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Synthesis of tetraarylthiophenes by regioselective Suzuki cross-coupling reactions of tetrabromothiophene

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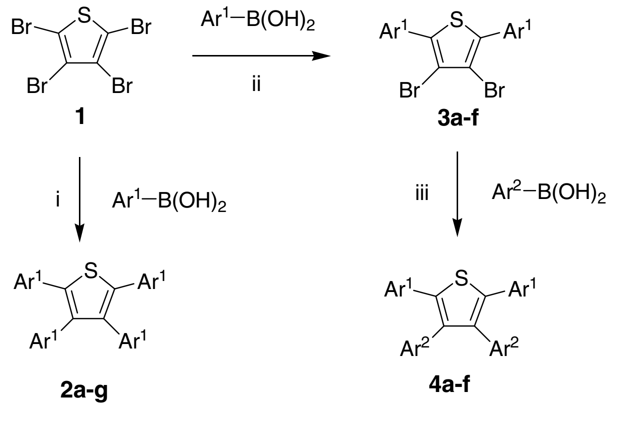
Abstract—Tetraarylthiophenes were prepared by regioselective Suzuki cross-coupling reactions of tetrabromothiophene.

Palladium catalyzed cross-coupling reactions represent an important method for carbon–carbon bond formations of heterocycles.[1] In recent years, the regioselectivity of polyhalogenated heterocycles as starting materials in such reactions has been extensively studied.[2] These reactions usually proceed by oxidative addition to the most electron-deficient carbon atom, while the other reactive positions remain unattacked. Thiophene-containing compounds are widely known as an important class of materials which show intrinsic electronic properties such as luminescence, redox activity, nonlinear optical chromism and electron-transport.[3] Therefore, their regioselective functionalization by palladium catalyzed reactions is of considerable importance. The Sonogashira coupling reaction of 2,3-dibromothiophene has been reported to allow a regioselective coupling of carbon atom C-2.[4] Likewise, the Kumada cross-coupling of 2,3- and 2,4-dibromothiophene proceeded with very good C-2 regioselectivity.[5] Whitesides et al. reported regioselective Sonogashira couplings of tetraiodothiophene to give 2,5-disubstituted thiophenes.[6] Later, related reactions of tetrabromothiophene were reported.[7] Herein, we report what are, to the best of our knowledge, the first Suzuki reactions of tetrabromothiophene. These reactions proceed with very good regioselectivity and allow an efficient synthesis of tetraarylthiophenes.

Tetrabromothiophene (**1**) was prepared, as previously reported,[8] by bromination of thiophene. The Suzuki reaction of **1** (1.0 equiv) with various boronic acids (5.0 equiv) afforded tetraarylthiophenes **2a**–**g** containing four identical aryl groups (Scheme 1, Table 1).[9] The reaction of **1** (1.0 equiv) with 2.2 equiv of boronic acids resulted in regioselective formation of 2,5-diaryl-3,4-dibromothiophenes **3a**–**f** (Table 2). The Suzuki reaction of **3a**,**b** (1.0 equiv) with various arylboronic acids (3.0 equiv) allowed the synthesis of tetraarylthiophenes **4a**–**f** containing two different types of aryl groups (Table 3). During the optimization, the stoichiometry,



Scheme 1. Suzuki reactions of **1**. Reagents and conditions: (i) **1** (1.0 equiv), $Ar^1B(OH)_2$ (5.0 equiv), $Pd(PPh_3)_4$ (10 mol %), K_3PO_4 (8.0 equiv), solvent (see Table 1); (ii) **1** (1.0 equiv), $Ar^1B(OH)_2$ (2.2 equiv), $Pd(PPh_3)_4$ (6 mol %), K_3PO_4 (4.0 equiv), solvent (see Table 2); (iii) **3a**,**b** (1.0 equiv), $Ar^2B(OH)_2$ (3.0 equiv), $Pd(PPh_3)_4$ (10 mol %), K_3PO_4 (4.0 equiv), solvent (see Table 3).

Keywords: Catalysis; Heterocycles; Palladium; Regioselectivity; Thiophenes.

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Table 1. Synthesis of tetraarylthiophenes **2a–g**

2	Ar^1	Solvent/H_2O (4:1)	% (**2**)
a	Ph	Toluene	37[a]
b	4-(MeO)C_6H_4	1,4-Dioxane	94[b]
c	2-(MeO)C_6H_4	1,4-Dioxane	38[b]
d	1-Naphthyl	Toluene	65[b]
e	4-MeC_6H_4	Toluene	87[a]
f	4-ClC_6H_4	Toluene	89[b]
g	4-FC_6H_4	Toluene	93[b]

[a] Isolated yields (conditions: 90 °C, 12 h).
[b] Isolated yields (conditions: 90 °C, 24 h).

Table 2. Synthesis of 2,5-diarylthiophenes **3a–f**

3	Ar^1	Solvent/H_2O (4:1)	% (**3**)
a	Ph	Toluene	32[a]
b	4-MeC_6H_4	Toluene	77[a]
c	4-MeOC_6H_4	1,4-Dioxane	43[b]
d	2-MeOC_6H_4	1,4-Dioxane	35[b]
e	3,5-$Me_2C_6H_3$	Toluene	54[b]
f	2-Thienyl	Toluene	48[b]

[a] Isolated yields (conditions: 90 °C, 12 h).
[b] Isolated yields (conditions: 90 °C, 24 h).

Table 3. Synthesis of tetraarylthiophenes **4a–f**

4	Ar^1	Ar^2	Solvent/H_2O (4:1)	% (**4**)
a	Ph	4-MeC_6H_4	Toluene	86[a]
b	4-MeC_6H_4	Ph	Toluene	51[a]
c	4-MeC_6H_4	4-(MeO)C_6H_4	Toluene + dioxane[c]	76[b]
d	4-MeC_6H_4	4-(EtO)C_6H_4	Toluene + dioxane[c]	93[b]
e	4-MeC_6H_4	4-(OH)C_6H_4	Toluene + dioxane[c]	82[b]
f	4-MeC_6H_4	4-ClC_6H_4	Toluene	91[b]

[a] Isolated yields (conditions: 90 °C, 12 h).
[b] Isolated yields (conditions: 90 °C, 24 h).
[c] Toluene/dioxane = 1:1.

temperature, solvent, and the presence of water played an important role.

The structure and configuration of the products were proved by spectroscopic methods. The structure of **3e** is supported by an X-ray crystal structure analysis (Fig. 1).[10]

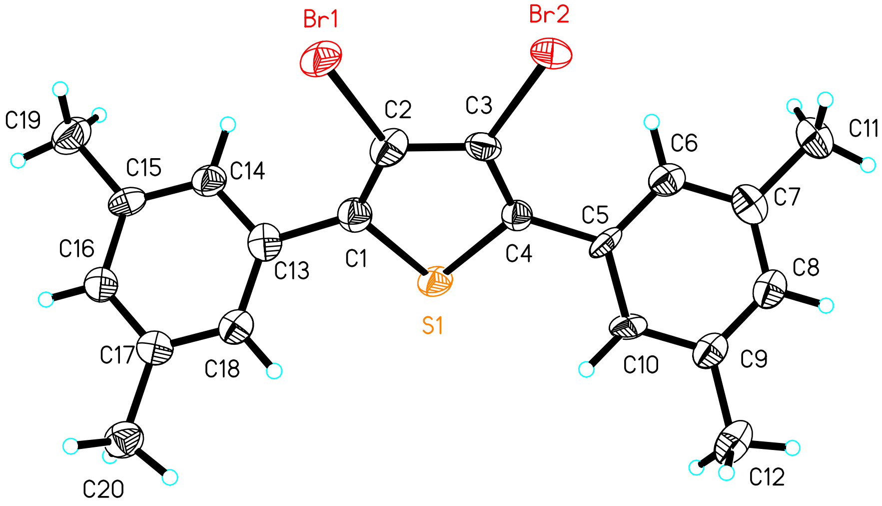

Figure 1. Crystal structure analysis of **3e**.

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9. *General procedure*: to a toluene solution (4 mL) of **1** (0.400 g, 1.0 mmol) was added $Pd(PPh_3)_4$ (0.070 g, 6 mol %) at 20 °C. After stirring for 30 min, the aryl-

boronic acid (2.2 mmol), K_3PO_4 (4.0 mmol), and water (1.0 mL) were added. The mixture was stirred at 90 °C for 12 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

Synthesis of 3,4-dibromo-2,5-di(p-tolyl)thiophene (**3b**). Starting with **1** (0.400 g, 1.0 mmol) and 4-tolylboronic acid (0.299 g, 2.2 mmol), **3b** was isolated (0.325 g, 77%) as a colorless solid, mp = 152–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.25$ (s, 6H, $2CH_3$), 7.22 (d, $^3J = 8.2$ Hz, 4H, Ar), 7.46 (d, $^3J = 8.2$ Hz, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.8$ (CH_3), 107.9 (CBr), 129.3, 129.8 (CH, Ar), 130.5, 137.9, 138.0 (C). IR (KBr, cm^{-1}): $\tilde{\nu} = 3432$ (br, m), 3021 (m), 2918 (w), 1489 (s), 1266 (w), 864 (m), 809 (m), 798 (s), 755 (m), 490 (s). MS (EI, 70 eV): *m*/*z* (%) = 424 (M^+, [^{81}Br, ^{81}Br], 49), 422 (M^+, [^{81}Br, ^{79}Br], 100), 420 (M^+, [^{79}Br, ^{79}Br], 45), 342 (11), 262 (37), 229 (5), 202 (10), 135 (6). HRMS (EI, 70 eV): calcd for $C_{18}H_{14}Br_2S$ (M^+, [^{79}Br]): 419.91775; found: 419.91769. All products gave satisfactory spectroscopic data and correct elemental analyses and/or high resolution mass data.

Synthesis of tetra(p-tolyl)thiophene (**2e**). Starting with **1** (0.400 g, 1.0 mmol) and 4-tolylboronic acid (0.680 g, 5.0 mmol), **2e** was isolated (0.384 g, 87%) as a colorless solid, mp 226–227 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.29$, 2.32 (2 × s, 12H, 2 × CH_3), 6.87, (d, $^3J = 8.2$ Hz, 4H, Ar), 6.96 (d, $^3J = 8.2$ Hz, 4H, Ar), 7.03 (d, $^3J = 8.2$ Hz, 4H, Ar), 7.14 (d, $^3J = 8.2$ Hz, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$, 21.4 (CH_3), 128.7, 129.1, 129.2, 130.9 (4CH, Ar), 131.8, 133.8, 136.0, 136.9,137.9, 138.6 (C, Ar). IR (KBr, cm^{-1}): $\tilde{\nu} = 3432$ (w), 3022 (m), 2918 (w), 1514 (s), 1495 (s), 1456 (m), 1182 (w), 1111 (w), 1109 (w), 834 (m), 818 (s), 807 (m), 733 (m), 556 (w), 527 (w), 507 (w). MS (EI, 70 eV): *m*/*z* (%) = 444 (M^+, 100), 355 (4), 299 (6), 207 (4), 155 (6), 115 (4), 91 (9), 71 (5), 57 (7), 44 (6). HRMS (EI, 70 eV): calcd for $C_{32}H_{28}S$ (M^+): 444.19062; found: 444.19071.

10. Reinke, H.; Rasool, N.; Langer, P., unpublished results.