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Palladium-Catalyzed Synthesis of 2,3-Disubstituted Benzothiophenes via the Annulation of Aryl Sulfides with Alkynes

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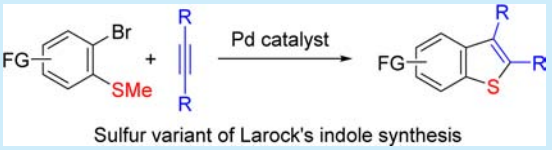
Supporting Information

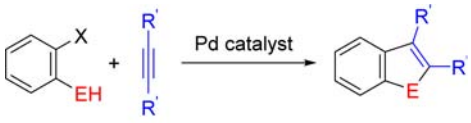
ABSTRACT: A new method has been developed for the synthesis of 2,3-disubstituted benzothiophenes involving the palladium-catalyzed annulation of aryl sulfides with alkynes. This convergent approach exhibited good functional group tolerance, providing rapid access to a diverse array of derivatives from simple, readily available starting materials. This protocol can also be used to synthesize 2-silyl-substituted benzothiophenes, which can be used as versatile platforms for the synthesis of 2,3-unsymmetrically substituted benzothiophenes.



Sulfur variant of Larock's indole synthesis

The catalytic heteroannulation of alkynes is a useful method for the convergent synthesis of a wide range of heteroarenes from simple, readily available building blocks.[1] For example, the palladium-catalyzed annulation of *o*-haloanilines with internal alkynes allows for the rapid construction of 2,3-disubstituted indole derivatives (Larock indole synthesis, Scheme 1, E = NR).[2] This approach was successfully extended to the synthesis of benzofurans by the annulation of the corresponding *o*-halophenol substrates (Scheme 1, E = O).[3] Naturally, it was envisioned that the corresponding sulfur variant would provide a valuable method for the synthesis of benzothiophene derivatives (Scheme 1, E = S), which can be found in numerous π-conjugated organic materials[4] and pharmaceutical agents.[5] However, to the best of our knowledge, there have been no reports in the literature pertaining to the development of a catalytic annulation reaction for the formation of benzothiophenes. As an alternative approach, radical annulation reactions involving the addition of carbon-[6] or sulfur-centered[7] radicals to alkynes have been reported.[8] Although these radical reactions are useful for synthesizing certain types of benzothiophenes, their application has been limited by several issues. For example, none of these methods are applicable to the annulation with an aliphatic alkyne, most likely because propargylic hydrogen can be abstracted by an aryl or thiyl radical intermediate. Moreover, some of these reactions require the use of hazardous reagents, such as peroxides,[6a−c] or a large excess (>5 equiv) of the alkyne.[7b,c] Herein, we report the development of a new method that successfully addresses all of these issues involving the palladium-catalyzed annulation of thiophenol derivatives with alkynes.

Scheme 1. Palladium-Catalyzed Synthesis of Heteroarenes via the Annulation of Aryl Halide Derivatives with Alkynes



E = NR known (Larock indole synthesis)
O known
S NOT achieved

The lack of a sulfur variant of the Larock indole synthesis can be attributed, in part, to the poisoning of the catalyst by the presence of a strongly coordinating SH group. Indeed, our initial attempts to synthesize benzothiophene via the palladium-catalyzed reaction of thiophenol **1-H** with alkyne **2a** afforded **1a** in only 9% yield (Table 1, entry 1). Our previous work involving the synthesis of heterocycles via the cleavage of a carbon−heteroatom bond[9−11] led us to examine the corresponding annulation reaction using sulfide derivatives. Pleasingly, the use of methyl sulfide **1-Me** or phenyl sulfide **1-Ph** led to a dramatic increase in the yield of **1a** (entries 2 and 3). Although switching the PPh_3 ligand to several other common ligands did not lead to an improvement in the yield of **1a**,[12] increasing the amount of PPh_3 to 1 equiv relative to the substrate afforded **1a** in excellent yield. The nature of the base also had a significant impact on the efficiency of this annulation reaction. For example, the use of an amine base instead of Na_2CO_3 generally resulted in a better yield of the desired product in the presence of a catalytic amount of PPh_3 (entries 4−6). Notably, DBU gave the best results of all of the bases examined in the current study. The use of DBU was particularly effective for the annulation with aromatic alkynes such as **2b** (entry 8), which performed much less efficiently when Na_2CO_3 was used as the base (entry 7). The suitability of methyl sulfide **1-Me**, rather than thiophenol **1-H** or phenyl sulfide **1-Ph**, was further corroborated by the low yields of **1b** obtained when DBU was used as the base (entries 9 and 10).

With two different sets of conditions in hand [conditions A: PPh_3 (1 equiv), Na_2CO_3 (3 equiv); conditions B: PPh_3 (30 mol

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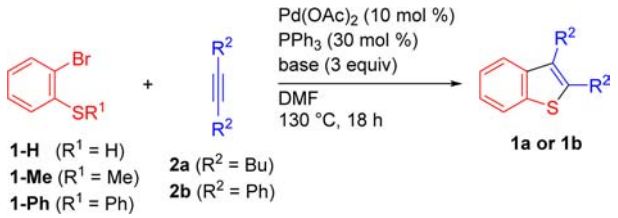
Table 1. Optimization of the Reaction Conditions[a]



entry	R^1	alkyne	base	NMR yield of **1**
1	H	**2a**	Na_2CO_3	9 (35)[b]
2	Me	**2a**	Na_2CO_3	39 (91)[b,c]
3	Ph	**2a**	Na_2CO_3	37 (95)[b]
4	Me	**2a**	Et_3N	65
5	Me	**2a**	DMAP	63
6	Me	**2a**	DBU	79
7	Me	**2b**	Na_2CO_3	6 (20)[b]
8	Me	**2b**	DBU	90[c]
9	H	**2b**	DBU	7
10	Ph	**2b**	DBU	0

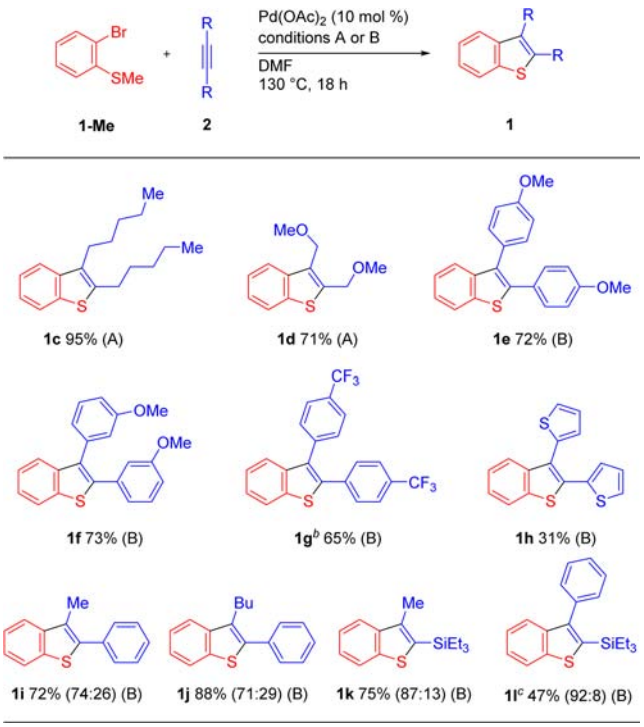
[a]Reaction conditions: **1** (0.30 mmol), **2** (0.45 mmol), $Pd(OAc)_2$ (0.030 mmol), PPh_3 (0.090 mmol), and base (0.90 mmol) in DMF (1.0 mL) at 130 °C for 18 h. The NMR yield was determined using 1,1,2,2,-tetrachloroethane as an internal standard. [b]PPh_3 (0.30 mmol) was used. [c]Isolated yield.

%), DBU (3 equiv)], we proceeded to explore the scope of this palladium-catalyzed intermolecular cyclization reaction using various alkynes (Scheme 2). Pleasingly, these methods allowed us to incorporate alkynes bearing both aliphatic (e.g., **1c** and **1d**) and aromatic (e.g., **1e**, **1f** and **1g**) substituents. 1,4-Dimethoxybut-2-yne can be successfully annulated under our conditions to form **1d**, with an oxygen functionality at the propargylic position remaining intact.[13] As shown in Table 1, the use of DBU as a base (conditions B) allowed for the annulation of an electronically diverse range of aromatic alkynes, as well as alkynes bearing thiophenes (e.g., **2e**). Several sets of unsymmetrical internal alkynes were also examined. In the case of alkynes bearing phenyl and alkyl groups, the phenyl group was preferentially incorporated at the 2-position of the resulting benzothiophene ring (**1i** and **1j**). In the case of alkynes bearing a $SiEt_3$ group, the silyl group was predominantly incorporated at the 2-position of the benzothiophene ring (**1k** and **1l**). In all of these cases, we observed a general trend toward the formation of benzothiophene rings with the larger of the two substituents from the alkyne substrate being incorporated at the 2-position of the product. The regioselectivity observed in this case was therefore similar to that reported for the Larock indole synthesis.[1d]

We subsequently investigated the palladium-catalyzed cyclization reaction of various sulfides with **2a** (Scheme 3). Several common functional groups, including chlorides (**3a**), cyano (**4a**), and ketones (**5a**), were found to be compatible, providing access to a wide range of functionalized benzothiophenes. Moreover, heterocyclic (**6a**) and π-extended (**7a** and **7b**) fused thiophenes can also be assembled successfully. A rapid buildup of increasingly complex ring systems was also possible via the double annulation on the substrates bearing two SMe groups using 2 equiv of alkynes (**8a** and **9a**).

Our annulation protocol was found to be amenable to gram-scale synthesis with a lower catalyst loading (5 mol %) (Scheme 4, top). Furthermore, the silyl-substituted benzothiophenes prepared using this method can serve as useful synthetic

Scheme 2. Pd-Catalyzed Synthesis of Benzothiophene Derivatives from 1-Me and Various Alkynes[a]



[a]Reaction conditions: **1-Me** (0.30 mmol), **2** (0.45 mmol), and $Pd(OAc)_2$ (0.030 mmol) in DMF (1.0 mL) at 130 °C for 18 h. Isolated yields are shown. The ratio in the parentheses refers to that of regioisomers. Compounds denoted A were synthesized under the conditions using PPh_3 (0.30 mmol) and Na_2CO_3 (0.90 mmol). Compounds denoted B were synthesized under the conditions using PPh_3 (0.090 mmol) and DBU (0.90 mmol). [b]**2** (0.90 mmol) was used at 160 °C. [c]**2** (0.90 mmol) was used. Conditions A: PPh_3 (0.30 mmol) and Na_2CO_3 (0.90 mmol). Conditions B: PPh_3 (0.090 mmol) and DBU (0.90 mmol).

intermediates. For example, the TFA-mediated desilylation of **1l** led to the formation of **10**, which represents the formal annulation product of a terminal alkyne. The silyl group in **1l** could also be substituted by various functional groups via halogenation, providing access to a broad range of benzothiophenes bearing different substituents at their 1- and 2-positions.

A proposed mechanism for the palladium-catalyzed cyclization reaction is shown in Scheme 5. The oxidative addition of the C−Br bond in **1-Me** to Pd(0)[14] would give the arylpalladium species **12**, which would subsequently add across the alkyne to form the six-membered palladacycle intermediate **13**. C−S bond-forming reductive elimination[15] from **13** would release the cyclic sulfonium salt **14** with the concomitant regeneration of Pd(0). The methyl group of **14** would be readily cleaved by Lewis basic species present in the reaction mixture (e.g., PPh_3, DMF or an external base), via an S_N2-type substitution process to afford the desired benzothiophene derivative **1**.[6b,c,8c] Indeed, the independently synthesized sulfonium salt **15** gave the demethylation product **16** in high yield when it was stirred in DMF at 130 °C.[12] This result therefore indicates that DMF can serve as a nucleophile required for the C−S bond cleavage. In addition, $MePPh_3^+Br^-$ was detected in the crude reaction mixture by ^{31}P NMR analysis when the reaction was conducted with 1 equiv of

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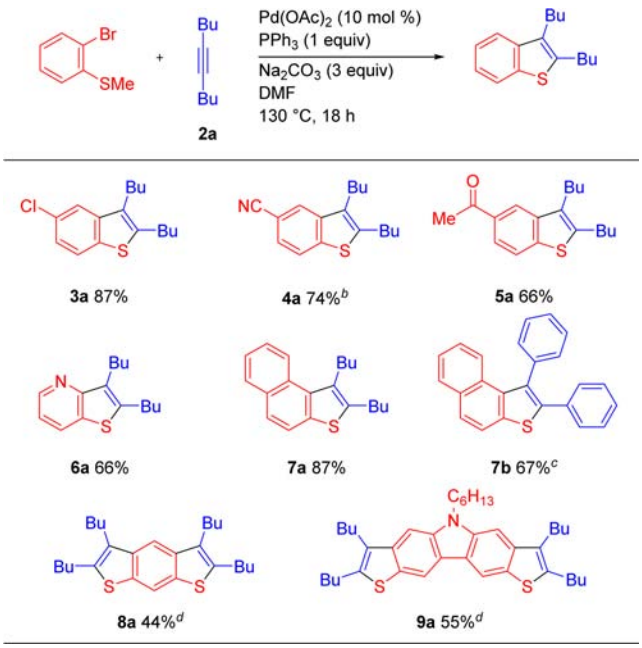
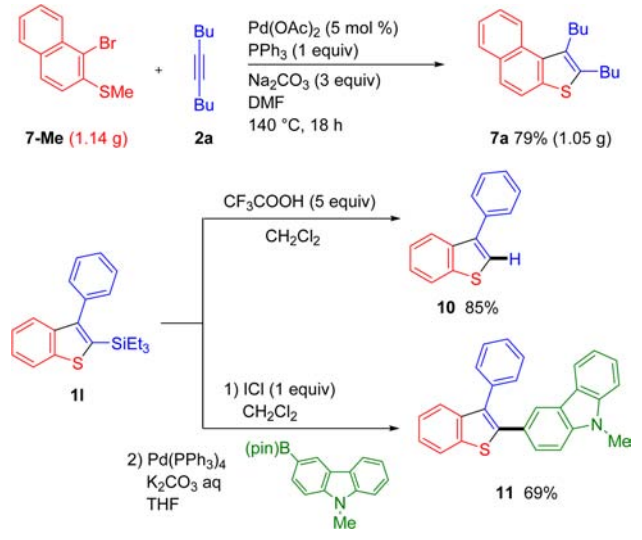
Scheme 3. Pd-Catalyzed Synthesis of Benzothiophene Derivatives from Various Aryl Sulfides and 2a[a]



[a]Reaction conditions: aryl sulfide (0.30 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (0.030 mmol), PPh_3 (0.30 mmol), and Na_2CO_3 (0.90 mmol) in DMF (1.0 mL) at 130 °C for 18 h. Isolated yields are shown. [b]**2** (0.90 mmol) was used at 160 °C. [c]Aryl sulfide (0.30 mmol), **2b** (0.45 mmol), $Pd(OAc)_2$ (0.030 mmol), PPh_3 (0.090 mmol), and DBU (0.90 mmol) in DMF (1.0 mL) at 130 °C for 18 h. [d]Aryl sulfide (0.15 mmol), **2a** (0.90 mmol), $Pd(OAc)_2$ (0.030 mmol), PPh_3 (0.30 mmol), and Na_2CO_3 (0.90 mmol) in DMF (1.0 mL) at 130 °C for 18 h.

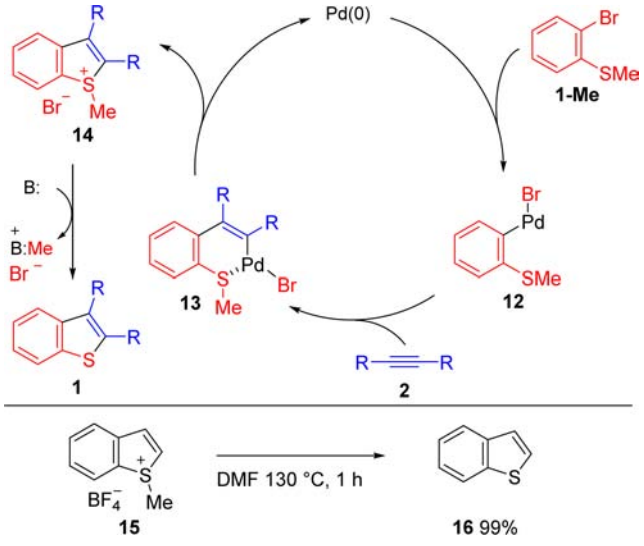
Scheme 4. Scalability and Transformation of Benzothiophene Derivatives



PPh_3,[12] indicating that PPh_3 could also behave as a nucleophile during the cleavage of the sulfonium intermediate **14**.

In summary, we have developed a new convergent method for the synthesis of benzothiophene derivatives from aryl sulfides and alkynes under palladium catalysis. This reaction represents the first reported sulfur variant of the Larock indole synthesis. Notably, this annulation protocol exhibited wide functional group compatibility, allowing for the rapid construction of molecular complexity using readily available building blocks. Based on these attractive features, it is envisioned that this newly developed method will be useful for the diversity-oriented synthesis of benzothiophenes. Further work toward the development of catalytic annulation reactions via the cleavage of a carbon−heteroatom bond is ongoing in our laboratories.

Scheme 5. Possible Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02055.

Detailed experimental procedures and characterization of products (PDF)

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Notes

The authors declare no competing financial interest.

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