JOC Article

Facile Synthesis of 6-Aryl 5-*N*-Substituted Pyridazinones: Microwave-Assisted Suzuki−Miyaura Cross Coupling of 6-Chloropyridazinones

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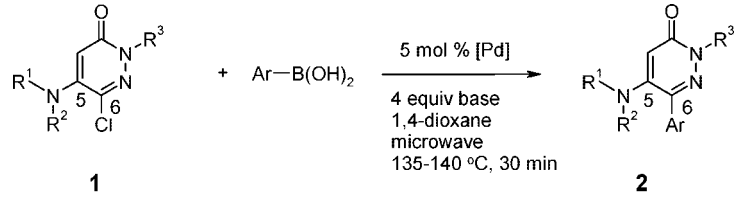
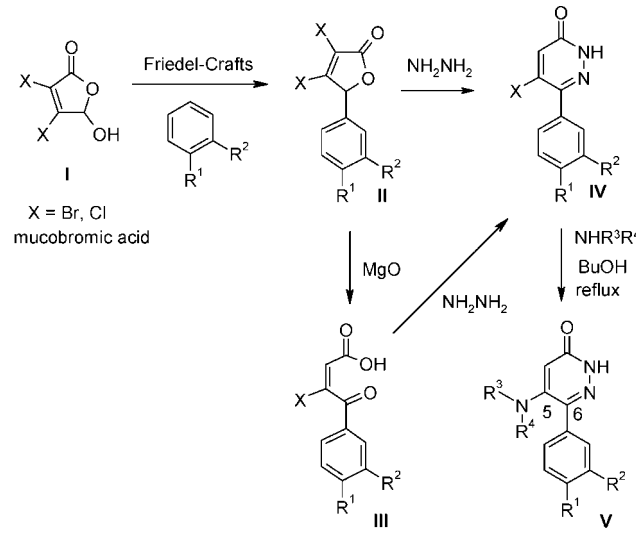


A facile synthesis of 5-dialkylamino-6-aryl-(2*H*)-pyridazin-3-one from 5,6-dichloropyridazinone was carried out by using a palladium-catalyzed Suzuki−Miyaura cross coupling of 6-chloro-5-dialkylaminopyridazinone **1** with various arylboronic acids (3 equiv) as the key transformation. The Suzuki−Miyaura cross-coupling reaction proceeded smoothly under microwave irradiation at 135−140 °C for 30 min with 5 mol % of Pd catalyst in moderate to good isolated yields. The use of a CombiPhos Pd6 mixture catalyst system and a single Pd-SPhos catalyst system was evaluated.

Introduction

The pyridazine nucleus and its 3-oxo derivative pyridazinones are recognized as versatile scaffolds with a wide range of biological activities that can also be used to support other pharmacophoric groups.[1−6] Most syntheses of 6-aryl 5-*N*-substituted pyridazinones **V** proceed via the traditional methods, involving condensation of hydrazine with appropriate substituted lactones or 1,4-dicarbonyl compounds **II** or **III**.[6] However, the major drawback of these synthetic routes is the necessity to "custom make" the required dicarbonyl components **II** or **III** (Scheme 1). Herein, we report the results of our approach leading to an efficient synthetic route from which a large number of analogues with variable substitutions at the N-2, C-5, and C-6 positions of the pyridazinone ring can be readily prepared.

SCHEME 1. Conventional Synthesis of 5-Dialkylamino-6-arylpyridazinones



As depicted in Scheme 2, our synthesis employs a very efficient microwave (MW) promoted Suzuki−Miyaura cross

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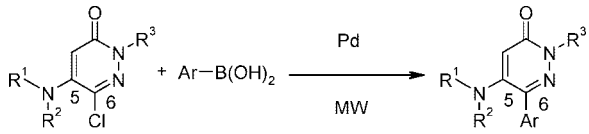
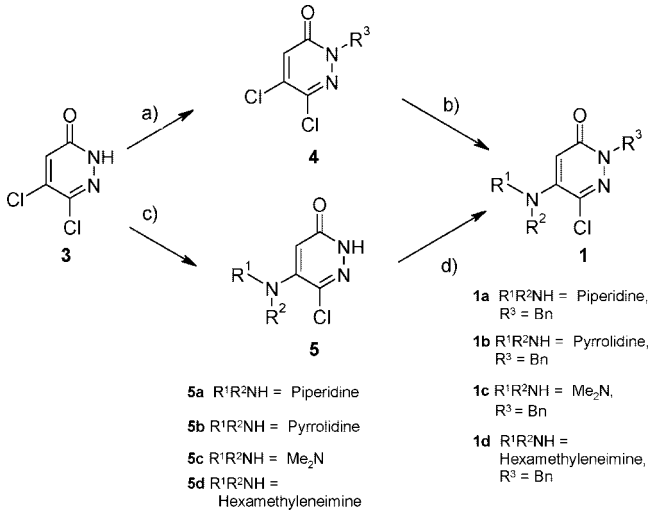
SCHEME 2. Route to 5-Dialkylamino-6-aryl-(2*H*)-pyridazin-3-one



1 **2**

SCHEME 3. Preparation of Key Intermediate 1[a]



[a] Reagents and conditions: (a) TMG (1,1,3,3-tetramethylguanidine) or PS-BEMP (polystyrene supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine), BnBr and dioxane as solvent, microwave, 100 °C, 10 min, quantitative yield; (b) DIEA, ethanol, microwave, 150 °C, 10−25 min, quantitative yields; (c) DIEA (diisopropylethylamine), ethanol, microwave, 150°C, 10−25 min, quantitative yields; (d) TMG or PS-BEMP, dioxane, microwave, 100 °C, 10 min, quantitative yield.

coupling between 6-chloro-5-dialkylaminopyridazinones **1** and arylboronic acids as the key transformation in the preparation of 6-aryl-5-dialkylamino-(2*H*)-pyridazin-3-one **2**. This method is attractive since it adds the aryl group toward the end of the synthesis, allowing one to take advantage of a wide selection of aryl boronic acids available from commercial sources. Although there are several reports on the preparation of pyridazinones using a Suzuki−Miyaura cross-coupling reaction,[7] there are no discussions on the synthesis of 5-dialkylamino-6-aryl-(2*H*)-pyridazin-3-one **2** with this transformation.

In addition, the key intermediate 6-chloro-5-dialkylaminopyridazinones **1** can be prepared in high yield in two steps starting from 5,6-dichloropyridazinone **3**[8] (Scheme 3). The synthesis of the intermediate **1** involved the nucleophilic substitution of amines at the C5 position to introduce the first diversity element, followed by an N-alkylation at N-2 to introduce the second diversity point or vice versa (Scheme 3).

Results and Discussion

Microwave-assisted chemical methods have been proven to be a powerful technique for increasing the throughput of chemical synthesis.[9] Microwave heating was chosen for the cross-coupling reaction in Scheme 2 to achieve the synthesis in short reaction time without the requirement of special reaction conditions such as inert gas. An initial attempt to couple 6-chloro-5-piperidylpyridazinone (**5a**) with phenylboronic acid, using Combiphos Pd6[10] catalyst in dioxane and Cs_2CO_3 as the base, at a temperature of 130 °C under microwave irradiation, gave no desired product. We suspected that the free N−H of pyridazinone interfered with the catalyst, as repeating the reaction with the *N*-benzyl-protected pyridazinone **1a** under the same conditions gave the desired coupling product (entry 1, Table 1). To define the conditions for the Suzuki−Miyaura cross coupling of 6-chloropyridazinones **1** with use of CombiPhos Pd6,[11] an intensive screening of reaction variables was undertaken, using 1-benzyl-6-chloro-5-piperidyl-(2*H*)-pyridazin-3-one (**1a**) and phenylboronic acid as representative substrates. It was uncovered that the cross coupling can proceed smoothly when a mixture of 1 equiv of **1a** and 3 equiv of phenyl boronic acid in 1,4-dioxane was irradiated under microwave conditions for 30 min at 135 °C in the presence of 4 equiv of Cs_2CO_3 and 3−15 mol % of palladium catalyst (Combiphos Pd6). At least 3 mol % Pd catalyst is required to achieve complete conversion. In addition to Cs_2CO_3, K_2CO_3 was identified as an alternative base providing similar results for the C−C bond formation.

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(10) CombiPhos-Pd6 is a mixture of POPd, POPd1, POPd2, POPd3, POPd4, POPd5, POPd6, POPd7, PXPd, PXPd2, PXPd3, PXPd4, PXPd6, PXPd7, and PXPd2-Br in equal mole amounts:

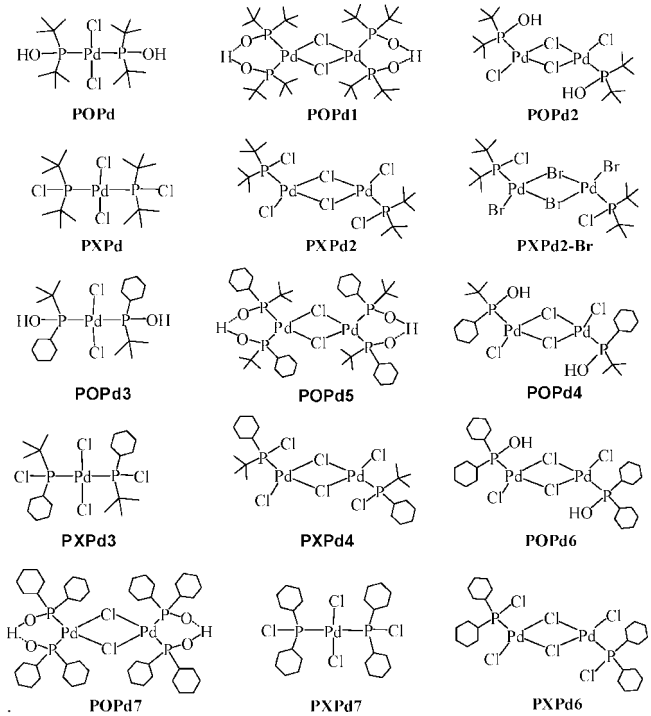

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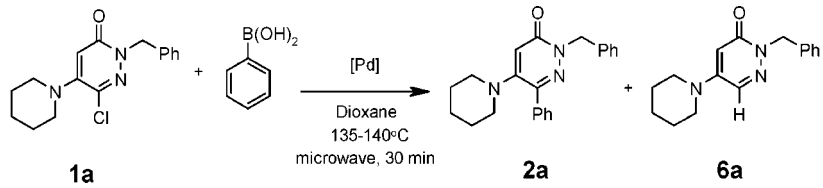
TABLE 1. Comparison of Catalyst Systems for Palladium-Catalyzed Suzuki Coupling of 6-Chloropyridazinone 4[a]



1a **2a** **6a**

entry	[Pd] (5 mol %)	base + solvent	product (%)[b]	byproduct **6a** (%)	entry	[Pd] (5 mol %)	base + solvent	product (%)[b]	byproduct **6a** (%)
1	**Pd6**	**Cs_2CO_3/dioxane**	**77**	**13**	11	$Pd_2(dba)_3$/SPHOS	Cs_2CO_3/THF	64	36
2	POPd2	Cs_2CO_3/dioxane	44	14	12	$Pd_2(dba)_3$/SPHOS	Cs_2CO_3/DMF	97	3
3	PXPd2	Cs_2CO_3/dioxane	88	12	13	$Pd_2(dba)_3$/SPHOS	Cs_2CO_3/toluene	48	42
4	PXPd	Cs_2CO_3/dioxane	88	12	14	$Pd_2(dba)_3$/SPHOS	K_2CO_3/dioxane	30	0
5	POPd6	Cs_2CO_3/dioxane	55	21	15	Pd6	K_2CO_3/dioxane	93	7
6	PXPd6	Cs_2CO_3/dioxane	84	16	16	$Pd_2(dba)_3$/SPHOS	K_3PO_4/dioxane	83	1
7	$Pd_2(dba)_3/PPh_3$	Cs_2CO_3/dioxane	90	10	17	**$Pd_2(dba)_3$/SPHOS**	**KF/dioxane**	**100**	**0**
8	$Pd_2(dba)_3$/xanthphos	Cs_2CO_3/dioxane	43	12	18	$Pd_2(dba)_3$/SPHOS	KOH/dioxane	49	5
9	$Pd_2(dba)_3$/dppf	Cs_2CO_3/dioxane	50	10	19	$Pd_2(dba)_3$/SPHOS	CsF/dioxane	50	2
10	$Pd_2(dba)_3$/SPHOS	Cs_2CO_3/dioxane	97	3	20	**$Pd_2(dba)_3$/SPHOS**	**KF/DMF**	**100**	**0**

[a] All reactions were carried out in 2.5 mL Biotage reaction process vials. The reaction mixture consists of 100 μmol of 6-chloropyridazinone **1a** and 5 mol % Pd catalyst, 3 equiv of phenylboronic acid, 4 equiv of base, and 1 mL of dioxane as solvent. The reaction mixture was irradiated at 135 °C for 30 min. Personal Chemistry (now Biotage) Smith Synthesized was used. [b] The conversion and yield of byproduct **6a** was detected by LC/MS.

DMF also can be a good alternative solvent in addition to dioxane. Some dehalogenation product of 6-chloropyridazinone **6a** was also detected (entry 1, Table 1).

The scope and limitation of using a palladium complex mixture as catalyst was also investigated. The activity of the individual catalysts (PXPd, POPd, PXPd2, POPd2, PXPd6, and POPd6) consisting of Combiphos Pd6 was examined for Suzuki coupling between 1-benzyl-6-chloro-5-piperidyl-(2*H*)-pyridazin-3-one (**1a**) and phenylboronic acid. The results are summarized in Table 1. The Palladium−phosphinic acid complexe catalysts are less reactive with 58% conversion for POPd2 (entry 2, Table 1) and 76% conversion for POPd6 (entry 5, Table 1). Palladium phosphinous chloride complexe catalysts are more reactive with 100% conversion for PXPd2, PXPd, and PXPd6 (entries 3, 4, and 6, Table 1). With a 90% conversion for Combiphos Pd6 catalyst, the less active catalysts POPd2 and POPd6 in the mixture did not interfere with the performance of the more active catalysts PXPd, PXPd2, and PXPd6. However, an observed limitation associated with using a mixture of catalysts, Combiphos Pd6, for Suzuki−Miyaura coupling is the dehalogenation of the 6-chloropyridazinone **1a** (dehalogenated product **6a**). To minimize and hopefully eliminate the undesirable dehalogenation reaction, a variety of palladium−phosphine complexes as catalysts were also investigated. A significant improvement on reducing dehalogenation side reaction was achieved when using palladium−2-(2′,6′-dimehtoxybiphenyl) dicyclohexylphosphine (Sphos[12]) as catalyst (100% conv., 3% **6a**, entry 10, Table 1). Further optimization of condition variables led to the optimal catalyst system that minimized dehalogenation by using KF as base in Dioxane (entry 17, Table 1). Improvement also was observed for Combiphos Pd6 when K_2CO_3 was used as base in dioxane. However, the reaction proceeded much slower compared to that with Cs_2CO_3 as base (entry 15, Table 1). In contrast, only sluggish reactivity was observed for the Pd-Sphos catalyst system with K_2CO_3 as base (30% conv., entry 14, Table 1).

For comparison, the reaction of **1a** with phenylboronic acid was also conducted with use of a preheated oil bath under otherwise identical conditions as for the microwave reaction, i.e., CombiPhos Pd6, at a temperature of 110 °C, for a period of 14 h. Although this thermal reaction took longer, it also gave complete conversion accompanied by the generation of around 10% dehalogenation product **6a**.

By weighing the pros and cons of the reaction systems, two sets of experimental conditions were selected as the cross-coupling method for the synthesis of 6-aryl 5-*N*-substituted pyridazinones. One set uses a mixture Pd catalyst Combiphos Pd6 and the other uses a Pd-Sphos catalyst system. In a typical experiment, a mixture of 1 equiv of **1a** and 3 equiv of phenylboronic acid in 1,4-dioxane was irradiated under microwave conditions for 30 min at 135 °C in the presence of 4 equiv of Cs_2CO_3 and 5 mol % of palladium catalyst (CombiPhos Pd6 or Pd-Sphos). No starting material (100% conversion to products) was detected by LC/MS analysis. It was found that at least 3 mol % of Pd catalyst was required to achieve complete conversion.

Under the typical microwave coupling conditions described above, the scope of cross coupling was investigated for the reaction between 6-chloropyridazinone **1** and arylboronic acids with CombiPhos Pd6 as catalyst for the synthesis of a diverse set of 6-aryl-5-dialkylaminopyridazinones **2**. The results are summarized in Table 2. Analysis of the crude reaction mixtures by LC/MS showed complete conversion in most cases (entries 1, 6−11, and 13, Table 2). Following preparative HPLC purification, satisfactory isolated yields were obtained though slightly lower than expected due to the generation of 6−23% dehalogentation product (Table 2).

The side chain effect at C5 of the pyridazinone was explored with different dialkylamino substitutions. Substrate **1b**, with a five-membered pyrrolidine side chain at C5, led to increased dehalogenation product (20% by LC/MS, entry 2, Table 2) compared with that of the piperidine side chain (13% by LC/MS. entry 1, Table 2). A significant reduction in the yield was observed with both substrate **1c**, bearing dimethylamine side chain, and **1d**, bearing the seven-membered ring hexamethyleneimine side chain at C5. These low yields were due to incomplete conversion (70% **1c** consumed by LC/MS for entry 3 and 86% by LC/MS for entry 4, Table 2) and to more profound dehalogenation product generation (23% by LC/MS for entry 3, 15% by LC/MS for entry 4,

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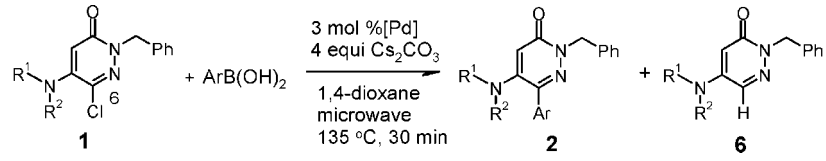
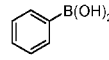
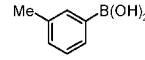
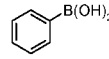
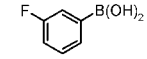
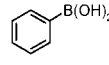
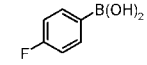
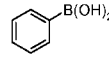
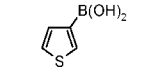
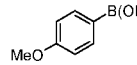
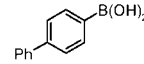
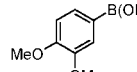
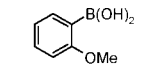
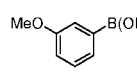
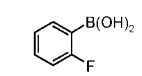
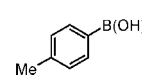
TABLE 2. Suzuki−Miyaura Cross Coupling of 6-Chloropyridazinones with Arylboronic Acids Catalyzed by Combiphos Pd6[a]



entry	prdct	NR^1R^2	$ArB(OH)_2$	yield%[b]	**6**(%[c])	entry	prdct	NR^1R^2	$ArB(OH)_2$	yield%[b]	**6**(%[c])
1	2a1			68	13	9	2a6			61	8
2	2b			60	20	10	2a7			64	14
3	2c			21	23	11	2a8			72	8
4	2d			37	15	12	2a9			30[e]	9
5	2a2			48[d]	6	13	2a10			63	4
6	2a3			58	9	14	2a11			11	-
7	2a4			77	8	15	2a12			15[f]	-
8	2a5			73	8						

[a] All reactions were carried out in 2.5 mL Biotage reaction process vials. The reaction mixture consisted of 100 μmol of 6-chloropyridazinone **1** and 5 mol % Combiphos Pd6, 3 equiv of arylboronic acid, and 4 equiv of Cs_2CO_3 as base, and 1 mL of dioxane as solvent. The reaction mixture was irradiated at 135 °C for 30 min. Personal Chemistry (now Biotage) microwave reactor Smith Synthesizer was used. 100% conversion was obtained for entries 1, 6−11, and 13. [b] Isolated yield by reverse HPLC. [c] Percent **6** is from LC/MS analysis of the reaction mixture. [d] 52% by LC/MS [e] 39% by LC/MS.S [f] Yield by LC/MS.

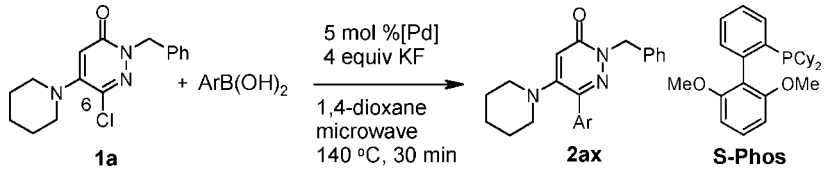
Table 2). The coupling of 6-chloropyridazinones proceeded well with boronic acids containing meta- and para-substituted electron-donating groups (entries 5−9, Table 2). Arylboronic acids with a strong electron-withdrawing group at the para-position and meta-position such as 3-nitro and 4-nitrobenzene boronic acids were unreactive even when 10% Pd catalyst was used (data not shown). The coupling with the heterocyclic 3-thienylboronic acid gave 30% isolated yield of the desired product **2** (entry 12, Table 2); this low yield resulted from incomplete conversion (39% **1a** consumed). No cross coupling occurred with other heterocyclic boronic acids, e.g., 2-furylboronic acid or 2-thienylboronic acid. The coupling reactions between ortho-substituted aryl boronic acids such as 2-methoxy and 2-fluorobenzene boronic acids were shown to be less successful giving 11% and 15% conversion by LC/MS (entries 14 and 15, Table 2).

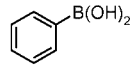
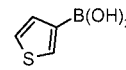
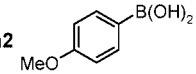
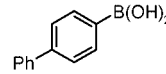
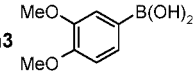
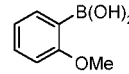
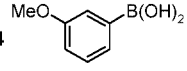
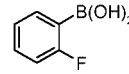
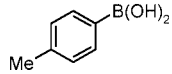
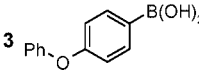
The mixture catalyst system CombiPhos Pd6 showed limited success for cross coupling due to the significant reductive dehalogenation reaction (6−23% by LC/MS). Employing much improved conditions with the Pd-SPhos catalyst system, cross coupling of 5-chloropyridazinones **1a** with various boronic acids proved to be more efficient. These results are summarized in Table 3. The Pd-SPhos catalyst gave excellent reactivity with ortho-substituted boronic acids, e.g., 2-methoxy- and 2-fluorobenzeneboronic acids (entries 8−9, Table 3): 100% conversion and dehalogenation free was achieved for both substrates. The Pd-SPhos catalyst system was also conducive for cross coupling between 6-chloropyridazinone **1a** and arylboronic acids bearing meta- or para-substituted electron-donating groups such as 4-OMe, 3-OMe-,and 4-Me (entries 2, 4, and 5, Table 3). However, the cross-coupling reaction of 4-phenoxybenzeneboronic acid only gave 67% conversion, with 35% reductive dehalogenation product **6** and 32% isolated yield after HPLC purification (entry 10, Table 3). A low isolated yield was also observed when using the biphenylboronic acid substrate (100% conversion and 50% **6** by LC/MS, entry 7, Table 3). Similarly to the CombiPhos Pd6 catalyst system, the heterocyclic boronic acids such as 2-furanyl- or 2-thienylboronic acids and arylboronic acids with strong electron-withdrawing groups, like 3-nitrobenzeneboronic acid, did not give any of the desired products.

Conclusions

In conclusion, applying a Pd-catalyzed Suzuki−Miyaura cross coupling of 6-chloro-5-dialkylaminopyridazinones as the key transformation, we have developed a facile synthesis of 6-aryl-5-dialkylaminopyridazin-3-ones. Two catalyst systems have been described. The preferred method utilized a Pd-SPhos complex as catalyst, 1,4-dioxane as solvent, KF as the base, and microwave irradiation as the heating source. The cross-coupling reaction proceeded efficiently at 135−140 °C with 3−5 mol % of Pd catalyst to form 6-aryl-5- dialkylaminopyridazinone in good yields.

TABLE 3. Suzuki−Miyaura Cross Coupling of 6-Chloropyridazinones with Arylboronic Acids Catalyzed by the Pd-SPhos Catalyst System[a]



entry	prod	$ArB(OH)_2$	yield%[b]	entry	prod	$ArB(OH)_2$	yield%[b]
1	2a1		95	6	2a9		71[c]
2	2a2		86	7	2a10		40[d]
3	2a3		90	8	2a11		95
4	2a4		93	9	2a12		95
5	2a5		73	10	2a13		32[e]

[a] All reactions were carried out in 2.5 mL Biotage reaction process vials. The reaction mixture consisted of 300 μmol of 6-chloropyridazinone **1a** and 5 mol % Sphos-Pd catalyst, 3 equiv of arylboronic acid and 4 equiv of base KF, and 2 mL of dioxane as solvent. The reaction mixture was purged with N_2 and irradiated at 140 °C for 30 min. Personal Chemistry (now Biotage) microwave reactor Smith Synthesizer was used. [b] Isolated yield by reverse HPLC. [c] 76% conv. by LC/MS. [d] 100% conv. 50% dehalogenation product **6** by LC/MS. [e] 67% conv. and 35% dehalogenation product **6** by LC/MS.

Additionally, we also demonstrated the possibility of using a mixture catalyst system consisting of CombiPhos Pd6, Cs_2CO_3 as base in dioxane to promote the Suzuki−Miyaura cross-coupling reaction. The catalyst system gave limited success due to the significant reductive dehalogenation reaction. However, the Combiphos Pd6 method allows quick access to many of the desired cross-coupling products of interest.

The Suzuki−Miyaura cross-coupling synthetic route described herein allowed the addition of diversity at the C6 position of the pyridazinone ring at a late stage in the synthesis. Further, this Suzuki−Miyaura cross-coupling-based procedure, used in conjunction with the efficient alkylation and nucleophilic substitution chemistries described for the preparation of **1**, offers a simple method to introduce a wide range of functional groups at N-2, C-5, and C-6 positions, which permits a rapid pharmaco-modulation of the pyridazinone scaffold. The results presented in this paper represent a significant improvement in the 5,6-disubstituted pyridazinone synthesis.

Experimental Section

General Procedures for the Palladium-Catalyzed Synthesis of 6-Aryl 5-*N*-Substituted Pyridazinones. (a) A Biotage Process Vial (2−5 mL) was charged with chloro-2-(phenylmethyl)-5-(1-piperidinyl)-3(2*H*)-pyridazinone (**1a**) (45.5 mg, 0.15 mmol), 3 mol % Combiphos Pd6 (3.4 mg, 4.5 umol), phenylboronic acid (55 mg, 0.45 mmol), and Cs_2CO_3 (195 mg, 0.6 mmol) in anhydrous 1,4-dioxane (2 mL). The resulting mixture was irradiated at 135 °C for 30 min on a microwave Smith Synthesizer. After irradiation, the sample was filtered through a thin pad of silica gel, washed with DCM, and concentrated. The crude was subjected to reverse-phase HPLC purification to give the desired product 43 mg, yield 61%.

(b) A typical experimental procedure with Pd-SPhos is as follows: A Biotage Process Vial (2−5 mL) was charged with 5 mol % of SPhos (6.15 mg, 15 umol), 2.5 mol % of $Pd_2(dba)_3$ (6.9 mg, 7.5 umol), chloro-2-(phenylmethyl)-5-(1-piperidinyl)-3(2*H*)-pyridazinone (**1a**) (91.0 mg, 0.3 mmol), phenylboronic acid (110 mg, 0.9 mmol), and KF (70 mg, 1.2 mmol). The vial was charged with 2 mL of anhydrous 1,4-dioxane, stirred at room temperature for 10 min, and then irradiated at 140 °C for 30 min, using the microwave reactor Smith Synthesizer. After irradiation, the sample was cooled, filtered, and purified by reverse-phase HPLC to give the desired product (98.2 mg, yield 95%).

6-Phenyl-2-(phenylmethyl)-5-(1-piperidinyl)-3(2*H*)-pyridazinone, 2a1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.25−7.48 (m, 8H), 6.64 (s, 1H), 5.35 (s, 2H), 2.89 (m, 4H), 1.50 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.06, 154.52, 144.26, 136.03, 135.80, 129.03, 128.80, 128.50, 128.44, 127.85, 127.46, 107.83, 55.08, 50.62, 24.74, 23.31. MS *m*/*z* 346.2 [M^+ + H]. HRMS (ES^+) calcd for $C_{22}H_{24}N_3O_1$ (M^+ + H) 346.1914, found 346.1915.

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Supporting Information Available: Experimental procedures and characterization data for 5-aminopyridazinone **1** and Suzuki−Miyaura cross-coupling products **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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