Microwave-Enhanced Efficient Synthesis of Diversified 3,6-Disubstituted Pyridazines

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Pyridazines have demonstrated versatile biological activities, for example, antibacterial,[1] antidepressant,[2] antihypertensive,[3−6] analgesic,[7] nephrotropic,[8−11] antiinflammatory,[2,12] anticancer,[12] cardiotonic,[3,13] antiaggregative,[14] and inhibitory activities of acetylcholinesterase,[15,16] aldose reductase,[17] MAO,[18] α_1-adrenoceptor,[19] CDKs,[20] COX-2,[21] and p38 MAP kinase.[22]

In the preparation of various pyridazines, 3-chloro-6-arylpyridazines are important intermediates.[15,16,23,26] Generally, the synthesis of 3-chloro-6-arylpyridazines was carried out by condensation of 1,4-dicarbonyl compounds with hydrazines,[24,25] followed by chlorination of pyridazones with $POCl_3$.[16,25,26] Recently, Parrot and co-workers reviewed the progress of palladium-catalyzed cross-coupling reactions on pyridazine moieties.[27] These metal-catalyzed approaches are remarkable in that they reach a large range of such important heterocyclic compounds for pharmacological and agrochemical studies. However, only one example described Suzuki coupling of 3,6-dichloropyridazine with phenylboronic acid under reflux in toluene for 24 h in 70% yield.[28] To select at the 3- and 6-positions of the electron-deficient pyridazine ring, Stanforth et al. replaced one of the two chlorine atoms with iodine which is easy to process via the palladium oxidative addition of 3-chloro-6-iodopyridazine for Suzuki coupling.[29] Other works also reported Suzuki coupling of 3-chloro-6-methoxypyridazine and 3-amino-6-chloropyridazine with a slow heating process.[28,30] Because this kind of scaffold exhibits the extensive bioactivity, the development of an efficient synthetic protocol to construct the diversified pyridazine derivatives library for high-throughput biological screening is very attractive to us. Here, we report optimized results for the rapidly synthesis of 3,6-disubstituted pyridazines from inactive 3,6-dichloropyridazine using microwave irradiation.

Microwave irradiation has been widely applied in organic synthesis.[31] Many organic transformations, such as Suzuki coupling,[32] have been accelerated under microwave irradiation. We screened various catalysts, bases, solvents, and microwave irradiation conditions (temperature and time) to optimize the Suzuki coupling reaction of inactive 3,6-dichloropyridazine with 4-methoxyphenylboronic acid (Table 1).

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As shown in Table 1, $PdCl_2(PPh_3)_2$ is the most effective catalyst to afford monosubstituted product **3e** (entry 1), compared with others (entries 2−8). With the use of Pd/C or TBAB instead of the "Pd" catalyst, the transformation didn't proceed. After the quantity of the catalyst, the reaction time, and temperature (entries 6−12) were optimized, the reaction using 3 mol % $PdCl_2(PPh_3)_2$ and K_2CO_3 as base at 120 °C for 10 min gave **3e** in 72% yield (entry 12). Different bases and solvents system were tested, K_2CO_3 as a base in acetonitrile/water (3:2) gave the best result with 72% yield of **3e** and less recovered starting material (entry 19). Although ionic liquids have been applied for Suzuki cross-coupling reaction, as an attractive clean media,[31] [BMIM]-BF_4 did not work as well in this reaction. Finally, we found that the reaction of 1.0 equiv of 3,6-dichloropyridazine, 1.2 equiv of arylboronic acid, 1.5 equiv of K_2CO_3, and 3 mol % $PdCl_2(PPh_3)_2$ in acetonitrile/water (3:2, 2 mL) under microwave irradiation at 120 °C with stirring for 10 min gave the best result (**3e** in 72% yield, entry 19)

We next applied different boronic acids to synthesize the corresponding 6-aryl-3-chloropyridazines under the optimized conditions. The results are shown in Table 2. Diverse boronic acids including steric-hindered, electron-donating, and electron-withdrawing arylboronic and heteroarylboronic acids gave the desired products **3** in moderate to good yields (53−93%). In entries 2 and 9, the disubstituted product was obtained as a byproduct. Obviously, 4-acetylphenylboronic acid with electron-withdrawing at the *para* position exhibited a low yield along with the self-coupling byproduct (entry 4).

Aminopyridazines with diverse biological activities[15,25,26] were prepared by refluxing 3,6-dichloropyridazine with an amine and ammonium chloride in 1-butanol for 48 h.[15] Alternatively, the amination was also performed by heating the reactants to 100−170 °C in DMF with K_2CO_3 as base.[32] However, when compound **3e** was mixed with benzylamine and K_2CO_3 as base in anhydrous DMF and the mixture was stirred at 120 °C for 18 h, no reaction occurred. We discovered that the use of neat benzylamine at reflux for 18 h provided the desired product **4a** with an acceptable yield of 78% (Table 3, entry 2). When this reaction proceeded under microwave irradiation at 195 °C for 15 min, an excellent result (97% yield of **4a**) was obtained without disubstituted amine as a byproduct (Table 3, entry 3).

According to the reaction conditions mentioned above, amination of compound **3e** with universal amines including alphatic amines, arylamines, and cyclic amines under microwave conditions afforded the excellent results in over 80% yields (Table 3, entries 3−8). An excess of *p*-toluidine with 3-chloro-6-(4-methoxyphenyl) pyridazine **3e** were ground together and heated under microwave irradiation (see entry 7); the desired product **4e** was obtained in a satisfactory yield

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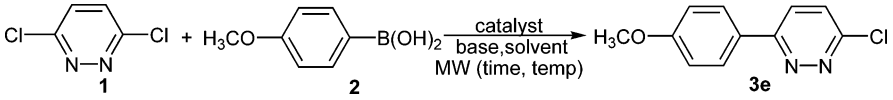
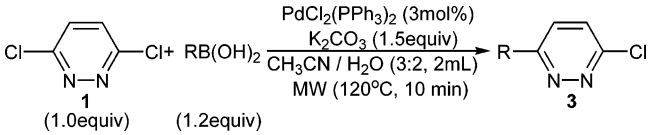
Table 1. Optimization for Microwave-Enhanced Suzuki Coupling of 3,6-Dichloropyridazine with 4-Methoxylphenylboronic Acid[a]



entry	catalyst	mol %	base	solvent	time (min)	temp (°C)	SM[b] (%)	yield[c] (%)
1	$PdCl_2(PPh_3)_2$	5	K_2CO_3	dioxane/water	5	120	14	67
2	$Pd(PPh_3)_4$	5	K_2CO_3	dioxane/water	5	120	11	64
3	$Pd(OAc)_2$/bpy (1:1)	5	K_2CO_3	dioxane/water	5	120	43	67
4	$PdCl_2[P(o\text{-toyl})_3]_2$	5	K_2CO_3	dioxane/water	5	120	16	33
5	10% Pd/C	10[d]	K_2CO_3	dioxane/water	5	120	79	0
6	$Pd(OAc)_2$/bpy (1:1)	5	K_2CO_3	dioxane/water	10	120	38	65
7	$Pd(OAc)_2$/bpy (1:2)	5	K_2CO_3	dioxane/water	10	120	31	54
8	$Pd(OAc)_2$/bpy (1:1)	5	K_2CO_3	dioxane/water	5	140	38	62
9	$PdCl_2(PPh_3)_2$	5	K_2CO_3	dioxane/water	10	120	24	70
10	$PdCl_2(PPh_3)_2$	3	K_2CO_3	dioxane/water	15	120	5	63
11	$PdCl_2(PPh_3)_2$	3	K_2CO_3	dioxane/water	10	140	7	57
12	$PdCl_2(PPh_3)_2$	3	K_2CO_3	dioxane/water	10	120	20	72
13	$PdCl_2(PPh_3)_2$	3	Cs_2CO_3	dioxane/water	10	120	0	68
14	$PdCl_2(PPh_3)_2$	3	$KF.2H_2O$	dioxane/water	10	120	3	47
15	$PdCl_2(PPh_3)_2$	3	K_3PO_4	dioxane/water	10	120	69	54
16	$PdCl_2(PPh_3)_2$	3	Na_2CO_3	dioxane/water	10	120	40	66
17	TBAB	100	K_2CO_3	dioxane/water	10	120	100	0
18	TBAB	100	K_2CO_3	water	10	120	100	0
19	$PdCl_2(PPh_3)_2$	3	K_2CO_3	MeCN/water	10	120	4	72
20	$PdCl_2(PPh_3)_2$	3	K_2CO_3	toluene/DMF	10	120	5	40
21	$PdCl_2(PPh_3)_2$	3	K_2CO_3	$[BMIM]BF_4$	10	120	100	0
22	$PdCl_2(PPh_3)_2$	3	K_2CO_3	toluene/water	10	120	37	73

[a] 3,6-Dichloropyridazine (0.30 mmol), 4-methoxyphenylboronic acid (0.36 mmol), base (0.45 mmol), solvent (2 mL, dioxane/water = 4:1; MeCN /water = 3:2; toluene/DMF = 9:1; toluene/water = 4:1; all ratio in v/v). [b] Unreacted 3,6-dichloropyridazine, where was recovered. [c] Isolated yield based on initial reactant not present in excess. [d] 10 mg of 10% Pd/C was used.

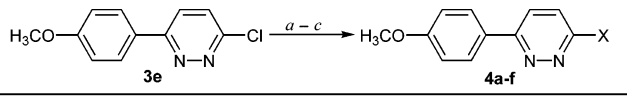
Table 2. Suzuki Coupling of 3,6-Dichloropyridazine with Diversified Boronic Acids under Microwave Irradiation[a]

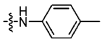
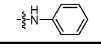


entry	R	product	yield[b] %
1	3-hydroxyphenyl	**3a**	72
2	4-*t*-butylphenyl	**3b**	64 (28)[c]
3	4-methylthiophenyl	**3c**	65
4	4-acetylphenyl	**3d**	53
5	4-methoxyphenyl	**3e**	73
6	4-chlorophenyl	**3f**	72
7	3-pyridiyl	**3g**	66
8	3-carboxylphenyl	**3h**	93
9	2-methoxyphenyl	**3i**	69 (25)[c]
10	2-fluorophenyl	**3j**	87

[a] Under optimized condition. [b] Isolated yield. [c] Yield of disubstituted product.

Table 3. Amination of 3-Chloro-6-(4-methoxyphenyl)pyridazine under Microwave Irradiation



entry	product	method	reactant	temp °C	time	X	isolated yield %
1	4a	a	benzylamine	120	18 h		0
2	4a	b	benzylamine	185	18 h		78
3	4a	c	benzylamine	195	15 min		97
4	4b	c	morpholine	130	15 min		95
5	4c	c	piperidine	110	15 min		91
6	4d	c	pyrrolidine	100	10 min		86
7	4e	c	*p*-toluidine	100	15 min		80
8	4f	c	aniline	190	10 min		86

[a] The mixture of **3e** (50 mg) with benzylamine (2 equiv) and K_2CO_3 (1.5 equiv) in DMF (2 mL) at 120 °C for 18 h. [b] The mixture of **3e** (50 mg) with benzylamine (excess) at reflux for 18 h. [c] The mixture of **3e** (50 mg) with aliphatic-, cyclic-, or arylamines (excess) under microwave irradiation.

without further amination. Both solid and liquid arylamines could smoothly react with 3-chloro-6-(4-methoxyphenyl) pyridazine **3e** under irradiation without the solvent.

In conclusion, we have developed an efficient method to generate the key intermediate 6-aryl-3-chloropyridazines by microwave-enhanced Suzuki coupling in moderate to good yields. Amination of the 6-aryl-3-chloropyridazine intermediate with various amines afforded 3-substitued-amino-6-arylpyridazines in high yields under microwave irradiation. This approach could be used to rapidly construct the diversified pyridazine compound libraries for high-throughput biological screening.

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Supporting Information Available. Experimental procedures, ^{1}H NMR spectra of all compounds, and ^{13}C NMR spectra of compounds **4a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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