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Synthesis of 6-aryl-2,4-diamino-pyrimidines and triazines using palladium catalysed Suzuki cross-coupling reactions

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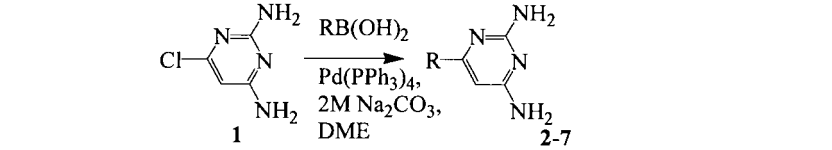
Abstract—The high yielding synthesis of 6-aryl-2,4-diaminopyrimidines and triazines via palladium catalysed Suzuki cross-coupling reactions of commercially available 6-chloro-2,4-diaminopyrimidine **1** or 6-chloro-2,4-diaminotriazine **8** and aryl boronic acids are described.

1. Introduction

The use of catalytic cross-coupling methodologies for preparing aryl functionalised heterocycles with pharmaceutical, agrochemical, materials and supramolecular applications is a burgeoning field of study.[1] In particular, the so-called Suzuki reaction,[2] which involves the palladium catalysed cross-coupling of heteroaryl-halides with aryl boronic acids, has received considerable recent attention. We are particularly interested in exploiting the versatility of the Suzuki cross-coupling procedure to prepare 6-aryl-2,4-diamino-pyrimidines and triazines, in view of their potentially interesting molecular recognition,[3] agrochemical and medicinal[4] properties. The synthesis of 6-aryl-2,4-diaminopyrimidines are largely unexplored, however, compound **2** has been previously synthesised by condensation reactions of guanidine with acetophenone,[5] 3-phenylpropynenitrile[6] or β-bromocinnamonitrile.[7] The synthesis of 6-aryl-2,4-diaminotriazines have been reported,[8] and typically involve the condensation of aryl-nitriles or esters with dicyandiamide or biguanide, respectively. Clearly, it would be advantageous to develop cross-coupling strategies utilising Suzuki procedures to allow rapid and convenient synthesis of a range of 6-aryl-2,4-diaminopyrimidines and 6-aryl-2,4-diaminotriazines from a common 6-halo-2,4-diamino-pyrimidine or triazine building block.



R	Reaction product (% yield)	R	Reaction product (% yield)
	2 (73 %)	F	**5** (86 %)
CH_3	**3** (73 %)	NC	**6** (86 %)
CH_3O	**4** (78 %)	O_2N	**7** (82 %)

Scheme 1.

Keywords: triazines; Suzuki cross-coupling; tetrakis(triphenylphosphine)palladium; pyrimidines.
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2. Results and discussion

In the present work, we report the first general, high yielding synthesis of 6-aryl-2,4-diaminopyrimidines **2**–**7** via Suzuki cross-coupling reactions of commercially available 6-chloro-2,4-diaminopyrimidine **1** with aryl boronic acids (Scheme 1).

We have extended our study to include the first synthesis 6-aryl-2,4-diaminotriazines **9**–**12** using Suzuki methodology from commercially available **8** and aryl boronic acids, which afforded the triazine derivatives **9**–**12** in good yield (Scheme 2).

3. Conclusions

In summary, we describe a general, versatile, high yielding method for preparing 6-aryl-2,4-diamino-pyrimidines and an improved method of preparing 6-aryl-2,4-diaminotriazines. Building blocks **1** and **8** will be further exploited to prepare highly functionalised pyrimidine and triazine derivatives, and their synthesis will be reported in due course.

4. Experimental

4.1. General

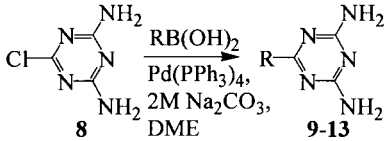
All reagents were obtained from commercial suppliers and were used without further purification. DME was distilled prior to use. Melting points were measured on a Reichert hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker DPX400 spectrometer. EI Mass spectral data were obtained using a Finnigan MAT 900 XLT mass spectrometer. Elemental analysis data were obtained using an Exeter CE-440 elemental analyser.

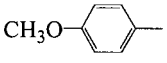
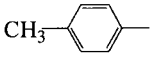
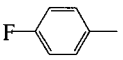
4.1.1. 2,4-Diamino-6-phenylpyrimidine 2. To a mixture 6-chloro-2,4-diaminopyrimidine **1** (0.65 g, 4.5 mmol) and tetrakis(triphenylphosphine)palladium (0.16 g, 0.13 mmol) in DME (10 ml) was added phenylboronic acid (0.823 g, 6.75 mmol) immediately followed by aqueous Na_2CO_3 (2 M, 4.7 ml). The mixture was flushed with N_2 for 5 min and the reaction mixture was then heated under reflux for 48 h. After cooling, the reaction mixture was evaporated under reduced pressure to dryness. THF (100 ml) was added and the suspension was placed in an ultrasonic bath for a few minutes. The mixture was filtered, washed thoroughly with THF and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as eluent, to afford **2** as a white solid (0.61 g, 73%); R_f (ethyl acetate) 0.1; mp 152–156°C (lit.[5] mp 160–161°C); ν_{max} (KBr) 3435, 3399, 3335, 3181, 1631; δ_H [400 MHz $(CD_3)_2SO$]: 7.94 (2H, d, J=3.0 Hz, Ph), 7.46 (3H, t, J=1.7 Hz, Ph), 6.40 (2H, s, NH_2), 6.26 (1H, s, N=CH), 6.01 (2H, s, NH_2); δ_C [100 MHz $(CD_3)_2SO$]: 165, 163, 162, 138, 129, 128, 126, 91; MS (EI) 186 (M^+, 100%). Found: C, 64.62; H, 5.42; N, 30.28. $C_{10}H_{10}N_4$ requires C, 64.52; H, 5.38; N, 30.11%.

4.1.2. 2,4-Diamino-6-(4-methylphenyl)-pyrimidine 3. This compound was synthesised analogously to **2** using **1** (1.0 g, 7 mmol), 4-methylphenylboronic acid (1.41 g, 10.4 mmol), Na_2CO_3 (2 M, 7.4 ml) and tetrakis(triphenylphosphine)palladium (0.24 g, 0.19 mmol). Compound **3** was obtained as an off-white solid (1.02 g, 73%); R_f (ethyl acetate) 0.15; mp 118–120°C; ν_{max} (KBr) 3435, 3399, 3335, 3181, 1631; δ_H [400 MHz $(CD_3)_2SO$]: 7.80 (2H, d, J=8.3 Hz, Ph), 7.23 (2H, d, J=7.9 Hz, Ph), 6.33 (2H, s, NH_2), 6.18 (1H, s, N=CH), 5.92 (2H, s, NH_2), 2.33 (3H, s, CH_3); δ_C [100 MHz $(CD_3)_2SO$]: 165, 163, 162, 140, 135, 129, 126, 90, 21; MS (EI) 200 (M^+, 100%). Found: C, 65.82; H, 5.98; N, 28.28. $C_{11}H_{12}N_4$ requires C, 66.00; H, 6.00; N, 28.00%.

4.1.3. 2,4-Diamino-6-(4-methoxyphenyl)-pyrimidine 4. This compound was synthesised analogously to **2** using **1** (1.0 g, 7 mmol), 4-methoxyphenylboronic acid (1.58 g, 10.4 mmol), Na_2CO_3 (2 M, 7.4 ml) and tetrakis(triphenylphosphine)palladium (0.24 g, 0.19 mmol). Compound **4** was obtained as an off-white solid (1.18 g, 78%); R_f (ethyl acetate) 0.11; mp 212–215°C; ν_{max} (KBr) 3435, 3399, 3335, 3181, 1631; δ_H [400 MHz $(CD_3)_2SO$]: 7.95 (2H, d, J=2.9 Hz, Ph), 6.99 (2H, d, J=2.9 Hz, Ph), 6.30 (2H, s, NH_2), 6.17 (1H, s, N=CH), 5.98 (2H, s, NH_2), 3.76 (3H, s, OCH_3); δ_C [100 MHz $(CD_3)_2SO$]: 165, 164, 162, 160, 131, 128, 114, 90, 55; MS (EI) 216 (M^+, 100%). Found: C, 61.22; H, 5.52; N, 26.17. $C_{11}H_{12}N_4O$ requires C, 61.11; H, 5.55; N, 25.93%.

4.1.4. 2,4-Diamino-6-(4-fluorophenyl)-pyrimidine 5. This compound was synthesised analogously to **2** using **1** (0.69 g, 4.76 mmol), 4-fluorophenylboronic acid (1.0 g, 7.14 mmol), Na_2CO_3 (2 M, 5 ml) and tetrakis(triphenyl-phosphine)



R	Reaction product (% yield)	R	Reaction product (% yield)
	**9** (70 %)		**11** (76 %)
	**10** (73 %)		**12** (77 %)

Scheme 2.

palladium (0.16 g, 0.13 mmol). Compound **5** was obtained as an off-white solid (0.84 g, 86%); R_f (ethyl acetate) 0.26; mp 233–236°C; ν_{max} (KBr) 3435, 3399, 3335, 3188, 2287, 1635; δ_H [400 MHz $(CD_3)_2SO$]: 7.92 (2H, q, J=2.9 Hz, Ph), 7.31 (2H, t, J=6.7 Hz, Ph), 7.21 (2H, s, NH_2), 6.83 (2H, s, NH_2), 6.25 (1H, s, N=CH); δ_C [100 MHz $(CD_3)_2SO$]: 165, 164, 162, 130, 116, 92; MS (EI) 204 (M^+, 100%). Found: C, 58.90; H, 4.42; N, 27.32. $C_{10}H_9N_4F$ requires C, 58.82; H, 4.41; N, 27.50%.

4.1.5. 2,4-Diamino-6-(4-cyanophenyl)-pyrimidine 6. This compound was synthesised analogously to **2** using **1** (0.69 g, 4.76 mmol), 4-cyanophenylboronic acid (1.05 g, 7.14 mmol), Na_2CO_3 (2 M, 5 ml) and tetrakis(triphenylphosphine)palladium (0.16 g, 0.13 mmol). Compound **6** was obtained as an off-white solid (0.86 g, 86%); R_f (ethyl acetate) 0.24; mp 220–224°C (dec). ν_{max} (KBr) 3435, 3399, 3335, 3181, 1631; δ_H [400 MHz $(CD_3)_2SO$]: 8.05 (2H, d, J=8.0 Hz, Ph), 7.93 (2H, d, J=8.0 Hz, Ph), 6.47 (2H, s NH_2), 6.26 (1H, s, N=CH), 6.06 (2H, s, NH_2); δ_C [100 MHz $(CD_3)_2SO$]: 165, 164, 160, 143, 132, 127, 119, 112, 92; MS (EI) 211 (M^+, 100%). Found: C, 62.56; H, 4.27; N, 32.28. $C_{11}H_9N_5$ requires C, 62.56; H, 4.27; N, 33.18%.

4.1.6. 2,4-Diamino-6-(3-nitrophenyl)-pyrimidine 7. This compound was synthesised analogously to **2** using **1** (0.50 g, 3.46 mmol), 3-nitrophenyl boronic acid (0.87 g, 5.19 mmol), Na_2CO_3 (2 M, 3.6 ml) and tetrakis(triphenylphosphine)palladium (0.12 g, 0.095 mmol). Compound **7** was obtained as an off-white solid (0.70 g, 82%); R_f (ethyl acetate) 0.33; mp 213–216°C; ν_{max} (KBr) 3435, 3399, 3335, 3181, 1631; δ_H [400 MHz $(CD_3)_2SO$]: 8.76 (1H, s Ph), 8.30 (2H, d, J=1.3 Hz, Ph), 7.72 (1H, t, J=8.0 Hz, Ph), 6.51 (2H, s NH_2), 6.34 (1H, s, N=CH), 6.14 (2H, s, NH_2); δ_C [100 MHz $(CD_3)_2SO$]: 165, 164, 159, 148, 140, 132, 130, 124, 121, 91; MS (EI) 231 (M^+, 100%). Found: C, 51.72; H, 3.90; N, 30.38. $C_{10}H_9N_5O_2$ requires C, 51.95; H, 3.90; N, 30.30%.

4.1.7. 2,4-Diamino-6-phenyl-1,3,5-triazine 9. This compound was synthesised analogously to **2** using **8** (1.0 g, 6.87 mmol), phenylboronic acid (1.25 g, 10.3 mmol), tetrakis(triphenylphosphine)palladium (0.21 g, 0.19 mmol) and Na_2CO_3 (2 M, 7.2 ml). Compound **9** was obtained as a white solid (0.90 g, 70%); R_f (ethyl acetate) 0.1; mp 222–224°C; ($_H$ [400 MHz $(CD_3)_2SO$]: 8.47 (2H, m, J=6.9 Hz, Ph), 7.47 (3H, m, Ph), 3.80 (4H, s, NH_2),; MS (EI) 187 (M^+, 100%). Found: C, 57.62; H, 4.98; N, 37.28. $C_9H_9N_5$ requires C, 57.75; H, 4.81; N, 37.43%.

4.1.8. 2,4-Diamino-6-(4-methylphenyl)-1,3,5-triazine 10. This compound was synthesised analogously to **2** using **8** (0.25 g, 1.72 mmol), 4-methylphenylboronic acid (0.35 g, 2.58 mmol), tetrakis(triphenylphosphine)palladium (0.09 g, 0.08 mmol) and Na_2CO_3 (2 M, 2 ml). Compound **10** was obtained as a white solid (0.25 g, 73%); R_f (ethyl acetate) 0.1; mp 234–235°C; δ_H [400 MHz $(CD_3)_2SO$]: 8.20 (2H, d, J=8.3, Ph), 7.20 (2H, d, J=7.9, Ph), 3.70 (4H, s, NH_2), 2.30 (3H, s, CH_3); MS (EI) 201 (M^+). Found: C, 59.62; H, 5.48; N, 34.78. $C_{10}H_{11}N_5$ requires C, 59.70; H, 5.47; N, 34.82%.

4.1.9. 2,4-Diamino-6-(4-methoxyphenyl)-1,3,5-triazine 11. This compound was synthesised analogously to **2** using **8** (0.25 g, 1.72 mmol), 4-methoxyphenylboronic acid (0.39 g, 2.58 mmol), tetrakis(triphenylphosphine)palladium (0.09 g, 0.08 mmol) and Na_2CO_3 (2 M, 2 ml). Compound **11** was obtained as a white solid (0.28 g, 76%); R_f (ethyl acetate) 0.1; mp>200°C; δ_H [400 MHz $(CD_3)_2SO$]: 8.42 (2H, d, J=9.0 Hz, Ph), 6.99 (2H, d, J=9.0 Hz, Ph), 3.90 (3H, s, OCH_3), 3.70 (4H, s, NH_2); MS (EI) 217 (M^+). Found: C, 55.59; H, 5.00; N, 32.38. $C_{10}H_{11}N_5O$ requires C, 55.30; H, 5.07; N, 32.26%.

4.1.10. 2,4-Diamino-6-(4-fluorophenyl)-1,3,5-triazine 12. This compound was synthesised analogously to **2** using **8** (0.25 g, 1.72 mmol), 4-fluorophenylboronic acid (0.36 g, 2.58 mmol), tetrakis(triphenylphosphine)palladium (0.09 g, 0.08 mmol) and Na_2CO_3 (2 M, 2 ml). Compound **12** was obtained as a white solid (0.27 g, 77%); R_f (ethyl acetate) 0.1; mp>200°C; δ_H [400 MHz $(CD_3)_2SO$]: 8.27 (2H, t, J=9.0 Hz, Ph), 7.28 (2H, t, J=9.0 Hz, Ph), 6.76 (4H, s NH_2); MS (EI) 205 (M^+). Found: C, 52.62; H, 3.98; N, 34.28. $C_9H_8N_5F$ requires C, 52.68; H, 3.90; N, 34.15%.

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