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DOI:

[10.1002/ange.201801982](https://doi.org/10.1002/ange.201801982)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

He, Z., Shrives, H., Fernandez-Salas, J. A., Abengozar, A., Neufeld, J., Yang, K., Pulis, A., & Procter, D. (2018). Synthesis of C2 Substituted Benzothiophenes via an Interrupted Pummerer/[3,3]-Sigmatropic/1,2-Migration Cascade of Benzothiophene S-Oxides. *Angewandte Chemie*. <https://doi.org/10.1002/ange.201801982>

Published in:

Angewandte Chemie

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A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

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International Edition

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Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201801982
Angew. Chem. 10.1002/ange.201801982

Link to VoR: <http://dx.doi.org/10.1002/anie.201801982>
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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 H₂O₂ and TFA,^[24] or with *m*CPBA and BF₃•OEt₂,^[25] without over oxidation.

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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, where phenols (**2**) react through oxygen,^[12,17] and allyl (**5**)^[14a,b,18b] and propargyl (**6**) silanes^[14c-e] react through 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 regioselectivity 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 $BF_3 \cdot OEt_2$, 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**, rearomatization 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.

Acknowledgements

We thank EPSRC (Postdoctoral Fellowships to Z.H. and J.A.F.-S.; Established Career Fellowship to D.J.P.), The University of Manchester (Lectureship to A.P.P.; Studentship to H.J.S.), Novartis (Studentship to H.J.S.) Ministerio de Educación, Cultura y Deporte, Spain (Predoctoral FPU Fellowship to A.A.), and Erasmus+ (placement for J.N.) for their generous support.

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

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COMMUNICATION

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