First Site-Selective Suzuki–Miyaura Reactions of 2,3,4-Tribromothiophene

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Abstract: The first Suzuki–Miyaura reactions of 2,3,4-tribromothiophene are reported. These reactions provide a convenient and site-selective approach to 2-aryl-3,4-dibromothiophenes, 2,4-diaryl-3-bromothiophenes, and 2,3,4-triarylthiophenes.

Key words: catalysis, palladium, Suzuki–Miyaura reaction, site selectivity, thiophene

Aryl-substituted thiophenes are of considerable pharmacological relevance.[1] Thiophenes have also been isolated as natural products.[2] Thiophenes are of great importance in the field of material science, because of their electronic properties (e.g., redox activity, luminescence, nonlinear optical chromism, and electron transport).[3] In this context, the synthesis of terthiophenes and thienyldiynes play an important role.[4]

Site-selective palladium(0)-catalyzed cross-coupling reactions of polyhalogenated heterocycles constitute a powerful tool in organic synthesis.[5] The site selectivity often relies on electronic parameters [oxidative additions of palladium(0) species to carbon–halogen bonds are usually more rapid for electron-poor than for electron-rich carbon atoms]. In addition, steric parameters play an important role. It has been reported that Sonogashira and Kumada reactions of 2,3- and 2,4-dibromothiophene proceed with very good site selectivity (the first attack occurs at carbon atom C-2).[6] 2,3,5-Tribromothiophene undergoes site-selective metal–halide exchange, Kumada, and Suzuki cross-coupling reactions.[7] Sonogashira reactions of 2,3,4,5-tetraiodothiophene and 2,3,4,5-tetrabromothiophene have been reported to proceed selectively at positions 2 and 5.[8] Aryl-substituted thiophenes and selenophenes have been prepared by site-selective Suzuki reactions of 2,3,4,5-tetrabromothiophene and 2,3,4,5-tetrabromoselenophene, respectively.[9] Herein, we report what are, to the best of our knowledge, the first Suzuki–Miyaura reactions of 2,3,4-tribromothiophene. This substrate is of special synthetic and mechanistic interest since it contains three positions with different reactivity (compared to only two positions in case of 2,3,4,5-tetrabromothiophene). The reactions reported herein provide a convenient site-selective approach to 2-aryl-3,4-dibromothiophenes, 2,4-diaryl-3-bromothiophenes, and 2,3,4-triarylthiophenes which are not readily available.

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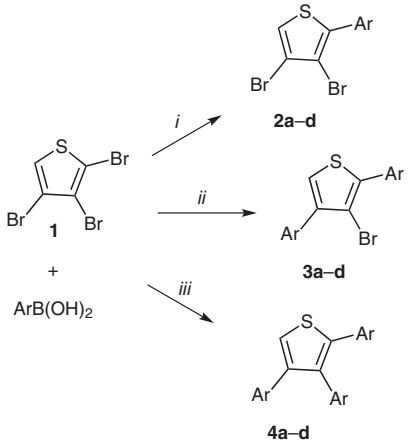
The Suzuki–Miyaura reaction of commercially available 2,3,4-tribromothiophene (**1**) with various arylboronic acids (1.1 equiv) afforded the 2-aryl-3,4-dibromothiophenes **2a–d** in 85–94% yield (Scheme 1, Table 1).[10] The Suzuki–Miyaura reaction of **1** with 2.1 equivalents of arylboronic acids afforded the 2,4-diaryl-3-bromothiophenes **3a–d** in 46–55% yield (Scheme 1, Table 2). The employment of 4.0 equivalents of arylboronic acids resulted in the formation of 2,3,4-triarylthiophenes **4a–d** in very good yields (Scheme 1, Table 3).



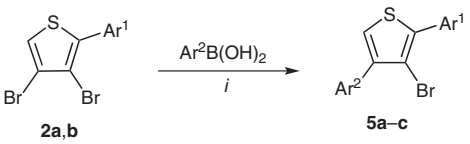
Scheme 1 Synthesis of **2a–d**, **3a–d**, and **4a–d**. *Reagents and conditions*: *i*, **1** (1.0 equiv), $ArB(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 M), 1,4-dioxane–toluene (1:1), 100 °C, 5 h (see Table 1); *ii*, **1** (1.0 equiv), $ArB(OH)_2$ (2.1 equiv), $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (4.0 equiv), 1,4-dioxane–toluene (1:1), H_2O (1 mL), 100 °C, 12 h, (see Table 2); *iii*, **1** (1.0 equiv), $ArB(OH)_2$ (4.0 equiv), $Pd(PPh_3)_4$ (6 mol%), K_2CO_3 (2 M, H_2O), 1,4-dioxane, 90 °C, 12 h (see Table 3).

The Suzuki–Miyaura reaction of 2-aryl-3,4-dibromothiophenes **3a**,**b** with 1.1 equivalents of arylboronic acids resulted in site-selective formation of the 2,4-diarylthiophenes **5a–c** containing two different aryl groups (Scheme 2, Table 4). Preliminary results show that the

Table 1 Synthesis of 2-Aryl-3,4-dibromothiophenes **2a–d**

2	Ar	Yield of **2** (%)[a]
2a	4-MeC_6H_4	89
2b	4-EtC_6H_4	87
2c	4-*t*-BuC_6H_4	94
2d	2-$MeOC_6H_4$	85

[a] Yields of isolated products.



Scheme 2 Synthesis of **5a–c**. *Reagents and conditions*: *i*, **2a**,**b** (1.0 equiv), $Ar^2B(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (4.0 equiv), 1,4-dioxane–toluene (1:1), H_2O (1 mL), 100 °C, 12 h.

Table 2 Synthesis of 3-Bromo-2,4-diarylthiophenes **3a–d**

3	Ar	Yield of **3** (%)[a]
3a	4-MeC_6H_4	55
3b	4-EtC_6H_4	51
3c	3,5-$Me_2C_6H_3$	46
3d	4-*t*-BuC_6H_4	49

[a] Yields of isolated products.

Table 3 Synthesis of 2,3,4-Triarylthiophenes **4a–d**

4	Ar	Yield of **4** (%)[a]
4a	4-MeC_6H_4	93
4b	3,5-$Me_2C_6H_3$	86
4c	4-*t*-BuC_6H_4	94
4d	4-$MeOC_6H_4$	96

[a] Yields of isolated products.

Table 4 Synthesis of 3-Bromo-2,4-diarylthiophenes **5a–c**

5	Ar^1	Ar^2	Yield of **5** (%)[a]
5a	4-MeC_6H_4	2-$MeOC_6H_4$	87
5b	4-EtC_6H_4	2-$MeOC_6H_4$	81
5c	4-EtC_6H_4	2,6-$(MeO)_2C_6H_3$	53

[a] Yields of isolated products.

reaction of these products with 2.0 equivalents of boronic acids allows the synthesis of 2,3,4-triarylthiophenes containing three different aryl groups.

In all reactions, the best yields were obtained when $Pd(PPh_3)_4$ was used as the catalyst. The use of other catalysts (such as $Pd(OAc)_2$/X-Phos) proved to be less successful in terms of yield. All reactions were carried out at 90–100 °C. For the synthesis of **2a–d** and **4a–d** K_2CO_3 and for the synthesis of **3a–d** and **5a–c** K_3PO_4 was used as the base. 1,4-Dioxane or a 1:1 mixture of 1,4-dioxane and toluene was used as the solvent.

The structures of all products were established by spectroscopic methods (NOESY, HMBC). The structures of **3a** and **4c** were independently confirmed by X-ray crystal-structure analyses (Figure 1 and Figure 2).[11]

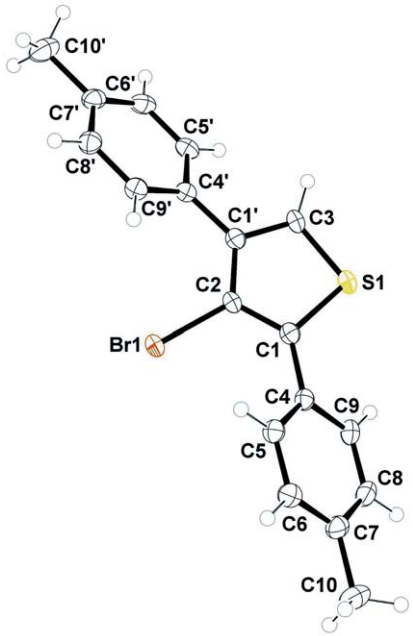


Figure 1 Crystal structure of **3a**

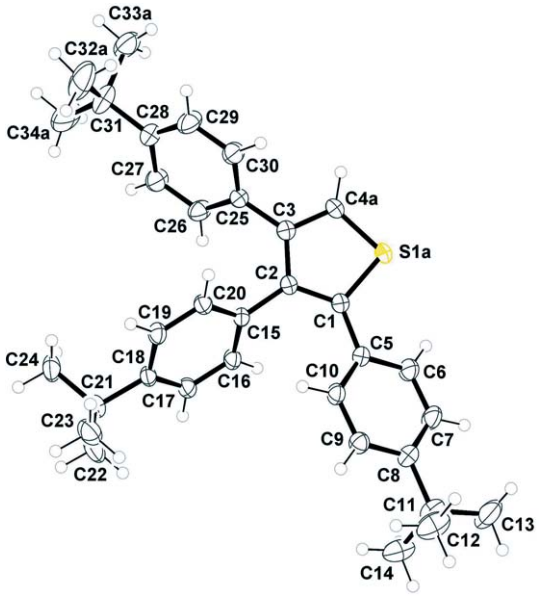


Figure 2 Crystal structure of **4c**

The yields of 2-aryl-3,4-dibromothiophenes **2a–d** and of 2,3,4-triarylthiophenes **4a–d** were significantly higher than those of 2,4-diaryl-3-bromothiophenes **3a–d**. The high yields of **4a–d** can be explained by the fact that no issue of site selectivity exists. The high yields show that the last step, the reaction of carbon atom C-3, must also proceed in good yields. The high yields of **2a–d** suggest that the rate of the reaction of carbon C-2 is considerably higher than that of carbon C-4. This can be explained by electronic reasons (Scheme 3). Inspection of selected crude spectra of **2** and **3** showed that no significant amounts of other heterocyclic products were formed. The moderate yields of products **3** can be explained by practical prob-

lems during the chromatographic purification. In fact, the transformation of thiophenes **2** into **5** proceeded in very good yields (except for **5c** which is derived from sterically hindered 2,6-dimethoxyphenylboronic acid). These results suggest that the rate of the reaction of carbon C-4 is considerably higher than that of carbon C-3.

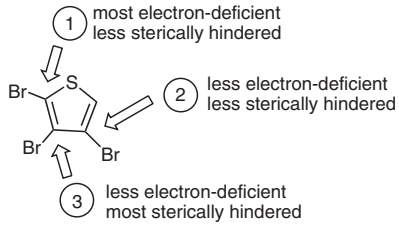


Figure 3 Possible explanation for the site selectivity of the reactions of **1**

As discussed above, the regioselectivites reported herein can be explained based on the different electronic and steric properties of the three different C–Br bonds of **1**. Carbon atom C-2 is the most reactive position because of its electron-deficient character and because it is easily sterically accessible (Scheme 3). From the electronic viewpoint, carbon C-3 is similar to C-4, but C-3 is more sterically hindered than C-4 because of the neighborhood of two bromine atoms.

In conclusion, we have reported the first Suzuki–Miyaura reactions of 2,3,4-tribromothiophene. The reaction with one, two, and three equivalents of arylboronic acids resulted in formation of 2-aryl-3,4-dibromothiophenes, 2,4-diaryl-3-bromothiophenes, and 2,3,4-triarylthiophenes with very good site selectivity, respectively.

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(10) **General Procedure for the Synthesis of 2-Aryl-3,4-dibromothiophenes 2**

To a mixture of **1** (0.159 g, 0.5 mmol), arylboronic acid (0.55 mmol), $Pd(PPh_3)_4$ (5 mol%) were added a mixture of 1,4-dioxane and toluene (1:1, 5 mL) and an aq solution of K_2CO_3 (2 mL, 2 M) under argon atmosphere. The reaction mixture was stirred at 100 °C for 5 h and was subsequently allowed to cool to 20 °C. The solution was poured into H_2O and CH_2Cl_2 (25 mL each), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 25 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (flash silica gel, heptanes).

Synthesis of 3,4-Dibromo-2-(4-ethylphenyl)thiophene (2b)

Starting with **1** (0.320 g, 1.0 mmol) and 4-ethylphenylboronic acid (0.165 g, 1.1 mmol), **2b** was isolated (0.298 g, 87%) as a colorless oil. ^{1}H NMR (300 Hz, $CDCl_3$): δ = 1.32 (t, ^3J = 7.6 Hz, 3 H, CH_3), 2.75 (q, ^3J = 7.6 Hz, 2 H, CH_2), 7.32 (d, ^3J = 8.4 Hz, 2 H, Ar), 7.38 (s, 1 H, Ar), 7.58 (d, ^3J = 8.3 Hz, 2 H, Ar). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 15.4 (CH_3), 28.7 (CH_2), 111.0, 114.7 (CBr), 122.0 (CH, thiophene), 128.2 (2 CH, Ar), 128.9 (2 CH, Ar), 130.3, 139.7, 145.7 (C). IR (KBr): ν = 3107 (w), 3020 (w), 2961 (m), 2927 (m), 2630 (w), 2306 (w), 1903 (w), 1524 (w), 1484 (m), 1308 (w), 1126 (w), 963 (w), 877 (s), 828 (s), 785 (m), 722 (s), 645 (w), 585 (m), 539 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 348 (44) [M$^+$, ^{81}Br, ^{81}Br], 346 (83) [M$^+$, ^{81}Br, ^{79}Br], 344 (41) [M$^+$, ^{79}Br, ^{79}Br], 333 (54), 331 (100) [M$^+$], 329 (50), 186 (11), 171 (38), 139 (11). HRMS (EI, 70 eV): *m/z* calcd for $C_{12}H_{10}Br_2S$ [M$^+$, Br, ^{81}Br]: 345.88440; found: 345.88457.

(11) CCDC 760153 and 760154 contain all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ; Fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.