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Article

Coupling Reaction of Organoboronic Acids with Chloropyrimidines and Trichlorotriazine†

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Pd-catalyzed cross-coupling reactions of chloropyrimidines with alkenylboronic acids readily proceed to give the corresponding alkenylpyrimidines in high to excellent yields. The coupling reaction of 2,4-dichloropyrimidine or 2,4,6-trichloropyrimidine with one equivalent of alkenylboronic acid occurred more easily on 4-position than on 2-position, which implied that the reaction is highly regioselective. The reaction is stereospecific since the configuration of C=C remained intact. The preliminary study on the cross-coupling reactions of 2,4,6-trichlorotriazine with one equivalent of arylboronic acids showed that the reactions afforded the monosubstituted triazines in moderate yields. The effect of steric hindrance of the substitutents on the reactions was found.

Keywords Suzuki-Miyaura cross-coupling reaction, organoboronic acid, chloropyrimidine, 2,4,6-trichloro-[1,3,5]triazine, alkenylpyrimidine, aryltriazine

Introduction

Pyrimidines and triazines frequently possess desired physiological activitives,[1] thus, it is important to develop a convenient methodology for the syntheses of substituted pyrimidines and triazines. The use of catalytic cross-coupling methodologies for preparing aryl-functionalized heterocycles with pharmaceutical, agrochemical, material and superamolecular applications is a burgeoning field of study.[2] Many methods have been developed for syntheses of *C*-aryl substituted derivatives of pyrimidine in the past decades.[3] However, the pyrimidines containing the unsaturated carbon chain were reported scarcely. The Pd-catalyzed coupling reactions of stereospecific alkenylzinc, alkenylstannane[4] and alkenylzirconcene[5] reagents were used to prepare stereodefined alkenyl-substituted pyrimidines, but these methods have their problems, *e.g.* the starting materials are toxic or difficult to obtain, and the yields are poor. The general approaches to prepare triazine derivatives involve Grignard reaction,[6] chlorination of 6-aryl-[1,3,5]triazine-2,4-dione,[7] and the condensation of *N*,*N*-dimethyl-arylamide with the *N*-cyanochloroformamidine.[8] Usually these reactions have poor tolerance for a range of functional groups and the procedures are inconvenient. The Suzuki-Miyaura type reaction, for its attractive features (high yields, mild conditions, tolerance of many functional groups, being unaffected in presence of water, *etc.*), has received considerable attention. In 2002, Molander and co-workers[9] reported an example of the coupling reaction of potassium *trans*-styryltrifluoroborate with different equivalents of 2,4,6-trichloropyrimidine to give monosubstituted pyrimidine in 55% yield and trisubstituted derivatives in 72% yield, respectively. It would be advantageous to develop cross-coupling strategies via Suzuki procedures to synthesize alkenylpyrimidines and arylsubstituted triazines. Herein we reported the results of the cross-coupling of organoboronic acids with chloropyrimidines and trichlorotriazine.

Results and discussion

The cross-coupling conditions were optimized using *trans*-heptenylboronic acid and 2-chloropyrimidine as coupling partners. The experiments showed that the catalytic result of $PdCl_2(PPh_3)_2$ was better than that of $Pd(PPh_3)_4$ and $K_3PO_4{\cdot}3H_2O$ as the base was superior to $KF{\cdot}2H_2O$ or KOH, and polar solvent (THF) was prior to nonpolar solvent for the cross-coupling reaction.

The cross-coupling reactions of various chloropyrimidines with stereodefined alkenylboronic acids were carried out under the optimized conditions ($PdCl_2(PPh_3)_2$ as catalyst, $K_3PO_4{\cdot}3H_2O$ as base, and THF as solvent). The reactions were monitored by TLC and the results are shown in Table 1.

From Table 1, it can be seen that the coupling reactions of 2-chloropyrimidine, 2,4-dichloropyrimidine or 2,4,6-trichloropyrimidine with one equivalent of

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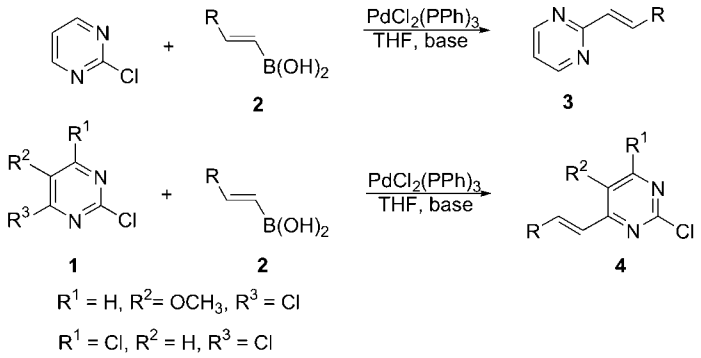
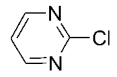
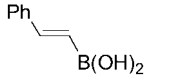
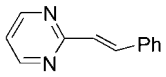
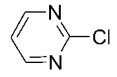
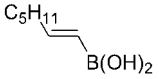
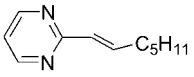
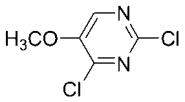
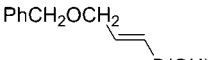
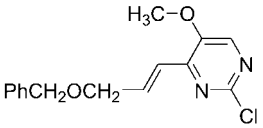
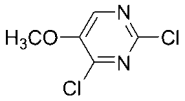
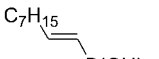
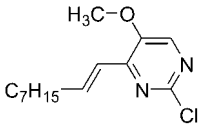
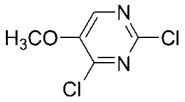
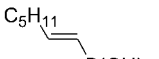
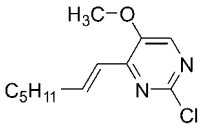
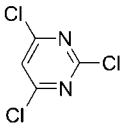
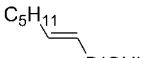
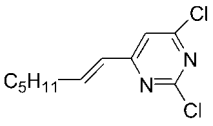
Table 1 Coupling reaction of chloropyrimidines with alkenylboronic acids[a]



Entry	Chloropyrimidine **1**	Alkenylboronic acid **2**	Product **3** or **4**		Yield[b]/%
1				**3a**	80[c]
2				**3b**	84[c]
3				**4a**	90[d]
4				**4b**	87[d]
5				**4c**	85[d]
6				**4d**	65[d]

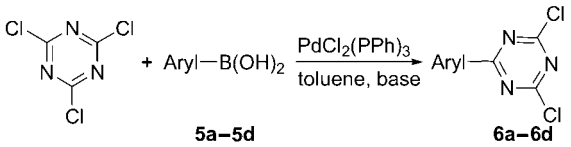
[a] The reactions were carried out using 3% mmol $PdCl_2(PPh_3)_2$, $K_3PO_4 \cdot 3H_2O$ (1 mmol), alkenylboronic acid (0.6 mmol), and chloropyrimidine (0.5 mmol) in 4 mL THF. [b] Isolated yield based on chloropyrimidines. [c] Refluxed for 24 h. [d] Refluxed for 17 h.

various trans-alkenylboronic acids gave the corresponding monoalkenyl substituted pyrimidines in good yields. The configurations of alkenyl groups are retentive as those in other Suzuki-Miyaura type reactions,[10] which was proved by the coupling constants ($J \geqslant 15.3$ Hz) of the olefinic protons of the coupling products. It also demonstrated that the reaction time for cross-couplings of 2,4-dichloropyrimidine and 2,4,6-tri-chloropyrimidine with alkenylboronic acids was shorter than that of 2-chloropyrimidine, because they had the C—Cl bond on the more electrophilic 4-position. The high regioselectivity of the cross-coupling reaction on 4-position was also observed. The ^{13}C NMR spectra confirmed the position of substitution. For example, the ^{13}C NMR spectrum of 4d showed four distinct carbon signals for pyrimidine ring, which indicates that there is an unsymmetrical substitution pattern for the pyrimidine ring, while the 2-heptenyl derivative would exhibit three signals. It is well in agreement with the previous results of coupling reactions of alkenylzincs and alkenylstannanes.[4,5] Compared with those reactions, the reaction has many advantages (high yield, starting materials are untoxic, easily available, and stable in the presence of moisture).

The preliminary experimental results showed that 2,4,6-trichloro[1,3,5]triazine reacted with one equivalent of arylboronic acids to give the monoaryl substituted coupling products in moderate yields (Table 2). The experiments showed that K_2CO_3 was a better base, and toluene was a good solvent for the coupling reaction.

In addition, the steric hindrance of the substituents seemed to have somewhat influences on the yields of coupling reaction (Table 2, Entries 2 vs. 3).

Table 2 Coupling reaction of the arylboronic acids with 2,4,6-trichloro[1,3,5]triazine[a]



5a–5d **6a–6d**

Entry	aryl	Arylboronic acid **5**	Product **6**	Yield [b]/%
1	phenyl	**5a**	**6a**	72
2	2-methylphenyl	**5b**	**6b**	44
3	4-methylphenyl	**5c**	**6c**	75
4	2-methoxyphenyl	**5d**	**6d**	49

[a] The reactions were carried out using 3% mmol of $PdCl_2(PPh_3)_2$, K_2CO_3 (1 mmol), arylboronic acid (0.5 mmol), 2,4,6-trichloro-[1,3,5]triazine (0.5 mmol) in 4 mL of toluene. [b] Isolated yield based on arylboronic acid.

In summary, we studied the Suziki-Miyaura type reaction of π-deficient heteroarylchlorides with one equivalent of organoboronic acids. The cross-coupling reactions of various chloropyrimidines with stereodefined alkenylboronic acids afforded the corresponding stereospecific alkenylpyrimidines in good to excellent yields under appropriate conditions. The regioselectivity of coupling reaction of 2,4-dichloropyrimidine and 2,4,6-trichloropyrimidine was examined, too, and it was found that the reaction occurred more easily on 4-position than on 2-position. The reaction provided a convenient route to prepare the stereodefined alkenylpyrimidines. Meanwhile the coupling reactions of trichlorotriazine with one equivalent of arylboronic acids gave monosubstituted aryltriazines in moderate yields.

Experimental

^1H and ^{13}C NMR spectra were measured at 300 MHz (MERCURY 300) using $CDCl_3$ as solvent and Me_4Si as the internal standard. IR spectra were determined by a Perkin-Elmer 983 spectrometer. Mass spectra were recorded on an HP-5989 instrument. HRMS were recorded on a Finnigan MA^+ instrument.

General procedures for the coupling reaction of 2-chloropyrimidine, or 2,4-dichloropyrimidine with alkenylboronic acids

Alkenylboronic acid (0.6 mmol), 2-chloropyrimidine (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol), and $K_3PO_4 \cdot 3H_2O$ (1.0 mmol) were placed in a flask under nitrogen atmosphere. Then 4 mL of THF was added and the reaction mixture was stirred under reflux. The reaction was monitored by TLC. After the reaction completed, the mixture was cooled to room temperature, quenched with water, and extracted with ether (3×5 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuum, followed by silica gel chromatography (ethyl acetate/hexane = 1/20) gave the corresponding coupling products.

3a: White solid, yield 80%, ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.73 (d, J=5.4 Hz, 2H), 8.00 (d, J=15.9 Hz, 1H), 7.64 (d, J=6.9 Hz, 2H), 7.38 (dt, J=15.9, 1.2 Hz, 3H), 7.25 (d, J=1.2 Hz, 1H), 7.12 (t, J=5.1 Hz, 1H) ; IR (KBr) v: 1636, 1550, 1413, 977, 803, 794, 691, 528 cm^{-1}; MS (70 eV) m/z (%): 182 (M^+, 26.45), 181 (100), 154 (3.27), 129 (4.79), 128 (7.85), 127 (3.61), 102 (6.67), 77 (4.46). Anal. calcd for $C_{12}H_{10}N_2$: C 79.10, H 5.53, N 15.37; found C 78.88, H 5.58, N 15.18.

3b: Colorless liquid, yield 84%; ^1H NMR ($CDCl_3$, 300MHz) δ: 8.64 (d, J=4.8 Hz, 2H), 7.16 (dt, J=7.2, 15.6 Hz, 1H), 7.05 (t, J=4.8 Hz, 1H), 6.54 (d, J=15.6 Hz, 1H), 2.30 (q, J=7.2 Hz, 2H), 1.60—1.21 (m, 6H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 64.68, 156.78, 142.20, 129.35, 118.16, 32.51, 28.17, 22.38, 13.89; IR (neat) v: 2959, 2929, 2858, 1654, 1569, 1555, 1421, 982 cm^{-1}; MS (70 eV) m/z (%): 176 (M^+, 27.44), 134 (19.74), 133 (84.75), 120 (25.85), 119 (100), 118 (27.54), 107 (21.74), 97 (30.60). HRMS calcd for $C_{11}H_{16}N_2$ 176.1301; found 176.1308.

4a: White solid, yield 90%, ^1H NMR δ: 8.17 (s, 1H), 7.25—7.42 (m, 6H), 7.01 (d, J=15.6 Hz, 1H), 4.62 (s, 2H), 4.29 (q, J=4.8 Hz, 2H), 3.95 (s, 3H) ; ^{13}C NMR (DMSO) δ: 152.84, 150.49, 143.63, 138.70, 138.04, 128.27, 127.52, 127.50, 119.97, 71.83, 69.08, 56.66; IR (KBr) v: 3059, 2843, 1562, 1365, 1010, 925, 698 cm^{-1}; MS (70 eV) m/z (%): 261 (11.51), 199 (7.63), 184 (9.15), 91 (100), 77 (6.31), 65 (9.39), 51 (5.30), 39 (5.40). Anal. calcd for $C_{15}H_{15}ClN_2O_2$: C 61.97, H 5.20, N 9.63; found C 62.10, H 5.17, N 9.34.

4b: White solid, yield 87%, ^1H NMR δ : 8.11 (s, 1H), 7.21—7.32 (dt, J=15.3, 6.9 Hz, 1H), 6.70 (d, J=15.3 Hz, 1H), 3.93 (s, 3H), 2.30 (q, J = 6.9 Hz, 2H), 1.20—1.59 (m, 10H), 0.88 (t, J=4.5 Hz, 3H); IR (KBr) v: 2925, 1684, 1561, 1425, 1356, 1278, 1015, 650 cm^{-1}; MS (70 eV) m/z (%): 197 (31.60), 171 (24.47), 86 (63.14), 85 (30.62), 84 (100), 71 (35.47), 57 (48.10), 43 (32.42). Anal. calcd for $C_{14}H_{21}ClN_2O$: C 62.56, H 7.8 7, N 10.42; found C 62.70, H 7.66, N 10.28.

4c: Colorless liquid, yield 85%, ^1H NMR δ: 8.11 (s, 1H), 7.21—7.33 (dt, J_1=15.6, 7.2 Hz, 1H), 6.72 (d, J= 15.6 Hz, 1H), 3.93 (s, 3H), 2.30 (t, J=7.2 Hz, 2H), 1.20—1.56 (m, 6H), 0.90 (t, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 155.09, 151.86, 148.63, 144.45, 141.12, 120.78, 56.24, 33.26, 31.38, 28.10, 22.42, 13.94; IR (neat) v: 3057, 2959, 2932, 1647, 1561, 1355, 1015, 651 cm^{-1}; MS (70 eV) m/z (%): 240 (M^+, 45.34), 205 (39.49), 197 (100), 183 (38.70), 182 (34.46), 171 (35.46), 41 (53.77), 39 (33.89). Anal. calcd for $C_{12}H_{17}$-

ClN_2O: C 59.87, H 7.12, N 11.64; found C 60.15, H 7.10, N 11.68.

4d: Colorless liquid, yield 65%, ^{1}H NMR δ: 7.13—7.25 (dt, J=15.6, 6.9 Hz, 1H), 7.11 (s, 1H), 6.32 (d, J=15.6 Hz, 1H), 2.29 (t, J=6.9 Hz, 2H), 1.50 (t, J=6.0 Hz, 2H), 1.31 (t, J=6.6 Hz, 4H), 0.89 (t, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 166.75, 162.32, 160.35, 145.92, 125.84, 116.05, 32.94, 31.30, 27.87, 22.39, 13.92; IR (neat) v: 2959, 2930, 1650, 1556, 1511, 1261, 1123, 980, 829 cm^{-1}; MS (70 eV) m/z (%): 203 (63.42), 201 (100), 175 (70.56), 162 (64.45), 71 (54.41), 57 (81.83), 43 (67.20), 41 (90.27). HRMS calcd for $C_{11}H_{14}Cl_2N_2$ 245.0615, found 245.0606.

General procedure for the coupling reaction of 2,4,6-trichloro-[1,3,5]triazine with arylboronic acids

Arylboronic acid (0.5 mmol), 2,4,6-trichlorotriazine (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol), and K_2CO_3 (1.5 mmol) were placed in a flask under nitrogen atmosphere. Then toluene (4 mL) was added, the mixture was stirred at 80 ℃ and monitored by TLC. After the reaction completed, the mixture was cooled to room temperature and filtered (washed with ether (3×5 mL)). The combined filtrate was evaporated and the residue was purified by silica gel chromatography to give the corresponding coupling products.

6a: White solid, yield 72%, ^{1}H NMR δ: 8.47—8.58 (m, 2H), 7.64—7.72 (m, 1H), 7.48—7.60 (m, 2H) ; IR (KBr) v: 1527, 1383, 1258, 1110, 840, 771, 697, 651 cm^{-1}; MS (70 eV) m/z (%): 226 (M^+, 16.44), 227 (64.76), 225 (100), 129 (76.78), 103 (56.24), 87 (47.30), 77 (22.37), 76 (34.39), 51 (22.82). Anal. calcd for $C_9H_5Cl_2N_3$: C 47.82, H 2.23, N 18.59; found C 48.11, H 2.50, N 18.73.

6b: White solid, yield 49%, ^{1}H NMR δ: 8.22 (d, J=8 Hz, 1H), 7.49 (t, J=8 Hz, 1H), 7.35 (t, J=8 Hz, 2 H), 2.71 (s, 3H) ; IR (KBr) v: 1602, 1528, 1301, 1245, 852, 844, 769, 645 cm^{-1}; MS (70 eV) m/z (%): 241 (57.53), 239 (89.07), 238 (100), 117 (96.87), 116 (84.81), 89 (74.40), 62 (62.71). Anal. calcd for $C_{10}H_7Cl_2N_3$: C 50.03, H 2.94, N 17.50; found C 50.32, H 3.03, N 17.32.

6c: White solid, yield 75%, m.p. 146.5—147 ℃, ^{1}H NMR δ: 8.39 (d, J=8 Hz, 2H), 7.33 (d, J=8 Hz, 2H), 2.46 (s, 3H); IR (KBr) v: 1611, 1531, 1388, 1261, 1246, 859, 842, 798 cm^{-1}; MS (70 eV) m/z (%): 240 (M^+, 10.75), 239 (60.02), 143 (30.30), 117 (100), 90 (22.31), 87 (32.13).

6d: White solid, yield, 44%, ^{1}H NMR δ: 8.01—8.06 (m, 1H), 7.54—7.62 (m, 1H), 7.04—7.13 (m, 2H), 3.93 (s, 3H); IR (KBr) v: 1529, 1484, 1239, 1017, 840, 811, 764 cm^{-1}; MS (70 eV) m/z (%): 214 (36.94), 158 (100), 129 (30.46), 124 (22.60), 104 (23.31), 90 (24.78), 87 (28.84), 63 26.51). Anal. calcd for $C_{10}H_7Cl_2N_3O$: C 46.90, H 2.76, N 16.41; found C 47.03, H 2.78, N 16.86.

References

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