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Synthesis of C2 Substituted Benzothiophenes via an Interrupted Pummerer/[3,3]-Sigmatropic/1,2-Migration Cascade of Benzothiophene *S*-Oxides

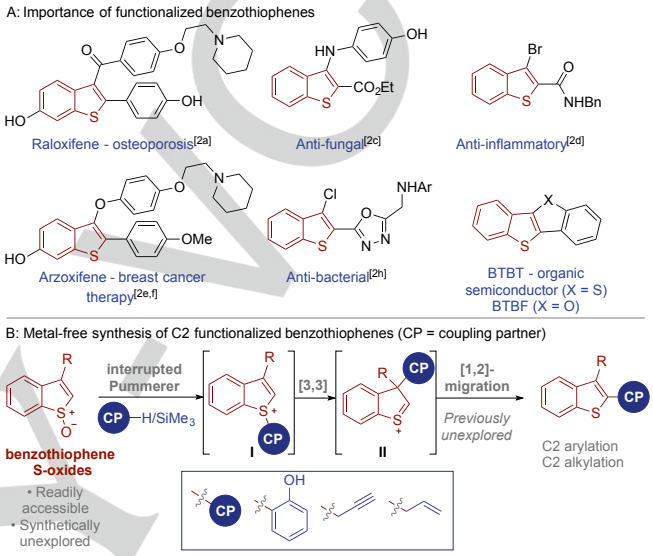
Zhen He, Harry J. Shrives, José A. Fernández-Salas, Alberto Abengózar, Jessica Neufeld, Kevin Yang, Alexander P. Pulis and David J. Procter*

Abstract: Functionalized benzothiophenes are important scaffolds found in molecules with wide ranging biological activity and in organic materials. We describe an efficient, metal-free synthesis of C2 arylated, allylated and propargylated benzothiophenes. The reaction utilizes synthetically unexplored yet readily accessible benzothiophene *S*-oxides and phenols, allyl- or propargyl silanes in a unique cascade sequence. An interrupted Pummerer reaction between benzothiophene *S*-oxides and the coupling partners yields sulfonium salts that lack aromaticity and therefore allow facile [3,3]-sigmatropic rearrangement. The subsequently generated benzothiophenium salts undergo a previously unexplored 1,2-migration to access C2 functionalized benzothiophenes.

Functionalized benzothiophenes are important heterocycles and are commonly found in molecules with wide ranging biological activity,[1,2] and are components in many organic functional materials (Scheme 1A).[3]

Substituted benzothiophenes can be constructed by annulation of either ring or by functionalization of the benzothiophene core.[4] An attractive strategy for the preparation of C2 substituted benzothiophenes involves functionalization of C-H bonds found in the parent heterocyclic motif.[5] Due to the increased acidity of the C2 C-H bond, classical methods for introducing carbon substituents at the expense of C-H bonds at C2 of benzothiophenes require stoichiometric metallation and such processes employ highly basic organometallic reagents.[6] Alternatively, Friedel-Crafts alkylation processes can be used but often give mixtures of C2 and C3 substituted products.[7] In addition to these limitations, both strategies are restricted to the use of electrophilic coupling partners.

Transition metals are able to mediate regioselective C-H arylation at the C2 position of benzothiophenes.[8] However, transition metal catalyzed C2 C-H alkylation of benzothiophenes is considerably more challenging as it requires high temperatures and is only reported in isolated cases.[9] Furthermore, metal contamination remains an issue when certain transition metals are used, especially when the products are destined for human consumption[10] or when trace metal contamination can affect product performance, such as in organic electronics.[11] Thus, a method that selectively introduces a carbon substituent at C2 in place of the C-H bonds of benzothiophenes under transition metal-free conditions is an attractive proposition.



Scheme 1. Importance of functionalized benzothiophenes and our metal-free strategy for their synthesis.

The groups of Yorimitsu,[12] Maulide,[13] Procter[14] and others[15] have contributed to a growing body of work describing the use of sulfonium intermediates[16-18] in the ortho C-H alkylation and arylation of aromatic sulfoxides. We have recently reported the use of benzothiophene *S*-oxides in the synthesis of C3-arylated and –alkylated benzothiophenes via an interrupted Pummerer[19]/[3,3]-sigmatropic rearrangement[16,20] cascade.[21] Herein we report a metal-free synthesis of C2 functionalized benzothiophenes (Scheme 1B). Using readily available, yet synthetically underutilized benzothiophene *S*-oxides as novel starting materials, we engage phenol, and allyl and propargyl silanes in a strategy that delivers C2 substituted benzothiophenes in a regioselective manner under mild conditions. The C2 C-H alkylation and arylation processes operate via an interrupted Pummerer/[3,3]-sigmatropic rearrangement sequence to generate 3,3-disubstituted benzothiophenium salts **II**, that subsequently undergo a previously unexplored 1,2-migration.

In comparison to regular aromatic sulfoxides, benzothiophene *S*-oxides (**1**) have received little attention as synthetic intermediates. Until recently, their use in Pummerer-type processes had not been described[21, 22] and reports of their reactivity was limited to cycloaddition and S_NAr type processes,[23] even though benzothiophene *S*-oxides are readily prepared from the parent benzothiophene by oxidation with H_2O_2 and TFA,[24] or with *m*CPBA and BF_3•OEt_2,[25] without over oxidation.

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We have shown that benzothiophene *S*-oxides **1** serve as precursors to benzothiophenium salts (*cf.* **I**) via an interrupted Pummerer reaction with suitable nucleophilic coupling partners.[21] We proposed that salts **I** would be predisposed to facile [3,3]-sigmatropic rearrangement, and that the 3,3-disubstituted benzothiophenium intermediates (*cf.* **II**) would then be able to undergo 1,2-migration and thus deliver C2 functionalized products. However, questions remained as to whether an existing substituent at C3 would affect the [3,3]-sigmatropic rearrangement, the key process that delivers the coupling partner to the benzothiophene scaffold, and whether selective migration of the coupling partner could be achieved. Notably, while 1,2-migrations of the related 3,3-disubstituted indolenines are well established,[26] the analogous reaction of 3,3-disubstituted benzothiopheniums (*cf.* **II**) has not been previously explored.[27]

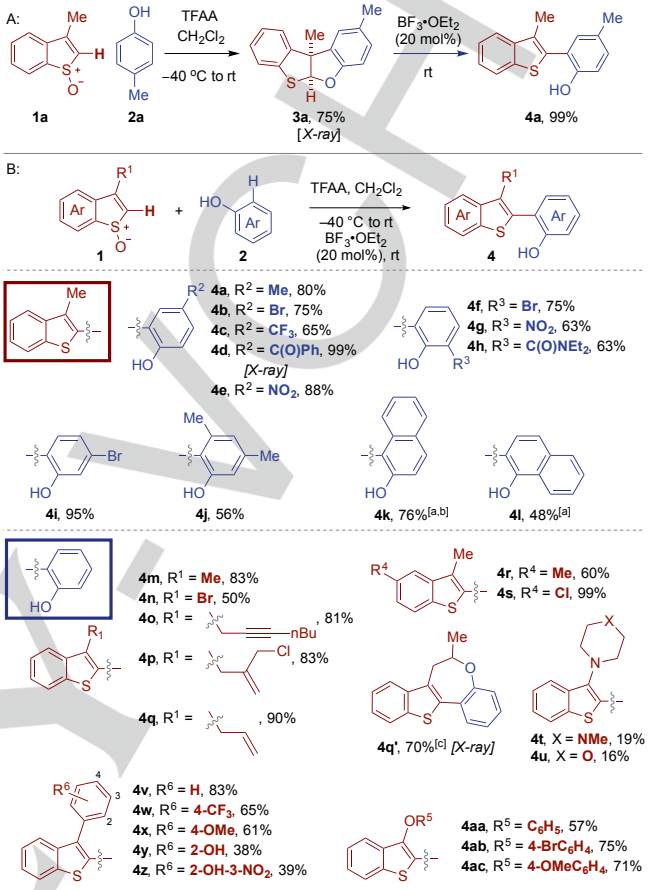
We began by investigating the coupling between C3 methyl benzothiophene *S*-oxide **1a** and *p*-cresol (**2a**) (Scheme 2A). Upon treating **1a** and **2a** with TFAA in CH_2Cl_2, isolable thioacetal **3a** was formed in 75% yield, indicating that the [3,3]-sigmatropic rearrangement occurs efficiently despite the presence of a C3 substituent. Pleasingly, reaction of 3,3-disubstituted thioacetal **3a** with catalytic BF_3•OEt_2 induced opening of the thioacetal and selective 1,2-migration of the aryl group to form the C2 functionalized benzothiophene **4a**.[28]

The coupling of **1a** and *p*-cresol (**2a**) could be carried out in a one-pot procedure, leading to **4a** in 80% isolated yield (Scheme 2B). The scope of the C2 C-H arylation was surveyed by varying the phenol and benzothiophene *S*-oxide coupling partners in the one-pot process. Functional groups, including bromo (**4b**,**f**,**i**), trifluoromethyl (**4c**), keto (**4d**), nitro (**4e**, **4g**), and amido (**4h**) were well tolerated in the phenol coupling partner. In the coupling of 3-bromophenol (formation of **4i**), complete selectivity for the least hindered ortho position was observed. Naphthalen-1-ol and naphthalen-2-ol coupling partners were also amenable to the process (**4k,l**), and the hindered biaryls **4j** and **4k** were formed in good yields. The regioselectivity of the metal-free C2-arylation was confirmed by NMR studies and by X-ray crystallographic analysis of **4d** and **4q'**.[29]

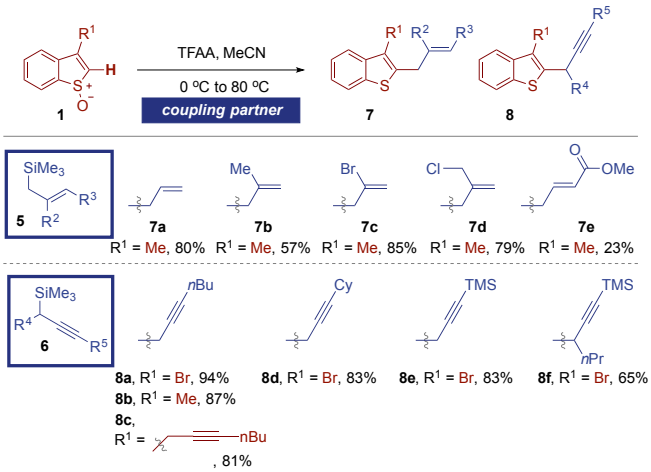
A variety of benzothiophene *S*-oxides **1** was also evaluated in the C2 arylation and we found that the reaction embraces many substitution patterns and functional groups (**4m**-**ac**). Alkyl (**4m**,**r**,**s**), bromo (**4n**), propargyl (**4o**), allyl (**4p**,**q**), and aryl (**4v**-**z**) proved to be compatible C3 substituents. The coupling of C3 allyl benzothiophene *S*-oxide with phenol, gave **4q** selectively under the standard conditions, whereas employing stoichiometric BF_3•OEt_2 and heating allowed for *in situ* cyclization of the phenolic oxygen onto the alkene to form the benzoxepine **4q'**.

Noteworthy is the efficient synthesis of the C3 bromo- (**4n**), and C3 oxygenated- C2 arylated products (**4aa**-**ac**) that bear the key structural features of some biologically active benzothiophenes (see Scheme 1). The analogous C3 nitrogen substituted benzothiophene *S*-oxides were also successfully arylated, albeit in lower isolated yields (**4t,u**).

Crucially, in all cases the phenol coupling partner exclusively migrated from C3 to C2 in the 3,3-disubstituted benzothiophenium intermediate (*cf.* **II**) formed after [3,3]-sigmatropic rearrangement, even when the existing C3 substituent had a comparable migratory aptitude: For example, in **4x** where C3 bears a para-methoxyphenyl group (vide infra).



Scheme 2. Development of the metal-free C2 arylation of benzothiophene *S*-oxide (A) and scope (B). Conditions: **1** (0.1 mmol), CH_2Cl_2 (1.0 ml), –40 °C; TFAA (0.15 mmol); **2** (0.15 mmol), 15 min; rt, overnight; BF_3•OEt_2 (0.02 mmol), rt, 1 h. Isolated yields. [a] THF used instead of CH_2Cl_2. [b] Heated at 45 °C after BF_3•OEt_2 added. [c] Heated at 60 °C after BF_3•OEt_2 added.



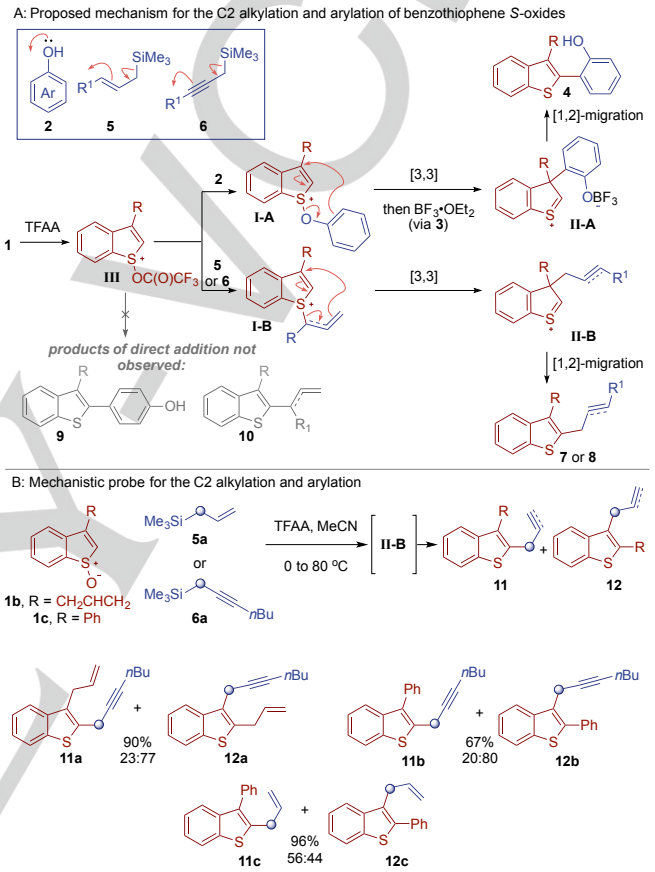
Scheme 3. Scope of the metal-free C2 alkylation of benzothiophene *S*-oxides **1**. Conditions: **1** (0.2 mmol), MeCN (2.0 ml), 0 °C; TFAA (0.4 mmol); **5** or **6** (0.3 mmol), 15 min; 80 °C, 3 h for allylation and 1 h for propargylation; Isolated yields.

We next investigated the coupling of allyl (**5**) and propargyl silanes (**6**) with benzothiophene *S*-oxides **1** in the interrupted Pummerer/[3,3]-sigmatropic rearrangement/1,2-migration cascade for the synthesis of C2 alkylated benzothiophenes (Scheme 3). The allylation proceeded smoothly, even when the allyl silane bore reactive functional groups such as *β*-bromo (**7c**), *β*-chloromethyl (**7d**), and *γ*-ester (**7e**) substituents. Similarly, propargyl silanes **6** containing alkyl (**8a**,**b**,**c**,**d**) and silyl (**8e**,**f**) substituents at the terminal position underwent efficient metal-free cross coupling. In addition, a more challenging, hindered secondary propargyl silane delivered branched product **8f** in 65% yield.

We propose that the metal-free C2 alkylation and arylation reactions follow common mechanistic steps (Scheme 5A). Electrophilic activation of the benzothiophene *S*-oxides **1** with TFAA forms sulfoxonium salts **III**. The coupling partner then engages **III** in an interrupted Pummerer reaction, were phenols (**2**) react through oxygen,[12,17] and allyl (**5**)[14a,b, 18b] and propargyl (**6**) silanes[14c-e] react though the γ-carbon in a S_E' fashion, to deliver sulfonium salts **I**. Sulfonium salts, analogous to **I**, have been formed and observed by NMR in the reaction of activated aryl sulfoxides with allyl and propargyl silanes.[14b,c] However, benzothiophenium salts **I** formed in the present study lack aromaticity[30] and undergo facile charge accelerated [3,3]-sigmatropic rearrangement[16,20] (at or below ambient temperature) and therefore were not observed. The [3,3]-sigmatropic rearrangement delivery mechanism ensures that C-C bond formation occurs in a completely site selective manner in terms of both the benzothiophene core and the coupling partner. Support for the interrupted Pummerer/[3,3]-sigmatropic rearrangement sequence is found in the regiospecificity of the reaction: only ortho substituted phenols are formed in the arylation, and allylated and propargylated products result from double S_E'-type substitution. Indeed, regioisomeric para substituted phenols (**9**), and allylated and allenylated products (**10**) were not observed.

In the case of C2 arylation, C-C bond formation also occurs initially at C3, as shown by X-ray crystallographic analysis of thioacetal **3a** (see Scheme 2A). Upon treating thioacetals **3** with BF_3•OEt_2, we propose that the formed 3,3-disubstituted benzothiophenium **II-A** undergoes 1,2-migration of the coupling partner to C2. Similarly, with allyl and propargyl silanes, intermediate **II-B** undergoes 1,2-migration. As previously reported, when R = H in **II**, rearomatisation occurs and C3 substituted benzothiophenes are formed.[21, 31]

The 1,2-migration, that transfers the coupling partner from C3 to C2, is a unique facet of the cascade. Literature precedent for this mechanistic pathway is scarce,[27] which is likely due to the challenge of synthesizing 3,3-disubstituted benzothiopheniums and their precursors. We therefore sought experimental evidence to shed light on this key process by coupling C3-allyl (**1b**), and C3-Ph (**1c**) benzothiophene *S*-oxides with propargyl (**6a**) and allyl (**5a**) silanes (Scheme 5B). In the case of C3-allyl benzothiophene *S*-oxide **1b** and propargyl silane (**6a**), the major product **12a** is formed as a result of allyl migration along with minor product **11a** arising from propargyl migration. Similarly, major product **12b** was formed as a result of phenyl migration when C3-Ph benzothiophene *S*-oxide **1c** was reacted with propargyl silane **6a**. When **1c** and allyl silane **5a** were reacted, phenyl (**12c**) and allyl (**11c**) migration occurred at similar rates. These results are inline with the hypothesis that 3,3-disubstituted benzothiophenium intermediates **II** are formed in the coupling process and that this is followed by 1,2-migration to effect C2 functionalization. Based on these observations and the results from Scheme 2, we are able to propose an order for migratory aptitudes in the metal-free C2 functionalization process to be: *o*-phenol>aryl~allyl >propargyl>alkyl.

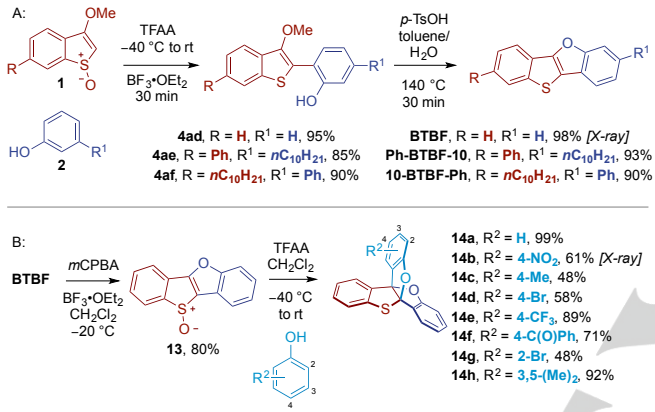


Scheme 5. Mechanistic hypothesis for the metal-free functionalization of benzothiophene *S*-oxides (A) and mechanistic probes (B).

We have begun to examine the synthetic utility of the products of metal-free C2 arylation (Scheme 6). In the field of organic electronics, benzothiophene ladder-type *p*-conjugated molecules such as benzothieno[3,2-*b*]benzothiophene (**BTBT**, see Scheme 1, X = S) and derivatives are key components in organic light-emitting diodes (OLEDs), organic field effect transistors (OFETs), and photovoltaic cells.[3a] Replacing one sulfur atom in **BTBT** leads to benzothieno[3,2-*b*]benzofuran (**BTBF**) type materials that have interesting yet underexplored physical and chemical properties, such as luminescence and liquid crystallinity.[32] Current synthetic strategies towards **BTBF** materials have high step counts or rely on transition metals.[33] Given that metal contamination can adversely affect the performance of organic materials,[11] a short, modular, transition metal-free route to **BTBF** materials is highly desirable. We therefore utilized a

benzothiophene *S*-oxide bearing a C3 OMe substituent and phenol in the coupling to generate benzothiophene **4ad** (Scheme 6A). Upon heating **4ad** under acidic conditions, the phenolic oxygen displaced the C3 OMe group to generate **BTBF** in high yield. Unsymmetrical **BTBT** materials display more uniform crystallinity in thin films which results in enhanced mobility and increased thermal durability.[34] The versatility of our metal free strategy was demonstrated in the modular synthesis of two novel **BTBF** analogues, **Ph-BTBF-10** and **10-BTBF-Ph**, whose structures are analogous to one of the best performing unsymmetrical **BTBT** materials.[34]

Finally, **BTBF** was readily oxidized to the corresponding *S*-oxide **13**. Subsequent metal-free coupling with phenols gave unusual and novel heteropropellane type thioacetal structures, **14a-h** (Scheme 6B).



Scheme 6. Transition metal-free synthesis of BTBF type materials (A) and heteropropellanes **14** (B).

We have described a metal-free, regioselective synthesis of C2 functionalized benzothiophenes. Synthetically underexplored benzothiophene *S*-oxides, prepared by simple oxidation of the corresponding benzothiophenes, serve as novel starting materials in coupling reactions with phenols, and allyl and propargyl silanes. The mechanism of both C2 alkylation and arylation processes operate via an interrupted Pummerer/[3,3]-sigmatropic rearrangement/1,2 migration cascade. Due to the lack of aromaticity in the intermediate thiophene ring in benzothiophenium salts, the subsequent [3,3]-sigmatropic rearrangement is facile. In addition, this rearrangement ensures complete regioselectivity with respect to the benzothiophene core and the coupling partner. The 3,3-disubstituted benzothiophenium salts formed after [3,3]-sigmatropic rearrangement undergo a 1,2-migration to deliver C2 substituted benzothiophenes, a mechanistic pathway that has seldom been reported or employed in a synthetically useful manner. The facile [3,3]-sigmatropic rearrangement and 1,2-migration allows for mild conditions to be employed, which in turn allows the scope of the reaction to be broad and encompass a range of reactive functional groups in both coupling partners.

Given the prevalence of benzothiophenes in bioactive molecules and materials chemistry, we anticipate that these metal-free alkylation and arylation processes will be of broad utility.

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Keywords: Sulfoxides • Pummerer reactions • Sulfur heterocycles • Sigmatropic rearrangement • Cascade reactions

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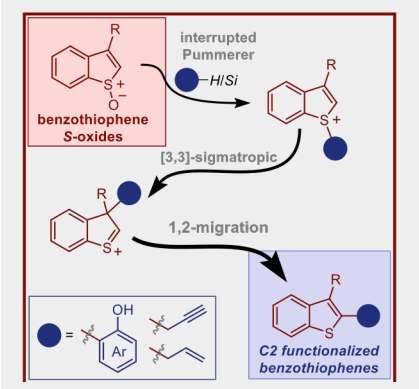
Benzothiophene *S*-oxides are transformed into C2 functionalized benzothiophenes in a cascade sequence involving an interrupted Pummerer, [3,3]-sigmatropic rearrangement, and an unexplored 1,2-migration. The reaction operates under metal-free conditions and delivers C2-arylated, -allylated and -propargylated benzothiophenes.



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Synthesis of C2 Substituted Benzothiophenes via an Interrupted Pummerer/[3,3]-Sigmatropic/1,2-Migration Cascade of Benzothiophene *S*-Oxides