Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5036

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COMMUNICATION

Palladium-catalyzed three-component domino reaction for the preparation of benzo[*b*]thiophene and related compounds†

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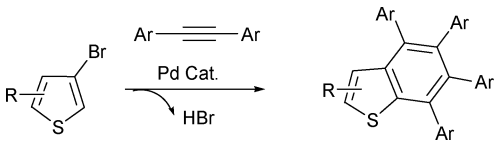
Received 11th April 2011, Accepted 17th May 2011
DOI: 10.1039/c1ob05571b

A simple and efficient palladium-catalyzed three-component domino reaction of bromothiophenes with internal alkynes has been developed to produce benzo[*b*]thiophenes in moderate to good yields.

Benzo[*b*]thiophenes display numerous applications in materials and biological chemistry.[1] The development of efficient and simple methods to synthesize these compounds has received considerable attention in recent years.[2–6,12]

Transition metal-catalyzed multi-component domino reactions are becoming more and more popular in modern organic synthesis.[7] In particular, the palladium-catalyzed reaction of aryl halides with alkynes to afford various polycyclic aromatic compounds has been highlighted in numerous reports.[8] The attractive points of these reactions are simplicity, efficiency, atom and step economy. Triggered by oxidative addition of palladium species to C–X (X = Br, I) bonds, all of the reactants are "*automatically assembled*" in one pot to produce the final polycyclic π-conjugated products. There is no need to isolate the intermediates. Several bonds (at least 3 bonds) are formed with the loss of only one molecule of HX (X = Br, I). This advantage has been previously used to construct different polycyclic aromatic hydrocarbons (PAHs),[1b] but there are limited examples of catalytic three-component domino reactions of alkynes with heteroaryl halides, especially the reaction with halothiophenes to produce benzo[*b*]thiophenes.[3,4,8a]

Palladium-catalyzed reaction of comparatively expensive *o*-dihalothiophenes with alkynes provided a simple and direct access to benzothiophenes,[3,8a] but the similar reaction with 2-iodothiophene was less effective.[4] Ir-catalyzed reaction of 2-thenoyl chloride with alkynes provided another efficient method.[5] Very recently, decarboxylation of heteroarene carboxylic acids and subsequent reactions with alkynes provided an efficient method for the preparation of various highly substituted indoles and benzofurans, but the reactions with thiophene derivatives were sluggish.[6] Herein, we would like to report the palladium-catalyzed three-component domino reaction of bromothiophenes with alkynes to form benzo[*b*]thiophenes selectively. The only by-product is HBr (Scheme 1).

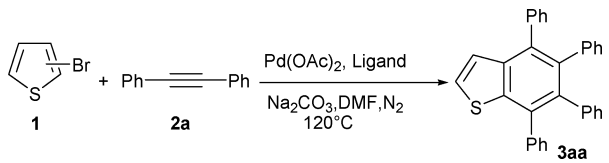


Scheme 1

We checked the reaction of 3-bromothiophene (**1a**) and 2-bromothiophene (**1b**), respectively, with diphenylacetylene (**2a**). As shown in Table 1, the reaction with 2-bromothiophene (**1b**) provided only a trace amount of the desired product (entry 11). But a promising result was obtained with 3-bromothiophene (entry 1). Encouraged by this result, we carried out a series of experiments with 3-bromothiophene to optimize the reaction parameters. Typical results are summarized in Table 1.

As a ligand, PCy_3 showed better results than PPh_3 (Table 1, entry 3 *vs.* entry 4) in terms of yield (according to GC analysis).

Table 1 Reactions of bromothiophenes(**1**) with diphenylacetylene (**2a**)[a]



Entry	**1**	Ligand[b]	LiBr (mmol)	Yield (%)[c]
1	**1a**	$P(Ph)_3$		61
2	**1a**	$P(Ph)_3$		31[d]
3	**1a**	$P(Ph)_3$	0.7	58
4	**1a**	$P(Cy)_3$	0.7	76(63)
5	**1a**	$P(Cy)_3$	1.0	16
6	**1a**	$P(Cy)_3$	0.7	89(82)[e]
7	**1a**	$P(Cy)_3$	0.5	67[e]
8	**1a**	$P(Cy)_3$		10[e]
9	**1a**		0.7	44(41)[e]
10	**1b**	$P(Ph)_3$		—
11	**1b**	$P(Cy)_3$		trace[f]

[a] Unless otherwise noted, $Pd(OAc)_2$ (5 mol%), ligand, and Na_2CO_3 were added to the DMF solution of 3-bromo- (**1a**) or 2-bromothiophene (**1b**) (1 mmol) and **2a** (3.0 mmol). The reaction mixture was stirred under N_2 at 120 °C for 24 h. [b] The ratio of ligand : Pd : Na_2CO_3 = 2 : 1 : 20. [c] GC yields. Isolated yields are given in parentheses. [d] The reaction was carried out under air. [e] 10 mol% $Pd(OAc)_2$ was used. [f] Reacted for 40 h.

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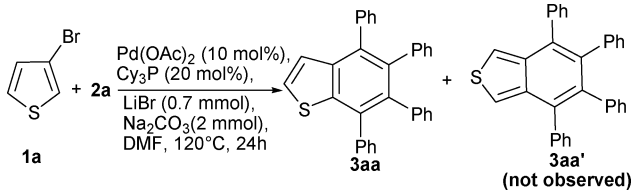
† Electronic supplementary information (ESI) available: Synthesis and characterization of products, ^1H and ^{13}C NMR, IR and UV spectra. See DOI: 10.1039/c1ob05571b

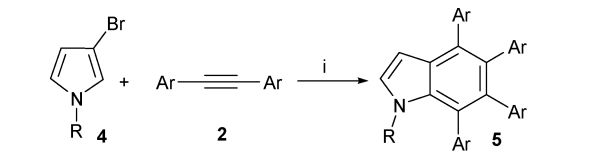
In the presence of $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), LiBr (0.7 mmol), and Na_2CO_3(2 mmol), the DMF solution of **1a** (1 mmol) and **2a** (3 mmol) was stirred at 120 °C for 24 h, leading to an 82% yield of benzothiophene **3aa** (entry 6). The reaction without phosphine ligand provided the desired product in low yield (entry 9). As shown in Table 1, LiBr additive plays an important role in this reaction (entries 3–8).[9] In all of the cases, only compound **3aa** was obtained selectively. The formation of **3aa′** was not observed (Scheme 2).[10] The different results obtained from 2- and 3-bromothiophenes, as well as the selective formation of **3aa**, may be due to the different reactivity of the α- and β-C–H bonds of thiophene.[11]



Scheme 2 The regioselective formation of **3aa**.

The reaction conditions of entry 6, Table 1, were chosen for further examination of the reaction scope with a variety of bromothiophenes and internal alkynes. Table 2 summarizes the results of the palladium-catalyzed reactions of bromothiophenes with alkynes. Clearly, various 3-bromothiophenes reacted smoothly with methyl- (**2b**), methoxy- (**2c**), and fluoro-substituted (**2d**) diphenylacetylenes to afford the corresponding benzothiophenes (entries 1–6) in moderate to good yields. Both CHO (entry 9) and CN (entry 10) groups are compatible with the present catalytic system. The versatile transformations of these functional groups will provide ready access to a wider range of benzothiophenes. It is worth noting that the reaction of 4-bromo-2-cyanothiophene (entry 10, **1g**) with diphenylacetylene was carried out without PCy_3 and the desired product could be isolated in 43% yield. The reaction with PCy_3 was sluggish.

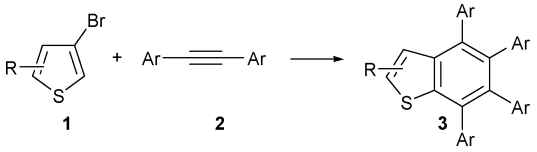
This catalytic system could also be used to synthesize indoles from the corresponding bromopyrroles (Scheme 3).

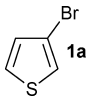
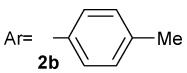
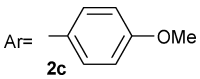
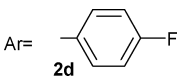
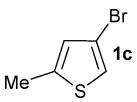
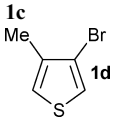
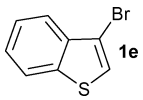
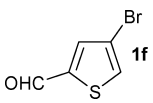
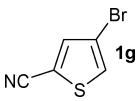


Scheme 3 The selective formation of indoles. *Reagents and conditions*: (i) $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), LiBr (0.7 mmol), Na_2CO_3(2 mmol), DMF, 120 °C, 24 h.

We propose the following reaction mechanism (Scheme 4): (1) oxidative addition of 3-bromothiophene **1** to Pd(0) gives a thienylpalladium(II) intermediate **6**; (2) *cis*-carbopalladation of the alkyne gives a vinylic palladium intermediate **7**; (3) next, cyclopalladation affords a five-membered palladacycle **8**; (4) the subsequent reaction with alkyne and reductive elimination affords the corresponding product **3** with regeneration of the Pd(0) species. The reaction pathway may also involve successive insertion of two molecules of alkynes to form **9**, which can also give **3**.[4]

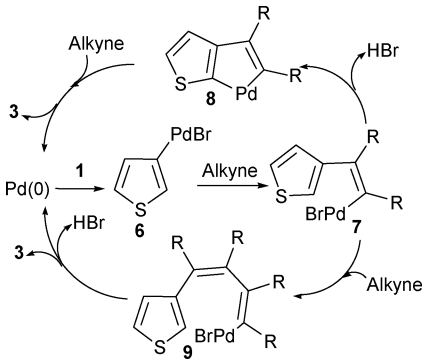
Table 2 Palladium-catalyzed reactions of bromothiophenes with alkynes[a]



Entry	Thiophene(**1**)	Alkyne(**2**)	Product	Yield (%)[b]
1		**2a**	**3aa**	89(82)
2	**1a**		**3ab**	(54)
3	**1a**		**3ac**	(61)
4	**1a**		**3ad**	(73)
5		**2a**	**3ca**	75(71)
6	**1c**	**2c**	**3cc**	(57)
7		**2a**	**3da**	(64)
8		**2a**	**3ea**	(52)[c]
9		**2a**	**3fa**	(47)
10		**2a**	**3ga**	(43)[d]

[a] Unless otherwise noted, $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%) and Na_2CO_3 (200 mol%) were added to the DMF solution of **1** (1 mmol) and **2** (3 mmol). The reaction mixture was stirred under N_2 at 120 °C for 24 h. [b] GC yields. Isolated yields are given in parentheses. [c] The reaction was carried out at 140 °C for 36 h with 10 mol% of PCy_3. [d] The reaction was carried out for 2 h without PCy_3.

In conclusion, a new and highly regioselective catalytic procedure was developed. It provides a simple and straightforward ring extension method for constructing substituted benzothiophenes from simple starting materials with high atom economy. Further studies to elucidate the optical and electronic properties of the resulting compounds and extension of the current scope towards the construction of polycyclic heteroaromatic compounds are now under way in our group.



Scheme 4 Plausible reaction mechanism for formation of **3**.

Acknowledgements

We would like to thank the National Natural Science Foundation of China (No. 21072179) for financial support. The authors thank Prof. Feng Shi for language polishing of this manuscript.

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