functional groups, and can be easily modified. Further, they are less expensive and less toxic than organometallic reagents. A variety of conditions, including different catalysts, bases, solvents and use of additives have been employed [6,7]. In the present paper, we report the palladium(0)-catalyzed coupling of benzenboronic acid with some derivatives of **2**.

Scheme 1

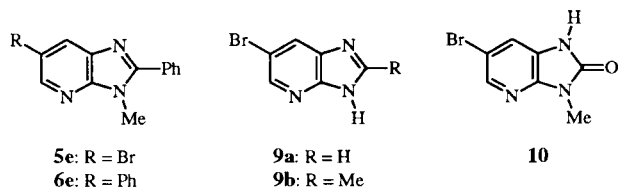


i: PhB(OH)₂, Pd(PPh₃)₄, 2 M Na₂CO₃, DME, reflux (see Table 1)

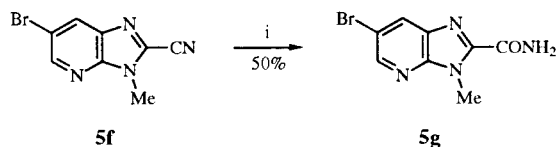
Results and Discussion.

As yet, there is no activity scale for the wide range of palladium catalysts available. Therefore, and in view of our previous experience from the Pd(0)-mediated arylation of pyridines [4], we chose to apply the Suzuki coupling methodology [8], with 3 mole percent tetrakis(triphenylphosphine)palladium(0) as catalyst and aqueous sodium carbonate as base. 1,2-Dimethoxyethane (DME) was used as solvent, as proposed by Gronowitz *et al.* [9]. The 1-methyl substituted **3** and the 3-methyl derivatives **5a** and **5b** all gave the respective 6-phenylated products **4**, **6a** and **6b** in good yields (Scheme 1 and Table 1). The yield of **6c** from **5c** was only 20%. However, the use of labelled boronic acid in the last step leads to labelled **6c** and analogues often required for bioassays and analytical studies [10]. The 6-bromo-2-chloro derivative **5d** afforded the 2,6-diphenyl derivative **6e** in 70% yield, if an excess of benzenboronic acid was used. If not, **5e**, **6d** and **6e** were obtained in 14, 33 and 23% yield, respectively. Conversion of the 2-chloro derivative **7** into compound **8** proceeded in 65% yield. The derivatives **9a** and **9b** with-

out an *N*-methyl group did not react at all. Likewise, the urea **10** did not enter the coupling reaction. Under the same conditions, nitrile **5f** was hydrolyzed to amide **5g**, but the bromine did not react (Scheme 2). These results are in agreement with reported unsuccessful phenylation attempts of chloronicotinamide and other substrates containing labile hydrogens, under similar conditions [11].



Scheme 2



i: PhB(OH)₂, Pd(PPh₃)₄, 2 M Na₂CO₃, DME, reflux

Table 1

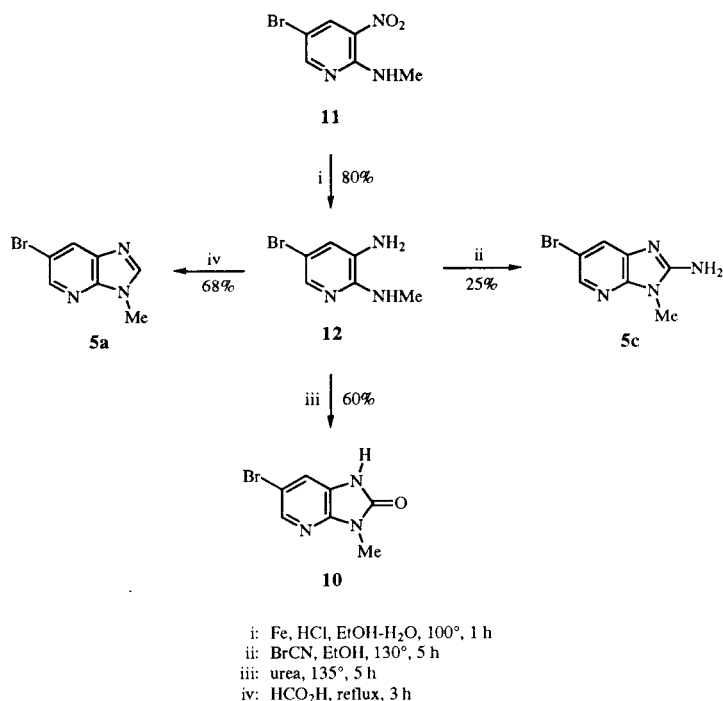
Reactions of Haloimidazo[4,5-*b*]pyridines (0.47 mmole) with PhB(OH)₂ (0.5 mmole), Pd(PPh₃)₄ (14 μmoles) and 2 M Na₂CO₃ (1.1 mmoles) in DME

Halide	Product	Reaction Time (h)	Isolated Yield (%)
3	4	2	76
5a	6a	3	70
5b	6b	5	66
5c	6c	4	20
5d	5e	5	14 [b]
5d	6d	5	33 [b]
5d	6e	5	23 [b]
5d [a]	6e	5	70
5f	5g	17	50
7	8	17	65

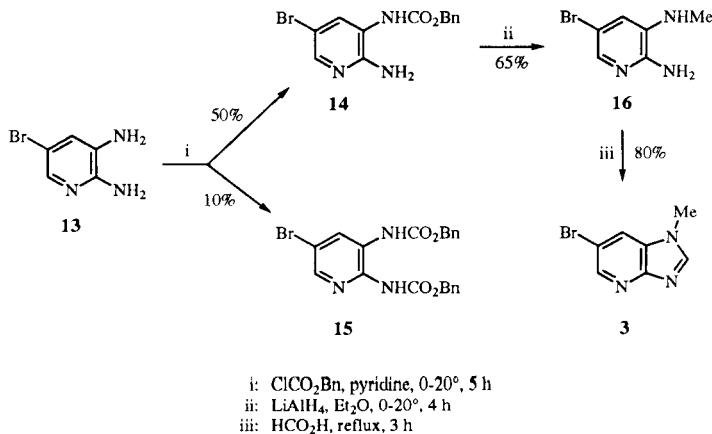
[a] 1.0 Mmole of PhB(OH)₂. [b] Yield is based on the ¹H nmr spectra.

Most of the 6-bromo derivatives **3**, **5** and **10** used as starting materials, had to be synthesized for the first time. The synthetic routes to these compounds are outlined in Schemes 3-5. Compounds **9a** and **9b** were prepared according to literature procedures [12]. Compound **5a** has been claimed to be prepared by treatment of **9a** with iodomethane [13]. No spectral data were given, but the reported melting point was in agreement with that of our 1-methyl isomer **3**, unequivocally prepared *via* **16** (Scheme 4), and not with that of **5a** prepared *via* **12** (Scheme 3). The intermediate **16** was prepared by a procedure for selective methylation of 2,3-diaminopyridine [14].

Scheme 3

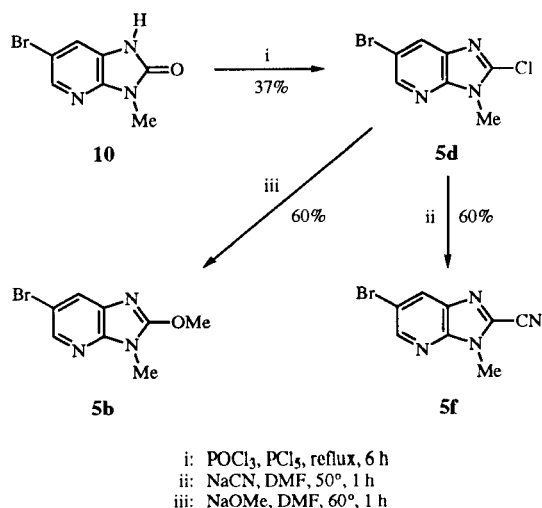


Scheme 4



This is the first report on the transition metal-mediated phenylation of imidazopyridines. In addition to other heteroaryl halides [7], 2-halo-, 6-halo- and 2,6-dihaloimidazo[4,5-*b*]pyridines can be efficiently coupled with benzeneboronic acid to yield the corresponding 2-phenyl, 6-phenyl, and 2,6-diphenyl derivatives, using mild reaction conditions and a commercially available palladium(0) catalyst. Under these conditions, the synthetic utility of the method is restricted to derivatives where one of the imidazole ring nitrogens is substituted. The method should prove useful, since there are very few general procedures for the introduction of aryl substituents into heteroaromatic compounds.

Scheme 5



EXPERIMENTAL

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° unless otherwise stated, and referenced to the solvent (deuteriochloroform 7.26 or dimethyl sulfoxide-*d*₆ 2.49 ppm). The coupling constants *J* are given in Hz and without sign. The mass spectra (70 eV) were obtained on a JMS-SX/SX 102A instrument with electron impact ionization. Perfluorokerosene was used as standard for the high resolution mass spectra (hrms). Unless otherwise stated, ions containing minor isotopes are not listed. Flash liquid chromatography (fc) was performed on silica gel (230-400 mesh ASTM, Merck). All reactions and purifications were monitored either by tlc (uv detection) on aluminium sheets coated with silica gel 60 F₂₅₄ (Merck) or by ¹H nmr spectroscopy. Petrol refers to petroleum ether boiling at 40-60°. Solvent mixtures are defined by volume ratios (v/v).

Starting Materials.

Compound **12** was prepared from **11** [4] by reduction with iron and hydrochloric acid [15]. Compound **13** was prepared from 2-amino-5-bromopyridine by nitration and subsequent reduction [15].

6-Bromo-1-methylimidazo[4,5-*b*]pyridine (**3**).

This compound was prepared from compound **16** (2.0 g, 9.9 mmol) and formic acid, by the procedure described below for compound **5a**. Recrystallization (chloroform-petrol) yielded **3** (1.7 g, 80%), mp 139-140°; ¹H nmr (deuteriochloroform): δ 3.87 (s, 3H, Me), 7.90 (d, *J* = 2.0, 1H, H-7), 8.09 (s, 1H, H-2), 8.62 (d, *J* = 2.0, 1H, H-5); hrms: Calcd. for C₇H₆N₃Br: 210.9745. Found: 210.9762.

6-Bromo-3-methylimidazo[4,5-*b*]pyridine (**5a**).

Diamine **12** (2.0 g, 9.9 mmol) was refluxed in formic acid (10 ml) for 3 hours. The excess formic acid was then distilled off and ice-water added. The precipitated product was filtered off and recrystallized from aqueous methanol to yield **5a** (1.4 g,

68%), mp 118-119°; ¹H nmr (deuteriochloroform): δ 3.91 (s, 3H, Me), 8.03 (s, 1H, H-2), 8.21 (d, *J* = 2.0, 1H, H-7), 8.46 (d, *J* = 2.0, 1H, H-5); hrms: Calcd. for C₇H₆BrN₃: 210.9745. Found: 210.9744.

6-Bromo-2-methoxy-3-methylimidazo[4,5-*b*]pyridine (**5b**).

Sodium methoxide (0.125 g, 2.3 mmol) was added to a solution of compound **5d** (0.5 g, 2.0 mmol) dissolved in dry *N,N*-dimethylformamide (10 ml). The mixture was heated at 60° under nitrogen atmosphere for 5 hours, then poured into ice-water and extracted with diethyl ether. The extract was washed with water, brine and dried over sodium sulfate. Evaporation of the filtrate and recrystallization of the residue (aqueous methanol) yielded pure **5b** (0.3 g, 60%), mp 128-129°; ¹H nmr (deuteriochloroform): δ 3.61 (s, 3H, NMe), 4.22 (s, 3H, OMe), 7.86 (d, *J* = 2.0, 1H, H-7), 8.21 (d, *J* = 2.0, 1H, H-5); hrms: Calcd. for C₈H₈BrN₃O: 240.9851. Found: 240.9841.

2-Amino-6-bromo-3-methylimidazo[4,5-*b*]pyridine (**5c**).

Diamine **12** (0.2 g, 0.99 mmol) was dissolved in 95% ethanol (15 ml). Cyanogen bromide (0.2 g, 1.9 mmol) was added and the reaction mixture was heated in a Teflon coated pressure bomb for 5 hours at 130°. After cooling, the mixture was evaporated to dryness. Water (50 ml) was added, and pH adjusted to ~11 with 5 *M* sodium hydroxide. The mixture was extracted with 1-butanol (5 x 30 ml). The extract was washed twice with water (2 x 10 ml) and brine (10 ml), then evaporated onto silica and purified by fc (chloroform-methanol, 8:1). Recrystallization (toluene-1-butanol) yielded **5c** (56 mg, 25%), mp 213-214°; ¹H nmr (DMSO-*d*₆): δ 3.48 (s, 3H, Me), ~7.0 (br s, 2H, NH₂), 7.56 (d, *J* = 1.9, 1H, H-7), 7.89 (d, *J* = 1.9, 1H, H-5); hrms: Calcd. for C₇H₇BrN₄: 225.9854. Found: 225.9869.

6-Bromo-2-chloro-3-methylimidazo[4,5-*b*]pyridine (**5d**).

Phosphorus pentachloride (0.82 g, 3.9 mmol) was added to a refluxing suspension of compound **10** (0.9 g, 3.9 mmol) in phosphorus oxychloride (5 ml). The mixture was refluxed for 6 hours. The solvent was then removed under reduced pressure. The residue was treated with water and basified (5 *M* sodium hydroxide) with external cooling. The solution was extracted with diethyl ether. The extract was washed with brine and dried with sodium sulfate. Evaporation of the filtrate onto silica, followed by fc (petrol-ethyl acetate, 5:2) and recrystallization (aqueous methanol) yielded **5d** (0.36 g, 37%), mp 116-117°; ¹H nmr (deuteriochloroform): δ 3.86 (s, 3H, Me), 8.09 (d, *J* = 2.0, 1H, H-7), 8.42 (d, *J* = 2.0, 1H, H-5); ms: *m/z* 245 (M⁺, 71%).

Anal. Calcd. for C₇H₅N₃BrCl: C, 34.1; H, 2.0; N, 17.0. Found: C, 34.0; H, 1.8; N, 17.1.

6-Bromo-2-cyano-3-methylimidazo[4,5-*b*]pyridine (**5f**).

Sodium cyanide (24 mg, 0.49 mmol) was added to a solution of compound **5d** (100 mg, 0.4 mmol) in *N,N*-dimethylformamide. The reaction mixture was heated at 60° for 1 hour, then poured into ice-water and extracted with diethyl ether. The extract was washed with water, brine and dried with sodium sulfate. Evaporation onto silica followed by fc (petrol-ethyl acetate, 5:2) and recrystallization (aqueous methanol) yielded **5f** (57 mg, 60%) mp 164-165°; ¹H nmr (deuteriochloroform): δ 4.07 (s, 3H, Me), 8.32 (d, *J* = 2.0, 1H, H-7), 8.64 (d, *J* = 2.0, 1H, H-5); ms: *m/z* 236 (M⁺, 100%).

Anal. Calcd. for C₈H₅BrN₄: C, 40.5; H, 2.1; N, 23.6. Found: C, 40.6; H, 1.8; N, 23.6.

6-Bromo-3-methylimidazo[4,5-*b*]pyridin-2-one (**10**).

Diamine **10** (6.0 g, 30 mmol) was fused with urea (6.0 g, 100 mmol) at 135° for 5 hours. The crude product was washed with boiling 95% ethanol (2 x 50 ml) and recrystallized (methanol-*N,N*-dimethylformamide) to yield **10** (4.0 g, 60%), mp 273–274°; ¹H nmr (DMSO-*d*₆): δ 3.26 (s, 3H, Me), 7.47 (d, *J* = 2.0, 1H, H-7), 8.03 (d, *J* = 2.0, 1H, H-5), ~11.3 (br s, 1H, NH); hrms: Calcd. for C₇H₆BrN₃O: 226.9694. Found: 226.9695.

Benzyl 2-Amino-5-bromopyridine-3-carbamate (**14**) and Dibenzy 5-Bromopyridine-2,3-dicarbamate (**15**).

Benzyl chloroformate (4.35 g, 26 mmol) was added dropwise to a stirred suspension of compound **13** (4.0 g, 21 mmol) in dry tetrahydrofuran (100 ml) and pyridine (6 ml) cooled at 0°. After stirring at 0° for 1 hour, and at 20° for 4 hours, ethyl acetate was added in excess. The organic phase was washed with water, brine, dried and evaporated onto silica. Fc (ethyl acetate-methanol, 20:1) and recrystallization (petrol-chloroform) yielded **14** (3.3 g, 50%) and **15** (1.0 g, 10%).

Compound **14** had mp 157–158°; ¹H nmr (DMSO-*d*₆): δ 5.15 (s, 2H, CH₂), ~6.1 (br s, 2H, NH₂), 7.3–7.5 (m, 5H, Ph), 7.78 (d, *J* = 2.2, 1H, H-6), 7.86 (br s, 1H, H-4), ~8.9 (br s, 1H, NH); hrms: Calcd. for C₁₃H₁₂BrN₃O₂: 321.0113. Found: 321.0112.

Compound **15** had mp 143–144°; ¹H nmr (DMSO-*d*₆): δ 5.11 and 5.17 (2s, 2 x 2H, 2CH₂), 7.3–7.5 (m, 2 x 5H, 2Ph), 8.24 (d, *J* = 2.2, 1H, H-4), 8.31 (d, *J* = 2.2, 1H, H-6), ~9.2 and ~9.6 (2 br s, 2 x 1H, 2NH); hrms: Calcd. for C₂₁H₁₈⁸¹BrN₃O₄: 457.0453. Found: 457.0461.

2-Amino-5-bromo-3-methylaminopyridine (**16**).

Lithium aluminium hydride (1.4 g, 37 mmol) was added to a solution of compound **14** (3 g, 9.3 mmol) in dry diethyl ether (185 ml), cooled at 0°. The mixture was stirred under dry nitrogen for 15 minutes at 0°, then for 4 hours at 20°. The excess hydride was decomposed by careful addition of ethyl acetate with cooling on ice. The mixture was filtered and extracted with 2 *M* hydrochloric acid (3 x 50 ml). The combined extracts were basified with solid sodium carbonate with cooling. Extraction with ethyl acetate and recrystallization (aqueous methanol) of the evaporation residue yielded **16** (1.2 g, 65%), mp 137–138°; ¹H nmr (DMSO-*d*₆): δ 2.68 (d, *J* = 4.9, 3H, Me), 5.21 (d, *J* = 4.9, 1H, NH), ~5.6 (br s, 2H, NH₂), 6.55 (d, *J* = 2.1, 1H, H-4), 7.27 (d, *J* = 2.1, 1H, H-6); hrms: Calcd. for C₆H₈BrN₃: 200.9902. Found: 200.9902.

Coupling Reactions.

General Procedure.

The appropriate haloimidazopyridine (0.47 mmol) and tetrakis(triphenylphosphine)palladium(0) (14 μmol, 16 mg) were dissolved in the minimum amount of 1,2-dimethoxyethane and stirred for 10 minutes at 20° under a nitrogen atmosphere. Benzenboronic acid (0.5 mmol, 61 mg) was added, followed by 2 *M* aqueous sodium carbonate (0.55 ml). The mixture was refluxed, until no further changes in the ¹H nmr spectra were observed (see Table 1), diluted with water (10 ml) and extracted with ethyl acetate. The extract was washed with water, then with brine, dried with sodium sulfate and evaporated to dryness. Recrystallization of the residue afforded the pure product. If necessary, fc was performed before recrystallization.

1-Methyl-6-phenylimidazo[4,5-*b*]pyridine (**4**).

The yield was 76%, mp 140–141° (petrol-chloroform) (lit [16]

mp 131–133°); ¹H nmr (DMSO-*d*₆): δ 3.92 (s, 3H, Me), 7.4 (m, 1H, H-4'), 7.51 (m, 2H, H-3' and H-5'), 7.8 (m, 2H, H-2' and H-6'), 8.33 (d, *J* = 2.1, 1H, H-7), 8.45 (s, 1H, H-2), 8.72 (d, *J* = 2.1, 1H, H-5).

6-Bromo-2-carbamoyl-3-methylimidazo[4,5-*b*]pyridine (**5g**).

The solvent for fc was petrol-ethyl acetate, 3:1, yield 50%, mp 233–234° (1,2-dimethoxyethane-methanol); ¹H nmr (DMSO-*d*₆, 100°): δ 4.10 (s, 3H, Me), ~7.8 (br s, 2H, NH₂), 8.38 (d, *J* = 2.0, 1H, H-7), 8.56 (d, *J* = 2.0, H-5); hrms: Calcd. for C₈H₇BrN₄O: 253.9803. Found: 253.9812.

3-Methyl-6-phenylimidazo[4,5-*b*]pyridine (**6a**).

This compound has been reported [17], but no data were given. The solvent for fc was ethyl acetate-methanol, 12:1, yield 70%, mp 120–121° (aqueous methanol); ¹H nmr (deuteriochloroform): δ 3.97 (s, 3H, Me), 7.4 (m, 1H, H-4'), 7.5 (m, 2H, H-3' and H-5'), 7.6 (m, 2H, H-2' and H-6'), 8.09 (s, 1H, H-2), 8.25 (d, *J* = 1.9, 1H, H-7), 8.66 (d, *J* = 1.9, 1H, H-5); hrms: Calcd. for C₁₃H₁₁N₃: 209.0953. Found: 209.0948.

2-Methoxy-3-methyl-6-phenylimidazo[4,5-*b*]pyridine (**6b**).

The yield was 66%, mp 114–115° (chloroform-petrol); ¹H nmr (deuteriochloroform): δ 3.68 (s, 3H, NMe), 4.26 (s, 3H, OMe), 7.4 (m, 1H, H-4'), 7.5 (m, 2H, H-3' and H-5'), 7.6 (m, 2H, H-2' and H-6'), 7.96 (d, *J* = 2.0, 1H, H-7), 8.40 (d, *J* = 2.0, 1H, H-5); hrms: Calcd. for C₁₄H₁₃N₃O: 239.1059. Found: 239.1056.

2-Amino-3-methyl-6-phenylimidazo[4,5-*b*]pyridine (**6c**).

The solvent for fc was ethyl acetate-methanol, 10:2, yield 20%, mp 212–213° (toluene-1-butanol) (lit [10] mp 217°). The spectral data were in accordance with those reported [10].

6-Bromo-3-methyl-2-phenylimidazo[4,5-*b*]pyridine (**5e**), 2-Chloro-3-methyl-6-phenylimidazo[4,5-*b*]pyridine (**6d**) and 3-Methyl-2,6-diphenylimidazo[4,5-*b*]pyridine (**6e**).

The coupling reaction with **5d** gave a mixture of **5e**, **6d** and **6e** in the respective yields (¹H nmr) 14, 33, and 23%. Fc (petrol-ethyl acetate, 5:2) resulted in only their partial separation. The experiment was repeated with twice the amount of benzenboronic acid giving **6e** as the only product in 70% yield.

Compound **5e** had mp 205–206° (petrol-chloroform); ¹H nmr (deuteriochloroform): δ 3.97 (s, 3H, Me), 7.6 (m, 3H, H-3', H-4' and H-5'), 7.8 (m, 2H, H-2' and H-6'), 8.20 (d, 1H, H-5), 8.45 (d, 1H, H-7); hrms: Calcd. for C₁₃H₁₀BrN₃: 287.0058. Found: 287.0089.

Compound **6d** had mp 151–152° (petrol-chloroform); ¹H nmr (deuteriochloroform): δ 3.91 (s, 3H, Me), 7.4 (m, 1H, H-4'), 7.5 (m, 2H, H-3' and H-5'), 7.6 (m, 2H, H-2' and H-6'), 8.12 (d, *J* = 2.0, 1H, H-5), 8.60 (d, *J* = 2.0, 1H, H-7); ms: *m/z* 243 (M⁺, 100%).

Anal. Calcd. for C₁₃H₁₀ClN₃: C, 64.2; H, 4.1; N, 17.2. Found: C, 63.8; H, 4.0; N, 17.0.

Compound **6e** had mp 196–197° (aqueous ethanol); ¹H nmr (deuteriochloroform): δ 4.03 (s, 3H, Me), 7.4–7.9 (m, 10H, 2 x Ph), 8.25 (d, *J* = 1.9, 1H, H-5), 8.65 (d, *J* = 1.9, 1H, H-7); ms: *m/z* 285 (M⁺, 91%).

Anal. Calcd. for C₁₉H₁₅N₃: C, 80.0; H, 5.3; N, 14.7. Found: C, 80.4; H, 5.4; N, 14.8.

3-Methyl-2-phenylimidazo[4,5-*b*]pyridine (**8**).

The solvent for fc was ethyl acetate-petrol, 1:1, yield 65%,

mp 124-125° (chloroform-petrol); ¹H nmr (deuteriochloroform): δ 4.00 (s, 3H, Me), 7.27 (dd, J = 8.0 and 4.8, 1H, H-6), 7.6 (m, 3H, H-3', H-4' and H-5'), 7.8 (m, 2H, H-2' and H-6'), 8.08 (dd, J = 8.0 and 1.5, 1H, H-7), 8.42 (dd, J = 4.8 and 1.5, 1H, H-5); hrms: Calcd. for C₁₃H₁₁N₃: 209.0954. Found: 209.0952.

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