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Synthesis of functionalized benzothiophenes by twofold Heck and subsequent 6π-electrocyclization reactions of 2,3-dibromothiophene

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ABSTRACT

The Heck reaction of 2,3-dibromothiophene afforded 2,3-di(alkenyl)thiophenes which were transformed into benzothiophenes by domino '6π-electrocyclization/dehydrogenation' reactions.

Benzothiophenes are of considerable pharmacological relevance and are present in some natural products, such as antiangiogenic bryoanthrathiophene.[1] Parent benzothiophene is present in coffee beans. Benzothiophenes are also used in crop protection. For example, mobam (4-(*N*-methylcarbamoyl)benzo[*b*]-thiophene) represents a potent insecticide which inhibits, similar to its naphthalene analogue (1-(*N*-methylcarbamoyl)naphthalene), the enzyme acetylcholinesterase.[2] Benzothiophenes are often bioisosteric with naphthalenes and indoles. (Benzo[*b*]thien-3-yl)acetic acid accelerates, similar to its indole analogue, the growth of plants. 3-(2-Aminoethyl)benzo[*b*]thiophene is known to stimulate the CNS. Its activity is even higher than that of the indole analogue tryptamine.[3] Last but not the least, benzothiophenes are present in many dyestuffs. Prominent examples are thioindigo and its derivatives. Benzothiophenes are synthetically available by condensation of thiophenolates or 2-formyl- or 2-acylthiophenolates with α-haloketones and subsequent cyclization.[4,5]

In the recent years, it has been shown that polyhalogenated heterocycles can be regioselectively functionalized in palladium(0)-catalyzed cross-coupling reactions by selective activation of a single halogen atom. The regioselectivity is controlled by electronic and steric parameters.[6] Recently, we have reported the synthesis of aryl-substituted thiophenes,[7] pyrroles,[8] and selenophenes[9] based on regioselective Suzuki reactions of tetrabromothiophene, tetrabromo-*N*-methylpyrrole, and tetrabromoselenophene, respectively. Sonogashira,[10] Kumada,[11] Suzuki,[12] and Stille[13] coupling reactions of 2,3-dibromothiophene have been reported to regioselectively occur at position C-2. Recently, we have reported Heck reactions of 2,3-dibromobenzofuran[14] and of 2,3-dibromo-*N*-methylindole.[15] Herein, we report what are, to the best of our knowledge, the first Heck reactions of 2,3-dibromothiophene to give 2,3-di(alkenyl)thiophenes. Domino '6π-electrocyclization/dehydrogenation' reactions[16,17] of the products afforded functionalized benzothiophenes.

The Heck reaction of 2,3-dibromothiophene (**1**) with acrylates **2a–l** (2.5 equiv) afforded the 2,3-di(alkenyl)thiophenes **3a–l** in good yields (Scheme 1, Table 1).[18] The best yields were obtained when the reactions were carried out using $Pd(OAc)_2$ (5 mol %) and the biaryl monophosphine ligands SPhos or XPhos (10 mol %) which were recently developed by Buchwald and co-workers (Scheme 2).[19] The reactions were carried out in DMF at 120 °C for 12 h. The employment of $Pd(PPh_3)_4$ was less successful in terms of yield. Heating of a xylene solution of **3a–e** and **3h–l** in the presence of Pd/C resulted in the formation of benzothiophenes **4a–e** and **4h–l** in quantitative yield.[20] The formation of the products can be explained by thermal 6π-electrocyclization to give intermediate **A** and subsequent dehydrogenation. During the optimization, it proved to be important to carry out the reaction at 200 °C. No conversion was observed at lower temperatures.

The structures of all products were established by spectroscopic methods. The structure of **3b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[21]

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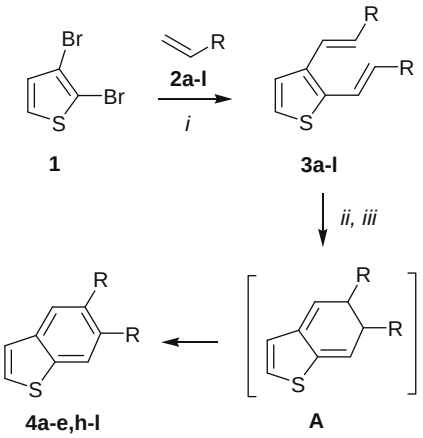
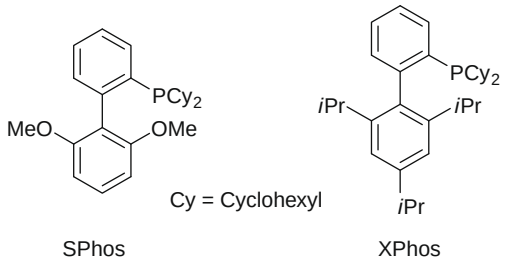


Scheme 1. Synthesis of **3a–l** and **4a–l**. Reagents and conditions: (i) **2a–l** (2.5 equiv), $Pd(OAc)_2$ (5 mol %), SPhos or XPhos (10 mol %), NEt_3, DMF, 120 °C, 48 h; (ii) xylene, 200 °C, 24 h; (iii) Pd/C (10 mol %), xylene, 200 °C, 48 h.

Table 1
Synthesis of **3a–l** and **4a–e** and **4h–l**

3,4	R	% (3)[a]	% (4)[a]
a	CO_2Me	81[b]	100
b	CO_2Et	90[c]	100
c	CO_2iBu	86[b]	100
d	CO_2nBu	93[c]	100
e	CO_2nHex	92[c]	100
f	CO_2tBu	89[b]	—[d]
g	CO_2iOct	87[c]	—[d]
h	$CO_2[CH_2CH(Et)(CH_2)_3CH_3]$	85[c]	100
i	Ph	91[c]	100
j	4-($tBuO$)C_6H_4	84[b]	100
k	4-$tBuC_6H_4$	94[c]	100
l	4-(MeO)C_6H_4	83[c]	100

[a] Yields of isolated products.
[b] XPhos was used.
[c] SPhos was used.
[d] Experiment was not carried out.



Scheme 2. Biaryl monophosphine ligands developed by Buchwald and co-workers (Ref.[19]).

The Heck reaction of **1** with only one equivalent of acrylates **2a–f** resulted in the formation of 2-alkenylthiophenes **5a–f** (Scheme 3, Table 2). The formation of these products can be explained by regioselective coupling of carbon atom C-2 of **1** with the acrylate and subsequent Pd(0)-catalyzed reduction.

In conclusion, 2,3-dialkenylthiophenes were prepared by the first Heck reactions of 2,3-dibromothiophene. Functionalized benzothiophenes were prepared by Pd/C-catalyzed domino '6π-electrocyclization/dehydrogenation' reactions of the 2,3-dialkenylthiophenes. The reaction of 2,3-dibromothiophene with one equivalent of alkenes resulted in the formation of 2-alkenylthiophenes.

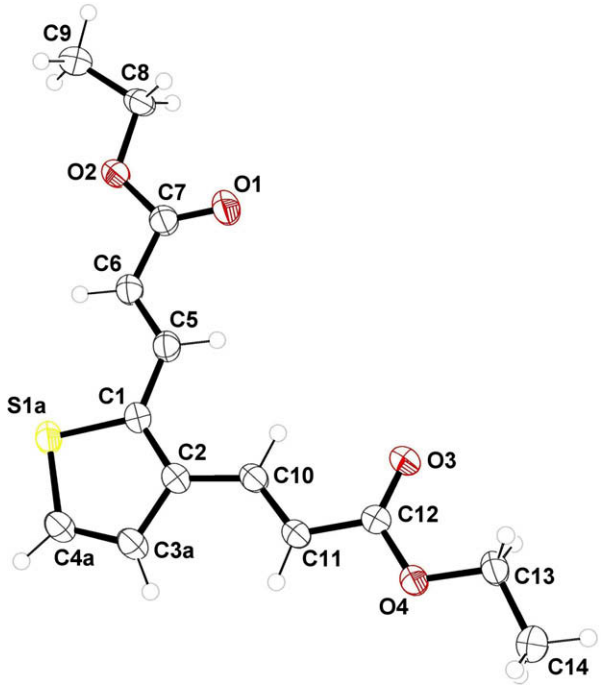
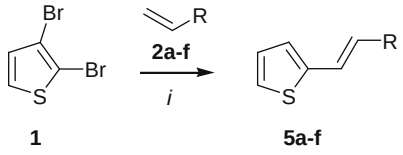


Figure 1. Crystal structure of **3b**.



Scheme 3. Synthesis of **5a–f**. Reagents and conditions: (i) **2a–f** (1.0 equiv), $Pd(OAc)_2$ (2.5–5 mol %), SPhos or XPhos (5–10 mol %), NEt_3, DMF, 120 °C, 24 h.

Table 2
Synthesis of **5a–f**

5	R	% (5)[a]
a	CO_2Me	75[b]
b	CO_2Et	78[c]
c	CO_2iBu	74[b]
d	CO_2nBu	85[c]
e	CO_2nHex	76[c]
f	CO_2tBu	87[b]

[a] Yields of isolated products.
[b] XPhos was used.
[c] SPhos was used.

Acknowledgments

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18. *General procedure A for the synthesis of* **3a–l**: In a pressure tube (glass bomb) a suspension of $Pd(OAc)_2$ (12 mg, 0.05 mmol, 5 mol %) and XPhos (47 mg, 0.10 mmol, 10 mol %) in DMF (5 mL) was purged with Ar and stirred at 20 °C to give a yellowish or brownish clear solution. To the stirred solution were added 2,3-dibromothiophene (**1**) (242 mg, 1.0 mmol), NEt_3 (1.1 mL, 8.0 mmol) and the acrylate (2.5 equiv per Br). The reaction mixture was stirred at 120 °C for 48 h. The solution was cooled to 20 °C, 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). The combined organic layers were washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes/EtOAc).
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20. *General procedure B for the synthesis of benzothiophenes* **4a–e** and **4h–l**. A xylene solution (3 mL) of **3a–e**, **h–l** was stirred at 200 °C for 24 h in a pressure tube. The solution was allowed to cool to 20 °C and Pd/C (30 mg, 10 mol %) was added. The solution was stirred at 200 °C for 48 h under argon atmosphere. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes/EtOAc). *Diisobutyl benzo[b]thiophene-5,6-dicarboxylate* (**4c**). Compound **4c** was prepared starting with 2,3-dibromothiophene (**1**) (242 mg, 1.0 mmol), following the general procedures A and B, as a light yellow highly viscous oil (287 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, 6H, J = 6.7 Hz, $2CH_3$), 0.94 (d, 6H, J = 6.7 Hz, $2CH_3$), 1.91–2.06 (m, 2H, CH), 4.05 (d, J = 6.8 Hz, $2CH_2O$), 7.35 (dd, 1H, J = 0.7, 5.6 Hz, ArH), 7.58 (d, 1H, J = 5.5 Hz, ArH), 8.10 (s, 1H, ArH), 8.20 (s, 1H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 19.1, 19.2 (CH_3), 27.7, 27.8 (CH), 71.8, 71.9 (CH_2O), 123.8, 124.0, 124.4 (CH), 127.8, 128.9 (C), 130.6 (CH), 140.8, 141.5 (C), 167.6, 168.3 (CO). IR (KBr): ν = 3106, 2958, 2873 (w), 1716 (s), 1626, 1601, 1545, 1490, 1468 (w), 1448, 1452, 1405, 1392, 1392, 1375, 1341 (m), 1314, 1271, 1239, 1190, 1167, 1119, 1097, 1073 (s), 1005, 982, 945, 904, 785, 775, 754, 702 (m), 682, 653, 626 (w) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 334 ($[M]^+$, 8), 222 (57), 206 (17), 205 (100), 178 (15), 160 (06). HR-MS (EI, 70 eV): calcd for $C_{18}H_{22}O_4S$ $[M]^+$: 334.12388; found: 334.12360.
21. CCDC-736137 contains 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, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.