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Site-selective mono-oxidative addition of active zinc into carbon-bromine bond of dibrominated-thiophenes: preparation of thienylzinc reagents and their applications

Hye-Soo Jung, Hyun-Hee Cho, Seung-Hoi Kim*

Department of Chemistry, Dankook University, 119 Dandaero, Cheonan 330-714, Republic of Korea

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ABSTRACT

A facile protocol for the preparation of 3-bromo-2-thienylzinc bromide **A** and 5-bromo-2-thienylzinc bromide **B** has been developed. It has been successfully accomplished by a site-selective oxidative addition of active zinc into a chemically pseudo-equivalent or equivalent carbon-bromine bond, respectively. The subsequent cross-coupling reactions of the organozincs were also successfully carried out under mild conditions providing the corresponding products in moderate to high yields.

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Poly-functionalized thiophene derivatives have been utilized for the preparation of valuable compounds in various fields such as optoelectrochemical materials, pharmaceuticals, and biologically active molecules.¹ Consequently, a variety of synthetic protocols for functionalized thiophene derivatives, especially 2,5disubstituted thiophenes, has been developed. Among those methodologies, a transition-metal-catalyzed ring-closure methodology has been successfully employed.² Along with this method, another approach to the synthesis of poly-functionalized thiophene molecules is to utilize a further functionalization of the preformed thiophenes. Most such approaches have been performed by the cross-coupling reactions of organometallics with multiple halogen-substituted thiophene derivatives, which are mostly disubstituted thiophenes such as 2,3-, 2,4-, 2,5-, and 3,4-dihalogenated thiophenes.³ Of those, 2,3- and 2,5-dibromothiophenes are mostly frequently utilized in the cross-coupling reactions of organometallics since these molecules are of special interest for both academic and industrial applications. The regio-selectivity in the cross-coupling reactions of 2,3- and 2,5-dibromothiophene molecules attracts more academic attention due to the chemical similarity of the two C-Br bonds presented in those compounds.

Christophersen et al. reported a protocol for the synthesis of 2,3-substituted thienylboronic acids and esters using a combination of halogen-magnesium exchange and borylation.⁴ Site-selective lithiation of 2,3-dibromothiophene and subsequent coupling

* Corresponding author. E-mail address: kimsemail@dankook.ac.kr (S.-H. Kim). reaction were utilized for the construction of a building block for polymeric systems.⁵ 2,3-Dibromothiophene was also successfully employed for the site-selective coupling reactions of Negishi,^{6a} Stille, Suzuki, and Sonogashira.^{6b} Selectivity between the α -position C–Br and the β -position C–Br of the thiophene ring was studied in the coupling reactions using 2,3,5-tribromothiophene and 2,3,4,5tetrabromothiophene, respectively. As expected, the coupling reactions preferred to take place at the α -position C–Br affording mono- or disubstituted thiophene products.⁷

In contrast, a relatively limited number of examples of the siteselective coupling reaction of 2,5-dibromothiophene bearing two chemically equivalent C-Br bonds was reported, presumably, due to the low selectivity.⁸ Instead of being used as a coupling partner, 2,5-dibromothiophene was generally used for the preparation of the corresponding Grignard reagent via a selective monobromine-magnesium exchange reaction.⁹ The resulting Grignard reagents were successfully applied to the preparation of unsymmetrical 2,5-disubstituted thiophene derivatives. From a synthetic point of view, it is of significance that this approach can be utilized as a somewhat different synthetic protocol for introducing more unique functional groups onto the thiophene ring. In addition, to the best of our knowledge, very limited number of research for the direct preparation of thienyl metallic reagents via a site-selective oxidative addition of a metal into the dihalogenated thiophenes has been performed.¹⁰

In our continuing study on the preparation and application of new organozinc reagents, we found that a very selective oxidative addition of active zinc into the C–Br bond of 2,3-dibromo- and





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Scheme 1. Preparation of 3-bromo-2-thienylzinc bromide (A).

2,5-dibromothiophene took placed yielding 3-bromo-2-thienylzinc bromide (\mathbf{A}) and 5-bromo-2-thienylzinc bromide (\mathbf{B}), respectively. The resulting organozinc reagents (\mathbf{A} , \mathbf{B}) were also utilized in various different types of coupling reactions under mild conditions.

As is well known, organozinc reagents have been widely used in synthetic organic chemistry mainly owing to their relatively high functional group tolerance and great efforts have been made to expand their applicability.¹¹ We, herein, report a facile protocol for the synthesis and application of a new type of organozinc reagent prepared by a site-selective oxidative addition of active zinc into a chemically equivalent or pseudo-equivalent C–Br bond.

In order to accomplish our challenge, we first tried the oxidative addition of active zinc with 2,3-dibromothiophene which possesses two chemically pseudo-equivalent C–Br bonds. The

 Table 1

 Cross-coupling reaction of 3-bromo-2-thienylzinc bromide (A)

oxidative addition reaction was carried out at room temperature using 1.2 equiv of active zinc. It was of interest that the oxidative addition occurred exclusively at the α -position leaving the β bromine atom intact and yielding the corresponding organozinc reagent, 3-bromo-2-thienylzinc bromide (**A**). This result could be rationalized by the NMR study performed by Handy and Zhang,¹² and was also confirmed by GC–MS analysis of the reaction mixture in our study (Scheme 1).

With this reagent, we attempted the cross-coupling reaction with a variety of coupling partners and the results are summarized in Table 1.

The formation of the organozinc reagent (**A**) was further confirmed by the cross-coupling reactions. Initial study was carried out with acid chlorides in the presence of Pd-catalyst at room temperature. Benzoyl chlorides containing an electron-withdrawing group required 24 h-stirring to complete the coupling reaction yielding the corresponding ketones (**1a** and **b**) in good yields (entries 1 and 2, Table 1). In the case of trimethylbenzoyl chloride, the coupling reaction was completed in a shorter reaction time yielding the ketone (**1c**) in 90% isolated yield (entry 3, Table 1). A less reactive acid chloride, 4-morpholinecarbonyl chloride, was also successfully employed for the coupling reaction at refluxing

Entry	Electrophile	Conditions	Product		Yield ^a (%)
1	Br	Pd(PPh ₃) ₂ Cl ₂ rt/24 h	S O Br	1a	80
2	F COCI	Pd(PPh ₃) ₂ Cl ₂ rt/24 h	S O F	1b	85
3	COCI	$Pd(PPh_3)_2Cl_2 rt/2 h$	S O	1c	90
4	O N COCI	$Pd(PPh_3)_2Cl_2 reflux/24 h$	S O N	1d	61
5	Br	Pd(PPh ₃) ₂ Cl ₂ rt/24 h	S Br	1e	92
6	Br	Pd(PPh ₃) ₂ Cl ₂ rt/24 h	S S	1f	86
7	Br	$Pd(PPh_3)_2Cl_2 reflux/24 h$	S Br	1g	52
8	Br	$Pd(PPh_3)_2Cl_2 rt/24 h$	S N Br	1h	66
9	H ₂ N	Pd(OAc) ₂ /SPhos/reflux Pd(PPh ₃) ₂ Cl ₂ /reflux/24 h	_		Nr ^b

^a Isolated yeild (based on electrophile).

^b No reaction occurred.



Scheme 2. Preparation of 5-bromo-2-thienylzinc bromide (**B**).

Table 2Coupling reaction of **B** with acid chlorides



Entry	Electrophile	Conditions	Product		Yield ^a (%)
1	Br	Cul/LiCl rt/2 h	Br S Br	2a	73
2	CI	Cul/LiCl rt/2 h	Br S CI	2b	79
3	CI	Cul/LiCl rt/2 h	Br	2c	63
4	F ₃ C COCI	Cul/LiCl rt/1 h	Br S O CF3	2d	90
5	NC	Cul/LiCl 0 °C/2 h	Br	2e	75
6	H ₃ CO	Cul/LiCl rt/2 h	Br S	2f	85
7	COCI	Cul/LiCl rt/2 h	Br	2g	75
8	COCI	Cul/LiCl rt/2 h	Br S S	2h	93
9	COCI	Cul/LiCl rt/2 h	Br S O	2i	84
10	CI	Cul/LiCl rt/1 h	Br S	2j	66
11	COCI	Cul/LiCl rt/2 h	Br S O	2k	79
12		Pd(PPh ₃) ₂ Cl ₂ reflux/24 h	Br S N	21	68

^a Isolated yield (based on electrophile).

Table 3Coupling of **B** with aryl halides





^a Isolated yield (based on electrophile).

temperature to give rise to the corresponding product (**1d**) in 61% isolated yield (entry 4, Table 1).¹³ By employing the aryl halides, more examples of 2-aryl-substituted thiophenes were obtained. Under the identical catalytic system, a successful C–C bond was formed to yield 2-(4'-bromophenyl)-substituted thiophene (**1e**) and 2-(2'-naphthyl)-substituted thiophene (**1f**) in 92% and 86% isolated yields, respectively (entries 5 and 6, Table 1). Interestingly, heteroaryl halides (entries 7 and 8, Table 1) were coupled well with the organozinc (**A**) in the presence of Pd-catalyst providing bisheteroaryl compounds (**1g** and **h**, Table 1) in moderate yields. Unfortunately, no desired coupling product was obtained from the reaction with 4-iodoaniline bearing an acidic proton, either using Pd(OAc)₂ or Pd(PPh₃)₂Cl₂ (entry 9, Table 1).

With these promising results obtained from employing 2,3-dibromothiophene in hand, our studies were expanded to assess whether this protocol could be used for a much more challenging molecule, 2,5-dibromothiophene possessing two chemically equivalent C–Br bonds.

Symmetrically disubstituted-thiophene was treated with 1.1 equiv of active zinc at room temperature in THF. Surprisingly, the oxidative addition of active zinc into C–Br bond occurred at one of the two C–Br bonds in a highly selective manner. From GC and GC–MS analyses of the reaction mixture, it was observed that less than 5% of diorganozinc reagent was formed in the reaction mixture. Prior to the study of this reagent on the coupling reactions, an aliquot of the solution was treated with iodine and analyzed by GC and GC–MS. Both analyses clearly showed the formation of 2-bromo-5-iodothiophene, which suggested the formation of 5-bromo-2-thienylzinc bromide (**B**). All of the spectroscopic data of the compound were consistent with the literature values (Scheme 2).

The minor product (diorganozinc bromide) obtained during the procedure of organozinc synthesis did not interfere with the subsequent cross-coupling reaction that provided the desired coupling products. Once again, the formation of the organozinc reagent (B) was further confirmed by the transition-metal-catalyzed crosscoupling reactions with various electrophiles and aryl halides. The results are summarized in Tables 2 and 3.

On the basis of the promising results obtained from the previous work utilizing A, we examined the coupling reaction of **B** with acid chlorides in the presence of a catalytic amounts of Pd(PPh₃)₂Cl₂. In contrast to the previous results, however, this catalytic system was not effective for the formation of the desired product. Interestingly, an efficient route for the completion of the coupling reaction was attained simply by switching the catalyst to copper. As depicted in Table 2, a copper catalytic system worked more effectively to give the corresponding ketone products in moderate to good yields. Regardless of the substituents on the benzoyl chloride such as bromo-, chloro-, trifluoromethyl-, cyano-, and methoxy-, the corresponding ketones (2a, b, d-f, Table 2) were successfully obtained in moderate to good isolated yields (entries 1, 2, 4-6, Table 2), respectively. 4-Chloromethylbenzoyl chloride was coupled effectively with B to produce the ketone 2c (entry 3, Table 2) in moderate yield, leaving a sensitive active site (benzyl chloride) intact. The coupling reaction of **B** with a bulky acid chloride resulted in the formation of the ketone (2g) in 75% isolated yield (entry 7, Table 2). In addition, heteroaryl acid chlorides were also employed to investigate the facility of this methodology under the same conditions. As shown in Table 2, the corresponding coupling products (2h-j, Table 2) were obtained in good to excellent isolated yields (entries 8-10, Table 2). The copper catalyst system also showed good reactivity in the coupling reaction of **B** with cyclohexanecarbonyl chloride to provide the heteroaryl alkyl ketone (2k) in 79% isolated yield (entry 11, Table 2). Interestingly, in the case of 4-morpholinecarbonyl chloride, the Pd-catalyst system (2 mol % of Pd(PPh₃)₂Cl₂ at refluxing temperature) was more efficient to complete the coupling reaction affording the product 21 in 68% isolated yield (entry 12, Table 2).

In continuation of ongoing coupling reaction of a new organozinc reagent **B**, more thiophene derivatives were prepared under the typical Pd-catalyzed coupling reaction conditions and the results are summarized in Table 3. In a standard experiment, iodinated aryl compounds were coupled with **B** in the presence of 2 mol % of Pd(PPh₃)₂Cl₂ in THF and the reaction was completed in 24 h at room temperature. Analytically pure products (3a and b, Table 3) were obtained in 63% and 84% yields, respectively. However, this catalyst system did not work well for the brominated aryl compound. Instead, as described in Table 3, the reaction of 2-bromoindene with **B** was completed at room temperature in 12 h using 1 mol % of $Pd(PPh_3)_4$ affording the coupling product **3c** in 43% isolated yield (entry 3, Table 3). Surprisingly, Pd(II)-catalyst worked very efficiently for both brominated and iodinated heteroarvl compounds. The reaction with brominated-thiophene resulted successfully in the formation of unsymmetrically disubstituted bithiophene **3d** in 62% yield (entry 4, Table 3). A similar reaction with 3-bromoquinoline was executed under the same conditions giving rise to the desired product 3e in 61% yield (entry 5, Table 3). A selective coupling reaction of **B**, as expected, was observed from the reaction with a pyridine containing both iodine and bromine atoms (entry 6, Table 3). The product **3f** with two bromine atoms was obtained in 72% isolated yield.

In conclusion, a site-selective oxidative addition of active zinc¹⁴ into both chemically equivalent and pseudo-equivalent carbon–bromine bonds has been developed and the subsequent coupling reactions of the resulting organozinc reagents were successfully demonstrated with a variety of electrophiles and aryl halides under mild conditions.¹⁵ The desired products were obtained in good to excellent isolated yields. Most of the coupling products obtained in this study may potentially be further transformed to the highly substituted thiophene derivatives due to the presence of a bromine atom on the thiophene ring. Such applications of the strategy proposed herein are presently being investigated.

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- 15. A typical procedure: (a) Preparation of 5-bromo-2-thienylzinc bromide (B); 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). 2,5-Dibromothiophene (4.82 g, 20.0 mmol) dissolved in 20 mL of THF was then cannulated neat into the flask at room temperature. The resulting mixture was stirred for 1 h at room temperature. The whole mixture was settled down and then the supernatant was used for the subsequent coupling reactions; (b) Cu-catalyzed crosscoupling reaction; Into a 25 mL round-bottomed flask were placed CuI (0.05 g, 10 mol%) and LiCl (0.02 g, 20 mol%). 5-Bromo-2-thienylzinc bromide (B) (5.0 mL, 0.5 M in THF, 2.5 mmol) was added into the flask under an argon atmosphere. Next, 6-chloronicotinoyl chloride (0.35 g, 2.0 mmol) was slowly added via a syringe while being stirred at room temperature. The resulting mixture was stirred at room temperature for 1 h. Quenched with saturated NH_4Cl solution, then extracted with ethyl ether (10 mL \times 3). Washed with saturated NaHCO₃, Na₂S₂O₃ solution and brine, then dried over anhydrous MgSO₄. Purification by column chromatography on silica gel (2% ethyl acetate/ 98% heptane) afforded 0.40 g of 2j in 66% isolated yield as a light yellow solid (mp 117 °C); ¹H NMR (CDCl₃, 400 MHz) δ = 8.84 (d, J = 2.4 Hz, 1H), 8.10 (dd, I = 2.4; 2.4 Hz, 1H, 7.51 (d, I = 8.0 Hz, 1H), 7.40 (d, I = 4.0 Hz, 1H), 7.20 (d, J = 4.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) $\delta = 183.7$, 155.2, 149.9, 144.2, 139.1, 135.2, 131.8, 131.6, 124.9, 124.6; FT-IR (solid) 3096, 1624, 1558, 1415 cm⁻¹ (c) Pd-catalyzed cross-coupling reaction procedure; Into a 25 mL roundbottomed flask were added Pd(PPh₃)₂Cl₂ (0.035 g, 2.0 mol %), ethyl 2-thienylzinc bromide (**B**) (0.5 M in THF, 2.5 mmol) under an argon atmosphere at room temperature. The resulting mixture was stirred at room temperature for 2 h. Quenched with 3 M HCl solution, then extracted with ethyl ether (10 mL \times 3). Washed with saturated NaHCO₃, Na₂S₂O₃ solution and brine, then dried over anhydrous MgSO4. Purification by column chromatography on silica gel (2% ethyl acetate/98% heptane) afforded 0.39 g of ethyl 5'-bromo-2,2'-bithiophene-5-carboxylate (3d) in 62% isolated yield as a yellow solid (mp 69–70 °C); ¹H NMR (CDCl₃, 400 MHz) δ = 7.70 (d, J = 4.0 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.03 (dd, J = 3.6; 4.0 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) $\delta = 161.9$, 142.8, 137.8, 134.0, 132.3, 130.9, 125.2, 124.1, 112.9, 61.3, 14.4; FT-IR (solid) 2978, 1699, 1558 cm^{-1} .