Synthesis of Trisubstituted Pyrimidines by Regioselective S_NAr and Suzuki Reactions of Polyhalopyrimidines

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Abstract: An efficient, regioselective approach to the synthesis of trisubstituted pyrimidines was developed. Sequential functionalisation of commercially available polyhalopyrimidines provided the target compounds in moderate to good overall yields.

Key words: regioselectivity, palladium, pyrimidine, Suzuki, cross-coupling

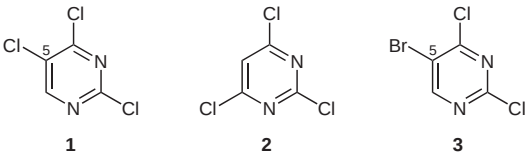
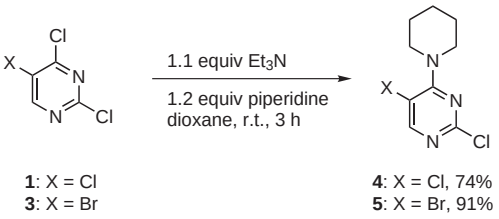


Figure 1

Functionalisation of halogenated aromatic compounds through metal-mediated cross-coupling reactions has become an important method for the rapid preparation of densely functionalised heterocycles.[1] A variety of such reactions have found applications in rapid analogue synthesis (RAS)[2], often with a view to generating sets of biologically interesting molecules.[3] In recent years, the development of cross coupling reactions of haloarenes has given rise to useful levels of selectivity for one position over another in substrates containing more than one halogen or pseudo-halogen.[4] This concept has been explored for a wide variety of important heterocyclic templates.[5]

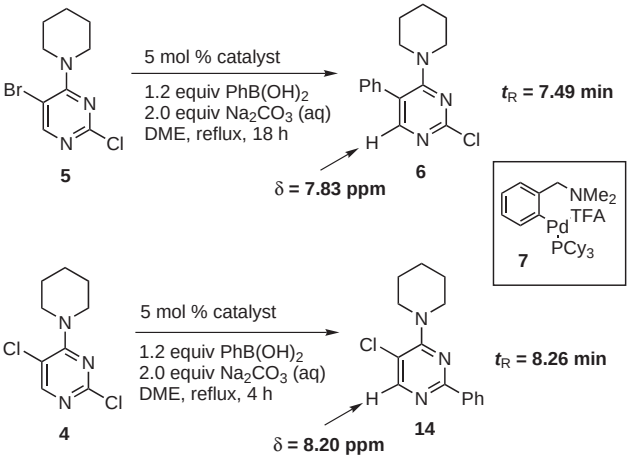
Within the context of an anti-cancer program to discover and develop small molecule lead-like compounds, we required a synthetic entry to 2,4,5-trisubstituted pyrimidines that would be amenable to rapid analogue synthesis. In the case of polyhalopyrimidines, a key report detailed the regioselective functionalisation of 2,4,5-trihalopyrimidines such as **1** (Figure 1) by means of sequential Stille couplings.[6] Reaction occurred sequentially at positions 4, 2 and finally 5. Palladium-catalysed regioselective couplings of 2,4-dichloropyrimidine with heteroaryl zinc halides have also been reported.[7] Studies concerning the more widely applicable Suzuki reaction have included preliminary work on trichloropyrimidine **2**, where mono-, di- or trisubstitution with phenylboronic acid was possible,[8] at positions 4, 6 and finally 2. A related reaction of 2,5-dibromopyrimidine with phenylboronic acid provided the 2-coupled product in only modest yield and selectivity.[9]

The work described in this report has resulted in a flexible and completely regioselective route to potentially useful trisubstituted pyrimidines from commercially available compounds **1** and **3**. The sequential modification of trihalopyrimidines such as **3** presented an attractive approach, wherein we planned to exploit established patterns of regioselectivity.[4] The key substrates **4** and **5** were easily prepared from **1** and **3** using standard nucleophilic aromatic substitution reactions (Scheme 1).[10]



Scheme 1

We initially considered the Suzuki coupling of bromochloropyrimidine **5** and conducted a brief screen of five common palladium catalysts using phenylboronic acid as the coupling partner. The catalysts employed were $Pd(Ph_3P)_4$, $PdCl_2(Ph_3P)_2$, $PdCl_2(o\text{-}Tol_3P)_2$, $PdCl_2$(dppf) and the Bedford palladacycle **7**[11] (Scheme 2).



Scheme 2

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Analysis of the crude reaction mixtures by LCMS (to determine the identity of the halogens in the product) suggested that the coupling had proceeded regioselectively at the 5-bromo position to give **6**; no reaction at the 2-chloro substituent was observed. A significant amount of unreacted starting material remained in the case of $Pd(Ph_3P)_4$, while **7** gave the desired product and the product of debromination[12] in a ratio of 6.5:1. $PdCl_2$(dppf) gave the cleanest conversion and was therefore selected as the most suitable catalyst for development. A similar catalyst screening protocol was conducted for **4**, this time including $PdCl_2$(dppb).[13] In this case the monosubstitution product **14** was obtained – this was distinguished from isomer **6** by HPLC and ^{1}H NMR spectroscopic analysis (see Scheme 2). These structural assignments were subsequently confirmed by dehalogenation experiments (vide infra). In contrast to compound **5**, $Pd(Ph_3P)_4$ was the catalyst of choice for substrate **4** – the other screened catalysts gave poorer conversions or generated substantial quantities of bis-coupled product.[9]

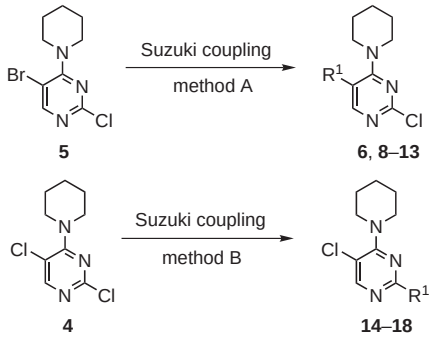
Selective Suzuki couplings of substrates **4** and **5** could be achieved in moderate to good yields using a variety of aromatic boronic acids (Table 1).[14] Single isomers were obtained in each case, and spectroscopic analysis showed them to be analogues of **6** and **14**, respectively. For bromide **5**, the use of more reactive coupling partners provided good yields of the desired cross-coupled products **6** and **8**–**13**.

The successful couplings of electron-deficient, vinyl and heteroaromatic boronic acids (entries 4, 6 and 7, respectively) are noteworthy. The 3-pyridyl case (entry 7) required use of the more active catalyst **7** – this catalyst was originally developed for couplings of less reactive but more widely available aryl chlorides.[11] We also found that using the more stable diethyl-3-pyridylborane gave a better yield than either a glycol boronate ester (poor conversion in a small scale test reaction) or pyridine-3-boronic acid (no reaction).[15] A sterically hindered boronic acid (entry 5) resulted in a less efficient reaction, which was also attended by a large amount of the corresponding debrominated side product.

In the case of chloride **4**, regioselective couplings at the 2-chloro position efficiently generated **14**–**18**, in agreement with the observations of sequential Stille reactions on 2,4,5-trichloropyrimidine.[6,16] This represents a complete reversal in regioselectivity as compared to couplings of compound **5**, where the more reactive bromo substituent undergoes palladium insertion first. The ability to introduce a 3-pyridyl moiety (entry 12) was significant, despite a modest yield of product **18**. Use of the diethylborane derivative was again preferable to boronate ester or boronic acid coupling partners.

As shown in Scheme 3, the regioselectivity of these reactions was unambiguously confirmed by reductive removal of the chlorine atoms in **8** and **15**, to give **19** and **20**, respectively, and analysis of the aromatic region in their respective ^{1}H NMR spectra.

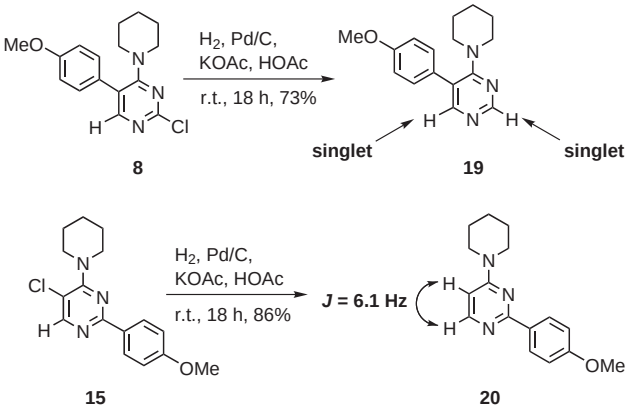
Table 1 Suzuki Couplings of Substrates **4** and **5**



5 **6**, **8**–**13** **4** **14**–**18**

Entry	Substrate	R^1	Method[a]	Product and yield (%)[b]
1	**5**	Ph	A	**6**, 75
2	**5**	4-$MeOC_6H_4$	A	**8**, 74
3	**5**	4-ClC_6H_4	A	**9**, 69
4	**5**	3-$O_2NC_6H_4$	A	**10**, 75
5	**5**	2-MeC_6H_4	A	**11**, 52
6	**5**	*trans*-Styryl	A	**12**, 95
7	**5**	3-Pyridyl	A[c,d]	**13**, 33
8	**4**	Ph	B	**14**, 72
9	**4**	4-$MeOC_6H_4$	B	**15**, 67
10	**4**	3-$O_2NC_6H_4$	B	**16**, 58
11	**4**	*trans*-Styryl	B	**17**, 88
12	**4**	3-Pyridyl	B[e]	**18**, 34[f]

[a] Method A: 0.05 equiv $PdCl_2$ (dppf), 1.2 equiv $R^1B(OH)_2$, 2.0 equiv Na_2CO_3 (aq), DME, reflux, 18 h. Method B: 0.05 equiv $Pd(Ph_3P)_4$, 1.5 equiv $R^1B(OH)_2$, 2.0 equiv Na_2CO_3 (aq), DME, reflux, 4 h.
[b] Yields are unoptimised and refer to isolated materials, homogeneous by HPLC and NMR analysis.
[c] Catalyst **7** (0.05 equiv) was used.
[d] Diethyl-3-pyridylborane as coupling partner.
[e] Reaction time was 18 h.
[f] 47% yield based on recovered starting material

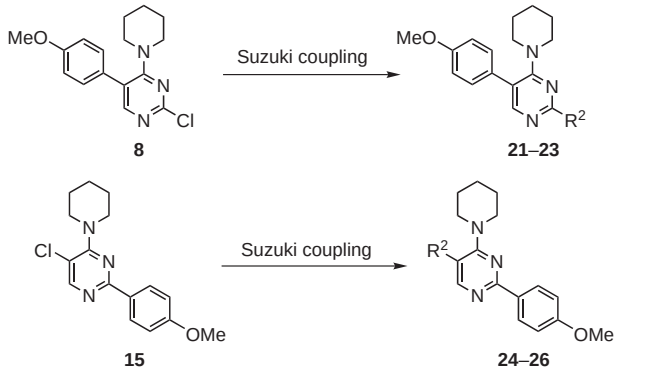


8 **19** **15** **20**

Scheme 3

The availability of remaining halogen substituents allowed for further functionalisation of the pyrimidine nucleus. For example, the regioisomeric pair of 4-methoxyphenyl-substituted chloropyrimidines **8** and **15** could be readily transformed to the fully trisubstituted materials by further palladium-catalysed coupling. Suzuki reactions of **8** using the Bedford catalyst **7** provided **21**–**23** in good yields (Table 2, entries 1–3). The nature of the boron coupling partner and catalyst were critical for efficient coupling in the 3-pyridyl case. A series of low yielding reactions using boronic acid and cyclic boronate ester derivatives eventually resulted in a much improved 60% yield when diethyl-3-pyridylborane was employed as the coupling partner (entry 3). Stille couplings using **8** and tributylphenyltin were significantly less efficient and afforded **21** in only 5–12% yield.[6]

Table 2 Suzuki Coupling of 4-Methoxyphenyl-Substituted Chloropyrimidines **8** and **15**



Entry	Substrate	R^2	Method[a]	Product and yield (%)[b]
1	**8**	Ph	A	**21**, 60
2	**8**	3-$MeOC_6H_4$	A	**22**, 85
3	**8**	3-Pyridyl[c]	A	**23**, 60
4	**15**	Ph	A	**24**, 39[d]
5	**15**	Ph	B	**24**, 50
6	**15**	3-$MeOC_6H_4$	A	**25**, 31
7	**15**	3-$OHCC_6H_4$	A	**26**, 43

[a] Method A: 0.05 equiv **7**, 3.0 equiv $R^2B(OH)_2$, 2.0 equiv Na_2CO_3 (aq), DME, reflux, 18 h. Method B: as method A but heating under microwave conditions, 145 °C, 1 h.
[b] Yields are unoptimised and refer to isolated materials, homogeneous by HPLC and NMR analysis.
[c] Diethyl-3-pyridylborane as coupling partner.
[d] 54% yield based on recovered starting material.

We anticipated that coupling of chloride **15** would be more challenging, due to the nature of the sterically hindered benzenoid chlorine atom. For the coupling of **15** with phenylboronic acid, a screen of three catalysts selected for their reactivity with chloroarenes was conducted. While $[Pd(t\text{-}Bu_3P)Br]_2$[17] gave a poor conversion, both palladacycle **7** and $Pd(t\text{-}Bu_3P)_2$[18] showed reasonable levels of activity. Bedford catalyst **7** was subsequently employed for Suzuki reactions of **15** (entries 4–7), which gave rise to fully functionalised compounds **24**–**26** in low to moderate yields. The use of microwave heating for high temperature reactions led to a modest improvement in the yield of **24** (entry 5).

In summary, we have explored a simple and flexible approach to the regioselective preparation of trisubstituted pyrimidines. This makes use of the predicted reactivity profile of the polyhalopyrimidine precursors to achieve selective sequential transformations. These reactions were shown to be of broad scope by using a variety of aryl and heteroaryl boronic acid derivatives. Further studies on the application of these findings are ongoing in our laboratories.

Acknowledgment

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(12) Analysis of the crude reaction mixture revealed that approximately 37% of the debrominated product was present. For all other coupling reactions of compound **5**, the same side-product was generated in quantities of less than 13%.

(13) The effective use of this catalyst in the coupling of electron-deficient heteroaryl halides has been reported. See: Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117.

(14) **Preparation of 6.**
To a solution of 5-bromo-2-chloro-4-(piperidin-1-yl)pyrimidine (**5**, 500 mg, 1.8 mmol) and phenylboronic acid (236 mg, 1.94 mmol) in DME (15 mL) was added $PdCl_2$(dppf) (66 mg, 0.08 mmol, 4.4 mol%). Then, 1 M Na_2CO_3 solution (3.75 mL, 3.75 mmol) was added, and the mixture heated at 85 °C for 18 h under an atmosphere of nitrogen. The solution was then cooled, and filtered through a plug of silica, washing with 10% MeOH–CH_2Cl_2. The filtrate was dried ($MgSO_4$), concentrated in vacuo and purified by flash column chromatography to yield the desired product (331 mg, 75%); R_f = 0.13 (hexane–EtOAc, 19:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33–1.44 (4 H, m), 1.45–1.56 (2 H, m), 3.17–3.26 (4 H, m), 7.23–7.40 (5 H, m), 7.85 (1 H, s). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.1, 25.3, 48.3, 119.1, 127.5, 127.9, 129.1, 137.1, 158.6, 159.0, 162.8. LCMS: t_R = 7.49 min. MS (ESI) for $C_{15}H_{16}Cl_1N_3$: *m/z* = 274 [MH^+].

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(16) **Preparation of 15.**
To a solution of 2,5-dichloro-4-(pyrimidin-1-yl)pyrimidine (**4**, 100 mg, 0.43 mmol) and 4-methoxyphenylboronic acid (74 mg, 0.607 mmol) in DME (3.6 mL) was added $Pd(PPh_3)_4$ (25 mg, 0.022 mmol, 5.0 mol%). Then, 1 M Na_2CO_3 solution (0.9 mL, 0.9 mmol) was then added, and the mixture heated at 85 °C for 4 h. The solution was then cooled to r.t., filtered through a plug of silica, washing with 10% MeOH–CH_2Cl_2. The solution was concentrated and then purified by flash column chromatography to yield the desired product (79 mg, 67%). R_f = 0.25 (hexane–EtOAc, 19:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.60–1.70 (6 H, m), 3.62–3.70 (4 H, m), 3.80 (3 H, s), 6.88 (2 H, d, *J* = 9.0 Hz), 8.20 (1 H, s), 8.23 (2 H, d, *J* = 9.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.6, 25.9, 48.5, 55.4, 113.7, 114.3, 129.7, 130.0, 156.6, 160.0, 161.0, 161.6. LCMS: t_R = 8.27 min. MS (ESI) for $C_{16}H_{18}Cl_1N_3O_1$: *m/z* = 303 [M^+].

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