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Microwave-assisted cross-coupling of 3-chloro-2-pyrazolines and 3-chloro-1-phenyl-1,4,5,6-tetrahydropyridazine with aryl boronic acids

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Abstract—3-Chloro-1-phenyl-2-pyrazoline and 3-chloro-1-phenyl-1,4,5,6-tetrahydropyridazine were coupled with aryl boronic acids in good yields under microwave heating conditions (140 °C, 5 min).

The palladium-catalyzed cross-coupling of aryl halides or triflates with organoboron reagents (Suzuki coupling) is one of the most versatile and utilized reactions for the construction of carbon–carbon bonds. The scope of Suzuki cross-coupling has been extended through the use of alkenyl halides, alkenyl triflates,[1] or alkyl halides[2] as coupling partners. Recently, Nadin and co-workers have reported the cross-coupling of the C-5 imidoyl chlorides of 1,4-benzodiazepines with organoboron reagents.[3] In contrast to the numerous studies on the transition metal-catalyzed cross-coupling reactions of alkenyl halides or triflates, examples involving imidoyl halides or triflates are rare. There have been a number of examples of the transition metal-catalyzed cross-coupling of imidoyl chlorides or triflates with organotin reagents,[4] alkynes,[5] organocopper reagents,[6] organomagnesium reagents,[7] organozinc reagents,[3,8] and primary amines.[9] Uneyama has reported the cross-coupling of the fluorinated imidoyl iodides, including the Pd(0)-catalyzed cross-coupling with alkenes and alkynes,[10] and the Rh(I)-catalyzed coupling cyclization with alkynes.[11] The cross-coupling of the lactam-derived imidoyl triflates with a chelated formate has also been reported recently.[12] Herein, we report the microwave-assisted cross-coupling of 3-chloro-1-phenyl-2-pyrazoline and 3-chloro-1-phenyl-1,4,5,6-tetrahydropyridazine with aryl boronic acids. To the best of our knowledge, it is the first time these two species have been used in the Suzuki-type cross-coupling.

Microwave irradiation has been widely applied in organic synthesis.[13] Many organic transformations, including Suzuki coupling,[14] have been accelerated by subjecting them to microwave irradiation. As a starting point for the development of our microwave-assisted methodology, we chose to study 3-chloro-1-phenyl-2-pyrazoline **2**, which can be prepared from commercially available 1-phenyl-3-pyrazolidinone following a procedure described by Dowlatshahi (Scheme 1).[15] Under microwave heating conditions, a list of Pd catalysts were screened in the cross-coupling of **2** with 2-naphthaleneboronic acid. In a typical experiment, a mixture of 1.0 equiv of **2** and 1.1 equiv of 2-naphthaleneboronic acid in acetonitrile was microwave heated for 5 min in the presence of 2.2 equiv of sodium carbonate (1.0 M aqueous solution) and 5 mol % of palladium catalyst. After aqueous work-up, the crude products were subjected to ^{1}H NMR analyses to determine the product/reactant ratios.

As shown in Table 1, $Pd(PPh_3)_4$ gave the best result with a conversion of 90% being achieved at 140 °C for 5 min (entry 1). When $Pd(PPh_3)_2Cl_2$ was used, the conversion

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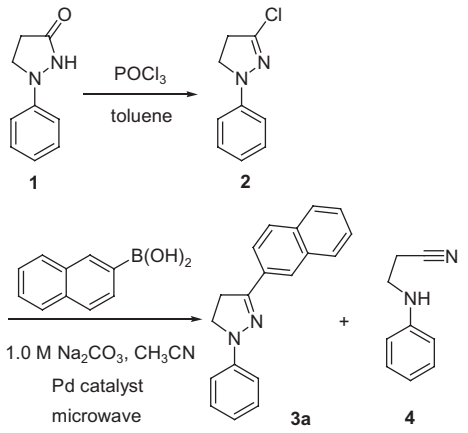


Scheme 1.

Table 1. Cross-coupling of **2** under different conditions

Entry	Microwave conditions[a]	Reactant/product ratio **2**:**3a**:**4**[b]
1	$Pd(PPh_3)_4$, 140 °C, 5 min	1:90:9
2	$Pd(PPh_3)_2Cl_2$, 140 °C, 5 min	0:85:15
3	$Pd(PPh_3)_2Cl_2$, 120 °C, 5 min	1:88:11
4	$Pd(dppf)Cl_2$, 140 °C, 5 min	8:78:14
5	$Pd(OAc)_2$, 140 °C, 5 min	67:9:24
6	10% Pd/C, 140 °C, 5 min	72:13:15
7	$Pd_2(dba)_3$, 140 °C, 5 min	93:0:7

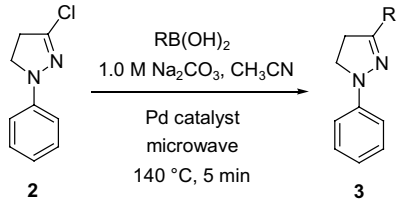
[a] Reaction conditions: 5 mol % of palladium catalyst, 1.1 equiv of boronic acid and 2.2 equiv of sodium carbonate were used.
[b] Determined by ^1H NMR analyses of the crude products after aqueous workup; errors estimated as ±5%.

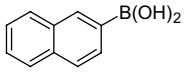
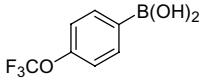
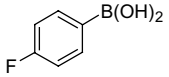
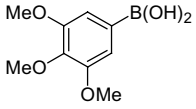
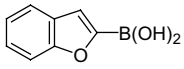
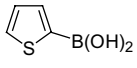
of **2** to **3a** was 85% at 140 °C (entry 2), and 88% at 120 °C (entry 3). $Pd(dppf)Cl_2$ gave a conversion of 78% at 140 °C for 5 min (entry 4). Under the same microwave condition, <15% conversion was observed with $Pd(OAc)_2$ (entry 5) and 10% Pd/C (entry 6). No product formation was observed when $Pd_2(dba)_3$ was used (entry 7). A ring-opening species **4** was detected as the only side product (entries 1–7).[16] The reduction or hydrolysis species was not observed in these reactions. It was surprising that pyrazoline **2** was very stable to the basic aqueous environment under microwave heating conditions (entries 5–7). Similar observation was reported in the cross-coupling of the C-5 imidoyl chlorides of 1,4-benzodiazepines with organoboron reagents.[3]

The microwave conditions from entry 1 and entry 2 in Table 1 were utilized for the cross-coupling of **2** with different boronic acids (Table 2). Good yields were observed for electron rich, electron deficient, and heteroaryl boronic acids. With 2-thiopheneboronic acid, the yield was improved from 43 (condition A) to 61 (condition C) by doubling the loading of catalyst and reagents.

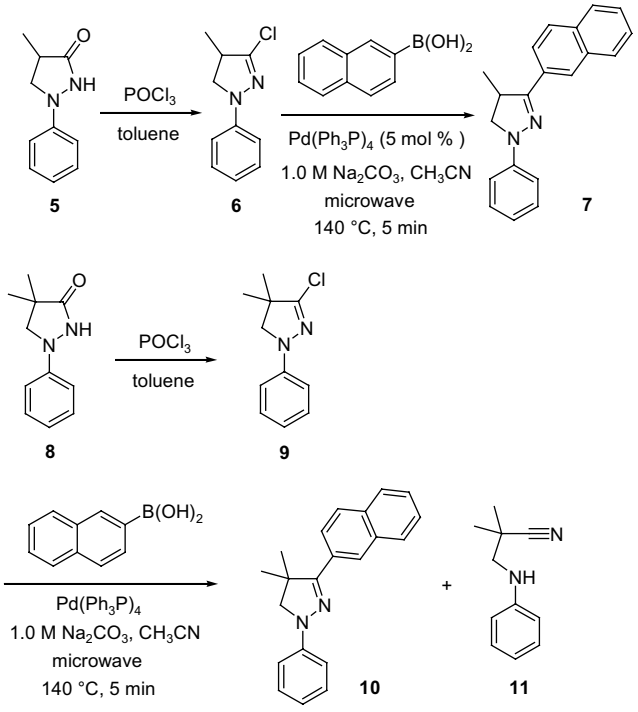
Two C4 substituted pyrazolines **6** and **9** were also prepared following the general $POCl_3$ procedure (Scheme 2).[15] The C4 monosubstituted pyrazoline **6** gave 64% isolated yield in the cross-coupling with 2-naphthaleneboronic acid (140 °C, 5 min). However, under the same condition, the C4 disubstituted pyrazoline **9** gave a much lower yield (34%) due to the increasing steric hindrance (Table 3, entry 1). With 10 mol % of $Pd(Ph_3P)_4$, a conversion of 46% was achieved (entry 2). Increasing the $Pd(Ph_3P)_4$ loading to 15 mol % led to a conversion of 48% (entry 3). No further conversion improvement was observed when 20 mol % $Pd(Ph_3P)_4$ was used (entry 4). It was surprising that 2.0 equiv of 2-naphthaleneboronic acid and 4.0 equiv of base caused a decrease of conversion (entries 2 and 5). The best reaction temperature was found to be 160 °C (entry 6), and above this temperature, the conversion decreased possibly due to the decomposition of the catalyst (entries 7 and 8). Increasing the reaction time to 15 min gave a conversion of 39%, while a higher percentage of ring-opening side product was also observed (entry 9). A combination of the advantageous factors (entries 3, 6 and 9) led to the best microwave condition (15 mol % of $Pd(Ph_3P)_4$, 160 °C, 15 min) with a conversion of 56%.

Table 2. Cross-coupling of **2** with different boronic acids



Entry	Boronic acid	Microwave condition[a]	Yield (%)[b]
a		A B	85 (66) 90
b		A	90 (83)
c		B	90 (82)
d		B	83 (57)
e		A B	84 (73) 94
f		B	54 (42)
g		A B C	43 (18) 49 61

[a] Reaction conditions: A. 5 mol % of $Pd(PPh_3)_2Cl_2$, 1.1 equiv of boronic acid and 2.2 equiv of sodium carbonate were used; B. 5 mol % of $Pd(PPh_3)_4$, 1.1 equiv of boronic acid and 2.2 equiv of sodium carbonate were used; C. 5 mol % of $Pd(PPh_3)_2Cl_2$, 2.0 equiv of boronic acid and 4.0 equiv of sodium carbonate were used.
[b] ^1H NMR yield (isolated yield); ^1H NMR yields were determined by ^1H NMR analyses of the crude products after aqueous workup; errors estimated as ±5%.



Scheme 2.

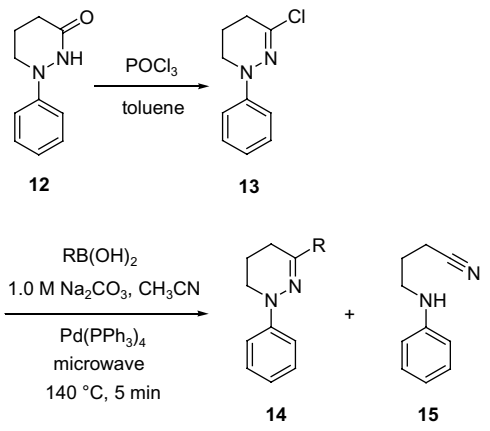
Table 3. Cross-coupling of **9** with 2-naphthaleneboronic acid

Entry	$Pd(PPh_3)_4$	Microwave condition[a]	Reactant/product ratio **9**:**10**:**11**[b]
1	5 mol %	140 °C, 5 min	59:34:7
2	10 mol %	140 °C, 5 min	45:46:9
3	15 mol %	140 °C, 5 min	42:48:10
4	20 mol %	140 °C, 5 min	45:44:11
5	10 mol %	140 °C, 5 min[c]	65:27:8
6	5 mol %	160 °C, 5 min	54:39:7
7	5 mol %	170 °C, 5 min	57:37:5
8	5 mol %	180 °C, 5 min	65:30:5
9	5 mol %	140 °C, 15 min	43:39:18
10	15 mol %	160 °C, 15 min	18:56:26

[a] Reaction conditions: 1.2 equiv of boronic acid and 2.4 equiv of sodium carbonate were used.
[b] Determined by ^1H NMR analyses of the crude products after aqueous workup; errors estimated as ±5%.
[c] Reaction conditions: 2.0 equiv of boronic acid and 4.0 equiv of sodium carbonate were used.

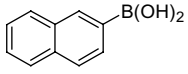
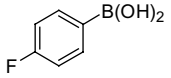
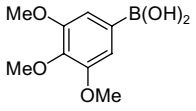
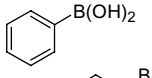
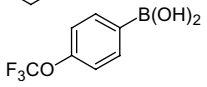
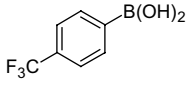
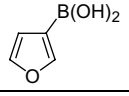
As shown in Scheme 3, 3-chloro-1-phenyl-1,4,5,6-tetrahydropyridazine **13** was prepared,[15,17–19] and subsequently coupled with a series of boronic acids to give good isolated yields under microwave heating conditions (140 °C, 5 min) (Table 4). Similar ring-opening side product **15** was formed in 10–25% yield.

In summary, we have demonstrated that the cross-coupling of 3-chloro-1-phenyl-2-pyrazoline and 3-chloro-1-phenyl-1,4,5,6-tetrahydropyridazine with aryl boronic acids can be achieved in good yields under microwave heating conditions (140 °C, 5 min). The cross-coupling of a sterically hindered pyrazoline **9** with 2-naphthaleneboronic acid afforded the product **10** in 56% yield under



Scheme 3.

Table 4. Cross-coupling of **13** with different boronic acids

Entry	Boronic acid	Yield (%)[a,b]
a		89(78)
b		85(81)
c		75(52)
d		81(80)
e		90(82)
f		88(76)
g		76(62)

[a] Reaction conditions: 5 mol % of palladium catalyst, 1.1 equiv of boronic acid and 2.2 equiv of sodium carbonate were used.
[b] ^1H NMR yield (isolated yield); ^1H NMR yields were determined by ^1H NMR analyses of the crude products after aqueous workup; errors estimated as ±5%.

the optimized microwave condition (15 mol % of $Pd(Ph_3P)_4$, 160 °C, 15 min).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.075.

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18. General procedure for the synthesis of the chloro substrates **2**, **6**, **9** and **13**: A solution of the precursor (**1**, **5**, **8** or **12**) (10 mmol) and $POCl_3$ (15 mmol, 1.4 mL) in toluene (20 mL) was heated at 70 °C for 1–2 h (monitored by TLC). After cooling to room temperature, the reaction mixture was slowly poured into a solution of sodium bicarbonate (50 mmol, 4.2 g) in ice water (100 mL), and extracted with methylene chloride (2×40 mL). The organic layers were combined, washed with brine (30 mL), diluted with hexane (80 mL), dried over sodium sulfate, and filtered through a pad of silica gel (40 mL). The silica gel was further eluted with 10% ethyl acetate/hexanes (100 mL). The organics were combined, and evaporated under vacuum to give the product, which was used in the cross-coupling reactions without further purification.
19. Typical procedure for the cross-coupling with boronic acids: A 2-5 mL Smith Process vial containing a magnetic stir bar was charged with the chloro substrate (**2**, **6**, or **13**) (0.30 mmol), boronic acid (0.33 mmol), 1.0 M Na_2CO_3 (0.66 mL, 0.66 mmol), $Pd(Ph_3P)_4$ (17.3 mg, 0.015 mmol), and acetonitrile (1.2 mL). The vial was sealed without degassing, and the suspension was heated at 140 °C for 5 min (fixed hold time) in the Smithcreator. The reaction mixture was partitioned between methylene chloride (40 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried over sodium sulfate, and filtered through Celite. The solvent was evaporated under vacuum, and the resulting crude product was purified by preparative TLC or flash chromatography.