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Pyridinyl- and Furanyl-methylzinc Chloride: Direct Preparation and Coupling Reactions

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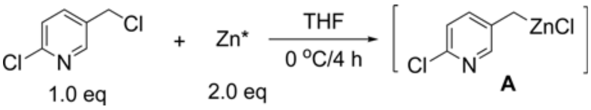
Benzylic organometal reagents are highly relevant for the synthesis of organic complex molecules, especially for the homologation of organometallics.[1] By utilizing these benzylmetallic reagents, the introduction of a diarylmethane-moiety presented in many natural compounds and biologically active materials has been successfully accomplished. To perform this strategy, a wide range of benzylic metal reagents have been used.[2] Along with the presence of a simple benzylic moiety in many natural materials, a non-functionalized or functionalized heterobenzylic moiety is also found and considered as an important class in biologically active pharmaceutical products.[3] For the synthesis of these active compounds, heterobenzylic halides were used mostly as a coupling partner of the corresponding organometallic reagents in the Stille, Suzuki and Negishi couplings.[3] However, some of the heterobenzylic halides are very unstable in the transition metal-catalyzed coupling reactions. To alleviate this difficulty, heterobenzylic sulfonium salts have also been participated in Pd-catalyzed coupling reactions of organometalllics.[4]

As described above, each heterobenzylic compound was used as a very efficient coupling partner in the cross-coupling reactions. In addition to this approach for the preparation of compounds containing a heterobenzylic moiety, utilizing the corresponding heterobenzylic organometal reagents would be another way to synthesize various different types of heterobenzyl-moiety-containing derivatives. Nevertheless, to the best of our knowledge, there is no report on the direct preparation of the heterobenzylic organometal reagent and its application in organic synthesis. In our continuing effort to explore the utility of organozinc reagents, it was found that several heterobenzylzinc reagents were easily prepared and their subsequent cross-coupling reactions were also carried out under mild conditions with some limitations. We herein report our first results of utilizing heterobenzylic zinc reagents.

For the preparation of heterobenzylzinc halides, readily available heterobenzyl halides such as 2-chloro-5-(chloromethyl)pyridine, 2-chloromethylpyridine, and 2-ethoxycarbonyl-5-(chloromethyl)furan were chosen. The oxidative addition of active zinc[5] was generally carried out in THF at room temperature.

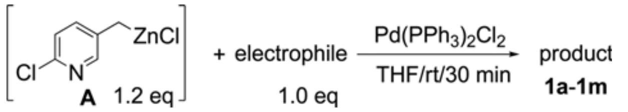
First attempt for the preparation of heterobenzylzinc was executed with 2-chloro-5-(chloromethyl)pyridine. In the presence of 2.0 equivalent of active zinc, the oxidative addition into the C-Cl bond of the benzylic position was completed in 4.0 h at room temperature to afford the corresponding organozinc reagent, (6-chloropyridin-3-yl)methylzinc chloride (**A**) without forming of any homocoupling product (Scheme 1).

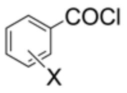
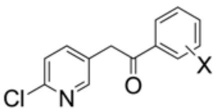
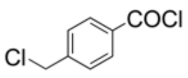
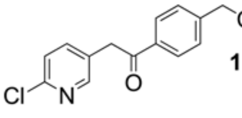
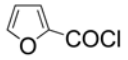
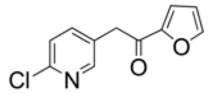
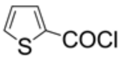
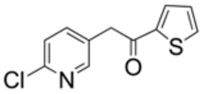
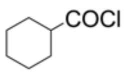
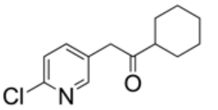
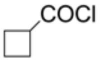
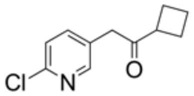
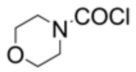
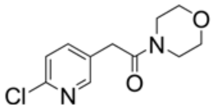
To investigate the applicability of the resulting organozinc reagent, we first examined the palladium-catalyzed cross-coupling reaction with a variety of acid chlorides. The results are summarized in Table 1. The reaction of **A** with benzoyl chloride was carried out in the presence of 1 mol % of $Pd(PPh_3)_2Cl_2$ at room temperature within 30 min providing the ketone **1a** in 65% isolated yield (entry 1, Table 1). During the coupling reaction, no detectable amount of homocoupling product of organozinc was observed. In addition, as we have developed a new catalytic system for the cross-coupling reaction of organozincs with acid chlorides,[6] coupling reaction has also been tried with 2 mol % of $Ni(acac)_2$-catalyst. Similar results were obtained in terms of yield and purity. Therefore, the rest of the reactions in this study were conducted using a Pd(II)-catalyst system. Not only bromobenzoyl chlorides (entries 2 and 3, Table 1) but chlorobenzoyl chloride (entry 4, Table 1) was successfully coupled with **A** under the Pd-catalyst system resulting in the formation of the ketones (**1b**, **1c**, and **1d**, Table 1) in moderate yields. Even higher yields were obtained from using benzoyl chlorides containing an electron-donating group. As depicted in Table 1, both 4-methyl- and 4-methoxybenzoyl chlorides reacted with **A** leading to ketones (**1f** and **1g**, Table 1) in 76% and 82% isolated yields, respectively. The reaction of **A** with 4-chloromethylbenzoyl chloride gave the expected product **1h** in 54% yield leaving benzyl chloride intact (entry 7, Table 1). By using heteroaromatic acid chlorides such as 2-furancarbonyl chloride and 2-thiophenecarbonyl chloride, the cross-coupling products (**1i** and **1j**, Table 1) were obtained in moderate yield (entries 8 and 9). The alkyl carbonyl chlorides (entries 10 and 11) were also suitable for the Pd-catalyzed coupling reaction, furnishing the



Scheme 1. Preparation of organozinc reagent **A**.

Table 1. Coupling reaction of (6-chloropyridin-3-yl)methylzinc chloride (**A**)

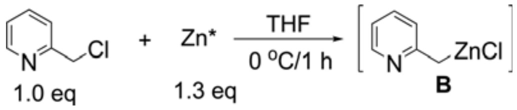


Entry	Electrophile	Product	Yield (%)[a]
			
1	X: H	**1a**	65
2	X: 3-Br	**1b**	45
3	X: 4-Br	**1c**	39
4	X: 3-Cl	**1d**	65
5	X: 4-Me	**1f**	76
6	X: 4-OMe	**1g**	82
7		 **1h**	54
8		 **1i**	60
9		 **1j**	34
10		 **1k**	58
11		 **1l**	67
12		 **1m**	54

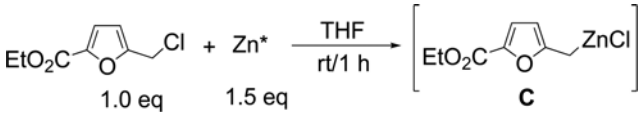
[a]isolated yield (based on electrophile)

corresponding ketones (**1k** and **1l**, Table 1) in moderate yields. It was of interest that a tertiary amide (**1m**) was achieved in 54% isolated yield from the coupling reaction of **A** with morpholinecarbonyl chloride (entry 12, Table 1).[7]

Following the observation of different reactivity from two regio-isomeric organozinc reagents such as 2-pyridylzinc bromide and 3-pyridylzinc bromide,[8] a further study has been performed with 2-pyridylmethylzinc chloride (**B**). Treatment of 2-(chloromethyl)pyridine with 1.3 equivalent of active zinc in THF at 0 °C resulted in the formation of 2-pyridylmethylzinc chloride (**B**) in 1.0 h. Prior to the application of **B** to the coupling reaction, it was treated with iodine and the resultant was analyzed by GC/MS showing more than 95% conversion to the iodinated product. With this promising reactivity, we have tried a typical transition-metal-catalyzed cross-coupling reaction using copper, nickel and palladium catalysts. Regardless of the catalysts used in this study, the coupling reactions proceeded smoothly with a variety of acid chlorides such as benzoyl chlorides, heteroaryl acid chlorides and alkyl acid chlorides. However, we have been confronted with a severe difficulty to purify the desired product. GC/GC-MS analysis of the reaction mixture clearly showed the formation of the desired ketone. Together with this, a newly formed spot on TLC plate was obtained and the corresponding product, which appeared as a single spot on TLC, was separated from the mixture by column chromatography. Despite this positive evidence of the successful cross-coupling reaction, we were not able to obtain an analytically-pure product. ^{1}H and ^{13}C NMR spectra definitely showed that the purified-product still contained an unidentified byproduct(s) that was impossible to separate by column chromatography. Once again, we could easily recognize the peaks attributed to the desired product on the NMR spectra along with other peaks. From the spectroscopic data, it could be inferred that the unidentified byproduct(s) was originated from the acid chlorides used in this study albeit there was no conclusive proof.

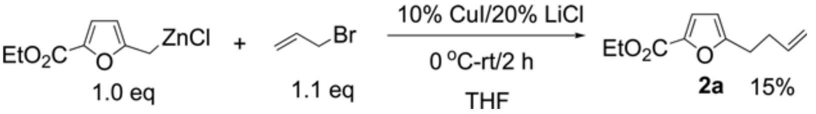


Scheme 2. Preparation of 2-pyridylmethylzinc chloride (**B**).



Scheme 3. Preparation of (5-ethoxycarbonylfuran-2-yl)methylzinc chloride (**C**).

In contrast to the previous studies performed with pyridylmethylzinc chlorides (**A** and **B**), more severe limitations were observed in the application of furan-derived heterobenzylzinc chloride. As described in Scheme 3, the preparation of the title organozinc reagent, 5-(ethoxycarbonylfuran-2-yl)methylzinc chloride (**C**), was readily accomplished from the direct insertion of active zinc into 5-ethoxycarbonyl-2-(chloromethyl)furan in THF at room temperature. To investigate the reactivity of the organozinc regent **C**, an aliquot was treated with iodine immediately after it was prepared and then analyzed by GC/GC-MS. Unlike the other organozinc reagents,[9] the low conversion (~77%) to the corresponding iodinated product was observed. Interestingly, an apparent change also occurred in the organozinc solution. Upon the storage even at a cold temperature, the color of the solution changed from a transparent light brown to a very viscous reddish brown.[10] It was also found that the reduced-form of the organozinc reagent was obtained as a major component in the solution from the iodine-quenching of the organozinc solution after being stored for two weeks at room temperature. Even though the instability and low reactivity of the



Scheme 4. The coupling reaction of **C** with allyl bromide.

organozinc **C**, we have tried a limited number of coupling reactions to explore the applicability. For a better result, the coupling reaction of **C** was conducted using a just-prepared solution. Its application was examined by the copper-catalyzed S_N2'-type reaction in a standard fashion (10 mol % CuI/20 mol % LiCl) affording the corresponding product (**2a**) in 15% yield (Scheme 4). Once again, on the basis of GC analysis of the reaction mixture, it could be concluded that the disappointed yield was attributed to the low reactivity of the organozinc **C**. No further conversion was observed after some amount of product was formed in the reaction mixture even in the extended reaction time. Additionally, Ni-catalyzed cross-coupling reaction with benzoyl chloride was carried out in THF at room temperature. The formation of coupling product was confirmed by GC/GC-MS. Unfortunately, however, the isolation of an analytically pure product turned out to be unsuccessful owing to the instability of the resulting product.[9] The purified-product from column chromatography was immediately turned into a dark oily product. As expected, ^1H and ^{13}C NMR spectra of the reformed-product showed complicated peaks which were attributed to both the expected product and unidentified product(s).

In conclusion, (6-chloropyridin-3-yl)methylzinc chloride (**A**), 2-pyridylmethylzinc chloride (**B**), and (5-ethoxycarbonylfuran-2-yl)methylzinc chloride (**C**) have been successfully prepared from the direct insertion of highly active zinc with readily available corresponding heterobenzyl halides. Significantly, it was found that the reactivity of the resulting organozinc reagents mainly depends upon the structure of the organozinc reagents. Further investigations are currently underway.

Experimental

Preparation of (6-Chloropyridin-3-yl)methylzinc Chloride (A). In an oven-dried 50 mL round-bottomed flask equipped with a stir bar was added 1.40 g of active zinc (Zn*, 22.0 mmol). 2-Chloro-5-(chloromethyl)pyridine (1.78 g, 11.0 mmol) dissolved in 10 mL of THF was then cannulated into the flask at 0 °C. The resulting mixture was stirred for 4 h at 0 °C. The whole mixture was settled down and then the supernatant was used for the subsequent coupling reactions.

A Representative Procedure for Pd-Catalyzed Coupling Reaction; 2-(6-Chloropyridin-3-yl)-2-thienylethanone (1j). Into a 25 mL round-bottomed flask were added $Pd(PPh_3)_2Cl_2$ (0.035g, 1.0 mol %) and 10 mL of (6-chloropyridin-3-yl)-methylzinc chloride (0.5 M in THF, 5.0 mmol). Next, thiophene-2-carbonyl chloride (0.59 g, 4.0 mmol) was added *via* a syringe while being stirred at room temperature. The resulting mixture was stirred at room temperature for 30 min. Quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel (5% ethyl acetate/95% heptane) afforded 2-(6-chloropyridin-3-yl)-1-(thiophene-2-yl)ethanone (**1i**, 0.57 g) as a light yellow solid in 60% isolated yield. mp 97-99 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, J = 2.4 Hz, 1H), 7.83 (dd, J = 0.8; 1.2 Hz, 1H), 7.73 (dd, J = 1.2; 0.8 Hz, 1H), 7.65 (dd, J = 2.4; 2.8 Hz, 1H), 7.33 (d, J = 4.4 Hz, 1H), 7.19 (dd, J = 4.0; 4.0 Hz, 1H), 4.23 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.6, 150.4, 150.3, 143.2, 134.7, 132.7, 128.8, 128.4, 124.2, 42.1; FT-IR (solid) 3099, 1659, 1566, 1460, 1232 cm^{-1}.

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9. In general, more than 95% conversion has been observed from most of the typical organozinc reagents utilized in our lab (unpublished data).
10. Instability of halogenated-furans is also described in reference 4.