One-Pot Cross-Coupling of Diborylmethane for the Synthesis of Dithienylmethane Derivatives

Kohei Endo,*[a,b] Takafumi Ishioka,[c] Takanori Shibata*[c]

[a] Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan
Fax +81(76)2645698; E-mail: kendo@se.kanazawa-u.ac.jp; E-mail: tshibata@waseda.jp

[b] PRESTO, Japan Science and Technology Agency (JST), 4-1-8 Honcho Kawaguchi, Saitama 332-0012, Japan

[c] Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Shinjuku, Tokyo 169-8555, Japan

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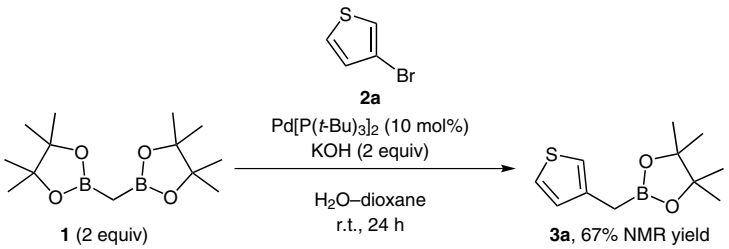
Abstract: The one-pot palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of a diborylmethane with bromothiophene derivatives realized the synthesis of various dithienylmethane derivatives. Cyclopentadithiophenes, which are promising compounds in material science, can be obtained in good yields. The in situ generation of an unstable thienylmethylboronate is a key step for the present reaction.

Key words: boron, cross-coupling, heterocycles, organometallic reagents, palladium

The cross-coupling reaction is a powerful approach to the synthesis of diarylmethane derivatives using aryl halides with benzylmetal intermediates or arylmetal intermediates with benzyl halides.[1,2] Typical reactions require the use of arylmetal- or benzylmetal-type intermediates, which sometimes degrade the reactions along with various side products. Especially, the incorporation of heteroaromatic moieties into the desired coupling products seems to be difficult, since intermediates for coupling reactions are often unstable.

During our studies using diborylmethane derivatives in cross-coupling reactions, we found that the use of heteroaryl halides did not give the desired products.[3] Extensive studies have shown that 3-bromothiophene (**2a**) could take part in the coupling reaction using diborylmethane (**1**) to give thienylmethylboronate derivative **3a** (Equation 1). Although the desired product **3a** was observed using NMR analysis, **3a** underwent decomposition after silica gel column chromatography. The only reported example of the synthesis of a thienylmethylboronate derivative was successful at a gram scale, but there was no mention of its stability.[4] We describe here the generation of thienylmethylboronate derivatives in situ via diborylmethane (**1**) for a one-pot coupling reaction. Various types of dithienylmethane derivatives and cyclopentadithiophenes were obtained in good to high yields.

Thiophene is an important building block for the synthesis of pharmaceutical and organic materials (Figure 1).[5] There have been numerous reports of methylene-bridged heteroaromatic compounds, including thiophene derivatives. We focused on the synthesis of dithienylmethane derivatives via a diborylmethane in one-pot. There are only a few conventional approaches to the synthesis of dithienylmethane derivatives.[6] The effect of the substituents of bromothiophenes was examined using diborylmethane (**1**); NMR yields are given due to the instability of products **3** (Table 1). The use of simple 3-bromothiophene (**2a**, 1 equiv) and diborylmethane (**1**, 2 equiv) in the presence of $Pd[P(t\text{-}Bu)_3]_2$ (10 mol%) and KOH (2 equiv) in H_2O–dioxane at room temperature gave the desired product **3a** in 67% NMR yield; protodeboronation seems to be a thorny problem (Table 1, entry 1).[7] We found that bromothiophenes bearing an electron-withdrawing group could give the desired products in relatively high yields. The reaction of acetyl derivative **2b** gave the product **3b** in high yield (Table 1, entry 2). The reaction of benzoyl derivative **2c** gave the product **3c** in good yield (Table 1,



Equation 1

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entry 3). The use of carboxylate derivatives **2d**, **2e**, and **2f** gave the products **3d**, **3e**, and **3f**, in good to high yields, respectively (Table 1, entries 4–6). The nitrile derivative **2g** can be compatible (Table 1, entry 7). In contrast, the reaction of a bromothiophene bearing an electron-donating group, even a methyl group, gave the product **3h** in low yield (Table 1, entry 8). Furthermore, regioisomers of **2b**, such as **2i** and **2j**, did not give the desired products at all (Table 1, entries 9 and 10). The reaction using 2-bromothiophene (**2k**) gave the product in low yield (Table 1, entry 11). Other heteroaromatic halides **2l** and **2m**, such as furan and pyridine derivatives, did not give the desired products (Table 1, entries 12 and 13).

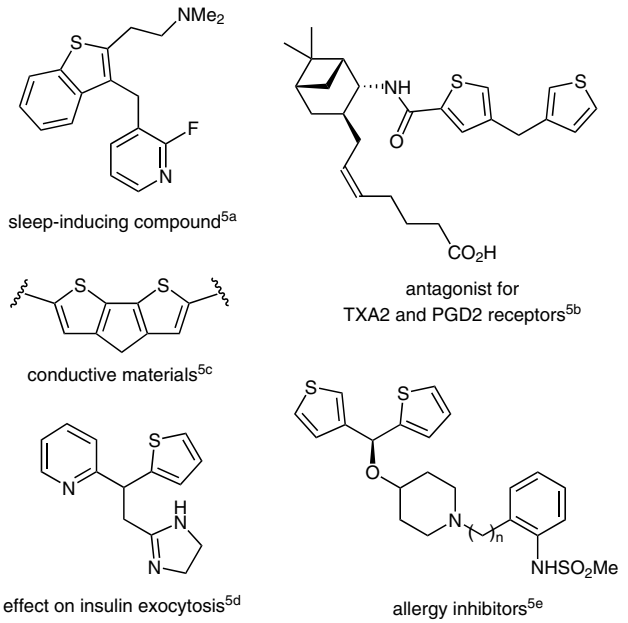
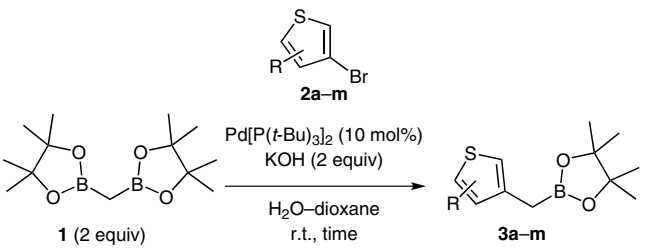
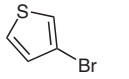
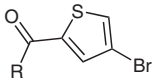
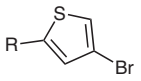
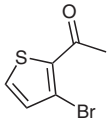
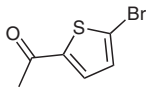
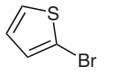
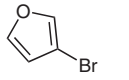
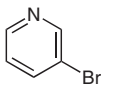


Figure 1 Examples of thiophene derivatives

The one-pot procedure for the synthesis of dithienylmethane derivatives and other heteroaromatic compounds is shown in Table 2, since the thienylmethylboronate derivatives **3** are not stable. An examination of the reaction conditions gave the desired products in high yield. The reaction required an appropriate amount of the second coupling partner and an additional KOH.[8] Various heteroaromatic halides were used for the synthesis of methylene-bridged products. The combination of **2a** and various second coupling partners showed that the second coupling reaction of thiophene derivatives bearing an electron-withdrawing group and/or an electron-donating group proceeded to give **4a**–**f** (Table 2, entries 1–6). The use of 2-bromothiophene (**2k**) gave the desired product **4g** in 71% yield (Table 2, entry 7). Interestingly, the use of 2,3-dibromothiophene (**2n**) gave the product **4h** chemoselectively (Table 2, entry 8).[9] The benzothiophene derivative **2o** could be used in the second coupling reaction to give the product **4i** in 75% yield (Table 2, entry 9). Furthermore, furan and pyridine derivatives participated in the second coupling reaction to give the products **4j** and **4k** in good yields (Table 2, entries 10 and 11). Other elec-

Table 1 Substituent Effect

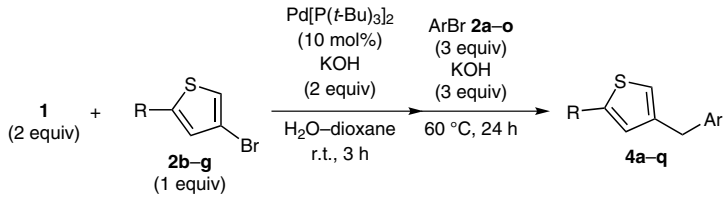


Entry	2	Time (h)	NMR yield (%)[a]
1	 **2a**	24	**3a** 67
2	 **2b** R = Me	3	**3b** 91
3	**2c** R = Ph	3	**3c** 79
4	**2d** R = OEt	3	**3d** 75
5	**2e** R = OPh	3	**3e** 75
6	**2f** R = O*t*-Bu	3	**3f** 90
7	 **2g** R = CN	3	**3g** 77
8	**2h** R = Me	4	**3h** 27
9	 **2i**	3	**3i** not detected
10	 **2j**	3	**3j** not detected
11	 **2k**	24	**3k**, 9
12	 **2l**	24	**3l** not detected
13	 **2m**	3	**3m** not detected

[a] NMR yield is given. Products were ascertained by MS–FAB.

tron-withdrawing groups were suitable for use under the conditions for the second coupling reaction and gave the products **4l–q**; however, the reaction using **2e** gave the product **2n** in low yield (Table 2, entries 12–17). Symmetrical dithienylmethanes were synthesized under the optimized reaction conditions (Scheme 1). The reaction of diborylmethane (**1**) and bromothiophene derivatives **2b**, **2c**, or **2f** (2.2 equiv) gave the desired products **4r**, **4s**, or **4t** in moderate to good yields.

Table 2 One-Pot Coupling Reaction



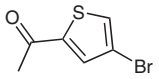
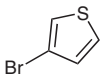
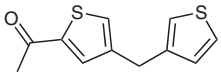
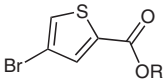
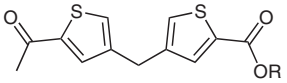
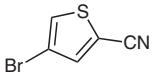
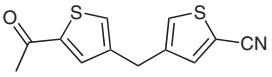
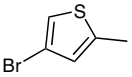
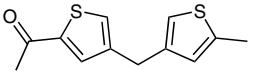
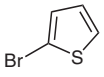
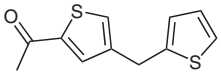
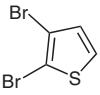
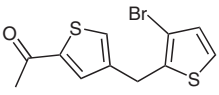
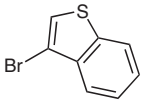
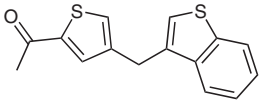
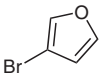
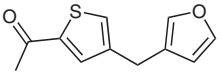
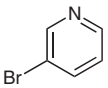
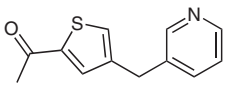
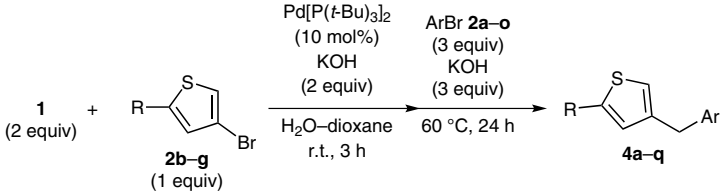
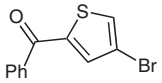
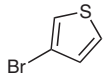
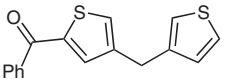
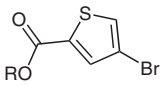
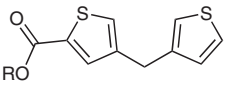
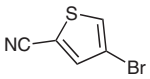
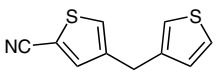
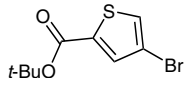
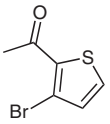
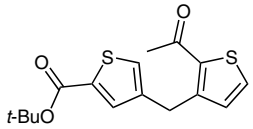
Entry	1st ArBr	2nd ArBr	Product (%)
1			
	2b	**2a**	**4a** 84
			
2	**2b**	**2d** R = Et	**4b** 64
3	**2b**	**2e** R = Ph	**4c** 51
4	**2b**	**2f** R = *t*-Bu	**4d** 91
5	**2b**		
		2g	**4e** 50
6	**2b**		
		2h	**4f** 63
7	**2b**		
		2k	**4g** 71
8	**2b**		
		2n	**4h** 52
9	**2b**		
		2o	**4i** 75
10	**2b**		
		2l	**4j** 65
11	**2b**		
		2m	**4k** 80

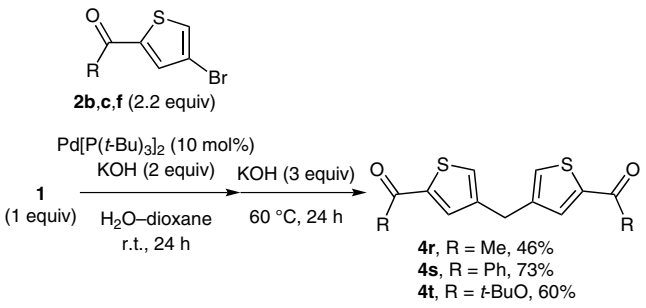
Table 2 One-Pot Coupling Reaction (continued)



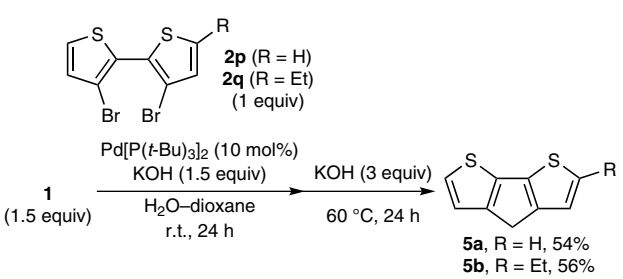
Entry	1st ArBr	2nd ArBr	Product (%)
12	 **2c**	 **2a**	 **4l** 91
			
13	**2d** R = Et	**2a**	**4m** 63
14	**2e** R = Ph	**2a**	**4n** 26
15	**2f** R = *t*-Bu	**2a**	**4o** 84
16	 **2g**	**2a**	 **4p** 74
17	 **2f**	 **2i**	 **4q** 54

Finally, the coupling reaction using diborylmethane (**1**) and 3,3′-dibromo-2,2′-bithiophene (**2p**) was performed for the synthesis of cyclopentadithiophene derivatives, which are conventionally synthesized via a copper-mediated intramolecular coupling or the Friedel–Crafts-type reactions.[8,10] After optimization of the reaction conditions, the desired cyclopentadithiophene **5a** was obtained in moderate yield (Scheme 2). Although bithiophene derivative **2q** bearing an alkyl group could take part in the reaction to give **5b**, a bithiophene derivative bearing an electron-withdrawing group, such as an acetyl group, gave only a trace amount of the desired product. Methylation products were observed as side products after protodeboronation (Scheme 3).

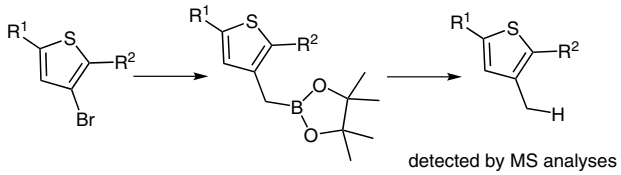
In conclusion, we have achieved a one-pot coupling reaction for the synthesis of dithienylmethane derivatives. The present reaction can provide unstable thienylmethylboronate derivatives in situ, which were used for the sequential coupling reactions without purification to give dithienyl methane derivatives. The products in the present paper should be useful for progress in pharmaceutical and material science.



Scheme 1 Synthesis of symmetrical dithienylmethanes



Scheme 2 Synthesis of cyclopentadithiophene



Scheme 3 Schematic results of protodeboronation

Representative Procedure of One-Pot Coupling Reaction

1-{4-[(Thiophen-3-yl)methyl]thiophen-2-yl}ethanone (4a)
To a solution of diborylmethane (**1**, 102.8 mg, 0.38 mmol, 2 equiv), 1-(4-bromothiophen-2-yl)ethanone (**2b**, 39.2 mg, 0.191 mmol), and $Pd[P(t\text{-}Bu)_3]_2$ (10.2 mg, 20 μmol, 10 mol%) in dioxane (2.0 mL) was added 8 N KOH aq (46 μL, 0.4 mmol, 2 equiv) at r.t. The mixture was stirred at r.t. for 3 h. Then, 8 N KOH aq (69 μL, 0.6 mmol, 3 equiv) and 3-bromothiophene (**2a**, 95.2 mg, 0.58 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 24 h and filtered through a pad of silica gel with Et_2O. Purification by silica gel column chromatography (hexane–EtOAc = 20:1) gave the product **4a** in 84% yield (0.160 mmol, 35.6 mg/42.5 mg); yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 7.32–7.25 (m, 2 H), 6.97 (s, 1 H), 6.92 (m, 1 H), 3.98 (s, 2 H), 2.52 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 144.4, 142.2, 139.9, 133.4, 129.9, 128.1, 126.1, 121.5, 31.0, 26.8. IR (neat): 2992, 2852, 1660, 1417, 1271, 777 cm^{-1}. ESI-HRMS (+): *m/z* calcd for $C_{11}H_{10}NaOS_2^+$ $[M + Na]^+$: 245.0065; found: 245.0066.

4*H*-Cyclopenta[1,2-*b*:5,4-*b*′]dithiophene (5a)[10c]
To a solution of diborylmethane (**1**, 80.2 mg, 0.30 mmol, 1.5 equiv), 3,3′-dibromo-2,2′-bithiophene (**2p**, 64.7 mg, 0.200 mmol), and $Pd[P(t\text{-}Bu)_3]_2$ (10.2 mg, 20 μmol, 10 mol%) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at r.t. The mixture was stirred at r.t. for 24 h. Then, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 24 h and filtered through a pad of silica gel with Et_2O. Purification by silica gel column chromatography (hexane) gave the product **5a** in 54% yield (0.107 mmol, 19.1 mg/35.6 mg); yellow solid; mp 74 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (m, 2 H), 7.08 (m, 2 H), 3.53 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 138.6, 124.4, 122.9, 31.8. IR (neat): 3074, 2922, 1660, 802, 685 cm^{-1}. ESI-HRMS (+): *m/z* calcd for $C_9H_7S_2^+$ $[M + H]^+$: 178.9984; found: 178.9984.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(8) See Supporting Information.

(9) The halogen–lithium exchange of **4h** using *n*-BuLi and subsequent protonation gave **4g**.

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