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A highly regioselective synthesis of 2-aryl-6-chlorobenzothiazoles employing microwave-promoted Suzuki–Miyaura coupling reaction

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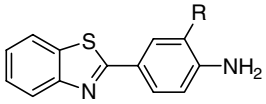
Abstract—Suzuki–Miyaura coupling reactions of 2,6-dichlorobenzothiazole with arylboronic acids, promoted by microwave heating, efficiently produce 2-aryl-6-chlorobenzothiazoles in a highly regioselective manner. This process serves as the foundation for a simple method to rapidly construct 2-aryl-6-chlorobenzothiazole libraries.

2-Arylbenzothiazoles have received much attention due to their unique structures and interesting biological properties that lead to their use as radioactive amyloid imaging agents,[1] anticancer agents,[2] antituberculotics,[3] calcium channel antagonists,[4] and biological photooxidizing agents.[5] Especially interesting are 2-(4-aminophenyl)-benzothiazole derivatives (e.g., **1** and **2**), which exhibit potent and selective in vitro antitumor activity against certain breast, ovarian, renal, colon, and lung tumor cell lines.[2] Although a large number of methods have been presented for the synthesis of 2-arylbenzothiazole,[6,7] the Suzuki–Miyaura coupling reaction[8] is one of the most efficient for this purpose.

In an earlier report, Kumar et al. described the Suzuki–Miyaura reaction of 2-bromobenzothiazole under conventional heating conditions.[9] The use of microwave heating[10,11] to promote these reactions would be of interest since it would allow for high-speed construction of products while potentially maintaining a high level of control of regioselectivity in dual functionalized substrates. In order to test this proposal, we have investigated Suzuki–Miyaura coupling reactions of commercially available 2,6-dichlorobenzothiazole (**3**) with arylboronic acids under microwave heating conditions. The results of this effort, presented below, show that this process can be used to produce a variety of 2-aryl-6-chlorobenzothiazoles with a high degree of regiochemical control.



R = CH_3 (**1**)
R = F (**2**)

Based on a consideration of the electronic nature of 2,6-chlorobenzothiazole, we anticipated that the C-2 position would be more reactive in palladium-catalyzed coupling processes.[12,13] Following a procedure developed earlier in our laboratory,[14] microwave-promoted Suzuki–Miyaura reaction of 2,6-chlorobenzothiazole (**3**) with phenylboronic acid (**4a**) was carried out by using $Pd(PPh_3)_4$ as the catalyst. This reaction efficiently provides the adduct **6a** with excellent regioselectivity. The structure assignment of **6a** was easily made by analysis of its spectroscopic data. Particularly informative is the characteristic chemical shift change that occurs at C-2 in ^{13}C NMR spectrum of **3** (153.8 ppm) and **6a** (168.5 ppm). In an attempt to obtain the bis-adduct, 2,6-diphenylbenzothiazole (**7**), the $Pd(PPh_3)_4$ catalyzed reaction of 2,6-chlorobenzothiazole (**3**) with a 3 equiv excess of phenylboronic acid was performed (Table 1, entry 1). However, this process provides 2-phenyl-6-chlorobenzothiazole (**6a**) exclusively. In contrast, when reaction of **3** with excess **4a** is conducted in the presence of $Pd(PPh_3)_4$ and the biphenyl substituted phosphine **5**, 2,6-diphenylbenzothiazole (**7**) is produced as the major

Keywords: Suzuki–Miyaura reaction; Palladium; Boronic acid; Microwave; Benzothiazole; Amination.
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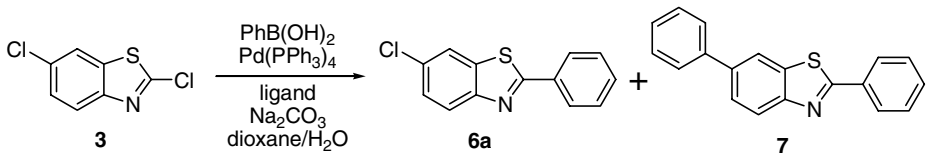
Table 1. Suzuki–Miyaura coupling reactions of 2,6-dichlorobenzothiazole (**3**) with excess phenylboronic acid (**4a**)[a]

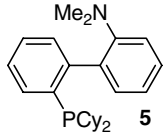


Entry	Ligand	Conditions[a]	Yield (%)[b]	
			6a	**7**
1	None	Microwave, 150 °C, 5 min	65	0
2	**5**[c]	Microwave, 150 °C, 15 min	(6)[d]	69 (77)[d]

[a] Reaction conditions: 2,6-dichlorobenzothiazole **3** (1 mmol), $Pd(PPh_3)_4$ (4 mol %), phenylboronic acid **4a** (3.0 mmol), Na_2CO_3 (2.4 mmol), dioxane/H_2O (4 mL/1 mL).

[b] Isolated yield.

[c] 2-*N*,*N*-Dimethylamino-2′-dicyclohexylphosphinobiphenyl (**5**) was used (8 mol %).

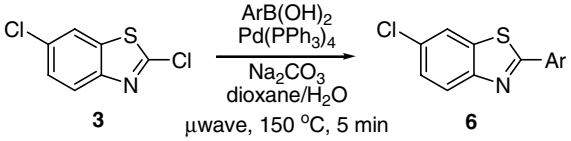


[d] GC yield.

product after a prolonged reaction time (entry 2). This observation suggests that the catalytic activity of palladium is activated by ligation with the biphenylphosphine **5**.[15]

Suzuki–Miyaura reactions of 2,6-dichlorobenzothiazole (**3**) with a broad variety of arylboronic acids were explored. As the results in Table 2 illustrate, these processes produce coupling products **6a**–**m** in moderate

Table 2. Suzuki–Miyaura coupling of 2,6-dichlorobenzothiazole (**3**) with arylboronic acids[a]



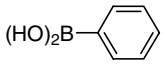
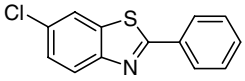
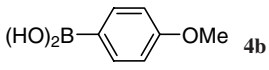
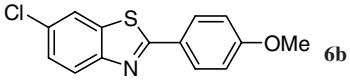
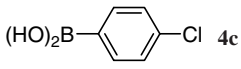
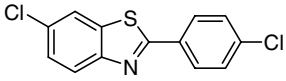
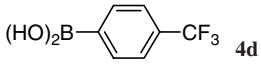
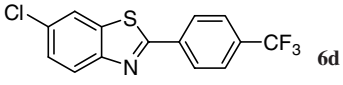
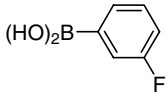
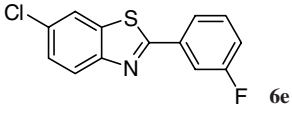
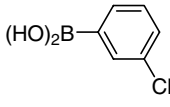
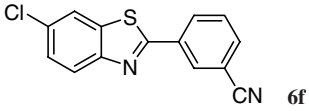
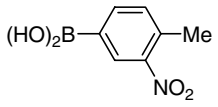
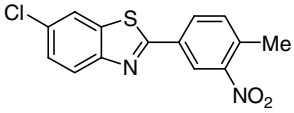
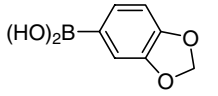
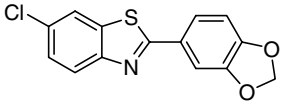
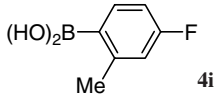
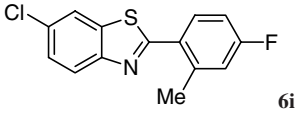
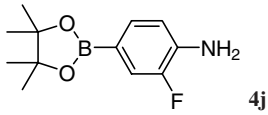
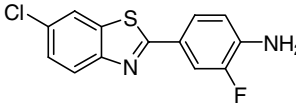
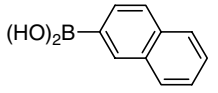
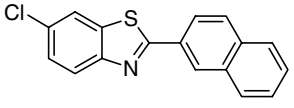
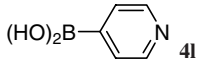
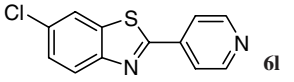
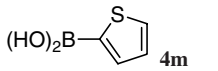
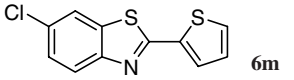
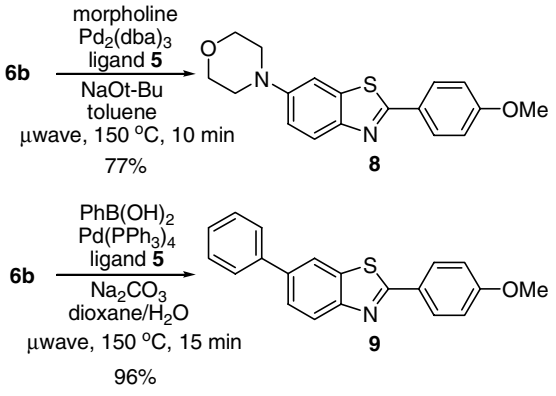
Entry	$ArB(OH)_2$	Product	Yield (%)[b]
1	 **4a**	 **6a**	75
2	 **4b**	 **6b**	79
3	 **4c**	 **6c**	65
4	 **4d**	 **6d**	67
5	 **4e**	 **6e**	77
6	 **4f**	 **6f**	65

Table 2 (*continued*)

Entry	$ArB(OH)_2$	Product	Yield (%)[b]
7	 **4g**	 **6g**	57
8	 **4h**	 **6h**	72
9	 **4i**	 **6i**	59
10	 **4j**	 **6j**	65
11	 **4k**	 **6k**	64
12	 **4l**	 **6l**	60
13	 **4m**	 **6m**	64

[a] Reaction conditions: 2,6-dichlorobenzothiazole (0.5 mmol), $ArB(OH)_2$ (**4**) (0.6 mmol), $Pd(PPh_3)_4$ (4 mol %), Na_2CO_3 (2.4 equiv), dioxane/H_2O (4 mL/1 mL), microwave, 150 °C, 5 min.
[b] Isolated yield.

to good yields.[16] It is noteworthy that the reaction takes place with both electron-withdrawing and electron-donating substituted arylboronic acids. However, the reaction of 4-methyl-3-nitrophenylboronic acid is sluggish and provides the mono-adduct **6g** in only moderate yield (entry 7). Suzuki–Miyaura coupling reaction of **3** with the *ortho*-methyl substituted boronic acid **4i** proceeds smoothly to afford the coupling product **6i** in 59% yield (entry 9). To demonstrate that this approach can be used to prepare aminophenyl-substituted benzothiazole, arylboronic acid **4j**[17] was reacted with **3** to form adduct **6j** in good yield (entry 10). The process is also effective with heteroarylboronic acids (entries 11–13), giving the corresponding coupling products in good yields.



Scheme 1.

To demonstrate the overall power of the microwave-promoted Suzuki–Miyaura coupling reaction, we have explored the use of the mono-adducts **6**, generated in this manner, as substrates for well-known palladium-catalyzed reactions (Scheme 1). For example, palladium catalyzed amination reaction of **6b** with morpholine in the presence of biphenylphosphine **5** under microwave heating conditions takes place efficiently to furnish 6-morpholinyl-benzothiazole **8** in 77% yield.[18] It is noteworthy that this amination process occurs at the less activated 6-chloro position of **6b** when the biphenyl ligand **5** is employed but not when BINAP is used. In addition, Suzuki–Miyaura reaction of **6b** with phenylboronic acid in the presence of **5** provides coupling product **9** in excellent yield. This result demonstrates that a sequential Suzuki–Miyaura reaction route can be used for the synthesis of orthogonally substituted diaryl-benzothiazoles.

In summary, we have developed a general and highly regioselective methodology for the efficient synthesis of 2-aryl-6-chlorobenzothiazoles based on Suzuki–Miyaura reactions of 2,6-dichlorobenzothiazole with arylboronic acids under microwave irradiation. In addition, the chloride functionality in the 2-aryl-6-chlorobenzothiazoles, produced in this manner, can be used to guide subsequent metal catalyzed transformations to form interesting target substances. Continuing studies are underway in our laboratory to biologically evaluate the benzothiazole derivatives produced in the current effort.

Acknowledgments

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16. General procedure for Suzuki–Miyaura reaction. Reactions were conducted by using a Biotage Initiator EXP™ microwave reactor. To a thick-well borosilicate glass vial (5 mL) was added 2,6-dichlorobenzothiazole **3** (1 mmol), $Pd(PPh_3)_4$ (4 mol %), arylboronic acid **4** (1.2 mmol), and Na_2CO_3 (2.4 mmol) sequentially. The mixture was dissolved in dioxane/H_2O (4 mL/1 mL) and degassed with argon over a 5 min period. Then, the reaction vial was sealed and placed in the microwave reactor and irradiated at 150 °C for 5 min. After being cooled to rt, the mixture was diluted with EtOAc, dried over $MgSO_4$, and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was subjected to silica gel flash column chromatography (EtOAc/hexanes) to yield the product. Adduct **6b**, mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, 2H, $J = 6.8$, 2.1 Hz), 7.92 (d, 1H, $J = 8.7$ Hz), 7.85 (d, 1H, $J = 2.1$ Hz), 7.42 (dd, 1H, $J = 8.7$, 2.1 Hz), 7.00 (dd, 2H, $J = 6.8$, 2.1 Hz), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 162.3, 153.0, 136.2, 130.8, 129.3, 127.2, 126.2, 123.7, 121.3, 114.6, 55.7; MS (EI) m/z M^+ for $C_{14}H_{10}ClNOS$ calcd 275.02, found 277 (34), 275 (M^+, 100), 260 (28), 232 (16), 197 (16), 188 (5), 149 (5).
17. Appukkuttan, P.; Eycken, E. V.; Dehaen, W. *Synlett* **2003**, *18*, 1204.
18. (a) Heo, J.-N.; Song, Y. S.; Kim, B. T. *Tetrahedron Lett.* **2005**, *46*, 4621; (b) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965; Procedure for palladium-catalyzed amination: To a thick-well borosilicate glass vial (5 mL) was added benzothiazole **6b** (149 mg, 0.54 mmol), $Pd_2(dba)_3$ (3 mg, 1 mol % of Pd), **5** (3 mg, 1.5 mol %), morpholine (56 μL, 0.65 mmol), and NaO*t*-Bu (73 mg, 0.76 mmol) sequentially. The mixture was dissolved in toluene (3 mL) and degassed with argon over 5 min. Then, the reaction vial was sealed and placed in the microwave reactor and irradiated at 150 °C for 10 min. After cooled to rt, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by silica gel flash column chromatography (40% EtOAc/hexanes) to provide **8** (136 mg, 77%): mp 180–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, 2H, $J = 8.8$ Hz), 7.84 (d, 1H, $J = 9.0$ Hz), 7.56 (d, 1H, $J = 2.3$ Hz), 7.21 (dd, 1H, $J = 9.0$, 2.4 Hz), 7.09 (d, 2H, $J = 8.8$ Hz), 3.84 (s, 3H), 3.77 (t, 4H, $J = 4.7$ Hz), 3.20 (t, 4H, $J = 4.7$ Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 163.4, 161.2, 149.1, 147.2, 135.9, 128.3, 125.9, 122.5, 116.0, 114.7, 106.5, 66.1, 55.4, 48.9; LC/MS (ESI) m/z M^+ for $C_{18}H_{18}N_2O_2S_2$ calcd 326.11, found 326.72.