Published in final edited form as:

Synthesis (Stuttg). 2010 August 1; 2010(16): 2721–2724. doi:10.1055/s-0030-1258150.

One-pot Double Suzuki Couplings of Dichloropyrimidines

Samantha C. Anderson and Scott T. Handy

Abstract

An effective one-pot, regioselective double Suzuki coupling of 2,4-dichloropyrimidine has been developed, which enables the quick and efficient synthesis of diarylated pyrimidines. The choice of solvent proved critical to the success of this reaction sequence, with alcoholic solvent mixtures affording much greater reactivity and correspondingly lower temperatures than the use of polar aprotic solvents.

Keywords

pyrimidines; Suzuki coupling; regioselectivity; catalyzed; one-pot

The pyrimidine nucleus is an important building block for a variety of compounds of biological and materials interest. For example, both the drugs Gleevec and Crestor feature pyrimidines at their core. (Figure 1) As a result of this importance, a variety of methods have been reported for the synthesis of substituted pyrimidines, including classical condensation routes such as the Bignelli synthesis and the Pinner synthesis.¹ Another approach for the synthesis of substituted pyrimidines is transition metal catalyzed cross coupling reactions.² This method has the advantages of wide functional group tolerance, allowing a single common intermediate to be diversified into a large number of related products.

Despite this versatility, though, cross coupling methods are less efficient if multiple substituents are to be installed. For example, using a conventional approach the installation of two substituents requires two separate coupling reactions and two separate halogenations for a total of four steps. (Scheme 1) When compared to a single step condensation approach, the cross-coupling approach is certainly less appealing.

In an effort to overcome this problem of greater linearity in coupling multiple substituents, we have been exploring the concept of regioselective polycoupling reactions on polyhaloheteroaromatics for the past few years.^{3,4} The general idea is to install all of the necessary halogens in one step, and then perform all of the couplings in a second step by taking advantage of the intrinsic differences in reactivity at different centers of the heteroaromatic ring to sequentially add each substituent.⁵ In light of the importance of pyrimidines in synthesis and our prior success with other dibromoheteroaromatics (including pyridines), we undertook a study of 2,4-dichloropyrimidine.

The regioselectivity of cross-coupling reactions of 2,4-dichloropyrimidine and 2,4,6-trichloropyrimidine has been established for a number of years.⁶ (Scheme 2) The observed preference for coupling initially at the 4-chloro position has been described as unusual,

though recent computational work by Merlic and Houk indicates that it is expected on the basis of calculated bond dissociation energies.⁷ Most of the experimental work on pyrimidines has focused on Suzuki couplings, with a variety of reaction conditions being employed with generally good success.^{8,9,10} It is interesting to note that in most cases, either complete regioselectivity is reported or no mention is made of the regioselectivity. However, Gong did report only moderate selectivity (2.8:1.0) in favor of the 4-coupled product when coupling with p-carboxyphenylboronic acid.⁹ By using a slow addition of an excess of the dichloropyrimidine, though, complete regiocontrol could be achieved. These same Gong reaction conditions, without slow addition of the dichloropyrimidine, have been employed by several other groups, though loss of regiocontrol has not been noted in any of these other reports.¹⁰

In light of our previous successes with one-pot double Suzuki couplings of dihaloheteroaromatics, we were interested in seeing if the same reaction conditions would be applicable to commercially available 2,4-dichloropyrimidine. Thus, the use of tetrakis(triphenylphosphine) palladium(0), with either potassium or sodium carbonate in either DMF/water or dioxane/water at 90 °C were all explored. Initial results were not promising. Although some reaction was clearly occurring (TLC and NMR analysis), attempts to isolate pure products were exceedingly difficult and isolated yields were below 20% of pure monocoupled product. These results were highly unexpected considering our earlier successes in other systems as well as the fact that some of these conditions had been employed in earlier literature reports of regioselective Suzuki couplings of pyrimidine.

Fortunately, further searching of the literature led to a patent report by Geneste and Sauer, which called for the use of tetrakis(triphenylphosphine) palladium(0) with potassium carbonate as base in methanol as the solvent at room temperature.¹¹ Gratifyingly, application of these conditions afforded the monocoupled product **1** with complete regioselectivity after 3–12 hours at room temperature. (Table 1, entries 1 and 2) The yields were fairly low (<40%), but the product was easily isolated from the reaction, so this appeared to be a promising starting point. Attempts were made to improve the yield by heating the reaction. Given the very limited temperature range accessible using methanol, the solvent was changed to ethanol. (Table 1, entries 3 and 4) Even at room temperature, this switch led to improved isolated yields, though heating to 55 °C resulted in very little further improvement.

A further question was if a coupling at the C2 position would also occur under the same reaction conditions. (Table 2) Not surprisingly, reactions at room temperature failed to afford any coupling product. By increasing the reaction temperature significantly, modest amounts of coupling products could be isolated. In this case, the use of ethanol as the alcoholic component was highly advantageous. (Table 2, entry 3) To further prevent the reaction from running dry, toluene was also included as a cosolvent and this modification resulted in further improvement.

With potential coupling conditions established for both the first and second couplings, a one-pot double coupling was attempted. (Table 3, entry 1) A solvent mixture of ethanol, toluene, and water was employed with potassium carbonate as the base and palladium tetrakis(triphenylphosphine) palladium(0) as the catalyst. The reaction was heated to 55 °C in order to achieve complete consumption of starting materials within 12 hours. In the absence of heat, many reactions were still not complete within 24–48 hours. At this point, the second boronic acid and more base was added and the reaction temperature increased to 90 °C for 12 hours. Initially, this approach was successful, but reproducibility issues were still noted. Two factors aided in overcoming these issues. First, brief degassing of the reaction mixture by bubbling argon through the reaction for 5 minutes helped to avoid

catalyst decomposition. Reproducibility was further improved by adding a second dose of catalyst (10 mol%) with the second boronic acid. The end result was a set of reaction conditions that reliably afforded >80% isolated yields of this double coupled product.

Armed with these reaction conditions, a range of boronic acids was studied, including electron-rich and electron-deficient aryls as well as an alkenyl boronic acid. Aryl boronic acids generally worked well, although the double coupling with p-methoxyphenylboronic acid followed by phenylboronic acid always afforded much lower yields. (Table 3, entry 2) The alkenyl boronic acid also underwent cross-coupling in moderate to high yields. (Table 3, entries 5 and 6) Electron-withdrawing substituents on the boronic acid had very little impact on the yield. It is worth noting that, in general, the reactions displaying lower yields were contaminated by larger amounts of boronic acid homocoupling products, which made purification more difficult and likely resulted in only partial conversion of the starting material and mono-coupled intermediate.

The cross-coupling reactions were not very successful for an *ortho*-substituted boronic acid. (Table 3, entries 7 and 8) This is not surprising, as earlier work done with *ortho*-substituted boronic acids has shown similar results. Harsher reaction conditions, employing a stronger base and higher reaction temperatures, could improve reactions with sterically hindered boronic acids.

In conclusion, an effective one-pot, regioselective double Suzuki coupling of 2,4-dichloropyrimidine has been developed. This method enables the quick and efficient synthesis of diarylated pyrimidines. The choice of solvent proved critical to the success of this reaction sequence, with alcoholic solvent mixtures affording much greater reactivity and correspondingly lower temperatures than the use of polar aprotic solvents. Sterically hindered boronic acids do not afford good yields of the dicoupled products, but alkenyl and several aryl boronic acids do work well. It is possible that the application of microwave reaction conditions may help to overcome some of these limitations.

EXPERIMENTAL

All ^1H and ^{13}C NMR spectra were recorded on a Jeol 300MHz NMR with an automatic sample changer, or on a Jeol AS 500MHz NMR, using CDCl_3 as solvent. All chemical shifts (δ) are reported in ppm, using TMS as a standard. All IR spectra were collected on a Varian 800 FT-IR. All reagents were ACS grade. All extractions from aqueous solution were dried over 97% anhydrous magnesium sulfate and evaporated using a Buchi rotary evaporator under reduced pressure. Thin-layer chromatography was performed using silica coated TLC plates. Preparatory thin-layer chromatography was performed using silica (60 Å thickness) coated, glass TLC plates.

2-chloro-4-phenylpyrimidine

2,4-dichloropyrimidine (100 mg, 0.67 mmol) was dissolved in a mixture of toluene (2.9 mL), ethanol (0.7 mL), and water (0.7 mL). The solution was degassed for five minutes with argon. At the end of five minutes, phenylboronic acid (82 mg, 0.67 mmol), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.18 mmol), and potassium carbonate (278 mg, 2.01 mmol) were added to the reaction vial. The vial was shaken at 55°C for 12 hours. The resulting crude product was partitioned between water and ethyl acetate, dried with anhydrous magnesium sulfate, and the solvent was removed in vacuo. The crude product was purified by flash-column chromatography on alumina (15% ethyl acetate in hexanes as eluent) to afford 65.2 mg (51%) of the 2-chloro-4-phenylpyrimidine as yellow solid.¹²

Mp: 109.5–111.5°C.

¹H NMR (300 MHz, CDCl₃), δ = 7.65 (m, 3H), 7.67 (d, 1H, J = 7.5), 8.10 (d, 2H, J = 7.0 Hz), 8.64 (d, 1H, J = 7.5 Hz).

Standard decoupling procedure, 4-phenyl-2-(4-methoxyphenyl)pyrimidine

2,4-dichloropyrimidine (100 mg, 0.67 mmol) was dissolved in a mixture of toluene (2.9 mL), ethanol (0.7 mL), and water (0.7 mL). The solution was degassed for five minutes with argon. At the end of five minutes, phenylboronic acid (82 mg, 0.67 mmol), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.18 mmol), and potassium carbonate (278 mg, 2.01 mmol) were added to the reaction vial. The vial was shaken at 55 °C for 12 hours. After 12 hours, p-methoxyphenylboronic acid (90 mg, 0.78 mmol), tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.09 mmol), and potassium carbonate (278 mg, 2.01 mmol) were added to the reaction vial. The vial was shaken at 90°C for an additional 12 hours. The resulting crude product was partitioned between water and ethyl acetate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with 0.5% methanol in dichloromethane to afford 147 mg (84%) of the purified, decoupled product as a brown solid.

Mp: 83–85°C.

IR (neat): 3003, 2879, 1712, 1554, 1437, 1331, 1215, 1177, 1119, 1040, 911, 770 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 3.90 (s, 3H), 7.05 (d, 2H, J = 7.0 Hz), 7.63–7.51 (m, 4H, J = 6 Hz), 8.28–8.19 (m, 2H), 8.55 (d, 2H, J = 7.0 Hz), 8.78 (d, 1H, J = 6 Hz).

¹³C NMR (75 MHz, CDCl₃) δ = 164.1, 162.7, 158.0, 127.5, 129.4, 128.8, 128.1, 127.5, 112.4, 112.0, 111.8, 110.6, 56.0.

HRMS (EI): *m/z* calcd for C₁₇H₁₄N₂O: 262.1106; found: 262.1105.

4-(4-methoxyphenyl)-2-phenylpyrimidine

The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with 0.5% methanol in dichloromethane to afford 70 mg (39%) of the purified, decoupled product as a brown oil.¹³

¹H NMR (300 MHz, CDCl₃) δ 3.88 (s, 3H), 7.03 (d, 2H, J = 7.5 Hz), 7.55–7.42 (m, 4H), 8.22 (d, 2H, J = 7.0 Hz), 8.64–8.48 (m, 2H), 8.76 (d, 1H, J = 6 Hz).

4-(2-methoxyphenyl)-2-phenylpyrimidine

The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with 0.5% methanol in dichloromethane to afford 38 mg (21%) of the purified, decoupled product as yellow oil.¹³

¹H NMR (300 MHz, CDCl₃) δ = 3.90 (s, 3H), 7.03 (d, 2H, J = 7.0 Hz), 7.59–7.51 (m, 4H), 8.28–8.16 (m, 2H), 8.55 (d, 2H, J = 6 Hz), 8.78 (d, 1H, J = 6 Hz).

2-(2-methoxyphenyl)-4-phenylpyrimidine

The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with 0.5% methanol in dichloromethane to afford 27 mg (15%) of the purified, decoupled product as yellow oil.

IR (neat): 3003, 2879, 1712, 1554, 1437, 1331, 1215, 1177, 1119, 1040, 911, 770 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ = 3.89 (s, 3H), 7.02 (t, 1H, J = 6.5 Hz), 7.17-7.40 (m, 6H), 7.89 (d, 1H, J = 7.0 Hz), 8.40 (d, 2H, J = 7.0 Hz), 8.78 (d, 1H, J = 6.0 Hz).

^{13}C NMR (75 MHz, CDCl_3) δ = 163.4, 161.4, 159.7, 157.3, 136.6, 129.0, 128.2, 128.0, 127.8, 127.4, 121.7, 119.5, 119.1, 114.3, 55.4.

HRMS (EI): m/z calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$: 262.1106; found: 262.1103.

2-(4-fluorophenyl)-4-phenylpyrimidine

The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with 40% ethyl acetate in hexanes to afford 109 mg (65%) of the purified, decoupled product as a yellow solid.¹⁴

Mp: 73–76°C.

^1H NMR (300MHz, CDCl_3) δ = 7.19-7.11 (m, 2H), 7.58-7.49 (m, 4H), 8.27-8.16 (m, 2H), 8.59 (dd, 2H, J = 24 Hz, 7.5 Hz), 8.78 (d, 1H, J = 6.0 Hz).

4-(4-fluorophenyl)-2-phenylpyrimidine

The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with 40% ethyl acetate in hexanes to afford 103 mg (62%) of the purified, decoupled product as a tan solid.

Mp: 53–57°C.

IR (neat): 3003, 2879, 1712, 1554, 1437, 1331, 1215, 1177, 1119, 1040, 911, 770 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ = 7.22-7.14 (m, 2H), 7.56-7.47 (m, 4H), 8.22-8.17 (m, 2H), 8.78 (d, 1H, J = 6.0 Hz).

^{13}C NMR (75 MHz, CDCl_3) δ = 165.1 (d, $^1J_{\text{CF}}$ = 185 Hz), 163.3, 161.0, 157.6, 136.8, 132.4 (d, $^4J_{\text{CF}}$ = 3 Hz), 129.8, 129.3 (d, $^3J_{\text{CF}}$ = 8 Hz), 129.9, 127.4, 126.9, 116.2 (d, $^2J_{\text{CF}}$ = 18).

HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{11}\text{N}_2\text{F}$: 250.0906; found: 250.0909.

2-(4-methoxyphenyl)-4-trans-heptenylpyrimidine

The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with a 40% ethyl acetate in hexanes to afford 112 mg (62%) of the purified, decoupled product as yellow oil.

IR (neat): 3003, 2879, 1712, 1554, 1437, 1331, 1215, 1177, 1119, 1040, 911, 770 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ = 0.79 (t, 3H, J = 7.0 Hz), 1.35-1.16 (m, 6H), 2.09-1.98 (m, 2H), 3.88 (s, 3H), 6.45 (d, 1H, J = 14 Hz), 7.08-6.98 (m, 3H), 7.25-7.14 (m, 1H), 8.51 (d, 2H, J = 7.5 Hz), 8.61 (d, 1H, J = 6 Hz).

^{13}C NMR (75 MHz, CDCl_3) δ = 164.0, 162.2, 161.7, 157.3, 140.1, 129.2, 128.7, 128.0, 113.1, 112.2, 55.0, 31.3, 30.4, 27.4, 20.8, 13.5.

HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$: 282.1732; found: 282.1731.

4-(4-methoxyphenyl)-2-trans-heptenylpyrimidine

The crude product was purified by preparatory thin-layer chromatography on silica gel (60 Å thickness) eluting with 40% ethyl acetate in hexanes to afford 180 mg (95%) of the purified, decoupled product as yellow oil.

IR (neat): 3003, 2879, 1712, 1554, 1437, 1331, 1215, 1177, 1119, 1040, 911, 770 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ 0.90 (t, 3H, $J = 8.0$ Hz), 1.25–1.45 (m, 6H), 3.88 (s, 3H), 6.41 (d, 1H, $J = 15$ Hz), 6.90–6.99 (m, 3H), 7.11–7.17 (m, 1H), 7.24–7.18 (m, 1H), 8.41 (d, 2H, $J = 7.5$ Hz), 8.68 (d, 1H, $J = 6$ Hz).

^{13}C NMR (75 MHz, CDCl_3) δ = 164.0, 162.7, 161.5, 127.3, 140.1, 129.9, 128.0, 127.3, 114.1, 113.0, 58.0, 32.0, 31.1, 28.4, 23.3, 14.5.

HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$: 282.1732; found: 282.1736.

Acknowledgments

Financial support by the NIH (2R15GM074662-02A1) and a gift of boronic acids by Frontier Scientific is gratefully acknowledged.

References

1. For examples, see: Li JJ. Name Reactions in Heterocyclic Chemistry. 2005 New York: John Wiley and Sons:536..
2. Li, JJ.; Gribble, GW. Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist. London: Elsevier; 2007. p. 475
3. (a) Varallo S, Handy ST. Synthesis. 2009;138.(b) Handy ST, Mayi D. Tetrahedron Lett. 2007; 46:8108. [PubMed: 19008934] (c) Handy ST, Wilson T, Muth A. J. Org. Chem. 2007; 72:48496.(d) Zhang Y, Handy ST. Open Journal of Organic Chemistry. 2008;58.(e) Handy ST, Zhang Y. Synthesis. 2006;3883.(f) Handy ST, Sabatini JJ. Org. Lett. 2006; 8:1537. [PubMed: 16597104]
4. For a review of regioselective couplings of heteroaromatic systems, see: Schroeter S, Stock C, Bach T. Tetrahedron. 2005; 61:2245..
5. Handy ST, Zhang Y. Chem. Commun. 2006;299.
6. For the earliest report of regioselectivity in a cross-coupling of 2,4-dichloropyrimidine, see: Solberg J, Undheim K. Acta Chem. Scand. 1989; 43:62...
7. Garcia Y, Schoenebeck F, Legault CY, Merlic CA, Houk KN. J. Am. Chem. Soc. 2009; 131:6632. [PubMed: 19368385]
8. (a) Rheault TR, Donaldson KH, Cheung M. Tetrahedron Lett. 2009; 50:1399.(b) Gong B, Hong F, Kohm C, Jenkins S, Tulinsky J, Bhatt R, de Vries P, Singer JW, Klein P. Bioorg. & Med. Chem. Lett. 2004; 14:2303. [PubMed: 15081029] (c) Blackaby WP, Atack JR, Bromidge F, Castro JL, Goodacre SC, Hallett DJ, Lewis RT, Marshall GR, Pike A, Smith AJ, Street LJ, Tattersall DFD, Wafford KA. Bioorg. & Med. Chem. Lett. 2006; 16:1175. [PubMed: 16406613] (d) Wang X, Chakrabarti PP, Ognyanov VI, Pettus LH, Tamir R, Tan H, Tang P, Treanor JJS, Gavva NR, Norman MH. Bioorg. & Chem. Lett. 2007; 17:6539.(e) Parry PR, Wang C, Batsanov AS, Bryce MR, Tarbit B. J. Org. Chem. 2002; 67:7541. [PubMed: 12375993] (f) Delia TJ, Schomaker JM, Kalinda AS. J. Heterocyclic Chem. 2006; 43:127.(g) Ceide SC, Montalban AG. Tetrahedron Lett. 2006; 47:4415.(h) Schomaker JM, Delia TJ. J. Org. Chem. 2001; 66:7125. [PubMed: 11597240] (i) Colombo M, Giglio M, Peretto I. J. Heterocyclic Chem. 2008; 45:1077.(j) Liu J, Fitzgerald AE, Mani NS. J. Org. Chem. 2008; 73:2951. [PubMed: 18331061] (k) Cocuzza AJ, Hobbs FW, Arnold CR, Chidester DR, Yarem JA, Culp S, Fitzgerald L, Gilligan PJ. Bioorg. & Med. Chem. Lett. 1999; 9:1057. [PubMed: 10230640]
9. Gong Y, Pauls HW. Synlett. 2000;829.

10. Mavunkel B, Xu Y, Goyal B, Lim D, Lu Q, Chen Z, Wang D, Higaki J, Chakraborty I, Liclican A, Sideris S, Laney M, Delling U, Catalano R, Higgins LS, Wang H, Wang J, Feng Y, Dugar S, Levy DE. *Bioorg. & Med. Chem. Lett.* 2008; 18:2404. [PubMed: 18334293]
11. Geneste H, Sauer D. Preparation of piperazinylalkylpyrimidinones as dopamine D3 receptor ligands. *Ger. Offen.* 2006
12. Colombo M, Giglio M, Peretto I. *J. Heterocyclic Chem.* 2008; 45:1077.
13. Abbiati G, Arcadi A, Canevari V, Rossi E. *Tetrahedron Lett.* 2007; 48:8491.
14. Seki M, Kubota H, Matsumoto K, Kinumaki A, Da-te T, Okamura K. *J. Org. Chem.* 1993; 58:6354.

Figure 1.
Representative substituted Pyrimidines

Stepwise Approach

Polycoupling Approach

Scheme 1.
Cross-coupling Approaches

Scheme 2.

Regioselectivity in the Suzuki coupling of 2,4-dichloropyrimidine

Table 1

Solvent and Temperature Studies for the Monocoupling of 2,4-dichloropyrimidine

Entry	Solvent	Temperature	Time	Yield
1	Methanol	RT	3 h	37%
2	Methanol	RT	Overnight	30%
3	Ethanol	RT	Overnight	47%
4	Ethanol	55 °C	Overnight	51%

Table 2

Coupling at C2

Entry	Solvent	Temperature	Yield
1	MeOH/Tol	RT	NR
2	MeOH/Tol	55 °C	NR
3	EtOH/Tol/H ₂ O	90 °C	52%

Table 3

One-pot Double Couplings

Entry	R	R'	Yield
1	Ph	p-MeOC ₆ H ₄	84%
2	p-MeOC ₆ H ₄	Ph	39%
3	p-FC ₆ H ₄	p-MeOC ₆ H ₄	65%
4	p-MeOC ₆ H ₄	p-FC ₆ H ₄	62%
5	Ph	Trans-Heptenyl	95%
6	Trans-Heptenyl	Ph	62%
7	o-MeOC ₆ H ₄	Ph	21%
8	Ph	o-MeOC ₆ H ₄	15%