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# Direct Benzothiophene Formation via Oxygen-Triggered Intermolecular Cyclization of Thiophenols and Alkynes Assisted by Manganese/PhCOOH

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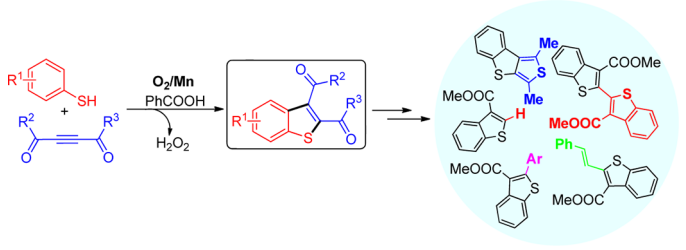
## ABSTRACT




**An intermolecular oxidative cyclization between thiophenols and alkynes for benzothiophene formation has been established. A variety of multifunctional benzothiophenes are synthesized. In addition, we demonstrated that the obtained benzothiophenes can be used for further transformation to give diverse benzothiophene derivatives efficiently and selectively.**

The benzothiophene skeleton is an important heterocycle.[1] Compared with other heteroaromatic rings, especially its analogues benzofuran and indole, the synthetic methods for the formation of benzothiophene skeleton are rather limited.[2] The most common approach is intramolecular cyclizations of α-arylthioketones,[3] *o*-alkynyl (or alkenyl or ynol) benzenthiols,[4] and alkynyl(aryl)thioethers.[5] These reactions are selective and efficient, but prefunctionalized thiophenols had to be synthesized for the cyclizations. The intermolecular cyclization of thiophenols with alkynes is envisioned as the most direct, simple, and atom-economical approach to benzothiophene skeleton. Suprisingly, although oxidative annulations of alkynes with phenols[6] and anilines[7] have been realized for the synthesis

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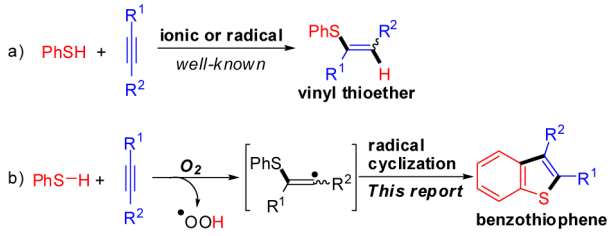
of benzofuran and indole rings, respectively, a similar strategy is not successful for benzothiophene formation,[8] possibly due to the following challenges: (1) the catalyst used could be poisoned by mercapto group in the starting materials; (2) the hydrothiolation of sulfur and hydrogen atoms from thiols to carbon−carbon triple bond is an efficient and feasible reaction (Scheme 1, a).[9] Herein, we disclose an efficient method for synthesis of benzothiophenes by the reactions of thiophenols with alkynes (Scheme 1, b).

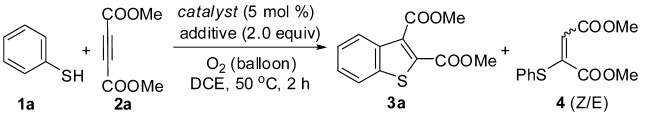
**Scheme 1.** Reaction Pathways of Thiophenol and Alkynes




The reactions of thiophenol **1a** with dimethyl acetylenedicarboxylate **2a** were investigated (Table 1). Delightedly, when **1a** reacted with **2a** under oxygen atmosphere, benzothiophene **3a** was obtained in 55% yield (entry 1). Subsequently, we focused on the metal screening to enhance the efficiency the desired reaction. Metal sources such as $FeCl_3$, $Fe(OAc)_2$, CuCl conducting in this transformation gave a trace amount of **3a**, while the hydrothiolation product of carbon−carbon triple bond **4** was obtained as the major product (entries 2−4). Although $Cu(OAc)_2$ and $CoCl_2$ also did not promote the efficiency of the benzothiophene formation (entries 5 and 6), manganese salts could help this process (entries 7 and 8). Importantly, further studies showed that the extra Brønsted acids as additives influenced the efficiency of oxidative annulations of **1a** and **2a** (entries 9−12, see more examples in the Supporting Information). Benzoic acid gave the best result, and **3a** could be obtained in 84% yield (entry 10).

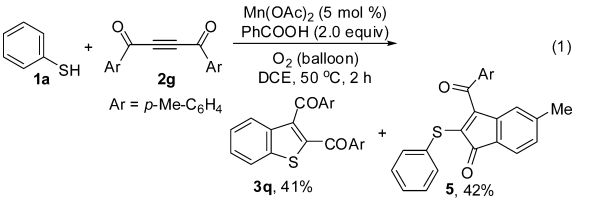
With the optimized reaction conditions in hand, we examined the scope of this transformation by synthesizing a variety of benzothiophenes (Figure 1). Electron-donating and electron-withdrawing substituted thiophenols all gave the desired benzothiophenes **3a**−**h** in good to excellent yields. *Ortho*- or *para*-substituted thiophenols all proceeded well under optimized reaction conditions. However, *m*-MeO-thiophenol **1h** utilized in this transformation showed poor regioselectivity (**3h**:**3h**′ = 45:35). It was found that *β*-naphthiophenol **1i** selectively cyclized at the α-position. A variety of alkynes were also tested to examine the applicability of the current reaction process. Symmetric or unsymmetrical alkynes all reacted well with thiophenol, giving various substituted benzothiophenes. It is noteworthy that thiophenol **1a** selectively reacted with unsymmetric alkyne **2m**, and a single isomer of benzothiophene **3m** was obtained. Monosubstituted benzothiophene **3n** was also generated by the use of terminal alkyne, while a low yield was obtained due to the formation of hydrothiolation products ( > 50% combined yield). Importantly, thiophenol-fused polycyclic aromatic compounds (**3o** and **3p**) could be synthesized utilizing *meta*- or *para*-dithiophenols, demonstrating a potential application in organic materials.[10] Interestingly, thiophenol **1a** reacted with 1,4-diphenylbut-2-yne-1,4-dione **2g** under optimized reaction conditions to give the benzothiophene **3q** in a 41% yield, along with a 42% yield of 2,3-substituted indanone **5** (eq 1). This result indicated that a radical cyclization most likely involves the present transformation.[11]

**Table 1.** Optimization of the Reaction Conditions[a]




| entry | catalyst | additive | **3a**[b] (%) | **4**[b] (%) |
|---|---|---|---|---|
| 1 | | | 55 | 2 (1:1) |
| 2 | $FeCl_3$ | | 4 | 49 (3:1) |
| 3 | $Fe(OAc)_2$ | | 6 | 12 (5:1) |
| 4 | CuCl | | 5 | 78 (9:1) |
| 5 | $Cu(OAc)_2$ | | 25 | 9 (4:1) |
| 6 | $CoCl_2$ | | 57 | 4 (1:1) |
| 7 | $Mn(OAc)_2$ | | 67 | 4 (1:1) |
| 8 | $MnO_2$ | | 64 | 4 (1:1) |
| 9 | $Mn(OAc)_2$ | AcOH | 27 | 13 (1:1) |
| 10 | $Mn(OAc)_2$ | PhCOOH | 84 | 4 (1:1) |
| 11 | $Mn(OAc)_2$ | HCOOH | 77 | 3 (2:1) |
| 12 | $Mn(OAc)_2$ | $CF_3COOH$ | 42 | |

[a] Conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), DCE (5.0 mL), 50 °C, 2 h, under $O_2$ (balloon). [b] Reported yields were based on **1a** and determined by $^1H$ NMR using an internal standard; the ratio of *Z*/*E* isomers is given in parentheses.




To further demonstrate the utility of the present reaction in synthesizing various benzothiophene derivatives, the

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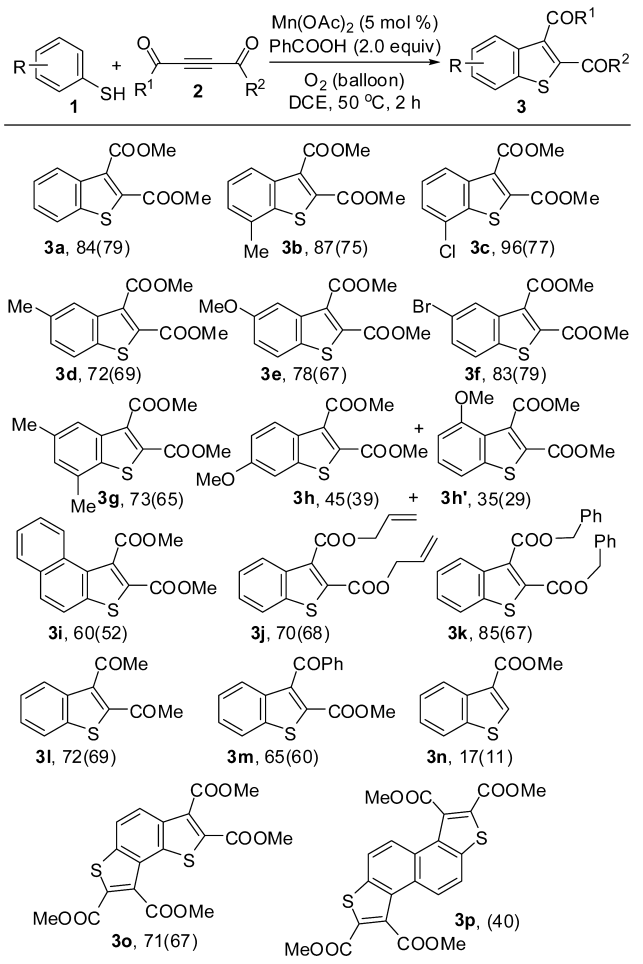
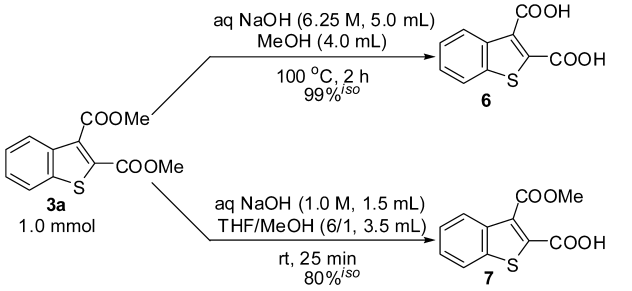


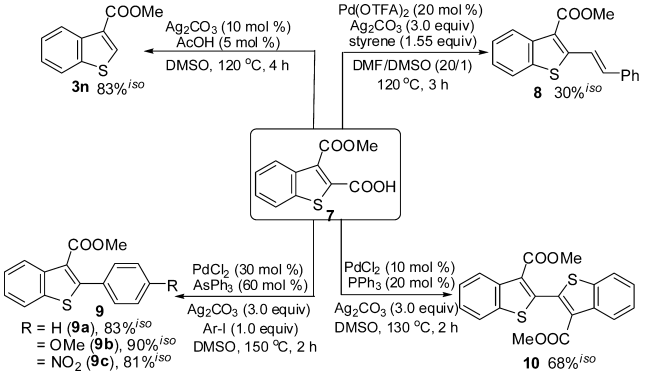

**Figure 1.** Representative results for the oxidative annulation of thiophenols with alkynes. (a) Conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Mn(OAc)_2$ (0.025 mmol), PhCOOH (1.0 mmol), DCE (5.0 mL), 50 °C, 2 h, under $O_2$ (balloon). (b) Reported yields were based on **1** and determined by $^1H$ NMR using an internal standard; isolated yields are given in parentheses. (c) For synthesis of **3o** and **3p**, **2a** (2.0 mmol) and PhCOOH (2.0 mmol) were used.

transformations of the dimethyl benzo[*b*]thiophene-2,3-dicarboxylate **3a** obtained above were then investigated. To our satisfaction, 2,3-dicarboxyl benzothiophene **6** and 2-carboxyl benzothiophene **7** were selectively and efficiently obtained by hydrolysis of **3a** under mild basic conditions (Scheme 2).[12] Using these selective hydrolyzed products, we examined the transformation of the **7** for synthesis of various benzothiophene derivatives through the developed decarboxylative reactions (Scheme 3).[13] The decarboxylation product **3n** was obtained in an excellent yield by a silver-catalyzed protodecarboxylation of **7**.[14] The Heck-type coupling product **8** could be also achieved using $Pd(OTFA)_2$ as a catalyst, although the yield of **8** is not satisfied at this stage.[15] By switching of $Pd(OTFA)_2$ to $PdCl_2$ and adding 0.6 equiv of $AsPh_3$, the decarboxylation−arylation products **9a**−**c** were smoothly synthesized in good yields.[16] To our satisfaction, a decarboxylation−homocoupling product **10** could be generated in moderate yield using $PdCl_2$ as a catalyst and $PPh_3$ as a ligand,[17] which is potentially applicable to synthesize extended $\pi$-conjugation of benzothiophene-based skeletons.

**Scheme 2.** Selective Hydrolysis of **3a**




**Scheme 3.** Synthetic Transformations of **7**




In an effort to realize our interests of generating synthetically useful structures, we also explored the transformation of **3l** (Scheme 4). Conversion of the compound **3l** using Lawesson reagent could easily synthesize the fused cyclic compound **11** in a good yield.[18] Hydrazinolysis of the acetyl-substituted **3l** with hydrazine hydrate afforded the heterocyclic compound **12** under mild reaction conditions. Furthermore, reduction of **3l** with sodium borohydride in

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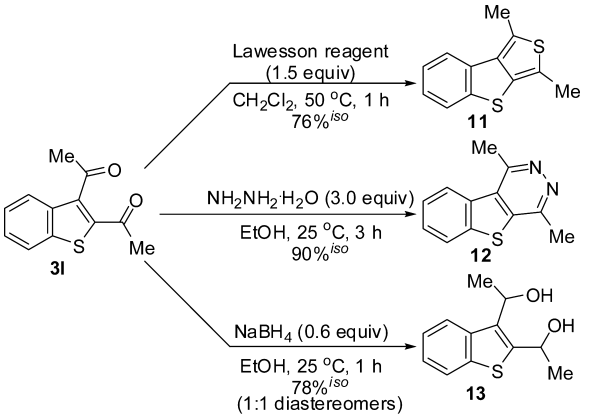
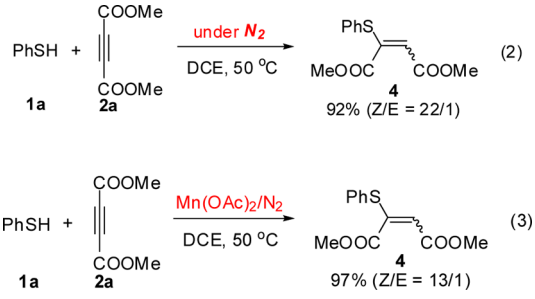
ethanol furnished a 1:1 diastereomer of diol **13** in a good combined yield.

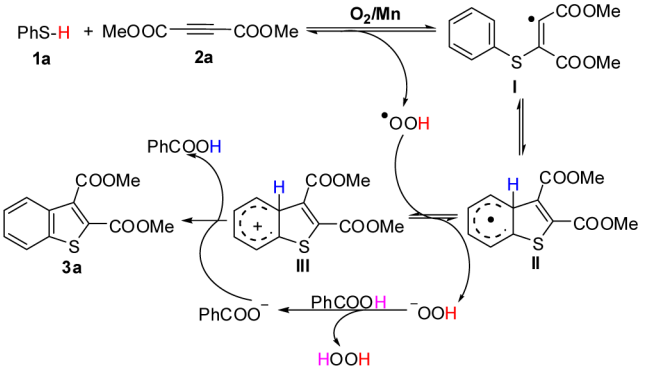
**Scheme 4.** Synthetic Transformations of **3l**




In order to clarify the possible pathways of the present oxidative annulation, the reactions of **1a** with **2a** were performed under nitrogen in the absence and presence of $Mn(OAc)_2$ (eqs 2 and 3). In both cases, vinyl thioether **4** was formed in excellent yields, while **3a** was not observed. Importantly, the transformation of **4** into **3a** could be excluded by the reaction of **4** under standard oxidative cyclization conditions. Furthermore, a series of controlled experiments, the starch iodide tests, were carried out (see details in the Supporting Information). The preliminary results indicated that $H_2O_2$ is generated simultaneously in the course of benzothiophene formation. On the basis of our results and literature reports,[19] a tentative mechanism for the oxidative annulation of thiophenol **1a** with dimethyl acetylenedicarboxylate **2a** to form benzothiophene **3a** is proposed in Scheme 5. Initially, a benzenesulfanyl radical is generated by oxygen-triggered hydrogen abstraction of **1a**, meanwhile releasing hydrogen peroxyl radical. The catalyst, $Mn(OAc)_2$, likely plays a role to activate oxygen and/or stabilize hydrogen peroxyl radical.[20] The addition of thiyl radical to alkyne **2a** leads to the vinyl radical intermediate **I**. The 5-($\pi$-endo)*ortho* cyclization gives the intermediate **II**, which is oxidized to the cationic intermediate **III** by hydrogen peroxyl radical. Benzoic acid plays a proton donor to neutralize hydrogen peroxide anion. Deprotonation of **III** assisted by benzoate leads to the final benzothiophene **3a**.




**Scheme 5.** Tentative Reaction Mechanism




In conclusion, we have developed an efficient and practical protocol for benzothiophene formation through direct intermolecular oxidative cyclization between simple thiophenols and alkynes. A variety of functionalized benzothiophenes was synthesized. In addition, the obtained benzothiophenes also can be used for further transformation, such as selective hydrolysis, decarboxylation/coupling, hydrazinolysis to give valuable compounds.

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**Supporting Information Available.** Representative experimental procedure, characterization of all new compounds, and $^1H$ and $^{13}C$ NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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