A Facile Synthetic Approach to the Preparation of 3-Pyridyl Derivatives: Preparations and Coupling Reactions of 3-Pyridylzinc and Its Analogues

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Abstract: A facile synthetic approach to the direct preparation of 3-pyridylzinc bromide has been demonstrated using Rieke zinc with 3-bromopyridine in the presence of a catalytic amount of lithium chloride. A variety of different electrophiles have been coupled to give the corresponding cross-coupling products in moderate to good yields. Also, this methodology has been expanded to the preparation of the corresponding organozinc reagents of 3-bromopyridine analogues.

Key words: 3-pyridylzinc bromide, coupling reaction, heterocyclic derivatives

Heterocyclic compounds which contain a pyridine function have frequently been found in natural products that have biological activity, especially in pharmaceutical, agrochemical and medicinal chemistry.[1] For example, bipyridine groups were found to be a key element in antibiotics such as caerulomycins and collismycins.[2] Other examples are the pyridylpyrimidines, which are used as fungicides, as well as tyrosine kinase inhibitors.[3] In addition, pyridine-containing oligomers are frequently found in liquid crystals used in material chemistry.[4]

As described above, the pyridine moiety has played a very significant role in a wide range of organic compounds. Consequently, new practical synthetic approaches for introducing pyridine rings into complex organic molecules are of high value.

Preparation of pyridyl derivatives are mostly performed using transition-metal-catalyzed cross-coupling reactions of pyridylmetallic reagents. However, the preparation of electron-deficient aryl organometallic reagents has been a challenging subject.

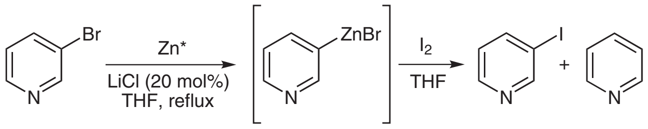
Even though there are many examples of the preparation of 2-pyridylmetallic halides from the reaction of halopyridines, only a limited number of studies have been reported on the preparation of 3-pyridylmetallic halides. 3-Pyridylmagnesium,[5] 3-pyridylzinc,[6] 3-pyridylindium halides[7] and Suzuki reagents[8] are the most widely used reagents for the preparation of pyridine-containing compounds.

Lithiation of 3-halopyridine followed by transmetallation with the appropriate metals (Mg, Zn, In) have afforded the corresponding 3-pyridylmetallic halides. However, this route has limitations such as cryogenic conditions, several side-reactions and limited functional-group tolerance.[9]

Very few studies have reported the direct synthesis of 3-pyridylmetallic halide reagents. Most of these reports include the treatment of 3-iodo- or 3-bromopyridine with highly active metals (Ca, Mg, Zn).[10] The subsequent coupling reactions were also carried out with a limited number of electrophiles. In these studies, 3-bromopyridine was generally used with active magnesium and calcium. Interestingly, for the preparation of 3-pyridylzinc halide via the direct method, 3-iodopyridine was exclusively used. To our best knowledge, there is only one example of the direct preparation of 3-pyridylzinc bromide utilizing 3-bromopyridine and, in this case, a very low yield was obtained from the subsequent cross-coupling reaction.[10a]

In our continuing study of active zinc and cross-coupling reactions of organozinc reagents, it has been found that Rieke zinc, in the presence of certain additives, exhibits a very high reactivity to 3-bromopyridine. Therefore, here we would like to report a facile synthetic method for the direct preparation of 3-pyridylzinc bromide and its coupling reactions.

The first attempt to synthesize 3-pyridylzinc bromide from the direct reaction of active zinc and 3-bromopyridine in tetrahydrofuran at room temperature under reflux resulted in low conversion (70%) to the organozinc reagent. Almost the same result was obtained after an extended reaction time (reflux, 24 h). However, as shown in Scheme 1, a dramatic improvement in the oxidative addition of active zinc was achieved by adding 10–20 mol% of lithium chloride to the reaction mixture. Even though the role of the lithium chloride has not been totally explained, more than 99% conversion of 3-bromopyridine into 3-pyridylzinc bromide was obtained in two hours at reflux in tetrahydrofuran. As was pointed out in 1989,[11] the rate-limiting step in the oxidative addition is electron transfer. Accordingly, this process will be accelerated by the presence of alkali salts, which can either be generated in the reduction process of forming the active metals or by addition of salts to the reaction mixture.[12]



Scheme 1 Preparation of 3-pyridylzinc bromide

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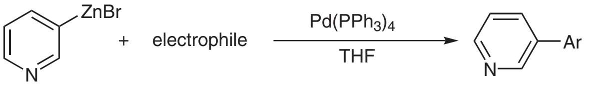
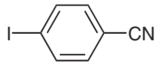
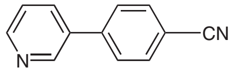
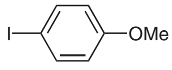
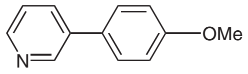
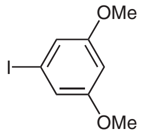
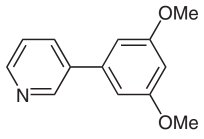
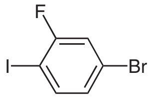
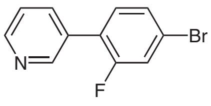
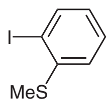
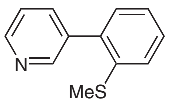
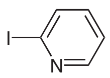
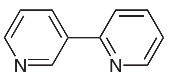
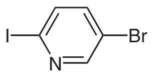
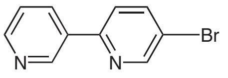
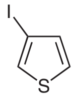
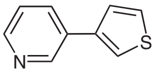
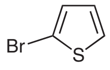
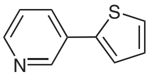
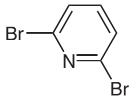
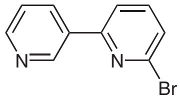
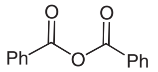
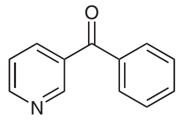
Table 1 Palladium-Catalyzed Coupling Reactions of 3-Pyridylzinc Bromide[a]



Entry	Electrophile	Time (h)	Product	Yield (%)[b]
1	 **2a**	1	 **3a**	65
2	 **2b**	1	 **3b**	81
3	 **2c**	1	 **3c**	63
4	 **2d**	24	 **3d**	63
5	 **2e**	12	 **3e**	32
6	 **2f**	1	 **3f**	71
7	 **2g**	1	 **3g**	62
8	 **2h**	1	 **3h**	71
9	 **2i**	48	 **3i**	86
10	 **2j**	48	 **3j**	29
11	 **2k**	12	 **3k**	38

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[a] Reaction conditions: electrophile (0.8 equiv), $Pd[P(Ph)_3]_4$ (1 mol%), r.t., THF.

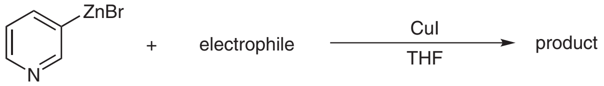
[b] Isolated yield (based on electrophile).

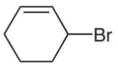
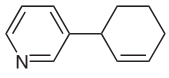
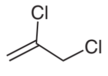
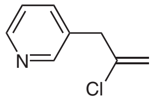
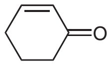
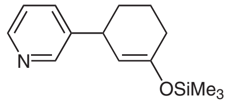
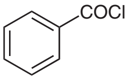
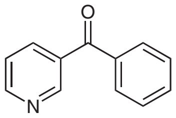
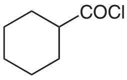
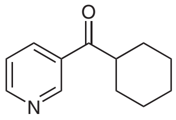
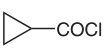
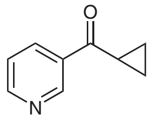
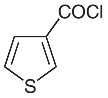
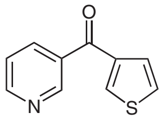
In order to confirm the formation of 3-pyridylzinc bromide, the resulting organozinc reagent was first treated with iodine to afford 90% 3-iodopyridine and 3% pyridine. The resulting 3-pyridylzinc bromide was added to a variety of electrophiles to give the corresponding coupling products in moderate to good yields. The results are summarized in Table 1. Palladium-catalyzed cross-coupling reactions with aryl iodides **2a–c** (Table 1) were complete in one hour at room temperature and gave the corresponding 3-pyridylbenzene derivatives in good yields (entries 1–3, Table 1). Longer reaction times were required with aryl iodides **2d** and **2e**, bearing a substituent in the 2-position (entries 4 and 5, Table 1), which is probably due to steric hindrance. With this result in hand, heteroaryl iodides **2f–h** were also coupled with 3-pyridylzinc bromide to afford the corresponding heteroaryls **3f–h** in good yields. Coupling reactions with heteroaryl bromides **2i** and **2j** required longer reaction times but also afforded the expected coupling products **3i** and **3j** in 86% and 29% isolated yields, respectively. As shown in entries 4 and 7 in Table 1, the carbon–iodine bond was selectively reacted in coupling reactions with the organozinc reagent **1a** to form the required carbon–carbon bond under the conditions used here. Even though a low yield was obtained from 2,6-dibromopyridine (**2j**), the coupling product **3j**, bearing a bromine atom, can serve as a valuable intermediate for the preparation of a variety of materials. Interestingly, it was also possible to obtain the aromatic ketone **3k** in moderate yield from the reaction of **1a** with benzoic acid anhydride (**2k**) in the presence of the palladium catalyst.

In order to expand the application of 3-pyridylzinc bromide, several copper-catalyzed coupling reactions were also investigated; the results are summarized in Table 2. S_N2'-type reactions were conducted with allyl halides to afford the expected products **4a** and **4b** (Table 2) in good to moderate yields, respectively. In the presence of TMSCl, silyl enol ether **4c** (Table 2) was obtained from the conjugate addition intermediate. Like other general organozinc reagents, 3-pyridylzinc bromide (**1a**) was also successfully used for the copper-catalyzed synthesis of ketone compounds. As shown in Tables 2, 10 mol% of copper(I) iodide promoted the coupling reaction with **1a** to give the ketones **3k** and **4d–f** in moderate yields under the conditions described in Table 2.

This study was expanded to include several analogues of 3-bromopyridine. As described in Tables 3, 3-bromoquinoline and 3-bromoisoquinoline were treated with active zinc along with 20 mol% of lithium chloride. It was found that the oxidative addition of active zinc was complete in two hours at reflux to give the corresponding organozinc reagents **1b** and **1c** (Table 3). The subsequent coupling reactions of **1b** were performed with aryl iodide (entry 1, Table 3) and heteroaryl iodides (entries 2 and 3, Table 3) in the presence of palladium catalyst, to afford the corresponding products **5a–c** in moderate to good isolated yields. Entries 4 and 5 in Table 3 show the results of the coupling reactions of **1c** with heteroaryl iodide and allyl

Table 2 Copper-Catalyzed Coupling Reaction[a]



Entry	Electrophile	Temp (°C)	Time (h)	Product	Yield (%)[b]
1		0	10 min	 **4a**	71
2		0	10 min	 **4b**	50
3[c]		0 to r.t.	24	 **4c**	48
4		0 to r.t.	12	 **3k**	50
5		0 to r.t.	12	 **4d**	69
6		0 to r.t.	12	 **4e**	38
7		0 to r.t.	12	 **4f**	50

[a] Reaction conditions: electrophile (0.8 equiv), CuI (10 mol%), THF.

[b] Isolated yield (based on electrophile).

[c] Reaction was conducted in the presence of TMSCl (1.0 equiv).

chloride. From these reactions, more new heteroaryl compounds **4d–e** were obtained in moderate yields (Table 3).

Finally, the regio-stability of 3-pyridylzinc bromide was confirmed by two additional coupling reactions. These results are listed in Table 4. It can be concluded that 3-pyridylzinc bromide prepared via direct oxidative addition of active zinc to 3-bromopyridine was stable enough to be used for the coupling reactions under the appropriate conditions without scrambling of the organometallic position.

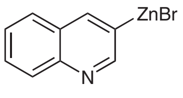
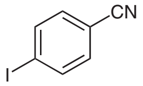
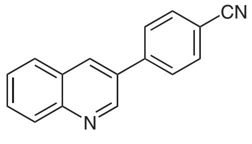
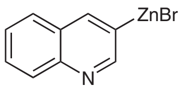
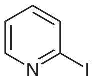
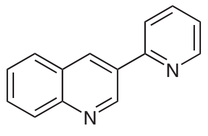
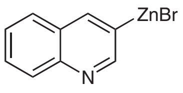
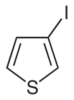
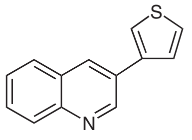
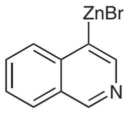
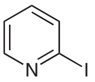
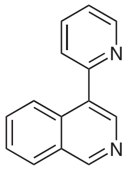
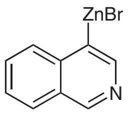
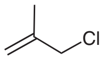
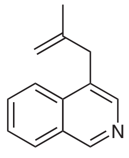
In conclusion, a facile synthetic approach to the direct preparation of 3-pyridylzinc bromide has been demonstrated. The reaction was easily performed using Rieke zinc with 3-bromopyridine, in the presence of a catalytic amount of lithium chloride. With the resulting 3-pyridylzinc bromide, a variety of electrophiles have been coupled to give the corresponding cross-coupling products in moderate to good yields. Furthermore, this methodology has been expanded to the preparation of the corresponding organozinc reagents of 3-bromopyridine analogues. Studies on more applications of this methodology are currently underway.

All reactions were performed under argon pressure. Active zinc was prepared by a literature method.[11] Other commercially available reagents including the solvent (THF, from Aldrich) were used without further purification. Flash chromatography was carried out on Kieselgel 60 (230–400 mesh). NMR spectra were recorded at 300 or 500 MHz using $CDCl_3$ (TMS). All melting points are uncorrected.

Preparation of 3-Pyridylzinc Bromide (1a)

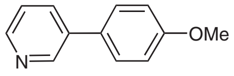
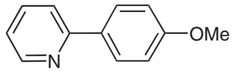
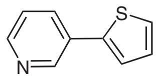
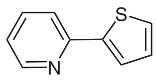
An oven-dried 100 mL round-bottomed flask was charged with active Zn (3.3 g, 50 mmol) in THF (30 mL) and LiCl (0.2 g, 20 mol%)

Table 3 Preparation of Quinoline and Isoquinoline Derivatives via Heteroarylzinc Reagents[a]

Entry	Organozinc	Electrophile	Catalyst	Temp	Product	Yield (%)[b]
1	 **1b**		$Pd(PPh_3)_4$	r.t.	 **5a**	70
2	 **1b**		$Pd(PPh_3)_4$	r.t.	 **5b**	65
3	 **1b**		$Pd(PPh_3)_4$	r.t.	 **5c**	53
4	 **1c**		$Pd(PPh_3)_4$	r.t.	 **5d**	37
5	 **1c**		CuI[c]	0 °C to r.t.	 **5e**	35

[a] Reaction conditions: electrophile (0.8 equiv), catalyst (1 mol%), 1 h, THF.
[b] Isolated yield (based on electrophile).
[c] 10 mol% catalyst used.

Table 4 Comparison of Physical Data[a]

Entry	Organozinc[b]	Electrophile	Product	Result	Mp (°C)
1	3-pyridylzinc bromide **1a**	**2b**	 **3b**	orange solid	56–58
2	2-pyridylzinc bromide	**2b**	 **3bb**	oil at r.t. (68%)[c]	–
3	3-pyridylzinc bromide **1a**	**2i**	 **3i**	oil at r.t.	–
4	2-pyridylzinc bromide	**2i**	 **3ii**	off-white solid (68%)[c]	61–62

[a] Reaction conditions: electrophile (0.8 equiv), $Pd(PPh_3)_4$ (1 mol%), r.t., THF.
[b] Prepared using active zinc.
[c] Isolated yield (based on electrophile).

under a positive pressure of argon gas. 3-Bromopyridine (3.9 g, 25 mmol) was added to the solution of active zinc at r.t. and the resulting mixture was then stirred at reflux for 2 h. After cooling to r.t., the supernatant was used for the subsequent coupling reactions.

Palladium-Catalyzed Cross-Coupling Reactions; Typical Procedure

3-(4-Methoxyphenyl)pyridine (3b)

A 50 mL round-bottomed flask equipped with a stirring bar, a thermometer and a septum, was charged with $Pd(PPh_3)_4$ (0.1 g) and then a solution of 3-pyridylzinc bromide (0.5 M in THF, 20 mL 10 mmol) was added into the flask via a syringe. Next, whilst being stirred at r.t., 4-iodoanisol (1.8 g, 8 mmol) in THF (5.0 mL) was added. After stirring at r.t. for 1.0 h, the reaction mixture was quenched with sat. NH_4Cl (20 mL), then extracted with Et_2O (3 × 20 mL), washed with sat. $Na_2S_2O_3$ (50 mL) and brine (50 mL), then dried over $MgSO_4$. The mixture was purified by flash column chromatography on a silica gel column (EtOAc–heptanes, 10%) to afford **2b** as a light-orange solid (1.2 g, 81% isolated yield).

Copper-Catalyzed Cross-Coupling Reactions; Typical Procedure

Cyclohexyl 3-Pyridyl Ketone (3d)

A 50 mL round-bottomed flask equipped with a stirring bar, a thermometer and a septum, was charged with CuI (0.2 g, 10 mol%) and a solution of 3-pyridylzinc bromide (0.5M in THF, 20 mL, 10 mmol). The flask was cooled to 0 °C and, whilst being stirred at 0 °C, cyclohexanecarbonyl chloride (1.16 g, 8 mmol) was added via syringe. The resulting mixture was allowed to warm gradually and then stirred at r.t. for 12 h. The reaction mixture was quenched with sat. NH_4Cl (20 mL) and then extracted with Et_2O (3 × 20 mL). The combined organic plases were washed with 7% NH_4OH (50 mL), sat. $Na_2S_2O_3$ (50 mL), $NaHCO_3$ (50 mL) and brine (50 mL), then dried over $MgSO_4$. The mixture was purified by flash column chromatography on a silica gel column (EtOAc–heptanes, 5%) to afford **3d** as a light-yellow oil (1.3 g, 69% isolated yield).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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