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Suzuki reaction of cyclopenta[*d*][1,2]oxazine in aqueous solvent with water-soluble phosphine ligand

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Abstract—A convenient and facile modification of cyclopenta[*d*][1,2]oxazines through Suzuki cross-coupling reaction by use of water-soluble phosphine ligand was accomplished. In aqueous solvent, 7-iodocyclopenta[*d*][1,2]oxazines readily afford the corresponding 7-arylcyclopenta[*d*][1,2]oxazines in moderate to excellent yields.
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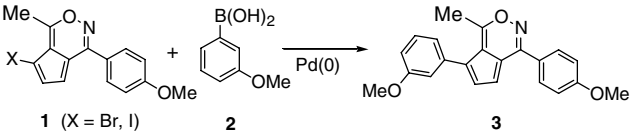
Cyclopenta[*d*][1,2]oxazine framework is seldom found in natural products or pharmaceuticals. There have been only a handful of reports on the synthesis of cyclopenta[*d*][1,2]oxazine and its derivatives, presumably due to limited stability of cyclopenta[*d*][1,2]oxazine skeletons.

Lloyd and Preston[1] first reported the synthesis of cyclopenta[*d*][1,2]oxazine by the reaction of diaroylcyclopentadiene with hydroxylamine. They also reported that treatment of cyclopenta[*d*][1,2]oxazine with *N*-bromosuccinimide afforded 7-bromocyclopenta[*d*][1,2]oxazine. In an effort to pursue inhibitors of the protein tyrosine phosphatase 1B (PTP1B),[2] it was required to synthesize the targeting compounds via Suzuki cross-coupling of 7-iodocyclopenta[*d*][1,2]oxazines. Palladium catalyzed cross-coupling reaction of aryl halides with boronic acid is a powerful synthetic method for arylation in carbon–carbon bond formation.[3] Aqueous-phase palladium catalyzed cross-coupling reactions are of interest with respect to environmental friendly synthetic process, the simplification of product separation and the economy of using water as a solvent in large-scale industrial syntheses.[4] In particular, aqueous palladium catalyzed cross-coupling reactions were considered to be highly versatile and useful method for heat or base labile compounds for decomposition, such as cyclopenta[*d*][1,2]oxazines. Herein, we report a synthetic method for halogenated cyclopenta[*d*][1,2]oxazines and palladium-catalyzed cross-coupling reaction of 7-iodocyclopenta[*d*][1,2]oxazines by use of water soluble phosphine.



1 (X = Br, I) **2** **3** (1)

For initial studies, we examined the coupling of **1** and **2** in the presence of palladium acetate. All experiments were run at 50 °C and at room temperature with **1** and 2.0 equiv of lithium acetate, Cs_2CO_3, K_2CO_3 in CH_3CN–H_2O (1:1) or 1,4-dioxane. We failed to produce any biaryl adduct of cyclopenta[*d*][1,2]oxazine **3** without remaining substrate **1**, even under a condition where triethylamine acted as a base in DMF at room temperature. From this result, we found that cyclopenta[*d*][1,2]oxazines were not tolerable under heated condition. Indeed, we turned our attention to aqueous Suzuki aryl coupling of cyclopenta[*d*][1,2]oxazines with water soluble phosphine ligand mediated by palladium acetate. Initially, all of the 7-iodo and 7-bromocyclopenta[*d*][1,2]oxazines were synthesized through several steps (Table 1).

For iodination reaction, treatment of cyclopenta[*d*]-[1,2]oxazine by *N*-iodosuccinimide in MeCN in the presence of trifluoroacetic acid gave **1b** in excellent yield. Water soluble phosphine ligand was prepared by a known procedure as cited in the literature.[5]

Keywords: Suzuki reaction; Cyclopenta[*d*][1,2]oxazine; Water-soluble phosphine ligand.
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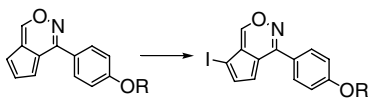
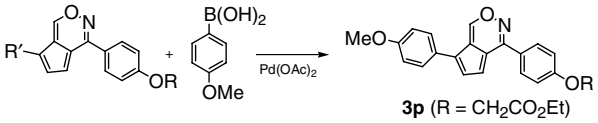
Table 1.



1b (R = CH_2CO_2Et)

Iodination reagent	Solvent	Yield (%)
ICI	AcOH	11
ICI	TFA/CH_2Cl_2	80
NIS	TFA/MeCN	91

Table 2.



3p (R = CH_2CO_2Et)

Entry	R′	Condition	Yield (%)
1	Br	CS_2CO_3, P(*o*-tolyl)$_3$, 1,4-dioxane, 50 °C	0[a]
2	I	CS_2CO_3, P(*o*-tolyl)$_3$, 1,4-dioxane, 50 °C	0[a]
3	Br	NaOAC, **I**, MeCN–H_2O (1:1)	0
4	I	NaOAC, **I**, MeCN–H_2O (1:1)	8
5	I	NaOAC, **I**, H_2O	7
6	I	CS_2CO_3, **I**, MeCN–H_2O (1:1)	8
7	I	NEt_3, **I**, MeCN–H_2O (1:1)	6
8	I	Toluene–MeOH–H_2O (1:1:1), **I**, CS_2CO_3	66

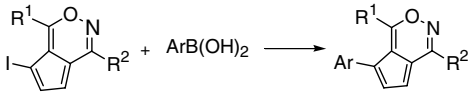
[a] No substrate was recovered.

For initial assessment of coupling reaction, Suzuki cross-coupling reactions were performed with a water soluble phosphine ligand, [2-(di-*tert*-butyl phosphanyl) ethyl] trimethyl ammonium iodide **I**, as cited in the literature.[6] The result given in Table 2 reveals that toluene was the solvent of choice to afford the desired 7-aryl-cyclopenta[*d*][1,2]oxazine along with CS_2CO_3 as a base without decomposition of the substrate at room temperature in moderate yield.

Suzuki reactions were not preceded under typical coupling condition with $Pd(OAc)_2$, tri(*o*-tolyl) phosphine in dioxane at 50 °C, and no substrate was recovered. (Table 2 entry 1 and 2) The reactions that were executed in water alone occurred more slowly than in water-miscible co-solvents (entry 5 in Table 2). With solvents, MeCN and water, the Suzuki reactions did not give rise to the desired product with satisfactory yields (entries 4–7). It was observed that the substrate was decomposed in either toluene or MeOH as a sole solvent without the addition of water. It was improved in yield with the addition of toluene in the reaction mixture, presumably because of better forming homogeneous reaction mixture (entry 8).

To evaluate the scope and limitation for this procedure to cyclopenta[*d*][1,2]oxazine acting as a substrate, we performed a number of coupling reaction with several aryl boronic acids and 7-iodocyclopenta[*d*][1,2]oxazines. All reactions were run at room temperature and cesium carbonate was used as a base of choice in toluene–MeOH–water (1:1:1) which was used as a solvent as given in Table 3. [2-(di-*tert*-butyl phosphanyl) ethyl] Trimethyl ammonium iodide **I** has allowed the first general coupling of aryl iodide to cyclopenta[*d*][1,2]oxazine at room temperature under nitrogen atmosphere. To

Table 3. Suzuki-coupling of 6-iodocyclopenta[*d*][1,2]oxazines



1 **3a - 3s**

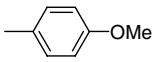
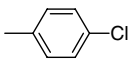
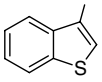
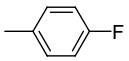
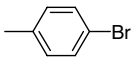
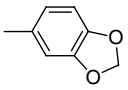
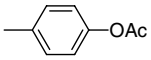
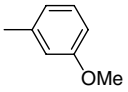
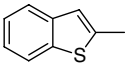
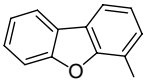
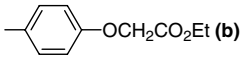
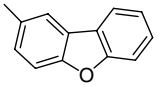
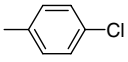
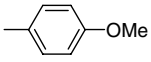
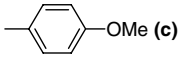
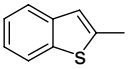
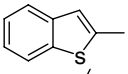
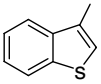
Compound no.	R^1	R^2	Ar	Yield (%)
3a	Me	–CO_2Me (**a**)		65
3b	Me	**a**		75
3c	Me	**a**		65
3d	Me	**a**		67
3e	Me	**a**		75
3f	Me	**a**		78

Table 3 (*continued*)

Compound no.	R^1	R^2	Ar	Yield (%)
3g	Me	**a**		72
3h	Me	**a**		77
3i	Me	**a**		59
3j	Me	**a**		93
3k	Me	**a**		51
3l	Me	**a**		65
3m	Me	**a**		68
3n	H			72
3o	H	**b**		65
3p	H	**b**		66
3q	H			80
3r	H	**c**		19[a]
3s	H	**c**		67

[a] 7-Bromocyclopenta[*d*][1,2]oxazine was used in place of 7-iodocyclopenta[*d*][1,2]oxazine.

date, there have been no examples of cross-coupling of cyclopenta[*d*][1,2]oxazines possessing limited stability in ordinary cross-coupling condition to construct carbon–carbon bond formation. 7-Iodo cyclopenta[*d*][1,2] oxazines **1b** provided coupled products in moderate to excellent yields at room temperature in aqueous solvent. It was unsatisfactory in yield when we used 7-bromocyclopenta[*d*][1,2]oxazine in place of its iodide (**3r**). Then, we applied this type of cross-coupling reaction in aqueous solvent with satisfaction. In summary, we observed that palladium catalyzed aryl boronic acid coupling reaction in water afforded a wide variety of 7-arylcyclopenta[*d*][1,2]oxazines, including base-sensitive or acid-sensitive ones which have tolerability in such conditions.

Typical procedure: To a stirred solution of 4-cyclopenta[*d*][1,2]oxazin-4-yl-phenoxy acetic acid ethyl ester (1.9 g, 6.39 mmol) in CH_3CN (40 mL) were added *N*-iodosuccinimide (1.58 g, 7.02 mmol) and trifluoroacetic acid (0.15 mL, 1.92 mmol). The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **1b** as a yellow solid (2.45 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, $J = 1.4$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 2H), 7.45 (d, $J = 2.8$ Hz, 1H), 7.06 (d, $J = 8.8$ Hz, 2H), 6.86 (dd, $J = 2.8$, 1.4 Hz, 1H), 4.70 (s, 2H), 4.30 (q, $J = 7.2$ Hz, 2H), 1.32 (t, $J = 7.2$ Hz, 3H); MS *m*/*e* (relative intensity) 423 (M^+, 0.8), 353 (0.9), 297 (46), 224 (7), 210 (100). Compound (**3a**): To a sealed tube were added 7-iodo-1-methylcyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (0.1 g, 0.32 mol), 4-methoxyphenyl boronic acid (0.07 g, 0.47 mol), $Pd(OAc)_2$ (0.01 g, 0.05 mmol),

[2-(di-*tert*-butyl phosphanyl) ethyl] trimethyl ammonium iodide (0.015 g, 0.05 mmol), Cs_2CO_3 (0.205 g, 0.63 mmol) and toluene–MeOH–H_2O (1:1:1, 4.5 mL) under nitrogen atmosphere. The reaction mixture was stirred for 15 h at room temperature. The resulting mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **3a** (62 mg, 65%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 3.1$ Hz, 1H), 7.32 (dd, $J = 6.7$, 2.1 Hz, 2H), 7.24 (d, $J = 3.1$ Hz), 6.98 (dd, $J = 6.7$, 2.1 Hz, 2H), 4.06 (s, 3H), 3.86 (s, 3H), 2.59 (s, 3H); MS *m*/*e* (relative intensity) 297 (M^+, 40), 223 (12), 207 (12), 70 (12), 59 (55), 43 (100).

Acknowledgements

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