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5-Bromo-2-pyridylzinc reagent; direct preparation and its coupling reactions

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ARTICLE INFO	ABSTRACT
Article history: Received 17 September 2010 Revised 26 October 2010 Accepted 4 November 2010 Available online 27 November 2010	A facile synthetic route to the direct preparation of 5-bromo-2-pyridylzinc iodide has been developed. Treatment of 5-bromo-2-iodopyridine with active zinc gave rise to the selective oxidative addition to C–I bond under mild conditions. The resulting organozinc iodide has been used in the variety of coupling reactions affording the corresponding cross-coupling product.

The use of pyridine-containing compounds has frequently appeared in a wide range of chemistry, such as natural product synthesis, pharmaceutical chemistry, and material science.¹ Many of the 2-pyridyl derivatives have been prepared using the Suzuki,² Stille,³ Grignard,⁴ and Negishi⁵ coupling reactions in the presence of a transition metal catalyst.

In spite of these intensive studies on the preparation and application of metalated-pyridine reagents, a very limited number of procedures have been reported using a selective metallation of dihalopyridines.

Especially, 5-bromo-2-metalated pyridine has received considerable attention in the pharmaceutical chemistry. To this end, several efforts have been performed by lithiation of 2,5-dibromopyridine. However, the preparation of stable pyridyl organometallics has been typically considered a problematic subject mainly because of its instability and the formation of byproducts.⁶ Along with this stability issue, selective lithiation of 2,5-dibromopyridine was a big challenging subject. As described in previous reports,⁷ the lithiation of 2,5-dibromopyridine occurred at the C(5)-position even at cryogenic conditions (*n*-BuLi, -100 °C). Wang et al. reported that 5-bromo-2-lithiopyridine resulted from the C(2)-selective lithiation of 2,5-dibromopyridine was obtained using *n*-BuLi under very low concentration (0.017– 0.085 M) at cold temperature $(-78 \circ C)$. However, the selectivity was highly dependent on the reaction conditions.⁸ Magnesiumhalogen exchange using 2,5-dibromopyridine with *i*-PrMgCl⁹ or n-Bu₃MgLi¹⁰ was also reported. Again, metallation at the C(5) was exclusively observed. Recently, Song et al. reported the synthesis of 5-bromopyridyl-2-magnesium chloride utilizing metal-halogen exchange method. Metallation took place selectively at the C(2)-position resulting in the formation of the corresponding Grignard reagent.^{4b}

As described above, several methods have been performed to make Grignard-type of pyridylmetallic reagents using 2,5-dihalopyridines. However, to our best knowledge, the preparation of the corresponding pyridylzinc reagent was not reported. We herein would like to report a practical procedure for the preparation of 5bromo-2-pyridylzinc iodide and subsequent coupling reactions.

Interestingly, in our continuing study on the preparation and application of organozinc reagents, it was found that 5-bromo-2-pyridylzinc iodide (I) was easily prepared using 5-bromo-2-iodo-pyridine and active zinc. It is of importance that the reaction proceeded via a selective oxidative addition of active zinc at the C(2)-position of pyridine under mild conditions. The resulting organozinc reagent (I) was treated with a variety of different electrophiles with/without any transition metal catalyst affording the coupling products.

The selective oxidative addition of the active zinc to carboniodine bond was completed at room temperature resulting in the formation of the corresponding 5-bromo-2-pyridylzinc iodide (I). According to GC–MS analysis of the reaction aliquot, more than 99% conversion into the corresponding organozinc reagent (I) was detected (Scheme 1).

Prior to the application of this organozinc (I) in the C–C bond forming reactions, the resulting 5-bromo-2-pyridylzinc iodide was treated with iodine to confirm the formation of organozinc reagent. The result showed the formation of 5-bromo-2-iodopyridine (85%), 3-bromopyridine (2%), and unidentified products by GC. Therefore, it could be concluded that the corresponding 5-bromo-2-pyridylzinc iodide was successfully prepared under the reaction conditions used in this study.



Scheme 1. Preparation of 5-bromo-2-pyridylzinc iodide (I).

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Table 1

Coupling reaction of I with aryl iodides



^a Isolated yield (based on ArI).

^b 20% conversion by GC/GC–MS, no isolated product.

In order to investigate the reactivity of this new organozinc reagent (I), it was treated with any iodides first in the presence of a catalytic amount of Pd(PPh₃)₄. As summarized in Table 1, most of the coupling reactions were performed at room temperature and the corresponding compounds were obtained in good to excellent yields. A simple iodobenzene reacted with I under the conditions depicted in Table 1. Interestingly, the coupling product 1a was obtained in excellent yield (94%, Table 1, entry 1). In the case of 4iodobenzonitrile containing an electro-withdrawing group (CN), an elevated temperature was more effective to complete the coupling reaction (Table 1, entry 2). Coupling reactions of I with other iodoaromatics containing an electron-donating group (OCH₃) and halogen (Br, F) also gave rise to the coupling products 1c and 1d in 70% and 78% isolated yields (Table 1, entries 3 and 4), respectively. Heteroaryl iodide was also a good coupling partner for the preparation of 2-heteroayl-substituted pyridine derivatives. A good result (1e, 79% yield) was obtained from the coupling reaction with 3-iodothiophene (Table 1, entry 5). It is of significance that the reaction conditions used for aforementioned coupling reactions worked well for the coupling reaction with aryl iodides containing an acidic proton. For example, coupling products, 1f and 1g, were successfully achieved from the coupling reactions with 3-aminoiodobenzene and 4-aminoiodobenzene (Table 1, entries 6 and 7), respectively.¹¹ Unfortunately, no reaction took place with iodophenol even with Pd(OAc)₂/SPhos (Table 1, entry 8).¹²

More results were obtained from the Pd(0)-catalyzed coupling reactions with bromoaromatic compounds. As shown in Table 2, treatment of **I** with functionalized aromatic (0.5 equiv of ethyl 5-bromothiophene-2-carboxylate) provided the coupling product

2a in 30% isolated yield (Table 2, entry 1). Interestingly, slightly higher yield (**2b**, 46%) was obtained from the reaction with the corresponding furan derivative (Table 2, entry 2) under the same conditions. 5-Bromofuran-2-carbaldehyde was also coupled with **I** at rt and resulted in the formation of 5-(5-bromopyridin-2-yl)furan-2-carbaldehyde **2c** in 78% yields (Table 2, entry 3).

Table 2

Coupling reaction with aryl bromides



^a Isolated yield (based on ArI).



Scheme 2. More examples of coupling reaction.

Several different types of coupling reactions of 5-bromo-2pyridylzinc iodide (**I**) have been investigated and the results are summarized in Scheme 2. Not only Pd-catalyzed coupling reaction but copper-catalyzed coupling reaction was accomplished. As described in Scheme 2, Pd(0) catalyst worked for the coupling reaction with 2-amino-5-iodopyridine to give an unsymmetrical 2,3bipyridine (**3d**) in 81% yield under mild conditions. This result is significant because considerable effort has been directed toward the preparation of unsymmetrical bipyridines.¹³

In the presence of Pd(II) catalyst, symmetrically substituted thiophene derivative (**3a**) was obtained in moderate yield. The coupling reaction was carried out with 0.3 equiv of 2,5-dibromothiophene at refluxing temperature for 24 h. This kind of product could be utilized for further application in material chemistry. A typical copper-catalyzed S_N2' -reaction was also successfully accomplished. Coupling reaction of **I** with 3-bromo-2-methylpropene gave rise to product **3e** in 71% at room temperature in 20 min.

Transition metal catalyst-free coupling reactions with acid chlorides were also carried out under mild conditions in this study.¹⁴ Even though low yields were obtained, a copper-free coupling reaction with benzoyl chlorides provided the corresponding ketones (**3b** and **3c**) in 24% and 29% isolated yields, respectively.

In conclusion, a practical synthetic route for the preparation of 2-substituted-5-bromopyridine derivatives has been demonstrated.¹⁵ It has been accomplished by utilizing a simple coupling reaction of a stable 5-bromo-2-pyridylzinc iodide (I), which was prepared via the direct insertion of active zinc to 5-bromo-2-iodopyridine. The subsequent coupling reactions with a variety of different electrophiles have been carried out under mild conditions. More applications of the organozinc reagent are currently under way.

Supplementary data

Supplementary data (experimental procedures and copies of ¹H, ¹³C NMR data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.041.

References and notes

- For recent examples, see: (a) Carey, J. S.; Laffan, D.; Thomson, C.; Wiliams, M. T. Org. Biomol. Chem. 2006, 4, 2337; (b) Bagley, M. C.; Glover, C.; Merritt, E. A. Synlett 2007, 2459; (c) Fang, A. G.; Mello, J. V.; Finney, N. S. Org. Lett. 2003, 5, 967.
- For recent examples, see: (a) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. Org. Lett. 2009, 11, 345; (b) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. Org. Lett. 2009, 11, 381; (c) Voisin-Chiret, A. S.; Bouillon, A.; Burzicki, G.; Celant, M.; Legay, R.; El-Kashef, H.; Rault, S. Tetrahedron 2009, 65, 607; (d) Hodgson, P. B.; Salingue, F. H. Tetrahedron Lett. 2004, 45, 685.
- (a) Schwab, P. F. H.; Fleischer, F.; Michl, J. J. Org. Chem. 2002, 67, 443; (b) Zhang, N.; Thomas, L.; Wu, B. J. Org. Chem. 2001, 66, 1500; (c) Schubert, U. C.; Eschbaumer, C.; Heller, M. Org. Lett. 2000, 2, 3373; (d) Gronowitz, S.; Bjork, P.; Malm, J.; Hornfeldt, A.-B. J. Organomet. Chem. 1993, 460, 127.
- (a) Sugimoto, O.; Yamada, S.; Tanji, K. J. Org. Chem. 2003, 68, 2054; (b) Song, J. J.; Yee, N. K.; Tan, Z.; Xu, J.; Kapadia, S. R.; Senanayake, C. H. Org. Lett. 2004, 6, 4905; (c) Duan, X.-F.; Ma, Z.-Q.; Zhang, F.; Zhang, Z.-B. J. Org. Chem. 2009, 74, 939.
- (a) Savage, S. A.; Smith, A. P.; Fraser, C. L. J. Org. Chem. **1998**, 63, 10048; (b) Fang, Y.-Q.; Hanan, G. S. Synlett **2003**, 852; (c) Trecourt, F.; Gervais, B.; Mallet, M.; Queguiner, G. J. Org. Chem. **1996**, 61, 1673; (d) Lutzen, A.; Hapke, M.; Staats, H.; Bunzen, J. Eur. J. Org. Chem. **2003**, 3948.
- For general examples of the coupling reactions of pyridylmetallics, see: Li, J. J.; Gribble, G. W. Palladium in Heterocyclic Chemistry, 2nd ed.; ELSEVIER, 2006.
- (a) Romero-Salguero, F. J.; Lehn, J.-M. *Tetrahedron Lett.* **1999**, 40, 859; (b) Parham, W. E.; Piccirlli, R. M. J. Org. Chem. **1977**, 42, 257; Preparation of 2bromo-5-pyridylboronic acid via lithiation of 2,5-dibromopyridine, see: (c) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. J. Org. Chem. **2002**, 67, 7541; (d) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, 58, 2885.
- Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E. J.; Reider, P. J. Tetrahedron Lett. 2000, 41, 4335.
- Trecourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Queguiner, G. Tetrahedron Lett. 1999, 40, 4339.
- (a) Mase, T.; Houpis, I. N.; Akao, A.; Dorziotis, I. K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Monila, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* 2001, *66*, 6775; (b) lida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* 2001, *42*, 4841.
- A recent example of coupling reaction with aminopyridine, see; Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. J. Org. Chem. 2005, 70, 388.
- 12. pK_a values (in DMSO); range between 10 and 19 for phenols, 20–30 for anilines, source from http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

- For a review, see: Kaes, C.; Katz, M.; Hosseini, M. W. Chem. Rev. 2000, 100, 3553. and see also:^{3c} references cited therein.
- For other example, see: Kim, S. H.; Rieke, R. D. *Tetrahedron Lett.* 2009, *50*, 5329.
 (a) *Preparation of 5-bromo-2-pyridylzinc iodide* (1): An oven-dried 100 mL round-bottomed flask equipped with stir bar and inlet valve was placed under an argon atmosphere. Next, Rieke zinc (0.5 M in THF, 33 mL, 50 mmol) was added via a syringe and then cooled the flask down in an ice-bath. 5-Bromo-2-iodopyridine (7.1 g, 25 mmol) dissolved in 20 mL of THF was cannulated into the flask while being stirred. After the addition was completed, the flask was allowed to warm up gradually, and then stirred at ambient temperature for 2 h. After settled down overnight, the supernatant was used for the subsequent coupling reactions. (b) A representative procedure of coupling reaction; In a 25 mL round-bottomed flask, Pd[P(Ph)₃]₄ (0.06 g, 1 mol %) and 2-amino-5-

iodopyridine (0.55 g, 2.5 mmol) were placed. Next, 10 mL (5 mmol) of 0.5 M solution of 5-bromo-2-pyridylzinc iodide (1) in THF was added into the flask at room temperature. After being stirred at room temperature for 6 h, the reaction mixture was heated to reflux for 2 h to complete the reaction. Cooled the mixture down to room temperature. Quenched with saturated NH₄Cl solution, then extracted with ethyl acetate (30 mL × 3). Combined organics were washed with saturated Na₂S₂O₃ solution and brine. Dried over anhydrous MgSO₄. A flash column chromatography (50% EtOAc/50% heptane) gave 0.51 g of **3d** as an off-white solid in 81% isolated. ¹H NMR (CDCl₃/DMSO-d₆, 500 MHz): δ 8.64 (s, 1H), 8.61 (s, 1H), 8.01 (d, *J* = 5 Hz, 1H), 7.82 (d, *J* = 10 Hz, 1H), 7.56 (d, *J* = 5 Hz, 1H), 6.60 (d, *J* = 10 Hz, 1H), 5.69 (s, 2H); ¹³C NMR (CDCl₃/DMSO-d₆, 125 MHz): δ 159.17, 153.18, 149.34, 145.99, 138.32, 134.70, 122.12, 119.12, 116.92, 107.38.