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Synthesis of 2-arylbenzimidazoles via microwave Suzuki–Miyaura reaction of unprotected 2-chlorobenzimidazoles

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ABSTRACT

A series of 2-arylbenzimidazoles were synthesized via microwave-mediated Suzuki–Miyaura coupling of 2-chloro benzimidazoles and either arylboronic acids or aryltrifluoroborate salts. The most notable aspect of the present work is that there is no need for protection of the benzimidazoles. In addition, reaction conditions were optimized to reduce homo coupling of pyridylboronic acids.

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Benzimidazoles are privileged structural units not only in the pharmaceutical industry but also in several other fields such as agricultural, electronic, and polymer chemistry.[1–4] Therefore, methods for the introduction of the benzimidazole unit are useful across a range of diverse areas. Although there are several methods for the synthesis of 2-arylbenzimidazoles via condensation of phenylene diamines onto benzaldehydes and benzoic acids,[5] we were interested in developing a more modular method for the direct introduction of preformed benzimidazoles onto an aryl nucleus. Such a strategy would be useful for the convergent synthesis of 2-arylbenzimidazoles.

As part of our efforts directed toward the synthesis of novel benzimidazole-containing structures for our histamine H_4 modulator program,[6] we required access to variously substituted 2-arylbenzimidazoles. Ideally, the approach should allow access to the free NH benzimidazoles utilizing readily available components and catalysts directly without the need for subsequent deprotection. Given the ready availability of arylboronic acids and aryl perfluoroborates,[7] the Suzuki–Miyaura[8] reaction was a logical starting point. Although the alternate disconnection was considered, the limited precedence for synthesis of 2-metallo benzimidazoles was discouraging.

Prior to the initiation of this work, there was only one literature example of a Suzuki coupling of a 2-chlorobenzimidazole.[9] This Letter nicely demonstrated the use of microwave conditions for the Suzuki coupling of halogen-substituted heterocycles, including one example of an *N*-methyl-protected benzimidazole. We used these optimized conditions as our starting point for investigating the use of the Suzuki–Miyaura reaction for the analogous coupling of unprotected 2-chlorobenzimidazoles. More recently, we became aware of the new catalyst systems reported by Nolan and co-workers,[10,11] which also effectively catalyze the Suzuki–Miyaura coupling with 2-chlorobenzimidazoles. This report prompted us to describe our work with coupling of 2-chlorobenzimidazoles and boronic acid derivatives under Suzuki–Miyaura conditions.

Following the optimized conditions of Gong and He,[9] the Suzuki–Miyaura reaction between an unprotected 2-chlorobenzimidazole and 3-benzyloxyboronic acid led to very clean conversion to the desired product in 23% isolated yield. Simply extending the reaction time to 30 min increased the yield to 80% (Table 1).[12]

In addressing the scope of the reaction, we were particularly interested in the behavior of *ortho*-substituted arylboronic acids in this coupling reaction since such couplings can be problematic. Application of the above-mentioned protocol to 2-methoxyphenylboronic acid with a 30 min reaction time resulted in clean conversion to the desired product, albeit in lower than desired yield (Table 1). The corresponding 5-chloro-2-methoxyboronic acid also coupled in low yield. When we extended this protocol to the synthesis of the 2-methoxy pyridine derivative, we obtained a moderate yield; in addition, we detected a substantial amount of by-product derived from the homo-coupling of the pyridylboronic acid.

At this point, we initiated an optimization strategy which involved a scan of commonly used Pd sources as well as investigation of the switch to trifluoroborate salts as coupling partners. As seen in Table 2, 10% $PdCl_2(PPh_3)_2$ combined with a perfluoroborate salt provided the best conversion.

With an efficient route for coupling the unprotected 2-chlorobenzimidazoles, we looked at examining the scope of coupling partners. As seen in Table 3, the reaction is quite general in regard to the perfluoroborate coupling partner. *ortho*-Substitution does not appear to dramatically inhibit the reaction, and coupling partners with electron donating and withdrawing groups couple well. However, neither 4-hydroxyphenyl perfluoroborate nor benzyl perfluoroborate yielded desired products under these conditions.

Although the reactions were generally very clean, we were plagued by presence of the homo-coupled product in the case of

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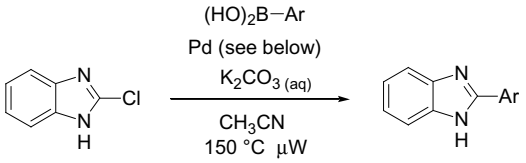
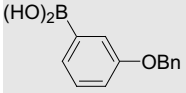
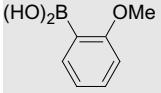
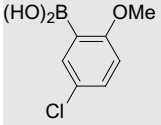
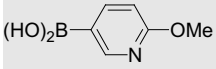
Table 1
Initial Suzuki–Miyaura conditions

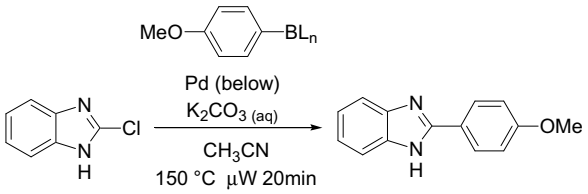


Ar–B(OH)$_2$	Pd source (10 mol %)	Time (min)	Yield (%)
	$PdCl_2(PPh_3)_2$	5	23
		30	80
	$PdCl_2(PPh_3)_2$	30	40
	$PdCl_2(PPh_3)_2$	30	27
	$PdCl_2(PPh_3)_2$	30	50

the pyridine cores. Switching our source of palladium to $PdCl_2(dppf)\cdot CH_2Cl_2$[13,14] significantly suppressed the homo-coupling such that we were able to access the 2-methoxy pyridyl derivative in >90% yield with less than 3% homo coupling product observed (Table 4).

Finally, we did a limited scan of the 2-chloro benzimidazoles and found that the reaction is generally tolerant of both electron-withdrawing- and electron-donating substituents (Table 5). Although the reaction with a 5-fluoro substituent consumed >95% of 2-chloro benzimidazole, the reaction was low yielding and contained many by-products. Interestingly, a similar coupling with 2-chloro-5-fluoro-4-methyl-benzimidazole gave a good yield of desired product (74%).

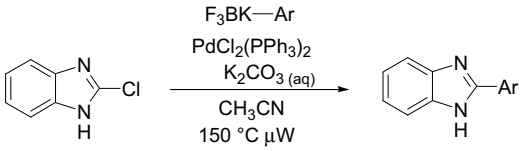
Table 2
Scan of Suzuki–Miyaura conditions

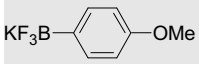
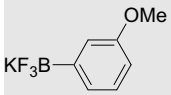
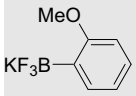
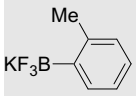
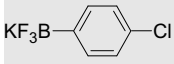
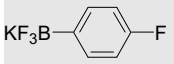
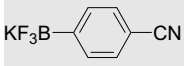
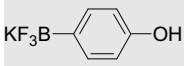
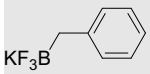


BL_n	Pd source	Pd (%)	Conv.[a] (%)
$B(OH)_2$	$Pd(OAc)_2$	10	56
KBF_3	$Pd(OAc)_2$	10	12
$B(OH)_2$	$Pd(DBA)_2$	10	24
KBF_3	$Pd(DBA)_2$	10	36
$B(OH)_2$	$Pd_2(DBA)_3$	10	23
KBF_3	$Pd_2(DBA)_3$	10	31
$B(OH)_2$	$PdCl_2(PPh_3)_2$	10	60
KBF_3	$PdCl_2(PPh_3)_2$	10	>99
KBF_3	$PdCl_2(PPh_3)_2$	1	45
KBF_3	$PdCl_2(dppf)\cdot CH_2Cl_2$	10	87
KBF_3	$PdCl_2(dppf)\cdot CH_2Cl_2$	5	78
KBF_3	$PdCl_2(dppf)\cdot CH_2Cl_2$	1	29

[a] Percent conversion judged by disappearance of 2-chloro benzimidazole via HPLC.

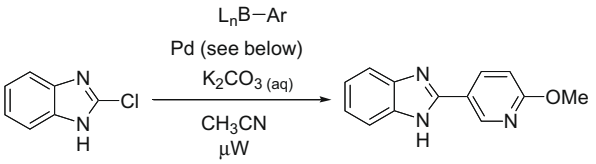
Table 3
Scope of aryl coupling partners



Ar–BF_3K	% Conv.[a]	Yield (%)
	>95	86
	>99	88
	>99	77
	89	72
	92	79
	90	68
	95	90
	95	0[b]
	95	0[b]

[a] Percent conversion judged by disappearance of 2-chloro benzimidazole by HPLC.
[b] No product detected by mass spectral analysis ESI(pos) or ESI(neg).

Table 4
Pyridyl coupling partners



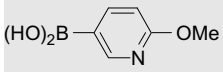
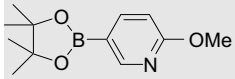
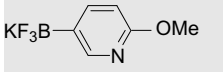
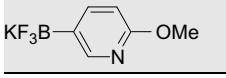
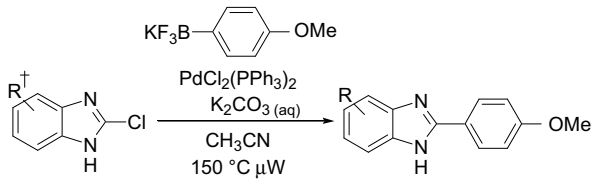
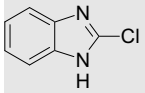
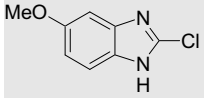
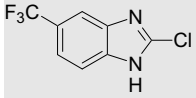
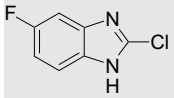
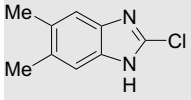
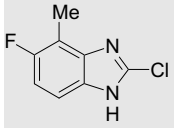
Ar–BL_n	Pd source (10 mol %)	Time (min)	Yield (%)
	$PdCl_2(PPh_3)2$	30	50
	$PdCl_2(PPh_3)_2$	30	40
	$PdCl_2(PPh_3)_2$	30	90
	$PdCl_2(dppf)\cdot CH_2Cl_2$	30	90

Table 5
Scope of benzimidazole coupling partners



Ar–Cl	% Conv.	Yield (%)
	>95	86
	>95	59
	>95	69
	>95	20
	>95	69
	>95	74[a]

[a] Coupling performed on *m*-*O*-benzylpotassium trifluoroborate.

In conclusion, we report a simple and efficient method for the direct synthesis of unprotected 2-aryl benzimidazoles using microwave-mediated Suzuki–Miyaura cross coupling of readily available trifluoroborates and 2-chlorobenzimidazoles.

Supplementary data

Supplementary data (synthetic procedures and spectral information) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.043.

References and notes

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11. Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685–692.
12. *Representative experimental procedure: 2-(4-Methoxy-phenyl)-1H-benzimidazole*: A suspension of 2-chlorobenzimidazole (76 mg, 0.50 mmol), 4-methoxy phenyl boronic acid (100 mg, 0.66 mmol) and $PdCl_2(PPh_3)_3$ (30 mg, 0.1 mmol) in CH_3CN (1.0 ml), and K_2CO_3 were heated to 150 °C for 30 min in microwave. The reaction mixture was cooled to room temperature and extracted with $CHCl_3$ or $CHCl_3$/IPA. The organic layers were dried over Na_2SO_4, and filtered and concentrated to give a crude solid that was often >90% pure. The solid could be further purified by SiO_2 chromatography with 0–4% acetone/CH_2Cl_2 and dried under vacuum to yield 96 mg, 86% yield of 2-(4-methoxy-phenyl)-1*H*-benzimidazole.
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