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Synthetic Routes to Nitroamino Precursors of the Food Carcinogen 2-Amino-1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridine and its 3-Methyl Isomer via Pd(0)-Catalysed Arylation

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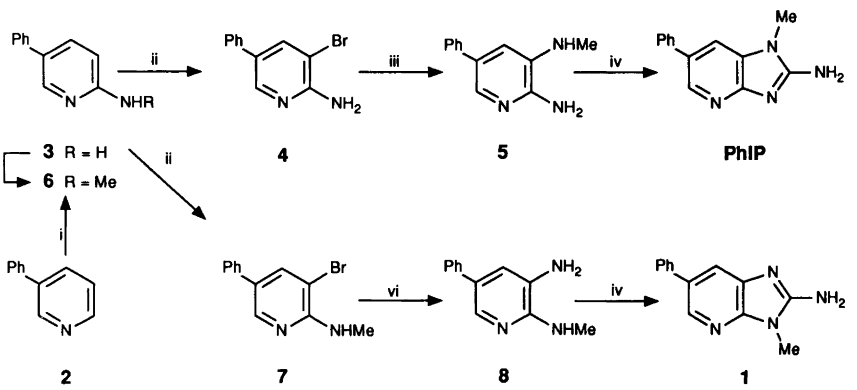
The synthesis of the novel key intermediates 3-methylamino-2-nitro- and 2-methylamino-3-nitro-5-phenylpyridine, and some of their derivatives substituted in the benzene ring, from 5-bromonicotinic acid, 3-bromo-5-methoxypyridine, 2-chloro-3-nitropyridine, 2-amino-5-bromopyridine or 5-bromo-2-methoxypyridine is described. Palladium(0)-mediated arylation of bromopyridines with areneboronic acids was an essential step in the syntheses.

The title imidazopyridine PhIP belongs to a group of potent mutagenic heterocyclic amines, the so-called aminoimidazoazaarenes (AIA, Fig. 1) isolated from the crust of fried or grilled meat and fish.[1,2] Some of the AIA have been found in model reaction systems consisting of creatinine, reducing sugars and essential amino acids.[2,3] Recently, such amines were also found in cigarette-smoke-polluted indoor air and rainwater.[4] The related 2-amino-3-methyl-1*H*-imidazo[4,5-*f*]quinoline (IQ) has been found to be carcinogenic to non-human primates, thus supporting the idea that these amines might be carcinogens for humans too.[5] Most recently, heart diseases have also been associated with these food mutagens.[6]

In connection with our synthetic work[7] related to the AIA compounds and their derivatives required for reference purposes, long-term animal feeding, human exposure studies, etc., we have investigated the preparation of the title carcinogen PhIP and its 3-methyl isomer **1**. The structure of PhIP was not unequivocally determined until it had been synthesized together with **1** as shown in Scheme 1.[8,9] There is, however, a bottleneck in these routes: the inefficient replacement of the unactivated bromine atom by methylamine or ammonia to give the sensitive diamines **5** and **8** under drastic conditions (pressure bomb, 200°C, 4 days). The aminopyridine **4** has been obtained by bromination of 2-amino-5-phenylpyridine.[8] This may be prepared by Chichibabin amination of commercial 3-phenylpyridine[8] (**2**) or more conveniently by Pd(0)-mediated phenylation[10] of commercial 2-amino-5-bromopyridine.



Scheme 1. Published[8,9] syntheses of the title imidazopyridines PhIP and **1**. *Reagents*: i, $NaNH_2$; ii, Br_2; iii, $MeNH_2$; iv, BrCN; v, (a) HNO_2/Br_2, (b) $MeNH_2$; vi, NH_4OH.

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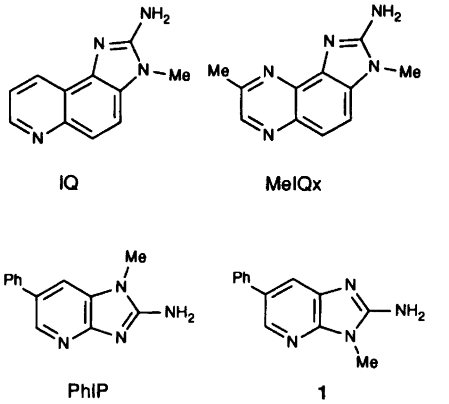
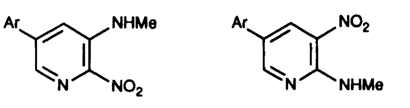


Fig. 1. Some aminoimidazoazaarenes (AIA).

Our main goal was to develop a procedure amenable to large scale, and leading to a pyridine nucleus with a nitro group *ortho* to a labile substituent which is thus rendered more easily replaceable by methylamine. From the resultant stable nitroamine, the mutagenic PhIP and **1** are obtained by reduction and subsequent cyclization with cyanogen bromide, without isolation of the intermediate diamine.[9] Thus, this paper deals with the synthesis of nitroamines **9** and **10**. These include four compounds substituted in the benzene ring and obtained in exploring the scope of the Pd(0)-catalysed arylation, which was the key step in the syntheses.



9 **10**

a Ar = Ph

b Ar = *p*-MeC_6H_4

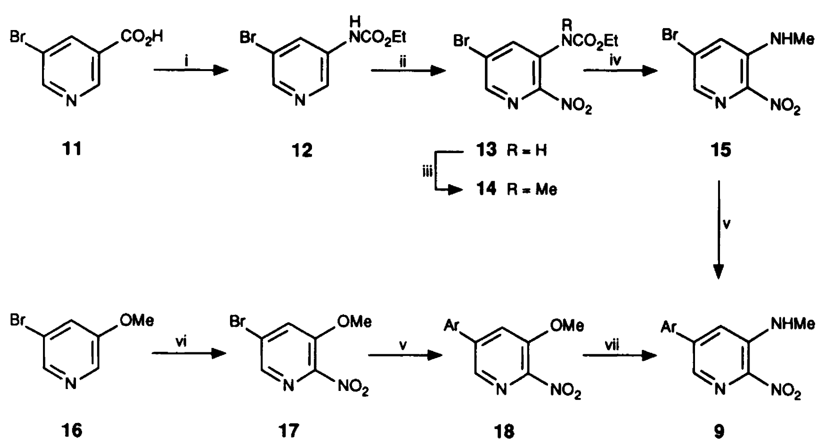
c Ar = *m*-$O_2NC_6H_4$

Results

Syntheses according to Scheme 2. The first route employs the commercially available **11** which was conveniently rearranged in one pot to the carbamate **12** by diphenyl phosphorazidate (DPPA).[11] Nitration of **12** followed by methylation of the resultant **13** yielded **14**, basic hydrolysis of which readily afforded the nitroamine **15**. The rather general cross-coupling of areneboronic acids with pyridyl bromides[10] mediated by tetrakis(triphenylphosphine)palladium(0) [$(PPh_3)_4Pd$] offered a method for the PhIP precursor **9a** from **15**. Treatment of **15** with benzene-, 4-methylbenzene- or 3-nitrobenzene-boronic acid afforded **9** in good yields. The second route we investigated starts from commercial 3,5-dibromopyridine. This was easily converted into the methoxypyridine **16** by methoxide in DMF.[12] Subsequent nitration afforded **17** in good yield. The pyridine **17** was successfully coupled with the areneboronic acids as described above and converted into the novel **18a–c**. Refluxing of methoxypyridines **18** with aqueous methylamine furnished **9** in good yields, with one exception: **18c** yielded **19** as the major product.

A third simple route from **4** via **20** to **9a** was not successful. To our disappointment, oxidation (H_2SO_5) of **4** to nitropyridine **20** failed, although we were successful with the oxidation of the 5-methyl analogue of **4** to the corresponding 2-nitropyridine.[13] Replacement of bromine with methylamine in pyridine **20** would most probably take place smoothly and under much milder conditions than in **4** (compare the route outlined in Scheme 1) yielding the stable nitroamine **9a** in good yield. However, being successful with the other two routes we did not attempt to obtain **20** in any other way.

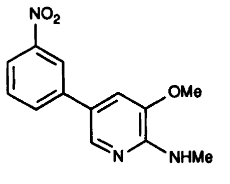
A recent method for the previously unknown arylation of chloropyridines[14] employing the more effective [1,4-bis(diphenylphosphine)butane]palladium(II) dichloride [$Pd(dppb)Cl_2$] as catalyst, prompted us to investigate a route starting from the much cheaper 3,5-dichloropyridine via **21**. Thus, nitration of **21** proceeded smoothly to give **22** in good yield, but further reaction with benzeneboronic acid did not work for this compound. However, the method worked nicely when we used 2-chloro-3-nitropyridine. Hydrolysis of **14** to **15** in aqueous ethanol was



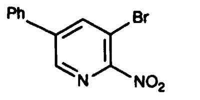
a Ar = Ph **b** Ar = *p*-MeC_6H_4 **c** Ar = *m*-$O_2NC_6H_4$

Scheme 2. Synthetic routes to nitroamines **9** of PhIP. *Reagents*: i, DPPA/abs. EtOH; ii, HNO_3; iii, Me_2SO_4; iv, aq. KOH; v, $Pd(0)/ArB(OH)_2$; vi, HNO_3; vii, $MeNH_2$.

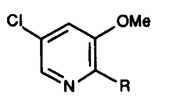
accompanied by some 5-ethoxy-3-methylamino-2-nitropyridine (**23**) which was easily separated from **15** by recrystallization. However, formation of the ethoxy by-product was significantly reduced by keeping the amount of ethanol to a minimum.



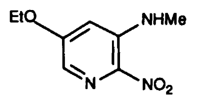
19



20



21 R = H
22 R = NO_2

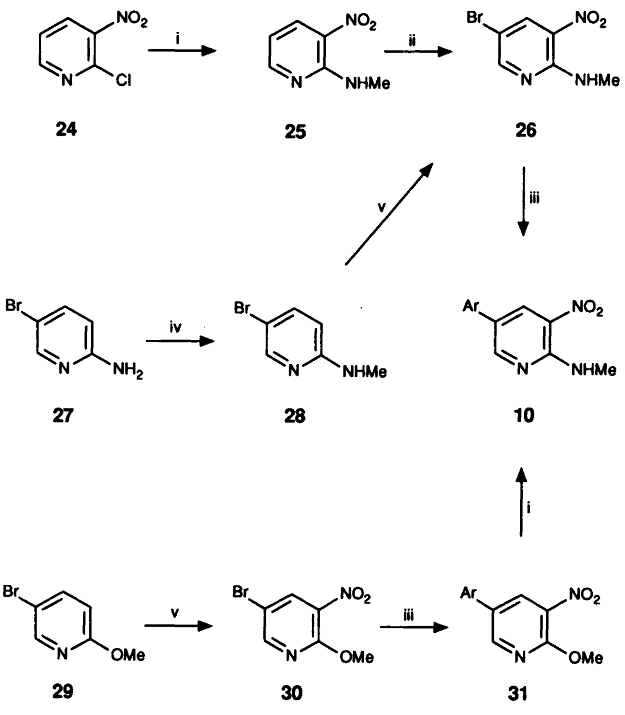


23

Syntheses according to Scheme 3. The routes investigated start from commercial 2-chloro-3-nitropyridine (**24**), 2-amino-5-bromopyridine (**27**) and 5-bromo-2-methoxypyridine[12] (**29**). The intermediate **25** was easily prepared by reflux of **24** with aqueous methylamine, which on subsequent bromination with pyridinium bromide perbromide furnished **26** in high yield. Alternatively, **26** was easily obtained by nitration of **28**. The latter was conveniently obtained by an efficient monomethylation method,[15] i.e., reduction ($NaBH_4$) of the adduct formed from 1-(1-hydroxymethyl)benzotriazole and **27**. The $(PPh_3)_4Pd$-catalysed arylation of **26** with benzeneboronic acid furnished the desired **10a** easily. The analogues **10b** and **10c** were obtained when 4-methyl- and 3-nitro-benzeneboronic acids were employed. The conversion of **26** into **10c** was slower than that leading to **10a** and **10b**.

In the third route, nitration of **29** did not afford exclusively the desired **30**, but a mixture of products, see below. Subsequent coupling of the bromopyridine **30** with the areneboronic acids was efficient and afforded the novel arylpyridines **31** readily. The latter were efficiently converted into **10** by reflux with methylamine.

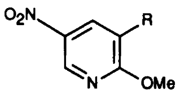
The by-products obtained in the nitration of **29** were 2-methoxy-5-nitropyridine[16] (**32**), its 3-bromo derivative **33**,[17] the dibromo derivative **34**,[18] and some unchanged starting material. The starting material (**29**), by-products **32**–**34** and the desired product **30** were present in a ca. 2:3:4:1:20 ratio according to GLC–MS and ^1H NMR analyses. However, it was possible to separate **30** from the unwanted products by flash chromatography in 22% yield. Again, we resorted to the chloro analogue **35** hoping for more selective formation[19] of the required nitro product. Indeed, nitration of **35** did not produce so many by-products but the ratio between the substrate **35** and product **36** was 2:5, the isolated yield (20%) of the



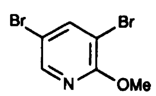
a Ar = Ph　b Ar = p-MeC_6H_4　c Ar = m-$O_2NC_6H_4$

Scheme 3. Synthetic routes to nitroamines **10** of **1**. *Reagents*: i, $MeNH_2$; ii, $C_5H_5NH^+Br_3^-$; iii, $Pd(0)/ArB(OH)_2$; iv, (a) 1-(1-hydroxymethyl)benzotriazole, (b) $NaBH_4$; v, HNO_3.

latter being not higher than that of the bromo analogue **30**. Furthermore, the yield for the conversion of chloropyridine **36**[20] into **31** was not more than 5% by using $Pd(dppb)Cl_2$[14] and most of the starting material was recovered. Therefore, no attempts were made to optimize the selectivity of the nitration leading to **36**.



32 R = H
33 R = Br



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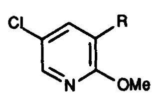

35 R = H
36 R = NO_2

Raney nickel-catalysed hydrogenation of **9a** and **10a** under ambient conditions, followed by treatment with cyanogen bromide as described[9] (pressure bomb, 200°C, 3 h) gave PhIP and **1** in 30% yield.

Discussion

The preparation of **9a** (Scheme 2) from commercially available **11** was the least satisfactory. This was mainly due to the variable and moderate yields (25–45%) of the modified Curtius rearrangement with DPPA.[11] This otherwise very practical transformation of acids into amines has been reported to proceed in higher yields with other pyridinecarboxylic acids.[11,21] The total yield of the arylnitroamines **9** from 5-bromonicotinic acid was ca.

10%. The route employing the methoxypyridine **16** was shorter and more efficient for preparing **9**. The overall yield of the nitroamines from commercial 3,5-dibromopyridine was ca. 15%. Reaction of **18c** with methylamine resulted in a mixture of the required **9c** and **19**, in which the latter was the predominant product according to ^{1}H NMR spectroscopy. Thus in the case of **9c**, the route via **15** is to be preferred.

Of the three routes investigated for the preparation of **10**, the one starting from **29** was the least satisfactory. This was mainly because of the low-yielding nitration of **29** to **30**. This is in accordance with the well-documented[22] competition of nitro-deprotonation and nitro-dehalogenation during the nitration of *p*-halomethoxyarenes. Fuming nitric and sulfuric acids at 100°C had to be used so that the rather difficult-to-control reaction would take place. Thus, the easiest way to prepare the nitroamines **10** was by starting either from commercial **24** or **27**. Both pathways were straightforward and efficient. The overall yields from **24** were 39, 42 and 28%, respectively. The respective yields from **27** were 43, 46 and 30%. The least convenient and efficient route via the novel **31** afforded **10** in only ca. 13% yield.

Important intermediates in our reaction routes were the bromopyridines **15**, **17**, **26** and **30** which allow the introduction of an arene into the pyridine nucleus by employing areneboronic acids. An improvement of the method has recently been reported.[23] We used benzeneboronic acid which leads to the desired nitroamine precursors of the title toxic imidazopyridines, and 4-methyl- and 3-nitro-benzeneboronic acids. Not surprisingly, we found no difference in the reaction times or yields when 4-methylbenzeneboronic acid was used, compared with benzeneboronic acid. The 3-nitro derivative, however, needed longer reaction times and in most cases gave lower yields compared with the parent benzeneboronic acid. This was presumambly due to the tendency of the areneboronic acids substituted with electron-withdrawing groups to undergo hydrolysis.

These results show that areneboronic acids allow the synthesis of PhIP and its analogues required for biological and structure–activity studies. For analytical and biological studies labelled areneboronic acids, methylamine and/or cyanogen bromide can be used in the last few steps.

Experimental

Melting points (uncorrected) were determined on a Mettler FP5 and FP62 instrument. The ^{1}H NMR spectra were obtained on a Varian VXR-400 spectrometer at 20°C if not otherwise stated and referenced to the solvent [δ($CHCl_3$) 7.26, (Me_2SO) 2.49, (Me_2CO) 2.09]. The coupling constants J are given in Hz. The mass spectra (70 eV, direct insertion) were obtained on a Finnigan 4021 instrument with electron impact ionization and an ion source temperature of 200°C. Ions containing isotopes other than ^{79}Br and ^{35}Cl are not listed. Flash liquid chromatography (FC) was performed on silica gel (230–400 mesh ASTM, Merck). Solvents were mixed on a volume basis. All reactions and purifications were monitored either by TLC (UV detection) on aluminium sheets coated with silica gel 60 F_{254} (Merck) or by means of a Varian 3300 GLC with an SE-30 column. Petroleum refers to petroleum ether boiling at 60–70°C.

*2-Amino-1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridine (PhIP) and 2-Amino-3-methyl-6-phenyl-3*H*-imidazo-[4,5-*b*]pyridine* (**1**). Standard Raney Ni hydrogenation of **9a** and **10a** in ethanol followed by treatment of the resulting diamines **5** and **8** with cyanogen bromide as described[9] afforded PhIP and **1** which were identical with authentic samples (TLC, ^{1}H NMR spectroscopy).

3-Methylamino-2-nitro-5-phenylpyridine (**9a**). *Method 1.* This compound was prepared from **15** (50 mg, 0.22 mmol) by method 1 for compound **9c**. Reaction time: 2 h (TLC: PhMe–MeCN, 6:1). FC was not necessary. Recrystallization (aq. EtOH) yielded 30 mg (61%) of **9a**.

Method 2. Compound **18a** (0.25 g, 1.1 mmol) was suspended in 40% aq. methylamine (6 ml, 70 mmol). The minimum amount of ethanol was added to obtain a clear solution. The reaction mixture was refluxed for 2–3 h (TLC: petroleum–EtOAc, 5:1). Water was added and the precipitated product was recrystallized (aq. EtOH) to yield 0.18 g (72%) of pure **9a**. M.p. 144–145°C. Found: C 62.3; H 4.4; N 17.9. Calc. for $C_{12}H_{11}N_3O_2$: C 62.9; H 4.8; N 18.3. MS, *m/z* (rel. int.): 229 (84, *M*), 199 (9), 195 (10), 183 (92), 154 (100). ^{1}H NMR ($CDCl_3$): δ 8.12 (6-H, d, *J* 1.9), 7.8 (NH, br s), 7.65–7.61 (2′-H and 6′-H, m), 7.56–7.49 (3′-H, 4′-H and 5′-H, m), 7.41 (4-H, d, *J* 1.9), 3.11 (NMe, d, *J* 5.1).

3-Methylamino-5-(4-methylphenyl)-2-nitropyridine (**9b**). *Method 1.* Compound **9b** was made from **15** (88 mg, 0.38 mmol) and 4-methylbenzeneboronic acid (57 mg, 0.42 mmol) by method 1 for compound **9c**. Reaction time: 3 h (FC & TLC: PhMe–MeCN, 7:1). Recrystallization (EtOH) yielded 60 mg (65%) of **9b**.

Method 2. Compound **18b** (0.15 g, 0.61 mmol) was dissolved in 40% aq. methylamine (10 ml, 104 mmol) and the minimum of ethanol to obtain a clear solution. The mixture was refluxed for 10 h (TLC: petroleum–EtOAc, 5:2), during which time more aq. methylamine (5 ml, 52 mmol) was added dropwise. The mixture was allowed to cool, a little water was added, and the precipitated product was recrystallized (aq. EtOH) to yield 90 mg (60%) of pure **9b**. M.p. 171–172°C. Anal. $C_{13}H_{13}N_3O_2$: C, H, N. MS, *m/z* (rel. int.): 243 (96, *M*), 213 (5), 209 (6), 197 (98), 168 (100). ^{1}H NMR ($CDCl_3$): δ 8.11 (6-H, d, *J* 1.9), 7.9 (NH, br s), 7.55–7.51 (2′-H and 6′-H, m), 7.39 (4-H, d, *J* 1.9), 7.37–7.31 (3′-H and 5′-H, m), 3.11 (NMe, d, *J* 5.1).

3-Methylamino-2-nitro-5-(3-nitrophenyl)pyridine (**9c**). *Method 1.* To a solution of **15** (73 mg, 0.31 mmol) and

$(PPh_3)_4Pd$ (11.6 mg, 10 µmol) in benzene (1 ml) was added 2 M sodium carbonate (0.5 ml, 1 mmol) and 3-nitrobenzeneboronic acid (58 mg, 0.35 mmol) dissolved in the minimum amount of ethanol. The reaction mixture was refluxed with vigorous stirring under nitrogen. After 15 h (TLC: PhMe–MeCN, 3:1) more 3-nitrobenzeneboronic acid (58 mg, 0.35 mmol) was added and the reaction was continued for another 15 h. Water (10 ml) was added to the mixture, which was then extracted with dichloromethane. The organic phase was filtered through a sintered-glass funnel packed with a little silica gel and evaporated. Recrystallization (aq. 2-methoxyethanol) of the residue yielded 60 mg (70%) of **9c**.

Method 2. Compound **18c** (100 mg, 0.36 mmol) was dissolved in 40% aq. methylamine (5 ml, 58 mmol) and DMF (15 ml). The reaction mixture was heated at 60°C for 24 h (TLC: PhMe–MeCN, 1:1). Removal of the solvent followed by recrystallization (aq. 2-methoxyethanol) of the residue yielded 80 mg of a mixture of **9c** and **19**. ^1H NMR analysis showed the product ratio to be 1:4. Compounds **9c** and **19** were separated by repeated FC (PhMe–MeCN, 10:1). Compound **9c** melted at 251–252°C (aq. 2-methoxyethanol). Anal. $C_{12}H_{10}N_4O_4$: C, H, N. MS, *m/z* (rel. int.): 274 (33, *M*), 228 (36), 226 (25), 199 (35), 182 (100). ^1H NMR ($CDCl_3$): δ 8.48 (2′-H, t, *J* 1.9), 8.35 (4′-H, ddd, *J* 7.9, 2.2 and 1.0), 8.12 (6-H, d, *J* 2.0), 7.96 (6′-H, ddd, *J* 7.9, 2.2 and 1.0), 7.9 (NH, br s), 7.74 (4′-H, dt, *J* 7.9), 3.15 (NMe, d, *J* 2.6).

2-Methylamino-3-nitro-5-phenylpyridine (**10a**). *Method 1.* Compound **26** (200 mg, 0.86 mmol) and $(PPh_3)_4Pd$ (30.4 mg, 26 µmol) were dissolved in benzene (3.2 ml). A solution of 2 M sodium carbonate (1.12 ml, 2.24 mmol) and benzeneboronic acid (117 mg, 0.96 mmol) dissolved in the minimum amount of ethanol were added. The mixture was refluxed under nitrogen for 1 h (TLC: petroleum–EtOAc, 5:2). Extraction with EtOAc and purification by FC (petroleum–EtOAc, 5:2) followed by recrystallization (EtOH) yielded 0.15 g (76%) of **10a**.

Method 2. Compound **31** (85 mg, 0.37 mmol) was dissolved in 40% aq. methylamine (2 ml, 23 mmol) and ethanol (0.5 ml). The reaction was refluxed for 2 h (TLC: hexane–EtOAc, 5:1). Cooling afforded orange crystals which on recrystallization (aq. EtOH) yielded 75 mg (87%) of pure **10a**. M.p. 130–131°C. Anal. $C_{12}H_{11}N_3O_2$: C, H, N. MS, *m/z* (rel. int.): 229 (70, *M*), 212 (41), 199 (2), 196 (3), 155 (100). ^1H NMR ($CDCl_3$): δ 8.74 (6-H, d, *J* 2.3), 8.65 (4-H, d, J 2.3), 8.3 (NH, br s), 7.57–7.53 (2′-H and 6′-H, m), 7.50–7.45 (3′-H and 5′-H, m), 7.41–7.36 (4′-H, m), 3.24 (NMe, d, *J* 5.0).

2-Methylamino-5-(4-methylphenyl)-3-nitropyridine (**10b**). *Method 1.* This compound was prepared from **26** (100 mg, 0.43 mmol) and 4-methylbenzeneboronic acid (65 mg, 0.48 mmol) by method 1 for compound **10a** (TLC: petroleum–EtOAc, 5:2; FC: petroleum–EtOAc, 5:1). Recrystallization (aq. EtOH) yielded 86 mg (82%) of **10b**.

Method 2. Compound **31b** (35 mg, 0.14 mmol) was suspended in ethanol (1 ml) and 40% aq. methylamine (1 ml, 1.5 mmol). The mixture was refluxed for 2 h (TLC: petroleum–EtOAc, 5:1). Cooling in an ice bath afforded orange crystals, which upon recrystallization (aq. EtOH) yielded 29 mg (83%) of pure **10b**. M.p. 143–144°C. Anal. $C_{13}H_{13}N_3O_2$: C, H, N. MS, *m/z* (rel. int.): 243 (86, *M*), 226 (42), 213 (1), 210 (3), 169 (100). ^1H NMR ($CDCl_3$): δ 8.72 (6-H, d, *J* 2.3), 8.62 (4-H, d, *J* 2.3), 8.2 (NH, br s), 7.45 (2′-H and 6′-H, dt, *J* 8.3 and 1.9), 7.28 (3′-H and 5′-H, dt, *J* 8.3 and 1.9), 3.23 (NMe, d, *J* 4.9), 2.40 (4′-Me, s).

2-Methylamino-3-nitro-5-(3-nitrophenyl)pyridine (**10c**). *Method 1.* This compound was prepared from **26** (125 mg, 0.54 mmol) and 3-nitrobenzeneboronic acid (100 mg, 0.6 mmol) by method 1 for compound **10a**. Reaction time: 18 h. FC: petroleum–EtOAc, 5:2. Recrystallization (EtOH) yielded 80 mg (54%) of **10c**.

Method 2. Compound **31c** (90 mg, 0.33 mmol) was dissolved in 2-methoxyethanol (5 ml) and 33% ethanolic methylamine (5 ml, 40 mmol). The solution was heated at 75°C for 4 h (TLC: petroleum–EtOAc, 5:1). Water (10 ml) was added and the solution was kept at 8°C overnight. Recrystallization (EtOH) of the crude product yielded 70 mg (78%) of pure **10c**. M.p. 150–161°C. Found: C 52.0; H 3.6; N 20.2. Calc. for $C_{12}H_{10}N_4O_4$: C 52.6; H 3.6; N 20.2. MS, *m/z* (rel. int.): 274 (62, *M*), 257 (38), 244 (2), 229 (3), 200 (100). ^1H NMR ($CDCl_3$): δ 8.78 (6-H, d, *J* 2.3), 8.69 (4-H, d, *J* 2.3), 8.42 (2′-H, t, *J* 2.1), 8.3 (NH, br s), 8.23 (4′-H, ddd, *J* 7.8, 2.1 and 1.0), 7.88 (6′-H, ddd, *J* 7.8, 2.1 and 1.0), 7.66 (5′-H, t, *J* 7.8), 3.25 (NMe, d, *J* 4.9).

Ethyl N-(5-bromo-3-pyridyl)carbamate (**12**). A mixture of commercial **11** (5 g, 24.8 mmol), DPPA (6.9 g, 25 mmol) and triethylamine (2.6 g, 25.7 mmol) in abs. ethanol (75 ml) was refluxed for 26 h (TLC: MeCN–EtOH, 5:1 and $CHCl_3$–MeOH, 5:1) and then evaporated to dryness. The residue was dissolved in toluene (900 ml) and washed successively with 5% citric acid (2 × 50 ml), water (50 ml), saturated aq. $NaHCO_3$ (2 × 50 ml) and saturated aq. NaCl (2 × 50 ml). Removal of toluene gave a sticky beige residue which was dissolved in hot cyclohexane and the minimum of ethanol. Cooling yielded 2.6 g (43%) of pure **12**. M. p. 152–153°C. Anal. $C_8H_9BrN_2O_2$: C, H, N. MS, *m/z* (rel. int.): 244 (100, *M*), 216 (2), 199 (8), 172 (97), 185 (66). ^1H NMR [$(CD_3)_2CO$]: δ 9.0 (NH, br s), 8.67 (6-H, d, *J* 2.1), 8.37 (4-H, t, *J* 2.1), 8.35 (2-H, d, *J* 2.1), 4.24 (CH_2, q, *J* 7.0), 1.31 (Me, t, *J* 7.0).

Ethyl N-*(5-bromo-2-nitro-3-pyridyl)carbamate* (**13**). Compound **12** (3.3 g, 13 mmol) was added portionwise to a cold mixture of conc. sulfuric (4 ml) and fuming nitric acids (2.8 ml, 66 mmol) with external cooling. The ice–water bath was removed and the mixture was stirred at 20°C for 20 h and at 80°C for 10 min (TLC:

MeCN–EtOH, 5:1). After cooling the mixture was poured onto ice and neutralized with aq. ammonia. The precipitated product was recrystallized (aq. EtOH) to yield 2.5 g (64%) of pure **13**. M.p. 122–123°C. Found: C 32.8; H 2.2; N 14.1. Calc. for $C_8H_8BrN_3O_4$: C 33.1; H 2.8; N 14.5. MS, *m/z* (rel. int.): 289 (2, *M*), 259 (1), 243 (5), 215 (80), 64 (100). ^{1}H NMR ($CDCl_3$): δ 9.6 (NH, br s), 9.32 (6-H, d, *J* 2.0), 8.28 (4-H, d, J 2.0), 4.31 (CH_2, q, *J* 7.1), 1.37 (Me, t, *J* 7.1).

Ethyl N-*(5-bromo-2-nitro-3-pyridyl)-N-methylcarbamate* (**14**). A solution of dimethyl sulfate (1.4 g, 11 mmol) in acetone (7 ml) was added to a boiling mixture of anhydrous potassium carbonate (2.0 g, 14.5 mmol) in acetone (10 ml) and compound **13** (2.0 g, 6.9 mmol). The mixture was refluxed for 6 h (TLC: $CHCl_3$–cyclohexane, 9:1), filtered and purified by FC ($CHCl_3$–cyclohexane, 9:1). Recrystallization (aq. EtOH) yielded 1.7 g (82%) of pure **14**. M.p. 59–60°C. Anal. $C_9H_{10}BrN_3O_4$: C, H, N. MS, *m/z* (rel. int.): 303 (1, *M*), 257 (13), 229 (72), 214 (5), 64 (100). ^{1}H NMR [$(CD_3)_2SO$, 100°C]: δ 8.62 (6-H, d, *J* 2.1), 8.54 (4-H, d, *J* 2.1), 4.04 (CH_2, q, *J* 7.1), 3.27 (NMe, s), 1.12 (Me, t, *J* 7.1).

5-Bromo-3-methylamino-2-nitropyridine (**15**). Compound **14** (700 mg, 2.3 mmol) was boiled with potassium hydroxide (325 mg, 5.8 mmol) in water (5 ml) and ethanol (1 ml) for 1 h (TLC: MeCN–EtOH, 5:1). The precipitated product from the cooled solution was recrystallized (aq. EtOH) to yield 400 mg (75%) of pure **15**. M.p. 180–181°C. Anal. $C_6H_6BrN_3O_2$: C, H, N. MS, *m/z* (rel. int.): 231 (47, *M*), 213 (4), 185 (64), 170 (7), 64 (100). ^{1}H NMR ($CDCl_3$): δ 7.90 (6-H, d, *J* 1.9), 7.8 (NH, br s), 7.48 (4-H, d, *J* 1.9), 3.05 (NMe, d, *J* 5.1).

5-Bromo-3-methoxypyridine (**16**). Commercial 3,5-dibromopyridine (25 g, 105 mmol) was dissolved in 450 ml DMF and kept under nitrogen. Sodium methoxide (14.3 g, 260 mmol) was added and the reaction mixture was heated at 75°C for 2 h (TLC: petroleum–EtOAc, 5:1). Ice–water was added to the mixture, which was extracted with ether. After removal of the solvent, the crude product was purified by FC (petroleum–EtOAc, 5:1) to yield 9.6 g (50%) of **16**. M.p. 30–31°C (lit.[24] 30–32°C). ^{1}H NMR ($CDCl_3$): δ 8.28 (2- or 6-H, d, *J* 1.9), 8.24 (6- or 2-H, d, *J* 2.6), 7.36 (4-H, dd, *J* 1.9 and 2.6), 3.86 (OMe, s).

5-Bromo-3-methoxy-2-nitropyridine (**17**). Compound **16** (9.6 g, 51 mmol) was added to a cold 1:1 mixture (50 ml) of fuming (65% SO_3) and conc. sulfuric acids with cooling in an ice–water bath. Fuming nitric acid (2.3 ml, 55 mmol) was added dropwise. The mixture was put in a 65°C oil bath and allowed to reach 100°C slowly, where it was kept for 90 min (TLC: petroleum–EtOAc, 5:1). The mixture was cooled and poured onto ice. Recrystallization (aq. EtOH) of the precipitate yielded 6.4 g (53%) of pure **17** as yellowish crystals. M.p. 112–113°C. Anal. $C_6H_5BrN_2O_3$: C, H, N. MS, *m/z* (rel. int.): 232 (16, *M*), 216 (1), 202 (5), 186 (45), 156 (100). ^{1}H NMR ($CDCl_3$): δ 8.15 (6-H, d, *J* 1.7), 7.67 (4-H, d, *J* 1.7), 3.99 (OMe, s).

3-Methoxy-2-nitro-5-phenylpyridine (**18a**). This compound was made from **17** (1 g, 4.3 mmol) by method 1 for compound **10a**. Reaction time: 2 h (FC & TLC: hexane–EtOAc, 10:3). Yield 0.94 g (95%). M.p. 98–99°C. Anal. $C_{12}H_{10}N_2O_3$: C, H, N. MS, *m/z* (rel. int.): 230 (29, *M*), 200 (2), 184 (20), 169 (11), 154 (100). ^{1}H NMR ($CDCl_3$): δ 8.29 (6-H, d, *J* 1.7), 7.63 (4-H, d, *J* 1.7), 7.61–7.58 (2′-H and 6′-H, m), 7.56–7.50 (3′-H, 4′-H and 5′-H, m), 4.06 (OMe, s).

3-Methoxy-5-(4-methylphenyl)-2-nitropyridine (**18b**). This compound was made from **17** (100 mg, 0.43 mmol) and 4-methylbenzeneboronic acid (65 mg, 0.48 mmol) by method 1 for compound **10a**. Reaction time: 3 h (TLC: petroleum–EtOAc, 5:2). FC was not necessary. Recrystallization (EtOH) yielded 130 mg (80%) of pure **18b**. M.p. 110–111°C. Anal. $C_{13}H_{12}N_2O_3$: C, H, N. MS, *m/z* (rel. int.): 244 (40, *M*), 198 (7), 183 (6), 168 (100), 167 (30). ^{1}H NMR ($CDCl_3$): δ 8.28 (6-H, d, *J* 1.8), 7.61 (4-H, d, *J* 1.8), 7.51 (2′-H and 6′-H, d, *J* 8.0), 7.33 (3′-H and 5′-H, d, *J* 8.0), 4.05 (OMe, s), 2.44 (4′-Me, s).

3-Methoxy-2-nitro-5-(3-nitrophenyl)pyridine (**18c**). This compound was made from **17** (200 mg, 0.86 mmol) and 3-nitrobenzeneboronic acid (158 mg, 0.95 mmol) by method 1 for compound **10a**. Reaction time: 30 h (GLC, 120–200°C, 10°C min^{-1}). Extraction with EtOAc, purification by FC (petroleum–EtOAc, 5:3) and recrystallization (2-methoxyethanol) yielded 0.17 g (72%) of pure **18c**. M.p. 207–208°C. Anal. $C_{12}H_9N_3O_5$: C, H, N. MS, *m/z* (rel. int.): 275 (16, *M*), 259 (1), 245 (10), 229 (36), 199 (100). ^{1}H NMR ($CDCl_3$): δ 8.47 (2′-H, t, *J* 1.9), 8.37 (4′-H, ddd, *J* 8.0, 2.0 and 1.0), 8.32 (6-H, d, *J* 1.9), 7.95 (6′-H, ddd, *J* 8.0, 2.0 and 1.0), 7.75 (5′-H, t, *J* 1.9), 7.67 (4-H, d, *J* 1.9), 4.10 (OMe, s).

3-Methoxy-2-methylamino-5-(3-nitrophenyl)pyridine (**19**). See method 2 under compound **9c**. M.p. 126–127°C. Anal. $C_{13}H_{13}N_3O_3$: C, H, N. MS, *m/z* (rel. int.): 259 (100, *M*), 244 (34), 231 (49), 216 (31). ^{1}H NMR ($CDCl_3$): δ 8.35 (2′-H, t, *J* 2.0), 8.13 (4′-H, ddd, *J* 8.0, 2.0 and 1.0), 8.03 (6-H, d, *J* 2.0), 7.84 (6′-H, ddd, *J* 8.0, 2.0, 1.0), 7.57 (5′-H, t, *J* 8.0), 7.04 (4-H, d, *J* 2.0), 5.1 (NH, br s), 3.94 (OMe, s), 3.09 (NMe, d, *J* 5.1).

5-Chloro-3-methoxy-2-nitropyridine (**22**). This compound was prepared from 5-chloro-3-methoxypyridine[12] (**21**) (5 g, 35 mmol) by the same procedure as for compound **16**. Recrystallization (aq. EtOH) yielded 4 g (60%) of pure **22**. M.p. 95–96°C. Anal. $C_6H_5ClN_2O_3$: C, H, N. MS, *m/z* (rel. int.): 188 (17, *M*), 172 (7), 158 (5), 142 (12), 64 (100). ^{1}H NMR ($CDCl_3$): δ 8.05 (6-H, d, *J* 2.0), 7.51 (4-H, d, *J* 2.0), 3.99 (OMe, s).

5-Ethoxy-3-methylamino-2-nitropyridine (**23**) was obtained during the hydrolysis of **14** to **15**. M.p. 179–180°C (aq. EtOH). Anal. $C_8H_{11}N_3O_3$: C, H, N. MS, *m/z* (rel. int.): 197 (95, *M*), 179 (1), 167 (1), 151 (30), 123 (100). ^{1}H NMR ($CDCl_3$): δ 8.0 (NH, br s), 7.60 (6-H, d, *J* 2.4), 6.51 (4-H, d, *J* 2.4), 4.17 (CH_2, q, *J* 7.0), 3.01 (NMe, d, *J* 5.1), 1.49 (Me, t, *J* 7.0).

2-Methylamino-3-nitropyridine (**25**). Commercial **24** (3 g, 19 mmol) was dissolved in 2-methoxyethanol (10 ml) and 33% ethanolic methylamine (7 ml, 80 mmol) was added. The mixture was kept in a 55°C oil bath for 10 min (TLC: petroleum–EtOAc, 5:3). Water (5 ml) was added and the mixture was kept at 8°C overnight. Recrystallization (aq. EtOH) of the crude product yielded 2.5 g (86%) of yellow **25**. M.p. 64–65°C (lit.[25] 63–64°C). ^{1}H NMR ($CDCl_3$): δ 8.45 (4-H, dd, *J* 4.5 and 1.8), 8.42 (6-H, dd, *J* 8.3 and 1.8), 8.26 (NH, br s), 6.65 (5-H, dd, *J* 8.3 and 4.5), 3.18 (NMe, d, *J* 4.9).

5-Bromo-2-methylamino-3-nitropyridine (**26**). *Method 1.* Commercial **27** was methylated[15] to **28**[26] which on nitration[27] afforded **26**. The overall yield from **27** was 56%.

Method 2. Compound **25** (0.5 g, 3.26 mmol) was dissolved in acetic acid (5 ml) and pyridinium bromide perbromide (0.9 g, 6.5 mmol) was added. The reaction mixture was kept at 20°C for 2 h (TLC: petroleum–EtOAc, 5:3). Water (5 ml) was added and the precipitated product was recrystallized (aq. EtOH) to yield 0.45 g (60%) orange crystals of **26**. M.p. 150–151°C (lit.[25] 149–150°C). ^{1}H NMR ($CDCl_3$): δ 8.54 (6-H, d, *J* 2.3), 8.45 (4-H, d, *J* 2.3), 8.2 (NH, br s), 3.16 (NMe, d, *J* 4.9).

5-Bromo-2-methoxy-3-nitropyridine (**30**). Of several procedures tried, the following was found to be the most satisfactory. 5-Bromo-2-methoxypyridine[12] (**29**) (2 g, 10.6 mmol) was dissolved in a cold 1:1 mixture (16 ml) of fuming (65% SO_3) and conc. sulfuric acids with cooling. The mixture was then gradually heated to 90–100°C. Fuming nitric acid (5 ml, 59 mmol) was added dropwise over a period of 1 h. After 6 h (TLC: petroleum–EtOAc, 5:1), the mixture was cooled, poured onto ice and carefully neutralized by addition of 30% NaOH with external cooling. Extraction with ether and separation by FC (petroleum–EtOAc, 5:1) yielded 0.54 g (22%) of **30**. M.p. 89–90°C. Anal. $C_6H_5BrN_2O_3$: C, H, N. MS, *m/z* (rel. int.): 232 (7, *M*), 216 (1), 202 (25), 186 (5), 64 (100). ^{1}H NMR ($CDCl_3$): δ 8.45 (6- or 4-H, d, *J* 2.3), 8.39 (4- or 6-H, d, *J* 2.3), 4.10 (OMe, s).

2-Methoxy-3-nitro-5-phenylpyridine (**31a**). This compound was made from **30** (0.75 g, 3.2 mmol) by method 1 for compound **10**. Reaction time: 3 h (TLC: hexane–EtOAc, 5:1). FC: petroleum–EtOAc, 6:1. Recrystallization (aq. EtOH) yielded 0.58 g (80%) yellow needles of pure **35**. M.p. 110–111°C. Anal. $C_{12}H_{10}N_2O_3$: C, H, N. MS, *m/z* (rel. int.): 230 (100, *M*), 214 (2), 200 (13), 183 (6), 169 (70). ^{1}H NMR ($CDCl_3$): δ 8.62 (6-H, d, *J* 2.2), 8.48 (4-H, d, *J* 2.2), 7.58–7.54 (3′-H and 5′-H, m), 7.52–7.48 (2′-H and 6′-H, m), 7.46–7.41 (4′-H, m), 4.17 (OMe, s).

2-Methoxy-5-(4-methylphenyl)-3-nitropyridine (**31b**). This compound was prepared from **30** (75 mg, 0.32 mmol) and 4-methylbenzeneboronic acid by method 1 for compound **10a**. FC was not necessary. Reaction time: 2.5 h (TLC: petroleum–EtOAc, 5:1). Recrystallization (EtOH) yielded 55 mg (70%) of pure **31b**. M.p. 117–118°C. Anal. $C_{13}H_{12}N_2O_3$: C, H, N. MS, *m/z* (rel. int.): 244 (100, *M*), 228 (4), 214 (6), 197 (6), 183 (56). ^{1}H NMR ($CDCl_3$): δ 8.62 (6-H, d, *J* 2.3), 8.46 (4-H, d, *J* 2.3), 7.46 (2′-H and 6′-H, dt, *J* 8.3 and 1.9), 7.30 (3′-H and 5′-H, dt, *J* 8.3 and 1.9), 4.16 (OMe, s), 2.42 (4′-Me, s).

2-Methoxy-3-nitro-5-(3-nitrophenyl)pyridine (**31c**). This compound was prepared from **30** (172 mg, 0.66 mmol) and 3-nitrobenzeneboronic acid (123 mg, 0.73 mmol) by method 1 for **10**. Reaction time: 4.5 h (TLC: hexane–EtOAc, 5:1). FC was not necessary. Recrystallization (Me_2CHOH) yielded 119 mg (62%) of pure **31c**. M.p. 196–197°C. Anal. $C_{12}H_9N_3O_5$: C, H, N. MS, *m/z* (rel. int.): 275 (91, *M*), 259 (2), 245 (51), 228 (4), 140 (100). ^{1}H NMR ($CDCl_3$): δ 8.68 (6- or 4-H, d, *J* 2.4), 8.54 (4- or 6-H, d, *J* 2.4), 8.44 (2′-H, t, *J* 2.0), 8.30 (4′-H, ddd, *J* 8.0, 2.0, 1.0), 7.90 (6′-H, ddd, *J* 8.0, 2.0, 1.0), 7.71 (5′-H, t, *J* 8.0), 4.20 (OMe, s).

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