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Synthesis of [1]benzothieno[3,2-*b*][1]benzothiophene (BTBT) and its higher homologs through palladium-catalyzed intramolecular decarboxylative arylation

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ABSTRACT

We report herein an effective method for the construction of 4- and 7-ring benzo-fused thieno[3,2-*b*]thiophenes, involving palladium-catalyzed intramolecular decarboxylative arylation as the key step.

Various poly-condensed arenes and heteroarenes are known to work as organic semiconductors. Particularly, thienoacene-based extended π-systems have attracted much attention, as they are robust and often show high hole mobilities in field effect transistor (FET) devises.[1] Benzo-fused thieno[3,2-*b*]thiophenes such as [1]benzothieno[3,2-*b*][1]benzothiophene (BTBT) (Fig. 1) derivatives are typical promising compounds. Thus, the synthesis of BTBT and its derivatives has been studied extensively in recent years. BTBT itself has been prepared by a number of methods including the reactions of 1,2-bis(2-bromophenyl)acetylene with S_8 or Na_2S,[2] 2,2′-dichlorostilbene with Na_2S,[3] *o*-chlorobenzaldehyde with NaSH,[4] and benzyl chloride with S_8.[5,6] Another effective method leading to BTBT is the iodine-promoted cyclization of 2,2'-bis(methylthio)stilbene, which was also applied to the synthesis of a largely extended thienoacene, that is, bis[1]benzothieno[2,3-*d*;2′,3′-*d*′]benzo[1,2-*b*;4,5-*b*′]dithiophene (BBTBDT) and its naphtho-analog.[7] BBTBDT was also prepared by a Pummerer-type biscyclization.[8] Recently, Takimiya and co-workers disclosed an elegant process for the construction of BTBT as well as its higher homologs by the sequential reactions of 2[2-(trimethylsilyl)ethynyl]thioanisole with PhSCl to form the corresponding 3-(phenylthio)benzo[*b*]thiophene and its 2-bromination followed by palladium-catalyzed intramolecular C–H arylation.[9] Despite these achievements for constructing the BTBT series of compounds, there still remains a substantial demand for further development of effective and flexible synthetic methods to enhance their utility. We herein describe a new synthetic sequence involving palladium-catalyzed intramolecular decarboxylative arylation as the key step, which enables to construct unknown bis[1]benzothieno[2,3-*d*;2′,3′-*d*′]benzo[1,2-*b*;5,6-*b*′]dithiophene (*iso*-BBTBDT) skeleton as well as BTBT and BBTBDT and their alkylated derivatives.

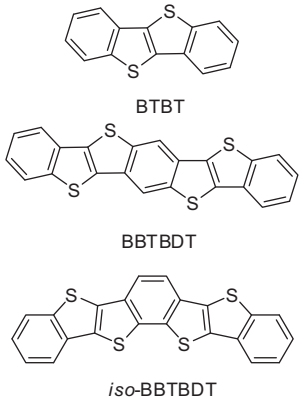

Figure 1. Structure of BTBT, BBTBDT, and *iso*-BBTBDT.

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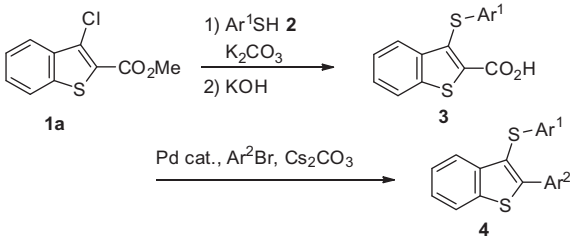
Decarboxylative arylation for constructing biaryl linkages using widely available arenecarboxylic acids as one of the coupling partners has recently emerged as an effective cross-coupling strategy that complements the relevant conventional methods employing arylmetal reagents.[10]

We previously reported the synthesis of 3-(arylthio)-2-arylbenzo[*b*]thiophene (**4**) of pharmaceutical interest (Scheme 1). The method with the readily available methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (**1a**) as the starting scaffold consists of nucleophilic 3-arylthiolation and palladium-catalyzed decarboxylative 2-arylation.[11] This sequence may allow various 2,3-disubstitution patterns on the benzo[*b*]thiophene framework. It may be conceived that using 2-bromobenzenethiols could afford BTBT and its derivatives via intramolecular decarboxylative arylation. Consequently, we have undertaken to their synthesis based on this strategy.

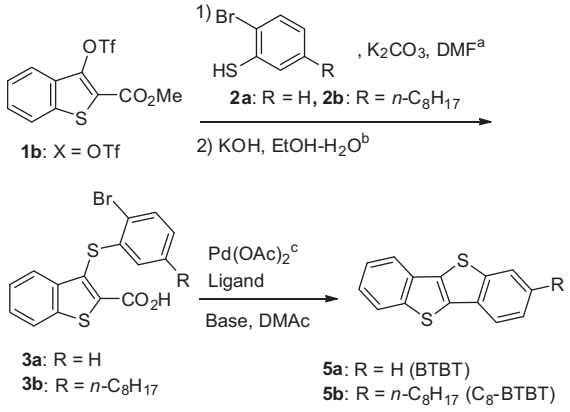
We first examined the synthesis of mother BTBT by using methyl 3-[(trifluoromethyl)sulfonyloxy]-benzo[*b*]thiophene-2-carboxylate (**1b**)[12] as the starting material to test the applicability of the triflate analog of **1a** (Scheme 2), since the leaving group is required to construct a higher BTBT analog (vide infra).

As expected, the reaction of **1b** with 2-bromobenzenethiol (**2a**) in the presence of potassium carbonate in DMF at 80 °C gave the corresponding phenylthiolated product in 53% yield and the subsequent hydrolysis with potassium hydroxide in ethanol/H_2O proceeded quantitatively to afford 3-[2-(bromophenyl)thio]-2-benzo[*b*]thiophenecarboxylic acid (**3a**). Then, the intramolecular decarboxylative arylation of **3a** was conducted in the presence of $Pd(OAc)_2$ as catalyst in combination with a number of bases and ligands in DMAc at 160 °C (Table 1). Using P(*o*-BP)Cy_2 (*o*-BP = biphenyl-2-yl, CyJohnphos) as ligand, various inorganic bases including Cs_2CO_3, Na_2CO_3, K_2CO_3, and CsOAc could be used to furnish BTBT in 71–77% yields (determined by GC, entries 1–4). The relatively strong Cs_2CO_3 was found to be superior to the other bases examined. However, a strong organic amine base, DABCO, was far less effective (entry 5). PCy_3 and P(*o*-BP)(*t*-Bu)$_2$ (Johnphos) in place of P(*o*-BP)Cy_2 afforded higher BTBT yields of 90% and 91%, respectively (entries 6 and 7). Thus, BTBT was isolated in 80% yield in entry 7. Similarly, the use of 2-bromo-5-octylbenzenethiol (**2b**)[13] in place of **2a** in the starting arylthiolation reaction of **1b** led to 2-octyl-BTBT **5b** (C_8-BTBT). The isolated yield of **5b** in the decarboxylative arylation step was 72% (entry 8). It is worth noting that not only a dialkyl-BTBT, but also a monoalkyl-BTBT has been reported to show a high hole mobility.[6]

We next examined the synthesis of BBTBDT by using di(2-ethylhexyl) 3,7-bis(trifluoromethanesulfonyloxy)benzo[1,2-*b*:4,5-*b*′]dithiophene-2,6-carboxylate (**1c**) as the synthetic scaffold (Scheme 3), the preparation of which starting from commercially available 2,5-dibromoterephthalic acid was recently described by us.[12] The reaction of **1c** with **2a** followed by hydrolysis gave the corresponding diacid **6a** in 42% yield (by two steps) and the subsequent decarboxylative cyclization afforded BBTBDT in 61% yield (18% after sublimation in vacuo). The physical properties of BBTBDT



Scheme 1. Preparation of 2-aryl-3-(arylthio)benzo[*b*]thiophene by nucleophilic arylthiolation and decarboxylative arylation (previous work).[11]

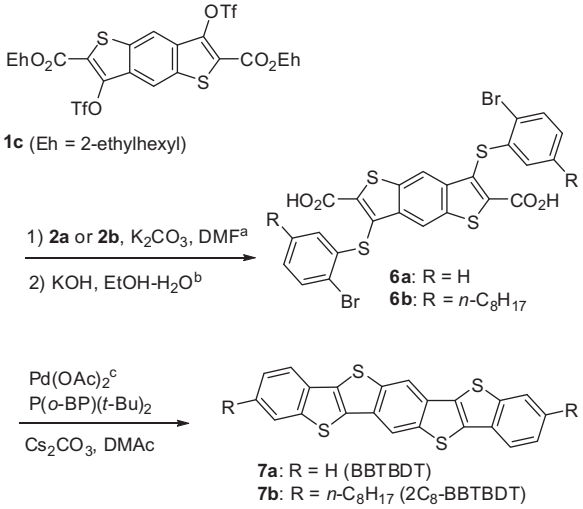


Scheme 2. Synthesis of BTBT and its alkylated derivative (C_8-BTBT). [a]Conditions: [**1b**]:[**2**]:[K_2CO_3] = 1:1.2:2 (7.1 mmol of **2a** and 0.6 mmol of **2b** were used), 80 °C, 8–24 h in DMF under N_2. [b]Conditions: [**2**]:[KOH] = 1:3, EtOH/H_2O = 10:1 (v/v), 100 °C, 6–14 h under N_2. Yields of **3a** and **3b** were 53% and 65%, respectively (by two steps). [c]See Table 1.

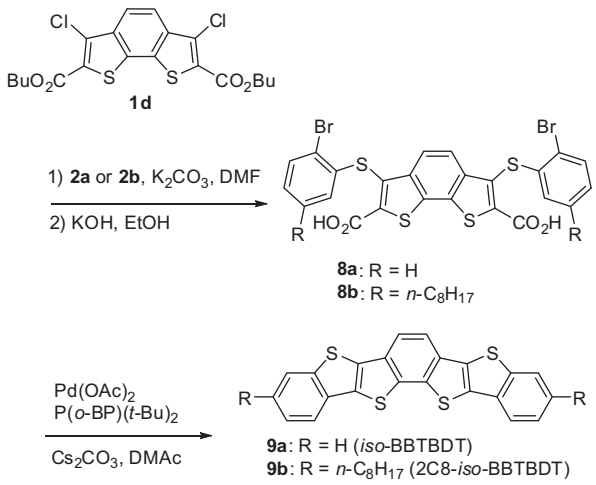
Table 1
Synthesis of BTBT and C_8-BTBT by intramolecular decarboxylative arylation[a]

Entry	Substrate	Ligand[b]	Base	Time (h)	Product, yield[c] (%)
1	**3a**	P(*o*-BP)Cy_2	Cs_2CO_3	2	**5a**, 77
2	**3a**	P(*o*-BP)Cy_2	Na_2CO_3	2	**5a**, 75
3	**3a**	P(*o*-BP)Cy_2	K_2CO_3	6	**5a**, 71
4	**3a**	P(*o*-BP)Cy_2	CsOAc	6	**5a**, 75
5	**3a**	P(*o*-BP)Cy_2	DABCO	6	**5a**, 15
6	**3a**	PCy_3	Cs_2CO_3	6	**5a**, 90
7	**3a**	P(*o*-BP)(*t*-Bu)$_2$	Cs_2CO_3	2	**5a**, 91 (80)
8	**3b**[d]	P(*o*-BP)(*t*-Bu)$_2$	Cs_2CO_3	2	**5b**, (72)

[a] Conditions: [**3**]:[$Pd(OAc)_2$]:[P(*o*-BP)(*t*-Bu)$_2$]:[Cs_2CO_3] = 1:0.1:0.2:2 (0.25 mmol of **3** was used), at 160 °C under N_2 in DMAc (2.1 mL).
[b] *o*-BP = biphenyl-2-yl.
[c] Determined by GC analysis. Value in parentheses is isolated yield.
[d] 0.13 mmol of **3b** was used in 1 mL of DMAc.



Scheme 3. Synthesis of BBTBDT and 2C_8-BBTBDT. [a]Conditions: [**1c**]:[**2**]:[K_2CO_3] = 1:2.4:4 (3 mmol of **2a** and 1.2 mmol of **2b** were used), 80 °C, 18 h in DMF under N_2. [b]Conditions: [**2**]:[KOH] = 1:6, EtOH/H_2O = 5:1 (v/v), 100 °C, 15–21 h under N_2. Yields of **6a** and **6b** were 42% and 75%, respectively (by two steps). [c]Conditions: [**6**]:[$Pd(OAc)_2$]:[P(*o*-BP)(*t*-Bu)$_2$]:[Cs_2CO_3] = 1:0.2:0.4:4 (0.3 mmol of **6a** and 0.114 mmol of **6b** were used). Yields of **7a** and **7b** were 61% (18% after sublimation in vacuo) and 26%, respectively.



Scheme 4. Preparation of *iso*-BBTBDT and $2C_8$-*iso*-BBTBDT. [a]Conditions: [**1d**]:[**2**]:[K_2CO_3] = 1:2.4:4 (5.2 mmol of **2a** and 1.6 mmol of **2b** were used), 80 °C, 8 h in DMF under N_2. [b]Conditions: [**2**]:[KOH] = 1:6, EtOH/H_2O = 5:1 (v/v), 100 °C, 15–21 h. Yields of **8a** and **8b** were 53% and 78%, respectively (by two steps). [c]Conditions: [**8**]:[$Pd(OAc)_2$]:[P(*o*-BP)(*t*-Bu)$_2$]:[Cs_2CO_3] = 1:0.2:0.4:4 (0.3 mmol of **8a** and 0.114 mmol of **8b** were used). Yields of **9a** and **9b** were 56% (32% after sublimation in vacuo) and 35% (25% after Soxhlet extraction), respectively.

have been reported.[7,8] Using **1c** and **2b** could also be obtained 2, 9-dioctyl-BBTBDT ($2C_8$-BBTBDT), albeit with a moderate yield.[14]

Butyl 3,6-bis(chloro)benzo[2,1-*b*:3,4-*b*′]dithiophene-2,6-carboxylate (**1d**) was found to be a useful scaffold for constructing an isomer of BBTBDT (*iso*-BBTBDT) **9a** and its dioctyl derivative **9b** (Scheme 4). Construction of the *iso*-BBTBDT skeleton is to date unprecedented. Diester **1d** can be readily prepared by the convenient double ring-closure reaction of commercially available 1,4-phenylenediacrylic acid with thionyl chloride in the presence of pyridine followed by esterification with butanol.[11,15] Decarboxylative cyclization of the intermediary diacids **8a** and **8b**, which were prepared from **1d** with **2a** and **2b**, gave rise to **9a** and **9b** in 56% and 36% yields, respectively.

In summary, we have demonstrated that 3-(chloro)- or 3-(trifluoromethanesulfonyloxy)-benzo[*b*]thiophene-2-carboxylic acid esters in combination with 2-bromobenzenethiols are useful building-blocks for constructing BTBT and its higher homologs. Thus, by using the present strategy including palladium-catalyzed decarboxylative arylation as the key step, not only BTBT and BBTBDT, but also a structurally new seven-ring theienoacene system, that is, *iso*-BBTBDT can be constructed effectively.[16] Further studies of the synthesis of related derivatives by this reaction sequence and their physical properties are underway and the details will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (characterization data of compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.084.

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16. *Dibutyl 3,6-bis[(2-bromophenyl)thio]benzo[2,1-b:3,4-b′]dithiophene-2,7-dicarboxylate (Scheme 4, the first step)*: In a 100 mL reaction flask were placed the dichloride **1d** (1.0 g, 2.18 mmol), the thiol **2a** (0.61 mL, 5.2 mmol), K_2CO_3 (1.2 g, 8.7 mmol), and DMF (20 mL), and the resulting mixture was stirred for 24 h at 80 °C under nitrogen. The reaction was quenched by adding water, extracted with chloroform, and dried over Na_2SO_4. Concentration followed by purification by column chromatography with hexane/ethyl acetate (20:1, v/v) gave the diarylthiolated diester (890 mg, 1.17 mmol, 53%) as a yellow solid. Mp 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 6H), 1.42 (tq, J = 7.6 Hz, 7.6 Hz, 4H), 1.70 (tt, J = 6.8 Hz, 6.8 Hz, 4H), 4.35 (t, J = 6.5 Hz, 4H), 6.58-6.61 (m, 2H), 6.93–7.00 (m, 4H), 7.52–7.55 (m, 2H), 7.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.87, 19.35, 30.67, 66.31, 121.30, 122.80, 126.99, 127.92, 127.95, 130.66, 133.10, 134.35, 136.84, 137.93, 140.33, 161.41; HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{32}H_{29}Br_2O_4S_4$: 764.9212, found: 764.9227.
*3,6-Bis[(2-bromophenyl)thio]benzo[2,1-b:3,4-b′]dithiophene-2,7-dicarboxylic acid (**8a**)*: To a mixture of the diester (870 mg, 1.14 mmol) and KOH (384 mg, 6.84 mmol), water (2 mL), and ethanol (10 mL)-dioxane (4 mL) were sequentially added, and the suspension was then heated at 100 °C for 6 h under nitrogen. The resulting mixture was allowed to cool to room temperature. The precipitate formed by addition of diluted aqueous HCl was collected and washed with water, ethanol, and hexane, and then, dried under high vacuum to provide dicarboxylic acid **8a** (755 mg, 1.14 mmol, quant.) as a yellow solid. Mp ca. 290 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.55–6.58 (m, 2H), 7.03–7.06 (m, 4H), 7.52–7.57 (m, 2H), 7.62–7.64 (m, 2H), 14.13 (bs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.10, 122.09, 127.32, 127.60, 128.33, 128.46, 132.88, 133.35, 137.14, 138.46, 139.40, 161.72; HRMS (FAB$^-$) m/z (M$^+$) calcd for $C_{24}H_{12}Br_2O_4S_4$: 649.7980, found: 649.7996.
*Bis[1]benzothieno[2,3-d;2′,3′-d′]benzo[1,2-b;5,6-b′]dithiophene (**9a**)*: In a 20 mL two-necked flask were placed the diacid **8a** (200 mg, 0.307 mmol), $Pd(OAc)_2$ (14 mg, 0.061 mmol) and Johnphos (37 mg, 0.123 mmol), Cs_2CO_3 (407 mg, 1.23 mmol), and DMAc (5 mL). The resulting mixture was stirred for 7 h at 160 °C under nitrogen and cooled to room temperature. The solid in the mixture was collected by filtration and washed with water, hexane, and acetone to give **9a** (69 mg, 0.171 mmol, 56%) as a yellow, practically insoluble solid. This was further purified by sublimation in vacuo under heating to give the analytical sample of **9a** (39.1 mg, 0.097 mmol, 32%). Mp >300 °C; HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{22}H_{11}S_4$: 402.9738, found: 402.9738; Anal. calcd for $C_{22}H_{10}S_4$: C, 65.64; H, 2.50. Found: C, 65.41; H, 2.63.
*2,9-Dioctylbis[1]benzothieno[2,3-d;2′,3′-d′]benzo[1,2-b;5,6-b′]dithiophene (**9b**)*: This compound was prepared as above by using **8b** (100 mg, 0.114 mmol). The collected solid was washed with water, hexane, acetone, and finally with chloroform to give **9b** (24.8 mg, 0.040 mmol, 35%) as a sparingly soluble yellow solid. A further purification was made by Soxhlet extraction with chlorobenzene to afford a somewhat clear colored sample of **9b** (17.5 mg, 0.028 mmol 25%). Mp ca. 210 °C (decomposed); ^{1}H NMR (400 MHz, toluene-d_8 at 100 °C) δ 0.90 (t, J = 6.4 Hz, 6H), 1.24–1.42 (m, 20H), 1.63 (tt, J = 6.4 Hz, 6.4 Hz, 4H), 2.61 (t, J = 7.4, 4H), 7.49 (s, 2H), 7.583 (s, 2H), 7.585 (d, J = 6.0 Hz, 2H) (one signal was overlapped by the solvent signal); HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{38}H_{43}S_4$: 627.2244, found: 627.2242.