SHORT PAPER

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Structural studies on bioactive compounds. Part 37.[1] Suzuki coupling of diaminopyrimidines: a new synthesis of the antimalarial drug pyrimethamine†

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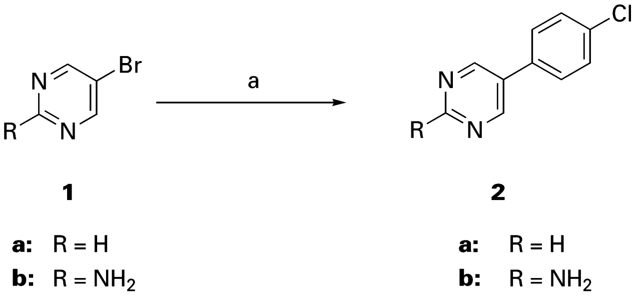
Suzuki reactions have been used successfully to effect cross-coupling of 5-halopyrimidines with 4-chlorobenzeneboronic acid and 2,4-diamino-5-(4-chloro-3-halo)-6-ethylpyrimidines with 4-methoxybenzeneboronic acid. The antimalarial drug pyrimethamine has been prepared by coupling 2,4-diamino-6-ethyl-5-iodopyrimidine with 4-chlorobenzeneboronic acid.

Keywords: bioactive compounds, diaminopyrimidines, pyrimethamine

Early efforts to exploit the Suzuki cross-coupling procedure[2] to attach aryl residues to halopyrimidines showed that neutral pyrimidine substrates coupled efficiently.[3] However, we have shown that amphoteric 2-amino-5-halopyrimidin-4(3*H*)-ones couple with difficulty even with normally reactive boronic acids, and dehalogenation is often the predominant result.[4] Presumably, under the basic conditions normally required, the aminohalo-pyrimidinone is in the anionic (electron-rich) state where cross-coupling is disfavoured. Conversely, it would be expected that aminohalo-pyrimidines should couple readily. We have demonstrated this principle and achieved a new synthesis of the antimalarial drug pyrimethamine (**6**).

In pilot experiments, 5-bromopyrimidine (**1a**) and 2-amino-5-bromopyrimidine (**1b**) were coupled with 4-chlorobenzeneboronic acid in 1,2-dimethoxyethane (DME) in the presence of potassium phosphate and the catalyst $Pd(OAc)_2(dppf)_2$, prepared *in situ* from 1,1′-(diphenylphosphino)ferrocene (dppf) and palladium acetate. 5-(4-Chlorophenyl)pyrimidine (**2a**) was isolated in 51% yield (Scheme 1) and the higher yield of **2b** (74%) from the aminobromo-pyrimidine (**1b**) encouraged the belief that diaminohalo-pyrimidines would be suitable substrates for cross-coupling reactions. However, despite a range of solvents, bases and catalysts being studied no 5-(2-chlorophenyl)pyrimidines were isolated when 2-chlorobenzeneboronic acid was employed as coupling partner in reactions with **1a** and **1b**.



Scheme 1
Reagents and conditions: a, $Pd(OAc)_2(dppf)_2$, 4-chlorobenzeneboronic acid, K_2HPO_4, DME, reflux under N_2

Our new route to pyrimethamine (**6**) started with the aminopyrimidinone (**3**), prepared (97%) from methyl propionylacetate and guanidine carbonate.[5] This was converted to the aminochloro-pyrimidine (**4**) (90%) with phosphorus oxychloride and thence to the diaminoiodo-pyrimidine (**5**) by (successive) amination and iodination reactions in overall 50% yield (Scheme 2). Coupling of **5** with 4-chlorobenzeneboronic acid using the (above) conditions afforded **6** in 76% recrystallised yield. No coupled products were detected when attempts were made to react **5** with 2-chlorobenzeneboronic acid or the *N,N'*-diacetyl-derivative of **5** with 4-chlorobenzeneboronic acid under the standard conditions employed.

The cross-coupling route represents a practical improvement over the historic synthesis of pyrimethamine by Russell and Hitchins[6] which involves interaction of a 3-carbon synthon and a guanidinium salt and employs diazomethane at one stage. A possible alternative route to pyrimethamine from **4** can be envisaged from (successive) methanolysis and bromination to form the bromomethoxy-pyrimidine (**7**), followed by cross-coupling with 4-chlorobenzeneboronic acid. The product (**8**) was only isolated in impure form (50%) after repeated chromatographic fractionation to remove starting material (**7**) and its debrominated analogue. Accordingly, **8** was not subjected to ammonolysis which would have led to pyrimethamine (**6**).

A further dimension can be added to the cross-coupling reactions of pyrimethamine starting from aminopyrimethamine (**9a**). Diazotisation of **9a** in tetrafluoroboric acid is known to yield the stable diazonium tetrafluoroborate salt (**9b**).[7] We have now shown that Sandmeyer reactions on diazonium salts from **9a** afforded the new bromo- (**9c**) and iodopyrimethamine (**9d**) in 74 and 85% yields: these substrates (**9b–d**) were coupled with 4-methoxybenzeneboronic acid to furnish the substituted biphenyl (**10**) in 47, 47 and 20% yields, respectively. Presumably, the chlorophenyl groups of both pyrimethamine (**6**) and the 3'-(4-methoxyphenyl)-pyrimethamine (**10**) would also undergo further cross-couplings, but this has not been explored.

Experimental

Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained on a Mattson 2020 Galaxy Series FT-IR spectrophotometer. All NMR spectra were acquired on a Bruker ARX 250 instrument. Chemical shifts are reported in δ units and referenced to tetramethylsilane as internal standard; coupling constants (*J*) are in Hz. New compounds were characterised by ^1H and ^{13}C NMR and HRMS because of the propensity of aminopyrimidines to undergo partial solvation resulting in variable elemental analyses.[8]

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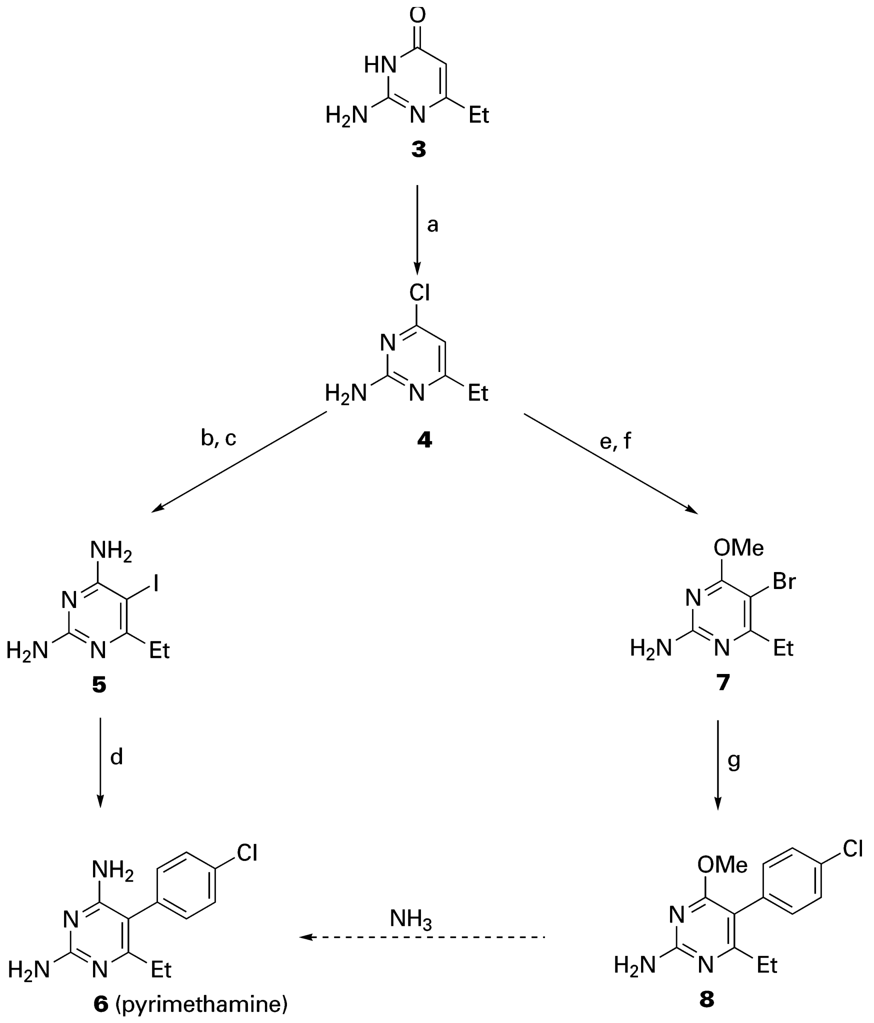
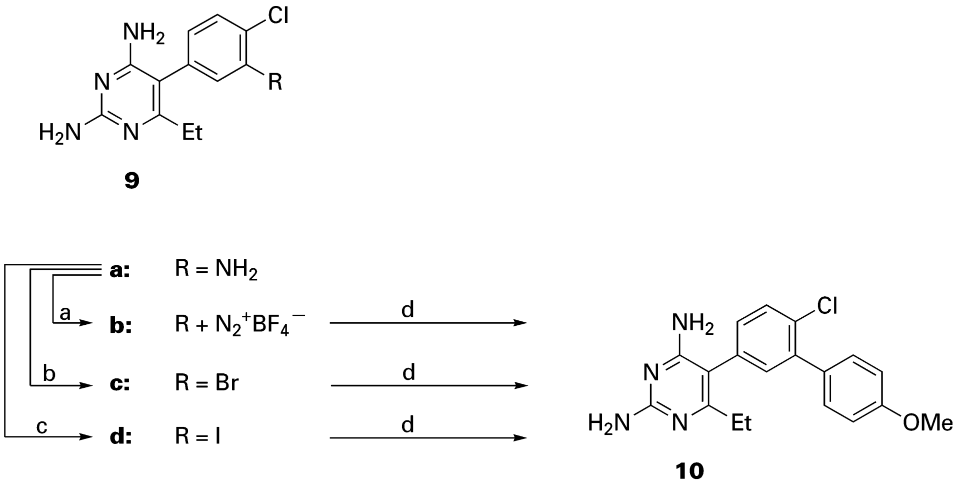
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2
Reagents and conditions: a, $POCl_3$, reflux; b, 35% aq NH_3, sealed tube; c, I_2 in aq NaOH; d, see a (Scheme 1); e, NaOMe, in MeOH, reflux; f, Br_2 in AcOH, 70°C; g, see a (Scheme 1)



Scheme 3
Reagents and conditions: a, $NaNO_2$ in 50 % aq HBF_4 at 0°C; b, $NaNO_2$ in HBr at 0°C, then Cu(I)Br; c, $NaNO_2$ in H2SO4 at 0°C, then KI; d, $Pd(OAc)_2(dppf)_2$, 4-methoxybenzeneboronic acid, K_2HPO_4, DME, reflux under N_2

Synthesis of halogenated substrates for Suzuki cross-coupling reactions: 2,4-Diamino-6-ethyl-5-iodopyrimidine (**5**). To a suspension of iodine (0.57 g, 2.23 mmol) in chloroform (20 ml) was added a solution of 2,4-diamino-6-ethylpyrimidine (0.27 g, 1.97 mmol) in water (7.5 ml) containing sodium hydroxide (0.16 g). The suspension was stirred (5 h). The product was collected, dried and crystallised from ethanol as white needles (56%), m.p. 150–152°C; ν_{max} (KBr/cm^{-1}) 3389. 3298, 3167, 1624, 1555, 1530, 1431; δ_H ($[^2H_6]$DMSO) 1.10 (3 H, t, *J* 7.5, CH_3), 2.57 (2 H, q, *J* 7.5, CH_2), 6.15 (2 H, br s, NH_2), 6.47 (2 H, br s, NH_2); δ_C ($[^2H_6]$DMSO) 12.5 (CH_3), 33.8 (CH_2), 63.6 (C), 162.4 (C), 163.3 (C), 170.3 (C); *m/z* (HRMS-EI) 263.9879 (M$^+$). $C_6H_9IN_4$ requires 263.9872. The diacetyl-derivative of **5**, formed with acetic anhydride and DMAP in boiling pyridine, crystallised from aqueous ethanol as brown crystals, m.p. 165°C; ν_{max} (KBr/cm^{-1}) 3462, 3231, 1676, 1580, 1497, 1424, 1381, 1317, 1526; δ_H ($[^2H_6]$DMSO) 1.20 (3 H, t, *J* 7.5, CH_3), 2.21 (6 H, s, $2 \times COCH_3$), 2.87 (2 H, q, *J* 7.5, CH_2), 9.86 (1 H, s, NH), 10.55 (1 H, s, NH); *m/z* (HRMS-EI) 348.0081 (M$^+$). $C_{10}H_{13}IN_4O_2$ requires 348.0083.

2-Amino-5-bromo-6-ethyl-4-methoxypyrimidine (**7**): Prepared (98%), from the bromination of 2-amino-6-ethyl-4-methoxypyrimidine in acetic acid at 70°C, this *pyrimidine* had m.p. 93–95°C; ν_{max} (KBr/cm^{-1}) 3459, 3162, 1632, 1561, 1481, 1447, 1379, 1044, 789; δ_H ($[^2H_6]$DMSO) 1.14 (3 H, t, *J* 7.5, CH_3), 2.63 (2 H, q, *J* 7.5, CH_2), 3.87 (3 H, s, OCH_3), 6.82 (2 H, br s, NH_2); δ_C ($[^2H_6]$DMSO) 12.1 (CH_3), 29.6 (CH_2), 54.3 (OCH_3), 90.4 (C), 161.7 (C), 165.3 (C), 169.8 (C).

2,4-Diamino-5-(3-bromo-4-chlorophenyl)-6-ethylpyrimidine (**9c**). Copper (II) sulfate pentahydrate (0.45 g, 1.8 mmol) and sodium bromide (0.91 g, 1.9 mmol) in water (1.5 ml) were heated to 45°C and sodium metabisulfite (0.12 g, 0.63 mmol) in water (1 ml) was added in portions. Additional sodium metabisulfite was added to the hot solution until the blue colour was discharged. The supernatant was removed and the precipitate was washed by decantation (water) and the solid dissolved in 48% hydrobromic acid (0.5 ml) to give a solution of copper (I) bromide. 2,4-Diamino-5-(3-amino-4-chlorophenyl)-6-ethylpyrimidine (**9a**, 1.02 g, 3.87 mmol)[7] in 48% hydro bromic acid (1.4 ml) at 0°C was diazotised by the addition of sodium nitrite (0.27 g, 3.87 mmol) in water (0.6 ml). The diazonium salt solution was added in portions to boiling copper (I) bromide solution (above). Addition of water followed by basification with concentrated aqueous ammonia/ice liberated the free base (**9c**; bromopyrimethamine) (74%), m.p. 222–223°C; ν_{max} (KBr/cm^{-1}) 3437, 3310, 3163, 1626, 1561, 1431, 1121, 1020, 812; δ_H ($[^2H_6]$DMSO) 1.07 (3 H, t, *J* 7.5, CH_3), 2.21 (2 H, q, *J* 7.5, CH_2), 5.83 (2 H, br s, NH_2), 6.04 (2 H, br s, NH_2), 7.31 (1 H, dd, *J* 2.0, 8.25, H-6'), 7.65 (1 H, d, *J* 2.0, H-2'), 7.76 (1 H, d, *J* 8.25, H-5'); δ_C ($[^2H_6]$DMSO) 13.2 (CH_3), 27.5 (CH_2), 104.5 (C), 122.0 (C), 131.0 (CH), 132.1 (C), 135.9 (CH), 137.3 (C), 162.1 (C), 163.2 (C), 166.4 (C); *m/z* (HRMS-EI) 325.9925 (M$^+$). $C_{12}H_{12}BrClN_4$ requires 325.9934.

2,4-Diamino-5-(4-chloro-3-iodophenyl)-6-ethylpyrimidine (**9d**): Prepared from **9a** by diazotisation in 2M-sulfuric acid, a Sandmeyer reaction with aqueous potassium iodide, followed by basification (aqueous concentrated ammonia), the free base (**9d**; iodopyrimethamine) (85%) was crystallised from aqueous ethanol, m.p. 205°C; ν_{max} (KBr/cm^{-1}) 3459, 3312, 3163, 1555, 1431; δ_H ($[^2H_6]$DMSO) 1.12 (3 H, t, *J* 7.5, CH_3), 2.25 (2 H, q, *J* 7.5, CH_2), 5.95 (2 H, br s, NH_2), 6.15 (2 H, br s, NH_2), 7.36 (1 H, dd, *J* 2.0, 8.25, H-6'), 7.76 (1 H, d, *J* 8.25, H-5'), 7.86 (1 H, d, *J* 2.0, H-2'); δ_C ($[^2H_6]$DMSO) 13.1 (CH_3), 27.1 (CH_2), 99.6 (C), 104.6 (C), 129.9 (CH), 132.6 (CH), 136.3 (C), 136.4 (C), 142.1 (CH), 161.3 (C), 162.4 (C), 165.0 (C); *m/z* (HRMS-EI) 373.9784 (M$^+$). $C_{12}H_{12}ClIN_4$ requires 373.9795.

General method for Suzuki cross-coupling reactions: Palladium acetate (6.7 mg, 0.03 mmol) and 1,1′-(diphenylphosphino)ferrocene (22 mg, 0.04 mmol) were heated in degassed 1,2-dimethoxyethane (4 ml) for 15 min under nitrogen. To the cooled solution was added the halo-pyrimidine (1.56 mmol), the substituted benzeneboronic acid 2.03 mmol), potassium phosphate (0.662 g, 3.12 mmol), 1,2-dimethoxyethane (6 ml) and water (3 ml). The mixture was heated at reflux for 24 h under nitrogen. After cooling, the reaction mixture was diluted with water (10 ml), extracted with chloroform (3 × 20 ml), washed with brine (20 ml) and water (20 ml), and the organic layer was evaporated. The residue was crystallised as appropriate (below).

The following cross-coupled products were prepared: *5-(4-chlorophenyl)pyrimidine* (**2a**), from **1a** (51%), from ethanol, m.p. 154–156°C (lit.,[9] m.p. 154–155°C); ν_{max} (KBr/cm^{-1}) 1555, 1418, 1354; δ_H ($[^2H_6]$DMSO) 7.63 (2 H, dt, *J* 2.5, 8.5, H-2′,6′), 7.89 (2 H, *J* 2.5, 8.5, H-3′,5′), 9.18 (2 H, s, H-4,6), 9.23 (1 H, s, H-2); δ_C ($[^2H_6]$DMSO) 128.9 (2 × CH), 129.4 (2 × CH), 132.2 (C), 132.8 (C), 134.1 (C), 154.8 (2 × CH); *2-amino-5-(4-chlorophenyl)pyrimidine* (**2b**), from **1b** (74%), from ethanol, m.p. 193–195°C (lit.,[10] m.p. 198°C); ν_{max} (KBr/cm^{-1}) 3298, 3163, 1665, 1597, 1491, 826; δ_H ($[^2H_6]$DMSO) 6.87 (2 H, br s, NH_2), 7.49 (2 H, d, *J* 7.5, H-2′,6′), 7.67 (2 H, *J* 7.5,H-3′,5′), 8.60 (2 H, s, H-4,6); δ_C ($[^2H_6]$DMSO) 121.0 (C), 127.1 (2 × CH), 129.1 (2 × CH), 131.8 (C), 134.4 (C), 156.1 (2 × CH), 163.2 (C); *2,4-diamino-5-(4-chloro-phenyl)-6-ethylpyrimidine* (**6**; pyrimethamine), from **5** (76%), m.p. 240–241°C, identical (m.p., IR, ^{1}H and ^{13}C NMR) to an authentic sample purchased from Sigma Chemical Company; *2-amino-5-(4-chlorophenyl)-6-ethyl-4-methoxypyrimidine* (**8**), from **7** (50%), after fractionation of the product by flash chromatography in ethyl acetate-hexane, 1:1), m.p. 172–174°C; ν_{max} (KBr/cm^{-1}) 3472, 3297, 1636, 1580, 1450, 1370, 1260; δ_H ($[^2H_6]$DMSO) 1.02 (3 H, t, *J* 7.5, CH_3), 2.27 (2 H, q, *J* 7.5, CH_2), 3.73 (3 H, s, OCH_3), 6.60 (2 H, br s, NH_2), 7.23 (2 H, d, *J* 8.5, H-2′,6′), 7.45 (2 H, *J* 8.5, H-3′,5′); δ_C ($[^2H_6]$DMSO) 13.2 (CH_3), 27.5 (CH_2), 53.4 (OCH_3), 107.6 (C), 128.3 (2 × CH), 131.7 (C), 132.6 (2 × CH), 134.1 (C), 162.3 (C), 167.1 (C), 169.3 (C); *m/z* (HRMS-EI) 264.0902 (M$^+$ +1). $C_{13}H_{15}ClN_3O$ requires 264.0902; *2,4-diamino-5-[4-chloro-3-(4-methoxyphenyl)phenyl]-6-ethylpyrimidine* (**10**), from **9b** (47%), **9c** (47%) and **9d** (20%), from 50% aqueous ethanol, m.p. 242–244°C; ν_{max} (KBr/cm^{-1}) 3453, 3314, 3179, 1630, 1555, 1435, 1238; δ_H ($[^2H_6]$DMSO) 1.00 (3 H, t, *J* 7.5, CH_3), 2.17 (2 H, q, *J* 7.5, CH_2), 3.82 (3 H, s, OCH_3), 5.71 (2 H, br s, NH_2), 5.91 (2 H, br s, NH_2), 7.05 (2 H, dt, *J* 2.5, 8.75, H-2″,6″), 7.17 (2 H, m, H-2',6'), 7.44 (2 H, dt, *J* 2.5, 8.75, H-3″,5″), 7.59 (1 H, d, *J* 8.0, H-5'); δ_C ($[^2H_6]$DMSO) 13.4 (CH_3), 27.7 (CH_2), 55.4 OCH_3), 105.4 (C), 113.8 (2 × CH), 130.2 (C), 130.5 (C), 130.8 (2 × CH), 131.0 (CH), 131.2 (CH), 133.7 (CH), 135.7 (C), 139.9 (C), 159.0 (C), 162.2 (C), 162.4 (C), 166.7 (C); *m/z* (HRMS-EI) 355.1324 (M$^+$ +1). $C_{19}H_{20}ClN_4O$ requires 355.1325.

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