Syntheses of 2-(Pentafluorophenyl)thiophene Derivatives via the Palladium-Catalyzed Suzuki Reaction

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This paper is dedicated to Professor Jan Becher on the occasion of his retirement.

Abstract: Various bis(pentafluorophenyl)-substituted thiophene and selenophene derivatives are effectively synthesized by the palladium-catalyzed Suzuki reaction using pentafluorophenyl boronic acid.

Keywords: boron, palladium, catalyst, cross-coupling, fluorine

A pentafluorophenyl group is an attractive functional in the growing field of material chemistry. Introduction of the group, with a strong electron-withdrawing nature,[1] into various π-electron systems was recently reported, proving that it is very effective in the perturbation of the electronic structure and/or crystal structure of the manipulated π-electron systems.[2] For example, Facchetti et al. reported that the introduction of the groups at the terminals of α-quaterthiophene brought about an inversion from *p*- to *n*-carrier type in field-effect transistor operation.[2a] Another example is the pentafluorophenyl-substituted dithienylethene derivative reported by Irie et al., which, thanks to the mutual strong interaction of the groups, underwent highly effective photocyclization and photocycloreversion in the crystal (and co-crystal) forms.[2b]

In these investigations, 2-(pentafluorophenyl)thiophene (**1**) and its derivatives are key compounds, which were previously synthesized by the palladium-catalyzed Suzuki reaction between pentafluoroiodobenzene (**2a**) and thiophene boric acid derivative[2b] or by the Stille reaction between pentafluorobromobenzene (**2b**) and 2-tributylstannylthiophene.[2a] Although other coupling approaches to **1** were reported using pentafluorobenzenesulfonyl chloride (**2c**)[3] or pentafluorophenylhydrazine (**2d**),[4] these methods are not likely to be applicable to the synthesis of its derivatives, because of the low yields, low selectivity, or requirement of excess reagents.

Considering the ready accessibility of α-halothiophenes by electrophilic substitutions of thiophenes, commercially available pentafluorophenylboronic acid (**3**)[5] is the counterpart of choice for the Suzuki coupling;[6] however, the reagent has been known to be rather inferior in the Suzuki reaction.[7] Very recently, Cammers-Goodwin et al. reported the synthesis of 2-(pentafluorophenyl)pyridine by the Suzuki reaction between **3** and 2-iodopyridine in the presence of Ag_2O.[8] This has impelled us to explore the synthesis of 2-(pentafluorophenyl)thiophene derivatives by a similar reaction. Although our initial trials using the Cammers-Goodwin protocol were not successful, we have finally found satisfactory reaction conditions, which are applicable to the synthesis of various pentafluorophenyl-substituted thiophene and selenophene derivatives.

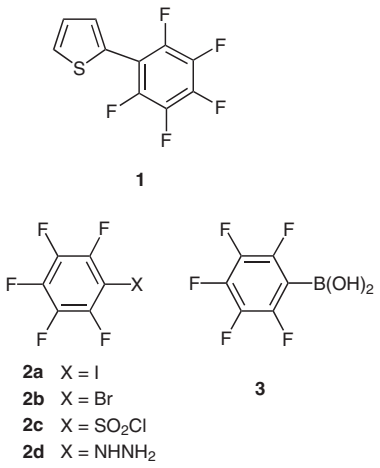

Figure 1

Table 1 summarizes results of the reaction of **3** with 2-bromothiophene under various reaction conditions including those generally employed for the Suzuki reaction (Table 1, entry 1) and those reported for the synthesis of 2-pentafluorophenylpyridine[8] (Table 1, entry 2). The reaction without Ag_2O as an additive gave no detectable **1** in the reaction mixture (Table 1, entry 1). Although a trace amount of **1** was detected upon changing the base to *t*-BuOK with Ag_2O as an additive (Table 1, entry 2), the main product in this reaction was 2-(4-*tert*-butyloxy-2,3,5,6-tetrafluorophenyl)thiophene (**4**, 26% isolated yield). Compound **4** is probably produced by a nucleophilic substitution reaction of the *tert*-butoxide anion at the *para* position of the thiophene ring. To avoid the use of nucleophilic *t*-BuOK as a base, sodium hydroxide (Table 1, entry 3) or potassium phosphate (Table 1, entry 4) were examined. With sodium hydroxide, **1** was obtained (8% yield), but the reaction gave an intractable complex mixture. The reaction with potassium phosphate also gave a complex mixture with a slightly increased

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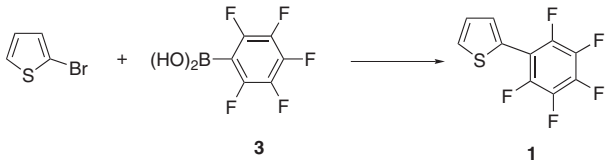
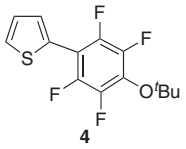
Table 1 The Suzuki Reactions of Pentafluorophenyl Boronic Acid (**3**) with 2-Bromothiophene



3 **1**

	Solvent	Catalyst	Base/ Additive	Temp (°C)	Time (h)	Result
1	DME	$Pd(PPh_3)_4$	K_2CO_3	85	20	0%
2	DME–*t*-BuOH	$Pd(PPh_3)_4$	*t*-BuOK Ag_2O	85	4	**1** (trace) **4**[a] (26%)
3	DME	$Pd(PPh_3)_4$	NaOH Ag_2O	85	20	**1** (8%)
4	DME	$Pd(PPh_3)_4$	K_3PO_4 Ag_2O	85	4	**1** (20%)
5	DMF	$Pd(PPh_3)_4$	K_3PO_4 Ag_2O	85	4	**1** (68%)

[a] 2-(4-*tert*-Butoxy-2,3,5,6-tetrafluorophenyl)thiophene.



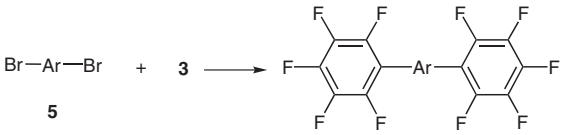
4

yield of **1** (20%). In contrast, a change of the solvent from DME to DMF dramatically increased the yield of **1** to 68% isolated yield (Table 1, entry 5).

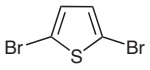
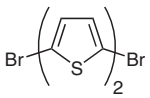
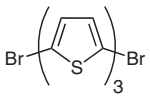
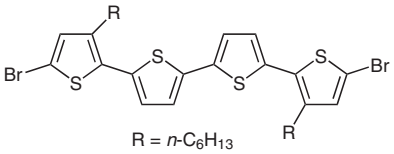
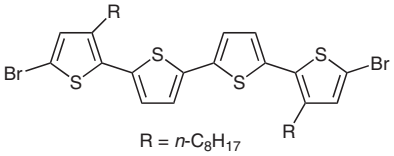
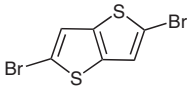
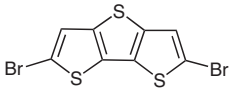
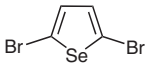
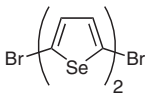
Using the optimized reaction condition (Table 1, entry 5), we attempted the synthesis of various bis(pentafluorophenyl)-substituted thiophene and selenophene derivatives (**6**) from the corresponding dibromo precursors (**5**). As shown in Table 2, this method is quite effective to synthesize a wide range of compounds, including oligothiophenes with various chain lengths (Table 2, entry 2–5), thiophene-fused system such as thieno[3,2:*b*]thiophene (entry 6,7), and several selenophene homologues.

In conclusion, we have established an effective method for the synthesis of pentafluorophenyl-substituted thiophene and selenophene derivatives using commercially available pentafluorophenyl boronic acid (**3**) and bromo-thiophenes and -selenophenes. Since the bromide precursors are easily accessible, the present method is potentially useful for the synthesis of various pentafluorophenyl substituted compounds for electronic or photochemical functional materials. Research in this area is currently underway.

Table 2 Suzuki Coupling Reactions of Pentafluorophenyl Boronic Acid (**3**) with Various Dibromothiophene and Dibromoselenophene Derivatives



5 **6**

Entry	BrArBr **5**	Product **6**	Yield (%)
1		**6a**	72
2		**6b**	66
3		**6c**	42
4		**6d**	84
5		**6e**	78
6		**6f**	60
7		**6g**	57
8		**6h**	78
9		**6i**	69

All reactions were carried out under a nitrogen atmosphere with anhydrous solvents. Column chromatography was carried out with Daisogel IR-60 (63–210 μm). Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL Lambda 400 spectrometer operating at 400 MHz and 100 MHz, respectively. ^{19}F NMR spectra were recorded on a JEOL AL-400S spectrometer operating at 372 MHz. Chemical shifts were reported as δ values (ppm) relative to internal standards, TMS for ^1H and ^{13}C NMR and $CFCl_3$ for ^{19}F NMR. EI-MS spectra were obtained on a Shimadzu QP-5050A spectrometer using an electron impact ionization procedure (70 eV). MALDI-TOF MS spectra were obtained on a Shimadzu KOMPACT-MALDI PROBE spectrometer using a dithranol matrix. The molecular ion peaks of the selenium-containing compounds showed a typical selenium isotopic pattern, and all the selenium-containing mass peaks are reported for ^{80}Se. Elemental analyses were performed by Mr. Hideaki Iwatani, Microanalytical Laboratory in Department of Applied Chemistry, Faculty of Engineering, Hiroshima University.

2-(Pentafluorophenyl)thiophene (1); Typical Procedure

A mixture of 2-bromothiophene (163 mg, 1.0 mmol), pentafluorophenyl boronic acid (212 mg, 1.0 mmol), tetrakis(triphenylphosphine)palladium (81.5 mg, 0.08 mmol), Ag_2O (460 mg, 2.0 mmol), and K_3PO_4·n-hydrate (1.7 g) in DMF (7 mL) was stirred at 85 °C for 4 h. The mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined extract was washed with water (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel eluted with CH_2Cl_2 to remove highly polar impurities followed by recrystallization from CH_2Cl_2–hexane (1:1) gave faint colorless fine crystals of 2-(pentafluorophenyl)thiophene (**1**, 170 mg, 68%); mp 42–43 °C.

^{1}H NMR ($CDCl_3$): δ = 7.19 (m, 1 H), 7.53 (m, 1 H), 7.56 (dd, *J* = 5.2, 1.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 126.27, 127.27, 128.22, 130.11, and a series of multiplets in the aromatic region (ArCF).

^{19}F NMR ($CDCl_3$): δ = –162.70 (m, 2 F), –156.49 (t, *J* = 21.0 Hz, 1 F), –140.50 (dd, *J* = 7.2 Hz, 21.6 Hz, 2 F).

MS (EI): *m*/*z* = 250 [M$^+$].

Anal. Calcd for $C_{10}H_3F_5S$: C, 48.01; H, 1.21. Found: C, 47.79; H, 1.10.

2,5-Bis(pentafluorophenyl)thiophene (6a)

Yield: 72%; pale yellow fine needles ($CHCl_3$–hexane, 1:1); mp 112–113 °C.

^{1}H NMR ($CDCl_3$): δ = 7.60 (br s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 129.19, 130.19, and a series of multiplets in the aromatic region (ArCF).

^{19}F NMR ($CDCl_3$): δ = –161.98 (m, 4 F), –154.88 (t, *J* = 21.8 Hz, 2 F), –139.75 (dd, *J* = 6.2, 20.6 Hz, 4 F).

MS (EI): *m*/*z* = 416 [M$^+$].

Anal. Calcd for $C_{16}H_2F_{10}S$: C, 46.17; H, 0.48. Found: C, 46.03; H, 0.42.

5,5′-Bis(pentafluorophenyl)-2,2′-bithiophene (6b)

Yield: 66%; yellow fine needles ($CHCl_3$–hexane, 1:1); mp 182–184 °C.

^{1}H NMR ($CDCl_3$): δ = 7.32 (d, *J* = 3.2 Hz, 2 H), 7.50 (d, *J* = 3.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 124.52, 126.07, 131.11, 138.85, and a series of multiplets in the aromatic region (ArCF).

^{19}F NMR ($CDCl_3$): δ = –162.26 (m, 4 F), –155.85 (t, *J* = 21.8 Hz, 2 F) –140.08 (dd, *J* = 6.2, 20.4 Hz, 4 F).

MS (EI): *m*/*z* = 498 [M$^+$].

Anal. Calcd for $C_{20}H_4F_{10}S_2$: C, 48.20; H, 0.81. Found: C, 48.13; H, 0.76.

5,5″-Bis(pentafluorophenyl)-2,2′:5′,2″-terthiophene (6c)

Yield: 42%; bright orange fine needles ($CHCl_3$); mp 90–191 °C.

^{1}H NMR ($CDCl_3$): δ = 7.15 (s, 2 H), 7.21 (d, *J* = 4.0 Hz, 2 H), 7.46 (d, *J* = 4.0 Hz, 2 H).

^{19}F NMR ($CDCl_3$): δ = –162.35 (m, 4 F), –156.12 (t, *J* = 20.8 Hz, 2 F), –140.18 (dd, *J* = 6.2, 20.9 Hz, 4 F).

MS (EI): *m*/*z* = 580 [M$^+$].

Anal. Calcd for $C_{24}H_6F_{10}S_3$: C, 49.66; H, 1.04. Found: C, 49.59; H, 1.07.

3,3‴-Dihexyl-5,5‴-bis(pentafluorophenyl)-2,2′:5′,2″:5″,2‴-quaterthiophene (6d)

Yield: 84%; orange needles ($CHCl_3$–hexane, ca. 1:2); mp 127–130 °C.

^{1}H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 7.1 Hz, 6 H), 1.30–1.46 (m, 12 H), 1.69 (quint, *J* = 7.8 Hz, 4 H), 2.83 (t, *J* = 7.8 Hz, 4 H), 7.12 (d, *J* = 4.0 Hz, 2 H), 7.19 (d, *J* = 4.0 Hz, 2 H), 7.38 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.09, 22.60, 29.16, 29.30, 30.50, 31.62, 124.14, 127.10, 127.13, 133.11, 133.25, 134.08, 137.27, 139.79, and a series of multiplets in the aromatic region (ArCF).

^{19}F NMR ($CDCl_3$): δ = –162.55 (m, 4 F), –156.50 (t, *J* = 20.2 Hz, 2 F), –140.31 (dd, *J* = 6.4, 22.3 Hz, 4 F).

MS (MALDI-TOF): *m*/*z* = 830 [M$^+$].

Anal. Calcd for $C_{40}H_{32}F_{10}S_4$: C, 57.82; H, 3.88. Found: C, 58.07; H, 3.79.

3,3‴-Dioctyl-5,5‴-bis(pentafluorophenyl)-2,2′:5′2 ″:5″,2‴-quaterthiophene (6e)

Yield: 78%; orange fine crystals ($CHCl_3$–hexane, ca. 1:2); mp 137–138 °C.

^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 6 H), 1.21–1.46 (m, 20 H), 1.66–1.74 (t, *J* = 7.7 Hz, 4 H), 2.83 (m, 4 H), 7.12 (d, *J* = 4.0 Hz, 2 H), 7.19 (d, *J* = 4.0 Hz, 2 H), 7.38 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.16, 22.77, 29.33 (× 2), 29.46, 29.56, 30.55, 31.92, 124.17, 127.09, 127.14, 133.14, 133.36, 134.13, 137.33, 139.75, and a series of multiplets in the aromatic region (ArCF).

^{19}F NMR ($CDCl_3$): δ = –162.55 (m, 4 F), –156.50 (t, *J* = 20.7 Hz, 2 F), –140.30 (dd, *J* = 6.4, 21.8 Hz, 4 F).

MS (MALDI-TOF): *m*/*z* = 886 [M$^+$].

Anal. Calcd for $C_{44}H_{40}F_{10}S_4$: C, 59.58; H, 4.55. Found: C, 59.65; H, 4.45.

2,5-Bis(pentafluorophenyl)thieno[3,2-*b*]thiophene (6f)

Yield: 60%; pale yellow needles ($CHCl_3$–hexane, ca. 2:1); mp 233–235 °C.

^{1}H NMR ($CDCl_3$): δ = 7.70 (s, 2 H).

^{19}F NMR ($CDCl_3$): δ = –161.94 (m, 4 F), –154.78 (t, *J* = 21.4 Hz, 2 F), –139.88 (dd, *J* = 5.8, 20.9 Hz, 4 F).

MS (EI): *m*/*z* = 472 [M$^+$].

Anal. Calcd for $C_{18}H_2F_{10}S_2$: C, 45.77; H, 0.43. Found: C, 45.60; H, 0.47.

2,6-Bis(pentafluorophenyl)dithieno[3,2-*b*:2′,3′-*d*]thiophene (6g)

Yield: 57%; yellow fine crystals($CHCl_3$); mp 244–246 °C.

^{1}H NMR ($CDCl_3$): δ = 7.75 (s, 2 H).

^{19}F NMR ($CDCl_3$): δ = –161.78 (m, 4 F), –154.99 (t, *J* = 21.0 Hz, 2 F), –139.88 (dd, *J* = 5.9, 20.6 Hz, 4 F).

MS (EI): *m*/*z* = 528 [M$^+$].

Anal. Calcd for $C_{20}H_2F_{10}S_3$: C, 45.46; H, 0.38. Found: C, 45.49; H, 0.40.

2,5-Bis(pentafluorophenyl)selenophene (6h)

Yield: 78%; pale yellow fine needles ($CHCl_3$–hexane, 1:1); mp 134–136 °C.

^{1}H NMR ($CDCl_3$): δ = 7.86 (br s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 132.55, 133.89, and a series of multiplets in the aromatic region (ArCF).

^{19}F NMR ($CDCl_3$): δ = –162.08 (m, 4 F), –155.19 (t, *J* = 21.8 Hz, 2 F), –139.83 (dd, *J* = 6.1, 21.0 Hz, 4 F).

MS (EI): *m*/*z* = 464 [M$^+$].

Anal. Calcd for $C_{16}H_2F_{10}Se$: C, 41.49; H, 0.44. Found: C, 41.38; H, 0.32.

5,5′-Bis(pentafluorophenyl)-2,2′-biselenophene (6i)
Yield: 69%; yellow needles ($CHCl_3$–hexane, 1:1); mp 202–203 °C.

^{1}H NMR ($CDCl_3$): δ = 7.33 (m, 2 H), 7.70 (d, *J* = 4.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 126.99, 127.24, 130.13, 133.37, and a series of multiplets in the aromatic region (ArCF).

^{19}F NMR ($CDCl_3$): δ = –162.34 (m, 4 F), –156.04 (t, *J* = 21.4 Hz, 2 F), –140.26 (dd, *J* = 5.8, 21.2 Hz, 4 F).

MS (EI): *m*/*z* = 594 [M$^+$].

Anal. Calcd for $C_{20}H_4F_{10}Se_2$: C, 40.57; H, 0.68. Found: C, 40.64; H, 0.65%.

Acknowledgment

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