ORGANIC LETTERS

2011
Vol. 13, No. 15
4100–4103

# Palladium-Catalyzed C–S Coupling: Access to Thioethers, Benzo[*b*]thiophenes, and Thieno[3,2-*b*]thiophenes

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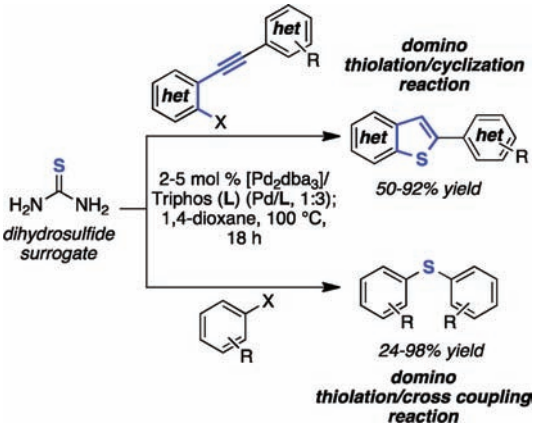
**Received June 15, 2011**

## ABSTRACT




**The first C–S bond formation/cross-coupling/cyclization domino reaction using thiourea as a cheap and easy to handle dihydrosulfide surrogate has been developed. Structurally important biarylthioether, benzo[*b*]thiophenes, and thieno[3,2-*b*]thiophene scaffolds are provided in high yield.**

Sulfur-containing functional groups and heterocycles are ubiquitous structural elements in pharmacologically active compounds and in material sciences.[1] In particular thioethers[2] and benzo[*b*]thiophenes[3] have been recognized as biological and physiological effectors. Novel methodologies for the synthesis of symmetric[4] and unsymmetric[5] biarylthioethers have been developed using copper[4,5a,6] and palladium[5c–e] catalyzed transformations.[7] Benzo[*b*]thiophenes are usually synthesized by the reaction of metalated arylalkenes with sulfur reagents[1a,b,8] or by

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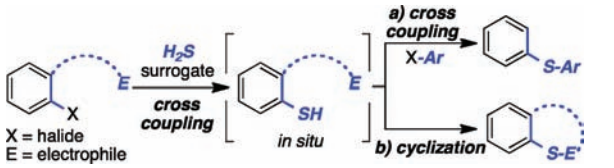
10.1021/ol2016093 
**Published on Web 07/06/2011**

nucleophilic aromatic substitution[9] with sodium hydrosulfide and subsequent cyclization at high temperatures (160−190 °C). Only few catalytic processes have been reported in the literature to circumvent these strong basic and harsh reaction conditions. Typical promotors or catalysts are strong electrophiles, such as AuCl,[10] stoichiometric cupric halides,[11] halonium ions,[3b,12] and strong acids (*p*-toluene sulfonic acid).[13] The cyclization requires the preformation of the corresponding alkynyl arylthioether, which subsequently undergoes endo-dig cyclization onto the alkyne moiety. Still, these reactions require the prerequisite formation of the aryl-thiols prior to cyclization. Efficient methodologies have been reported for the coupling of aryl iodides and bromides with dihydrosulfide surrogates, e.g. xanthate[5a] and tris(isopropyl)silylthiol,[5c] to furnish unsymmetric biarylthioether according to a consecutive addition−deprotection−addition protocol. However, the use of thiourea (**1**) as a surrogate[4,5a,5b,14] in the coupling of aryl bromides seems appealing since it is easy to handle and not affected by air or moisture. Yet, a palladium-catalyzed transformation has not been reported so far. This report concentrates on the application of **1** as a dihydrosulfide surrogate in a domino reaction[15] to access

**Scheme 1.** Domino C−S Bond Formation Cross-Coupling/Cyclization Reaction




symmetrical biarylthioether, benzo[*b*]thiophenes, and thieno[3,2-*b*]thiophenes in one step (Scheme 1).[16]

First, the aryl thiol[5d,6e,17] is generated *in situ*. Subsequent coupling with an aryl halide results in thioethers (Scheme 1a). Alternatively, in the presence of an alkyne an 5-endo-dig cyclization of the thiolate yields benzo[*b*]phiophene or thieno[3,2-*b*]thiophene derivatives (Scheme 1b). This *in situ* cross-coupling/cyclization sequence[12a,18] represents the first palladium-catalyzed one-pot synthesis of sulfur-heterocycles[3b,10−13] making these valuable structures readily available.

The catalyst system was optimized for the synthesis of symmetrical biarylthioether ensuring efficient C−S bond formation (see Supporting Information for details). The optimal catalyst system for the coupling of thiourea (**1**) with aryl halides (**2**) to form the symmetrical thioethers (**3**) consisted of the tridentate ligand Triphos (**L**), tris-(dibenzylideneacetone)dipalladium(0) ([$Pd_2dba_3$]), ceasium carbonate as base, and 1,4-dioxane as solvent (Table 1). In general, the reaction can be applied to aryl iodides and bromides, while aryl chlorides proved unreactive (entry 1, **2ac**). Diphenylsulfide (**3a**) was obtained from the coupling of iodo- (**2aa**) or bromobenzene (**2ab**) with **1** in 80% and 74% yield respectively (entry 1).

Interestingly, sterically encumbered aryl bromides (**2b** and **2c**) were converted into the thioethers **3b** and **3c** in excellent yields (93% and 98% yield, entries 2 and 3). The coupling of polyaromatic naphthyl derivatives (**2d** and **2e**) underwent thioether formation in good to excellent yields (77% and 92% yield, entries 4 and 5). The coupling of electron-rich thiophene **2f** (entry 6) proceeded in 44% yield indicating that the electronic nature of the aryl halide is crucial for efficient coupling. Indeed, electron-rich aryl iodides and bromides (**2ga**, **2gb**, entry 7) furnished the thioether **3g** in 18% yield. Interestingly only the free amino functionality

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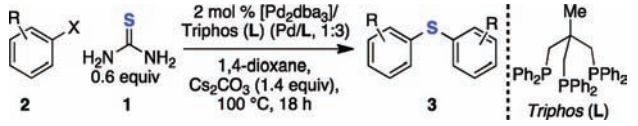
was tolerated in the coupling in comparison to the hydroxy functionality (entry 9 versus 8). However, electron-withdrawing groups are well tolerated (entries 10–16, 67–98% yield).

**Table 1.** Domino Reaction for the Synthesis of Biarylthioether Using Thiourea (**1**) as Dihydrosulfide Surrogate[a]

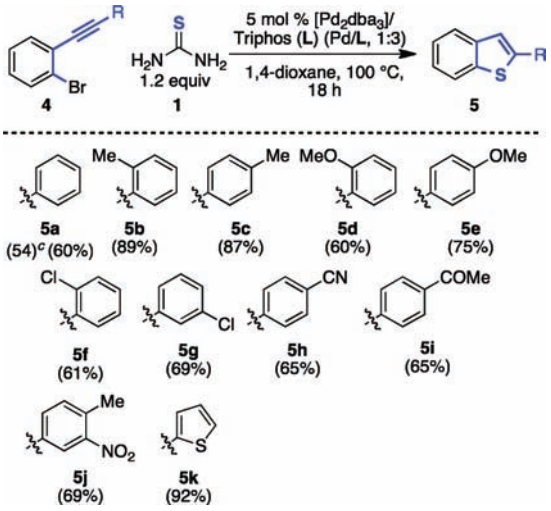



| entry | aryl halide **2** | product **3** | yield/%[b] |
|---|---|---|---|
| 1 | $C_6H_5$-X; X = I (**2aa**), Br (**2ab**), Cl (**2ac**) | **3a** | X = I (80), Br (74), Cl (0) |
| 2 | 2-$CH_3$-$C_6H_4$-Br (**2b**) | **3b** | 93 |
| 3 | 1,4-$(CH_3)_2$-$C_6H_3$-Br (**2c**) | **3c** | 98 |
| 4 | 2-naphthylbromide (**2d**) | **3d** | 77 |
| 5 | 1-naphthylbromide (**2e**) | **3e** | 92 |
| 6 | 2-bromothiophene (**2f**) | **3f** | 44 |
| 7 | 4-$OCH_3$-$C_6H_4$-X; X = I (**2ga**), Br (**2gb**) | **3g** | X = I (18), Br (18) |
| 8 | 4-OH-$C_6H_4$-Br (**2h**) | **3h** | 0 |
| 9 | 2-bromoaniline (**2i**) | **3i** | 24 |
| 10 | 4-chlorobromobenzene (**2j**) | **3j** | 78 |
| 11 | 3,4-dichlorobromobenzene (**2k**) | **3k** | 67 |
| 12 | 4-$CF_3$-$C_6H_4$-Br (**2l**) | **3l** | 67 |
| 13 | 4-acetyliodobenzene (**2m**) | **3m** | 80 |
| 14 | 4-$CO_2$Et-$C_6H_4$-X; X = I (**2na**), Br (**2nb**) | **3n** | X = I (95), Br (98) |
| 15 | 4-nitrobromobenzene (**2o**) | **3o** | 75 |
| 16 | 4-bromobenzonitrile (**2p**) | **3p** | 98 |

[a] 0.5 mmol of **2**, 0.33 mmol of **1**, 2 mol % $Pd_2dba_3$/**L** (Pd/**L**; 1/3), 100 °C, 18 h. [b] The yield was determined after column chromatography.

Having the efficient thiolation of aryl bromides established employing thiourea (**1**) as a dihydrosulfide surrogate we turned our attention to the intramolecular trapping of the formed arylthiolate with alkynes accessing benzo[*b*]thiophenes in good to excellent yields in a single process.[19] When 1-bromo-2-(phenylethynyl)benzene (**4a**, Scheme 2) was reacted with 1.2 equiv of **1** under the same reaction conditions as developed for the thioethers **3** the heteroaromatic product **5a** was obtained in 54% yield (Scheme 2). An increase of catalyst loading from 2 to 5 mol % resulted in an improved yield of 60%.[20] The substrate scope of this first domino thiolation/cyclization reaction was investigated (Scheme 2). The reaction proceeded in high yield for *ortho* and *para* substituted aryl groups (**5b** and **5c**). The reaction is relatively independent of the electronic nature of the aryl substituent. Electron-rich (**5d**–**e**) and electron-poor aromatic systems (**5f**–**j**) underwent cyclization in good to high yields irrespective of the substitution pattern. Functional

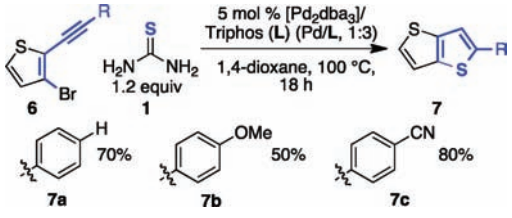
**Scheme 2.** Benzo[*b*]thiophene Synthesis Applying Thiourea (**1**) as Dihydrosulfide Surrogate[a–c]




[a] 0.2–0.7 mmol **4**, 0.3–0.9 mmol **1**, 5 mol % $Pd_2dba_3$/**L** (Pd/**L**; 1/3), 100 °C, 18 h. [b] The yield was determined after column chromatography. [c] The reaction was performed with 2 mol % $Pd_2dba_3$/**L**.

groups, such as nitrile (**5h**), ketone (**5i**), or nitro (**5j**), were well tolerated. The thiolation/cyclization reaction proved very efficient for the thiophene derivative **4k**. 2-Thiophenylbenzo[*b*]thiophene (**5k**) was obtained in excellent yield (92%) making the presented domino-reaction process a valuable methodology for efficient benzo[*b*]thiophene syntheses. Furthermore, the described domino thiolation/cyclization reaction can be applied for the synthesis of thieno[3,2-*b*]thiophenes.

**Scheme 3.** Palladium-Catalyzed Thieno[3,2-*b*]thiophene Synthesis[a,b]




[a] 0.5 mmol of **6**, 0.6 mmol of **1**, 5 mol % $Pd_2dba_3$/**L** (Pd/**L**; 1/3), 100 °C, 18 h. [b] The yield was determined after column chromatography.

In fact, when **6a** was subjected to the reaction with **1** under palladium catalysis the thieno[3,2-*b*]thiophene **7a** was obtained in 70% yield (Scheme 3).

The cyclization is more susceptible to the electronic nature of the aryl substituent than the cyclizations with the benzo

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(20) 5 mol % catalyst loading improved the yield for the other substrates **4** from 30 to 34% to 56–89% yield.

(21) **7b** was isolated in 80% yield. However, the isolated material was contaminated with 30% debrominated starting material (**6b**), which was impossible to separate from the product by all techniques applied. The yield was calculated from the integration of the OMe resonances in the $^1$H NMR spectrum.

derivatives **4** since the electron-rich 3-bromothiophene **6b** underwent annelation in lower yield (50%)[21] compared to its electron-deficient analogue **6c**, which was generated in excellent yield (80%).

In summary, an efficient methodology for the C–S coupling of aryl bromides and iodides applying thiourea as a cheap and easy to handle dihydrosulfide surrogate was developed. The new methodology was used to synthesize symmetrical biarylthioethers in high to excellent yields. The reaction conditions were successfully transferred to the domino thiolation/cyclization reaction furnishing benzo[*b*]thiophenes and thieno[3,2-*b*]thiophenes in high yield. This unprecedented domino coupling/cyclization reaction provides straightforward access to valuable structures for drug discovery and material sciences.

**Acknowledgment.** We thank the Fonds der Chemischen Industrie for a Fonds-fellowship to F.C.F. and a Liebig-Grant to J.P. and Prof. Dr. Stefan Bräse for his kind support.

**Supporting Information Available.** Experimental procedures, product characterization data, and $^{1}H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.