Polyaromatic Hydrocarbons

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Metal-Free Synthesis of Benzothiophenes by Twofold C–H Functionalization: Direct Access to Materials-Oriented Heteroaromatics

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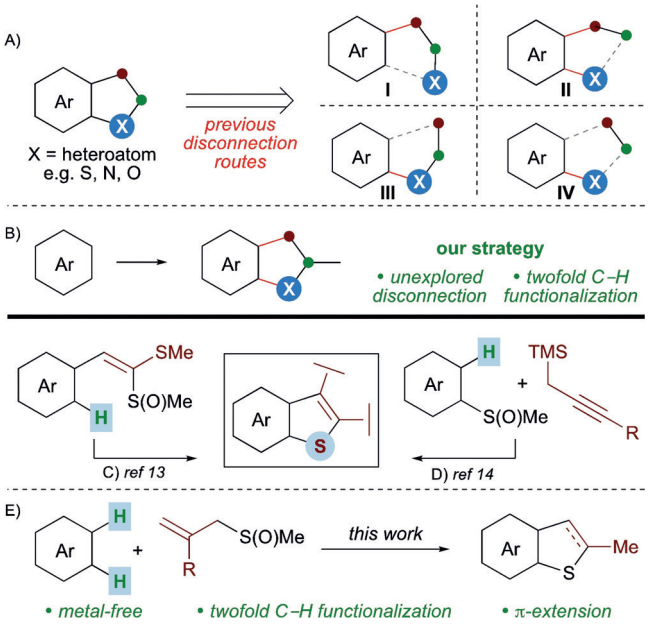
Abstract: *Due to their ubiquity in nature and frequent use in organic electronic materials, benzothiophenes are highly sought after. Here we set out an unprecedented procedure for the formation of benzothiophenes by the twofold vicinal C–H functionalization of arenes that does not require metal catalysis. This one-pot annulation proceeds through an interrupted Pummerer reaction/[3,3]-sigmatropic rearrangement/cyclization sequence to deliver various benzothiophene products. The procedure is particularly effective for the rapid synthesis of benzothiophenes from non-prefunctionalized polyaromatic hydrocarbons (PAHs).*

Heterocyclic systems are fundamental molecular motifs in nature and key components in some of society's most important molecules, including blockbuster drugs.[1] Benzothiophenes are particularly sought-after heteroaromatics as, not only are they found in many natural products and drug molecules,[2] but they are also widely used in organic electronic materials.[3] The most common approaches to benzo-fused heteroaromatic ring synthesis employ a side chain, destined to form the heterocyclic ring, already installed on the benzene ring (red bonds) before fusion occurs to give the target.[4,5] Thus, annulation can occur through; 1) an intramolecular cyclization of an arene bearing a suitable tethering group (**I**, **II**, **III**); or 2) an intermolecular reaction between a heteroatom-substituted arene and a suitable coupling partner (**IV**) (Scheme 1 A).

We considered an alternative approach to benzo-fused heteroaromatic ring synthesis that involves the fusion of arenes, which do not require prefunctionalization, with a suitable coupling partner (Scheme 1 B). This is a direct method for the construction of benzo-fused heteroaromatics that proceeds via the twofold functionalization of arenes at the expense of vicinal C–H bonds. Our approach parallels the C–H annulation of simple arenes with simultaneous construction of a new all-carbon aromatic region, recently termed an annulative π-extension (APEX) reaction.[6] Recent advancements by Itami,[7] Scott,[8,9] and others[10] have showcased this tool, which generally requires transition metals, for the assembly of carbocyclic frameworks. We are unaware of this strategy being used for the grafting of heteroaromatic rings to polyaromatic hydrocarbons (PAHs).



Scheme 1. A) Current routes for heteroarene synthesis. B) Our strategy: direct synthesis of benzo-fused heteroaromatics. C/D) Interrupted Pummerer chemistry for benzothiophene synthesis. E) This work: metal-free synthesis of (dihydro)benzothiophenes.

Interrupted Pummerer reactivity has been utilized in recent years for transition metal-free C–H bond functionalization[11] and for the synthesis of benzo-fused heteroarenes, in particular benzothiophenes.[12] Oshima, Yorimitsu and co-workers have described a method for the preparation of benzothiophenes from aryl substituted ketene dithioacetal *S*-oxides (Scheme 1 C).[13] More recently, we reported the combination of aryl sulfoxides and alkynes in a route to substituted benzothiophenes (Scheme 1 D).[14] These methods are appealing as they avoid the use of platinum group metals, which are costly, at risk in terms of supply, often toxic to living systems,[15] and can affect the performance of organic electronic materials.[16]

Here, we present a method for installing heteroaromatic regions on the edge of aromatic rings (Scheme 1 E). We utilise a one-pot sequence of intermolecular interrupted Pummerer reaction (Figure 1, *i*), [3,3]-sigmatropic rearrangement (Figure 1, *ii*), H^+ promoted cyclization (Figure 1, *iii*) and demethylation (Figure 1, *iv*) to give dihydrobenzothiophene products directly from arenes. Transition metals are not required in this thienannulation reaction,[17] which proceeds

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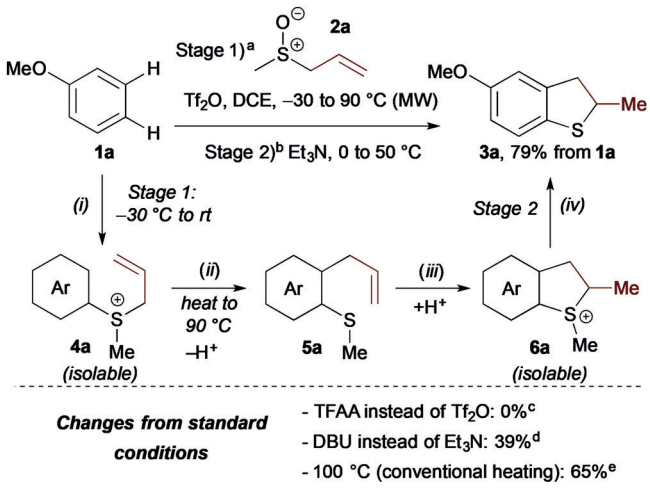
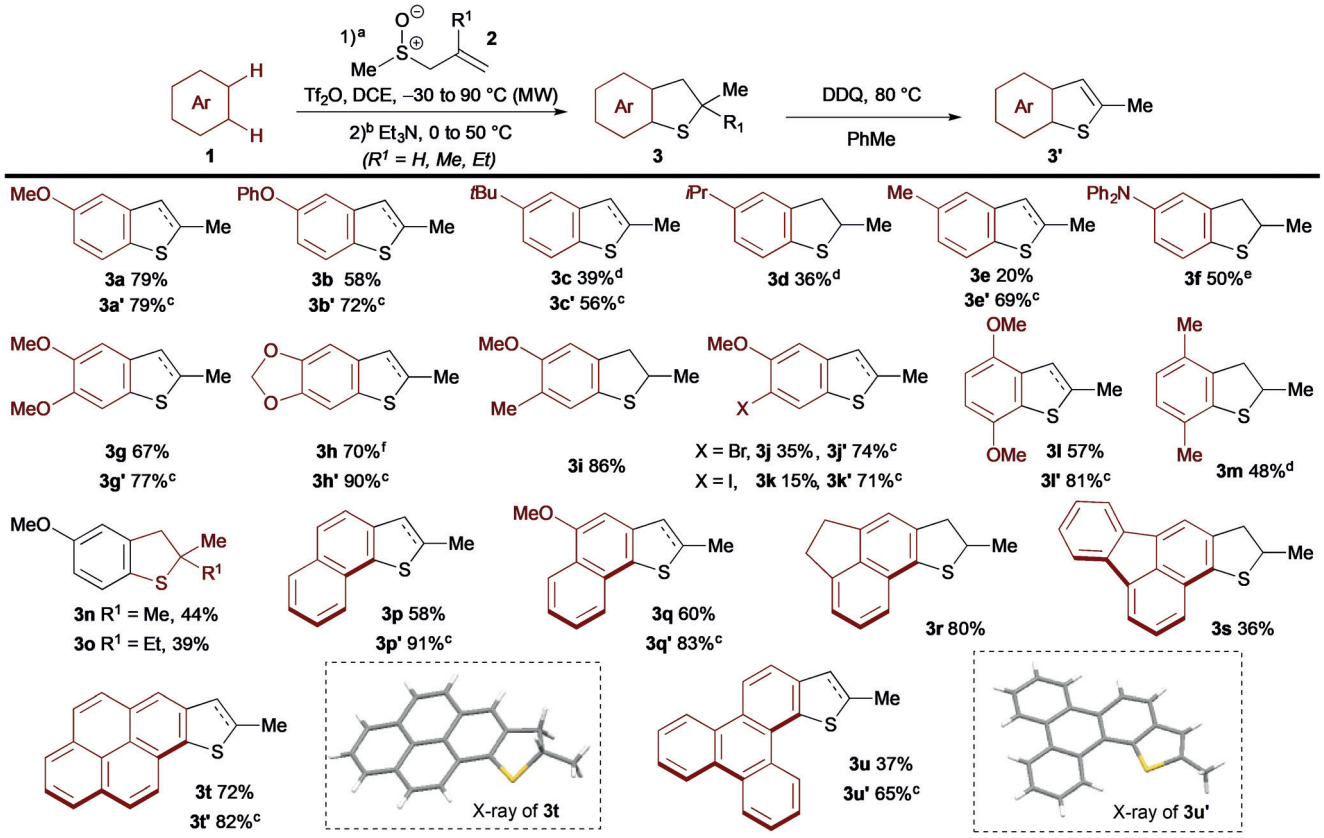


Figure 1. Transition metal-free, one-pot synthesis of 2,3-dihydrobenzothiophenes. [a] Stage 1: **1a** (0.5 mmol), **2** (0.5 mmol, 1.0 equiv), Tf_2O (0.55 mmol, 1.1 equiv), DCE (2.0 mL), −30 °C to 90 °C (MW heating). [b] Stage 2: Et_3N (3.0 mmol, 6.0 equiv), 0 °C to 50 °C. [c] Stage 1: TFAA (0.55 mmol, 1.1 equiv) used. [d] Stage 2: DBU (3.0 mmol, 6.0 equiv) used. [e] Stage 1: T = 0 °C to 100 °C (conventional heating), 18 h. DCE = 1,2-dichloroethane; TFAA = trifluoroacetic anhydride; Tf_2O = trifluoromethanesulfonic anhydride; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

through twofold C–H functionalization to give benzothiophene products. The method is particularly useful for the direct construction of important polyaromatic benzothiophenes.[3]

The first stage of this process relies on an intermolecular interrupted Pummerer reaction[18,19] between an activated sulfoxide, **2a**, and an arene **1a**. (Figure 1, *i*). In contrast to the intramolecular trapping of activated sulfoxides with arenes,[20] intermolecular reactivity is more challenging.[19l,m,r] We isolated the sulfonium intermediate **4a** by activating allyl sulfoxide **2a** with triflic anhydride and subsequent intermolecular trapping with anisole **1a**. Upon heating the mixture, the desired [3,3]-sigmatropic rearrangement of intermediate **4a** (Figure 1, *ii*), followed by spontaneous acid-promoted cyclization (Figure 1, *iii*) was observed. This provided diastereoisomeric sulfonium salt **6a**, which could be detected by ^1H NMR and mass spectrometry. Although the allylthioanisole intermediate **5a** was not observed under the standard reaction conditions, it could be isolated upon addition of an inorganic base to the standard reaction conditions. Addition of a nucleophilic base, NEt_3, to the same reaction pot led to conversion of sulfonium **6a** to the desired 2,3-dihydrobenzothiophene product **3a** in 79% isolated overall yield. Importantly, the transformation of **1a** into **3a** can be accomplished in one-pot and the isolation of intermediates is not required.

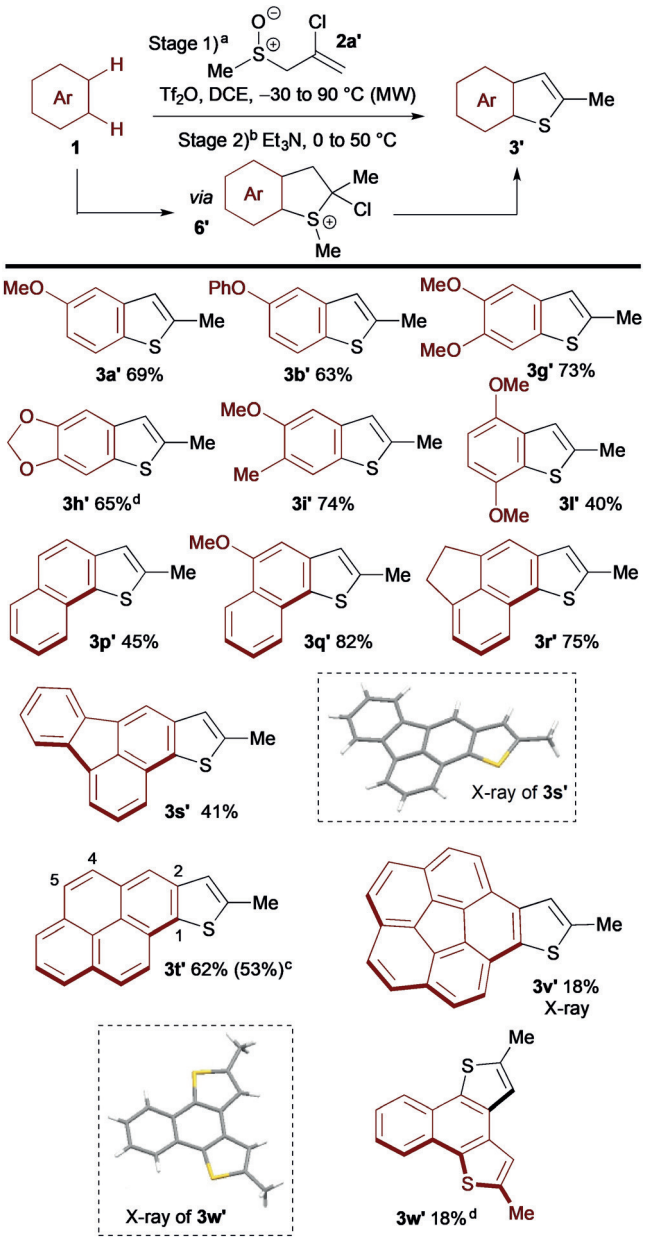


Scheme 2. Scope of the transition metal-free, one-pot synthesis of (2,3-dihydro)benzothiophenes. [a] Stage 1: **1** (0.5 mmol, 1.0 equiv), **2** (0.5 mmol, 1.0 equiv), Tf_2O (0.55 mmol, 1.1 equiv), DCE (2.0 mL), −30 °C to 90 °C (MW heating). [b] Stage 2: Et_3N (3.0 mmol, 6.0 equiv), 0 °C to 50 °C. [c] Oxidation: **3** (1.0 equiv), DDQ (1.1–1.6 equiv), PhMe (1.0 M), rt to 80 °C. Yield from **3**. [d] Stage 1: **1** (2.5 mmol, 5.0 equiv). [e] NMR yield. [f] Stage 1: −30 °C to 60 °C (MW heating). MW = microwave; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

We next set out to determine the generality of the procedure (Scheme 2). As the electron-donating ability of the aryl substituent was reduced, the overall yield of the process decreased (**3a**–**3e**). Toluene represents the current limit of the scope of our process; for example, benzene is unreactive under our current conditions. Aniline derivatives can also be used in the annulation; triphenylamine undergoes annulation to give **3f** in 50% NMR yield. For substrates where *ortho* and *para* substitution could arise, high *para*-selectivity was seen in the sulfenylation event. Disubstituted substrates also gave products in high yields (**3g**–**3m**). Halogen substituents were tolerated under the reaction conditions, but they reduced the yield of the reaction, likely due to a reduction in the nucleophilicity of the arene (**3j**–**3k**). 1,4-Disubstituted arenes reacted to provide sterically congested 4,7-disubstituted-dihydrobenzothiophenes (**3l**–**3m**). Sulfoxide coupling partners bearing alternative R^1 substituents gave 2,2-disubstituted-2,3-dihydrobenzothiophenes (**3n**, **3o**). Finally, polyaromatic hydrocarbons (PAHs) were tested in the reaction. Naptho-fused dihydrobenzothiophenes were prepared in good yield (**3p**–**3r**) and more complex polyaromatics, such as fluoranthrene and triphenylene, were transformed into polycyclic dihydrobenzothiophenes **3s** and **3u** in a highly regioselective twofold functionalization. Pyrene performed well under the reaction conditions to give the desired product **3t** in high yield.

It was clear that the oxidation/aromatisation of the 2,3-dihydrobenzothiophene products would lead to target molecules of considerable interest in the field of organic electronics.[3] By exposing the products **3** to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) we gained access to benzothiophene products **3′** (Scheme 2), including the π-extended benzothiophenes, **3p′**, **3q′**, **3t′** and **3u′**. Interestingly, crystallographic analysis[21] of **3u′** revealed this compound to adopt a slightly helical structure and the interplanar (dihedral) angle between the terminal rings of this [4]-thiahelicene derivative was calculated to be 11.8° (c.f. 26° for the parent [4]-helicene).[22] Overall, our approach constitutes a metal-free synthesis of various multiply substituted benzothiophenes from non-prefunctionalized arenes.

A more direct, one-pot approach to benzothiophenes from simple arenes could be achieved using a modified sulfoxide reagent: submitting readily-available sulfoxide **2a′** and an arene **1** to the standard reaction conditions formed intermediate **6′** and subsequent treatment with base resulted in dealkylation and elimination of chloride to give benzothiophene products **3′** directly (Scheme 3). The use of a chloride substituent as a place-holder for an alkene unit allows an additional oxidation step to be avoided in the formation of benzothiophenes. Furthermore, the equivalent of HCl formed is trapped and removed by the amine base. This constitutes an efficient, one-pot synthesis of benzothiophenes through a metal-free, thienannulative π-extension reaction. Our methodology proved amenable to the annulative π-extension of a range of arenes (**3a′, 3b′, 3g′**–**3i′, 3l′**). Importantly, the use of polyaromatic hydrocarbons such as naphthalene, fluoranthrene, pyrene and corannulene directly delivered a range of interesting polyaromatic benzothiophene products (**3p′**–**3t′**, **3v′**).[3] The regiochemistry of the transformation is also noteworthy—whereas transition metal-catalyzed procedures have shown selectivity for C–H functionalization at the K-region (4,5-positions) of pyrene, we observed exclusive π-extension at the 1,2-positions (**3t′**).[7] We have also demonstrated an iterative functionalization of simple arenes to obtain benzodithiophene (BDT) compounds. Thus, by consecutive C–H functionalization/π-extension we were able to prepare the cross-fused napthodithiophene derivative **3w′**, further illustrating the potential of this methodology for the rapid construction of interesting thienoacene materials.[3,23]



Scheme 3. Scope of the transition metal-free, one-pot synthesis of π-extended benzothiophenes. [a] Stage 1: **1** (0.5 mmol, 1.0 equiv), **2a′** (0.5 mmol, 1.0 equiv), Tf_2O (0.55 mmol, 1.1 equiv), DCE (2.0 mL), −30 °C to 90 °C (MW heating). [b] Stage 2: Et_3N (3.0 mmol, 6.0 equiv), 0 °C to 50 °C. [c] Yield on a larger scale; 0.50 g of **1t** gave 0.36 g of **3t′**. [d] Overall yield from **3p′**.

In conclusion we have developed a direct, metal-free method for the synthesis of benzothiophenes from non-prefunctionalized arenes and allyl sulfoxides. The method utilizes an interrupted Pummerer/[3,3] sigmatropic rearrangement/cyclization sequence to affect twofold C–H functionalization. The utility of the procedure is demonstrated through the facile synthesis of polyaromatic benzothiophenes by a one pot, π-extension process. We expect the process to be of particular value for the preparation of a wide-range of materials-oriented heteroaromatic frameworks.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: annulation · benzothiophene · Pummerer reaction · sulfur · π-extension

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