



## A facile synthetic route for 2-pyridyl derivatives: direct preparation of a stable 2-pyridylzinc bromide and its copper-free and Pd-catalyzed coupling reactions

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### ABSTRACT

Direct preparation of 2-pyridylzinc bromide has been developed. Interestingly, the subsequent coupling reactions with acid chlorides have been carried out without any transition metal catalyst. 2-Pyridylaryl compounds, symmetrical and unsymmetrical 2,2'-bipyridines were also successfully obtained from palladium-catalyzed coupling reactions of 2-pyridylzinc bromide under mild conditions.

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The use of pyridine-containing compounds has frequently appeared in a wide range of chemistries such as natural product synthesis, pharmaceutical chemistry, and material science.<sup>1</sup> Most of the 2-pyridyl derivatives have been prepared using the Suzuki,<sup>2</sup> Stille,<sup>3</sup> Grignard,<sup>4</sup> and Negishi<sup>5</sup> coupling reactions in the presence of a transition metal catalyst. Among these, the Suzuki coupling reaction is the most intensively studied and a very extensive work has been developed.<sup>6</sup> However, the preparation of stable 2-pyridyl organometallics has been typically considered a problematic subject mainly because of its instability and the formation of by-products.

Recently, several outstanding studies on the direct arylation of pyridine have been reported to avoid these inevitable difficulties. For example, Rh(I)<sup>7</sup> and Au(I)<sup>8</sup>-catalyzed arylation of pyridines, Pd-catalyzed arylation of pyridine N-oxide with unactivated arenes,<sup>9</sup> and haloarenes<sup>10</sup> have been developed. Also, the direct arylation of pyridine N-oxide by Grignard reagents was reported.<sup>11</sup>

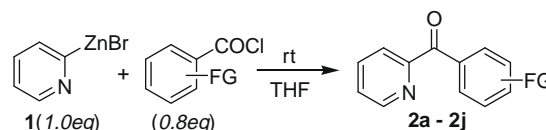
Interestingly, in our continuing study on the preparation and application of organozinc reagents, we found that 2-pyridylzinc bromide was easily prepared by treatment of 2-bromopyridine with active zinc under mild conditions. Significantly, the resulting organozinc reagent was able to react with a variety of different electrophiles with/without any transition metal catalyst affording the coupling products in good yields.

In general, the preparation of 2-pyridyl organometallics is mostly performed by lithiation of 2-halopyridine at cryogenic conditions followed by transmetalation with an appropriate metal halide. As mentioned above, this procedure causes some limitations on the use of the 2-pyridyl organometallics. In this study, readily available 2-bromopyridine was treated at rt with the active zinc prepared by the Rieke method.<sup>12</sup> The oxidative addition of the active zinc to carbon–bromine bond was completed in an hour at

refluxing temperature to give rise to the corresponding 2-pyridylzinc bromide (**1**).

In order to investigate the reactivity of the 2-pyridylzinc bromide (**1**), it was treated with benzoyl chlorides. As summarized in Table 1, the coupling ketone products were obtained in moderate yields. It should be emphasized that the coupling reaction with acid chlorides was carried out in the absence of any transition metal catalyst under mild conditions. Generally, a copper catalyst is widely used for the coupling reactions of organozinc reagents.<sup>13</sup> Halobenzoyl chlorides were easily coupled with 2-pyridylzinc bromide (**1**) at rt to give the corresponding ketones (**2a**, **2b**, **2c**, **2d**, and **2e**, Table 1) in moderate yields. Both benzoyl chlorides containing an electron-withdrawing group (CN and NO<sub>2</sub>) and an electron-donating group (Me and MeO) also successfully afforded the

**Table 1**  
Coupling reaction with benzoyl chlorides<sup>a</sup>



Entry	FG	Time (h)	Product	Yield <sup>b</sup> (%)
1	2-F	0.5	2-F ( <b>2a</b> )	65
2	3-F	0.5	3-F ( <b>2b</b> )	52
3	2-Br	0.5	2-Br ( <b>2c</b> )	45
4	4-Br	1	4-Br ( <b>2d</b> )	47
5	4-I	1	4-I ( <b>2e</b> )	36
6	3-CN	1	3-CN ( <b>2f</b> )	54
7	4-CN	1	4-CN ( <b>2g</b> )	50
8	4-Me	1	4-Me ( <b>2h</b> )	64
9	3,4-(OMe) <sub>2</sub>	2	3,4-(OMe) <sub>2</sub> ( <b>2i</b> )	40
10	4-NO <sub>2</sub>	1	4-NO <sub>2</sub> ( <b>2j</b> )	47

<sup>a</sup> No catalyst was used.

<sup>b</sup> Isolated yield (based on electrophile).

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**Table 2**  
Coupling reaction with acid chlorides<sup>a</sup>

Entry	Acid chloride	Product	Yield <sup>b</sup> (%)
1			62
2			53
3			42
4			63

<sup>a</sup> No catalyst used.<sup>b</sup> Isolated yield (based on electrophile).

corresponding ketones (**2f**, **2g**, **2h**, and **2i**, Table 1). Even with nitrobenzoyl chloride, ketone (**2j**, Table 1) was obtained in moderate yield. According to GC–MS analysis of the reaction mixture, a major by-product was the coupling product obtained from the reaction of acid chloride with THF.

More results obtained from the catalyst-free coupling reactions are shown in Table 2. Treatment of **1** with chloronicotinoyl chlorides (Table 2, entries 1 and 2) at rt for 3 h provided the corresponding ketones (**2k** and **2l**) in 62% and 53%, respectively. Alkyl carbonyl chlorides were also coupled with 2-pyridylzinc bromide (**1**) resulting in the formation of the ketones (**2m** and **2n**, Table 2) in good yields.

With these results in hand, we also explored the Pd-catalyzed coupling reaction of **1**. Even though 2-pyridylaryl derivatives were successfully prepared via the aforementioned direct arylation methods, relatively harsh conditions (excess amount of reactant, high temperature, protection/deprotection step, and addition of additives) were required. Interestingly, mild conditions were employed to complete the coupling reactions of 2-pyridylzinc bromide (**1**) in this study. As shown in Table 3, several different types of functionalized aryl halides and heteroaryl halides were coupled with **1** in the presence of 1 mol % of Pd[P(Ph)<sub>3</sub>]<sub>4</sub> at rt in THF. Functionalized iodobenzenes were first treated with 2-pyridylzinc bromide (**1**) and the results are shown in Table 3. 2-Pyridylaryl derivatives (**3a–d**) were obtained in good to excellent yields. Mono-substituted thiophenes were also easily coupled with 2-pyridylzinc bromide (**1**) to give rise to 2-(2'-pyridyl)thiophene (**3e**) and 3-(2'-pyridyl)-thiophene (**3f**) in 68% and 85% yields, respectively. Di- and tri-substituted thiophenes (Table 3, entries 7 and 8) were also good coupling partners to give interesting thiophene derivatives (**3g** and **3h**) in high yields. The coupling reaction with a furane derivative resulted in the formation of **3i** in an excellent yield (Table 3, entry 9).

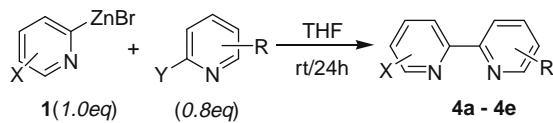
**Table 3**  
Pd-catalyzed coupling reactions

Entry	Electrophile	Time (h)	Product	Yield <sup>b</sup> (%)
1		24		81
2		24		88
3		24		68
4		4		90
5		24		68
6		3		85
7		24		89
8		24		80
9		3		91

<sup>a</sup> Performed with 1 mol %.<sup>b</sup> Isolated yield (based on electrophile).

More applications of 2-pyridylzinc bromide (**1**) were investigated and the results are summarized in Table 4. Not only symmetrical 2,2'-bipyridine (**4a**) but also unsymmetrical 2,2'-bipyridines (**4b–e**) were achieved in moderate yields. Again, the coupling reaction was completed in the presence of 1 mol % Pd[P(Ph)<sub>3</sub>]<sub>4</sub> in THF at rt. These results are significant because considerable effort has been directed toward the preparation of unsymmetrical 2,2'-bipyridines.<sup>14</sup>

In conclusion, we have demonstrated a practical synthetic route for the preparation of 2-pyridyl derivatives. It has been accomplished by utilizing a simple coupling reaction of a stable 2-pyridylzinc bromide (**1**), which was prepared via the direct insertion of active zinc to 2-bromopyridine. The subsequent coupling reactions with a variety of different electrophiles have been carried out under mild conditions. More applications of 2-pyridylzinc bromide (**1**) are currently under way.

**Table 4**  
Symmetrical and unsymmetrical 2,2'-bipyridines<sup>a</sup>

Entry	X	Y	R	Product	Yield <sup>b</sup> (%)
1	H	I	H		60
2	H	I	5-Br		72
3	H	Br	6-Me		65
4	H	Br	6-OMe		53
5	3-Me	I	5-Br		30

<sup>a</sup> Performed with 1 mol %.<sup>b</sup> Isolated yield (based on electrophile).**Supplementary data**

Supplementary data (experimental procedure, and copies of <sup>1</sup>H, <sup>13</sup>C NMR data) associated with this article can be found, in the on-line version, at doi:10.1016/j.tetlet.2009.07.004.

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