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Transition-Metal-Free Synthesis of C3-Arylated Benzofurans from Benzothiophenes and Phenols

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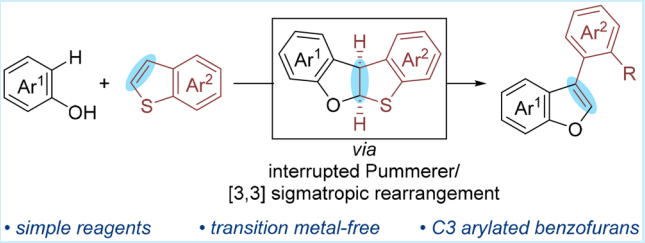
Supporting Information

ABSTRACT: We report a transition-metal-free synthesis of benzofurans from benzothiophenes and phenols that exploits the unique reactivity of sulfoxides. Through a sequence involving an interrupted Pummerer reaction and [3,3] sigmatropic rearrangement, phenols can be combined with readily accessible yet synthetically unexplored benzothiophene *S*-oxides to provide C3-arylated benzofuran products. The products from this approach can undergo subsequent functionalization to gain access to a range of important benzofuran derivatives.

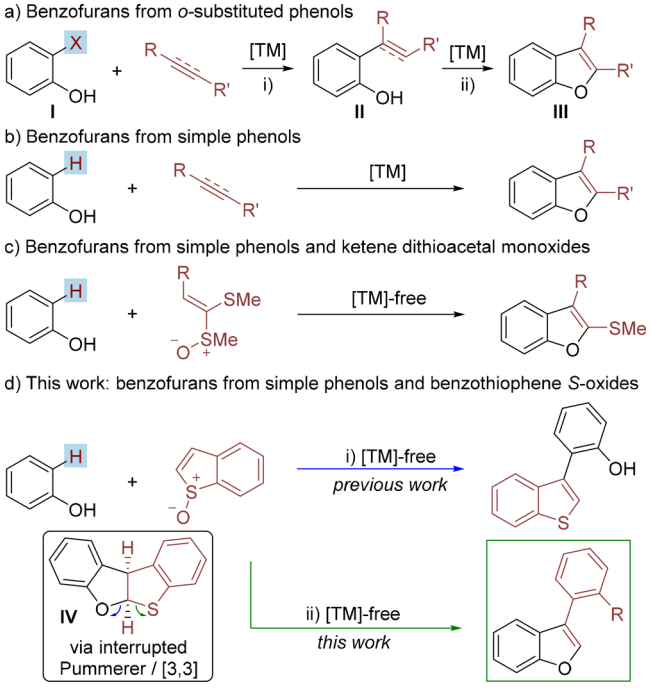


The benzofuran motif is a key structural unit found in a variety of functional molecules, from naturally occurring bioactive compounds to manmade organic electronics.[1] Demand for this important subunit has resulted in a range of methods for its construction.[2] A common route for benzofuran synthesis is through ring closure of *ortho*-substituted phenol derivatives (Scheme 1a).[3] However, the phenol generally requires prefunctionalization (i.e., *ortho*-halogenated phenols **I** are required), and the approach proceeds by (i) attachment of the alkynyl/alkenyl chain via transition-metal-catalyzed cross-coupling (**I** to **II**) followed by (ii) transition-metal-catalyzed ring closure (**II** to **III**). More recently, efforts have targeted a more direct synthesis of benzofurans via C−H coupling of simple phenols with alkenes and alkynes (Scheme 1b).[4] Despite this tremendous progress, most reactions require the addition of transition metals and the development of routes to benzofurans that do not require such metals remains an important goal.

The trapping of nucleophiles by activated sulfoxides through interrupted Pummerer-type processes has begun to spawn a variety of useful transformations.[5] In particular, this mode of reactivity has allowed the facile transformation of C−H bonds in the absence of transition metals.[6] This mode of reactivity has recently been harnessed by Yorimitsu and co-workers for the synthesis of 2-methylthiobenzofurans by reaction of simple phenols with ketene dithioacetal monoxides (Scheme 1c).[7,8]

We have recently described the arylation of benzothiophene *S*-oxides, readily prepared from the parent benzothiophene by simple oxidation, via an interrupted Pummerer-type reaction (Scheme 1d, (i)).[9] In this process, phenol substrates are captured by activated benzothiophene *S*-oxides before [3,3] sigmatropic rearrangement leads to the formation of the *S*,*O*-acetals **IV**. Acid-mediated ring-opening of these intermediates then provides the C3-arylated benzothiophenes through cleavage of the C−O bond. This provides a novel route to functionalized benzothiophenes and, importantly, does not require the use of transition-metal additives. In a proposed divergent approach, we speculated as to whether the intermediate thioacetals **IV** could also allow access to

Scheme 1. (a−c) Current Methods for the Synthesis of Benzofurans and (d) Using Sulfoxides for the Divergent Synthesis of Benzothiophenes and Benzofurans[a]



[a]TM = transition metal.

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benzofuran derivatives through selective cleavage of the C−S bond (Scheme 1d, (ii)).

Here, we describe a transition-metal-free synthesis of C3-arylated benzofurans via the C−H functionalization of simple phenol reagents. Our strategy represents a unique approach in which one molecule, the benzothiophene, is deconstructed for the assembly of another, the desired benzofuran. We also detail how the benzofuran products can undergo further derivatization through the use of desulfinylative cross-coupling methods. This procedure demonstrates that a variety of synthetically useful heterocyclic molecules can be constructed from simple phenols and previously unexploited benzothiophene *S*-oxides.

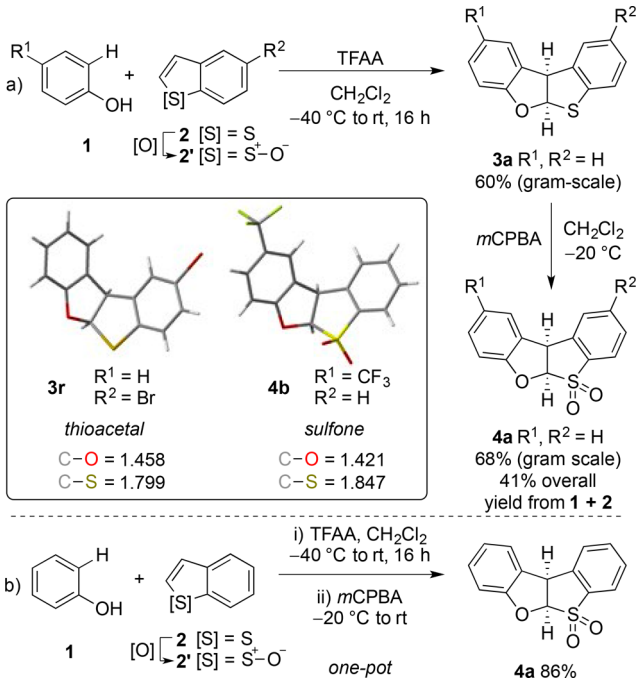
To begin our investigation, we set about synthesizing the key thioacetal intermediate **3a** (Scheme 2). Using our previously reported conditions, we found that thioacetal **3a** could be prepared through activation of the benzothiophene *S*-oxide **2′** with trifluoroacetic anhydride (TFAA) followed by addition of phenol **1**. This provided the thioacetal **3a** in 60% isolated yield. The benzothiophene *S*-oxides **2′** were easily prepared from the corresponding benzothiophenes **2**. After oxidation of the benzothiophene **2**, the crude material was filtered to provide the benzothiophene *S*-oxide **2′** as a solution in CH_2Cl_2 suitable for use in subsequent steps. Importantly, isolation of the sulfoxide was not required.

With the desired thioacetal in hand, we then considered methods for cleaving the C−S bond in favor of the C−O bond. From our previous report, we had observed cleavage of the C−O bond in the presence of acid, which led to the formation of C3-arylated benzothiophene products (Scheme 1d).[9] Our strategy for selective cleavage of the C−S bond was to first oxidize the thioacetal to the thioacetal *S,S*-dioxide. We hypothesized that converting the sulfide to the sulfone would render the C−S bond more susceptible to bond cleavage.[10] Upon treatment of thioacetal **3a** with *m*-CPBA, the desired sulfone **4a** was isolated in 68% yield. Both the thioacetal **3a** and the sulfone **4a** could also be prepared on gram scale without detriment to the yield.

The desired thioacetal *S,S*-dioxide **4a** could also be directly prepared from simple phenol and benzothiophene (Scheme 2b). Thus, following oxidation of benzothiophene **2** and filtration, benzothiophene *S*-oxide **2′** was activated using TFAA before addition of the phenol to form the thioacetal **3a** in situ. The addition of *m*-CPBA to the same pot resulted in the formation of the desired thioacetal *S,S*-dioxide **4a** in 86% overall yield. In general, the one-pot procedure provided greater overall yields than the stepwise procedure.

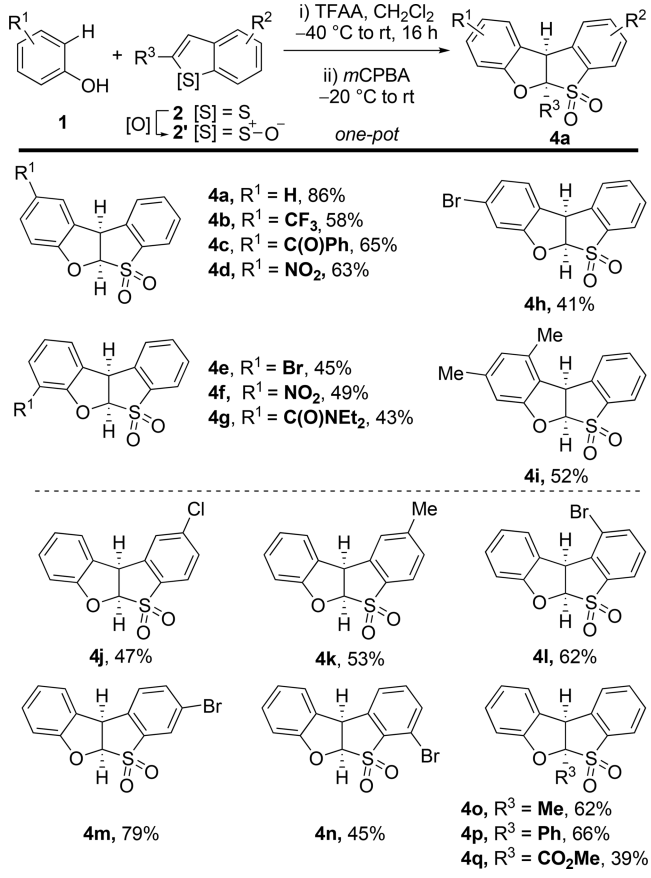
With an efficient method for the preparation of sulfones **4** in hand, we assessed the generality of this sequence. The yields provided in Scheme 3 are the result of the one-pot procedure, though we have also prepared and fully characterized each thioacetal intermediate **3**.[11] A range of electron-deficient phenols reacted well under the reaction conditions (**4b−h**). Substituents in both the *ortho* and *para* positions of the phenol were tolerated, although the *para*-substituted phenols provided superior yields, likely due to less steric hindrance around the

Scheme 2. (a) Preparation, Isolation, and X-ray Crystallographic Analysis of Thioacetal 3a and Thioacetal *S,S*-Dioxide 4a and (b) One-Pot Synthesis of Thioacetal *S,S*-Dioxide 4a[a]



[a]Reaction conditions. [O]: benzothiophene (1.0 equiv), *m*-CPBA (1.2 equiv), $BF_3{\cdot}OEt_2$ (8.0 equiv) then filtration. Sulfone formation: TFAA (1.5 equiv), phenol (1.5 equiv), then *m*-CPBA (2.4 equiv).

Scheme 3. Scope of the One-Pot Synthesis of Thioacetal *S,S*-Dioxides[a]



[a]Reaction conditions. [O]: benzothiophene (1.0 equiv), *m*-CPBA (1.2 equiv), $BF_3{\cdot}OEt_2$ (8.0 equiv) then filtration. Sulfone formation: TFAA (1.5 equiv), phenol (1.5 equiv), then *m*-CPBA (2.4 equiv).

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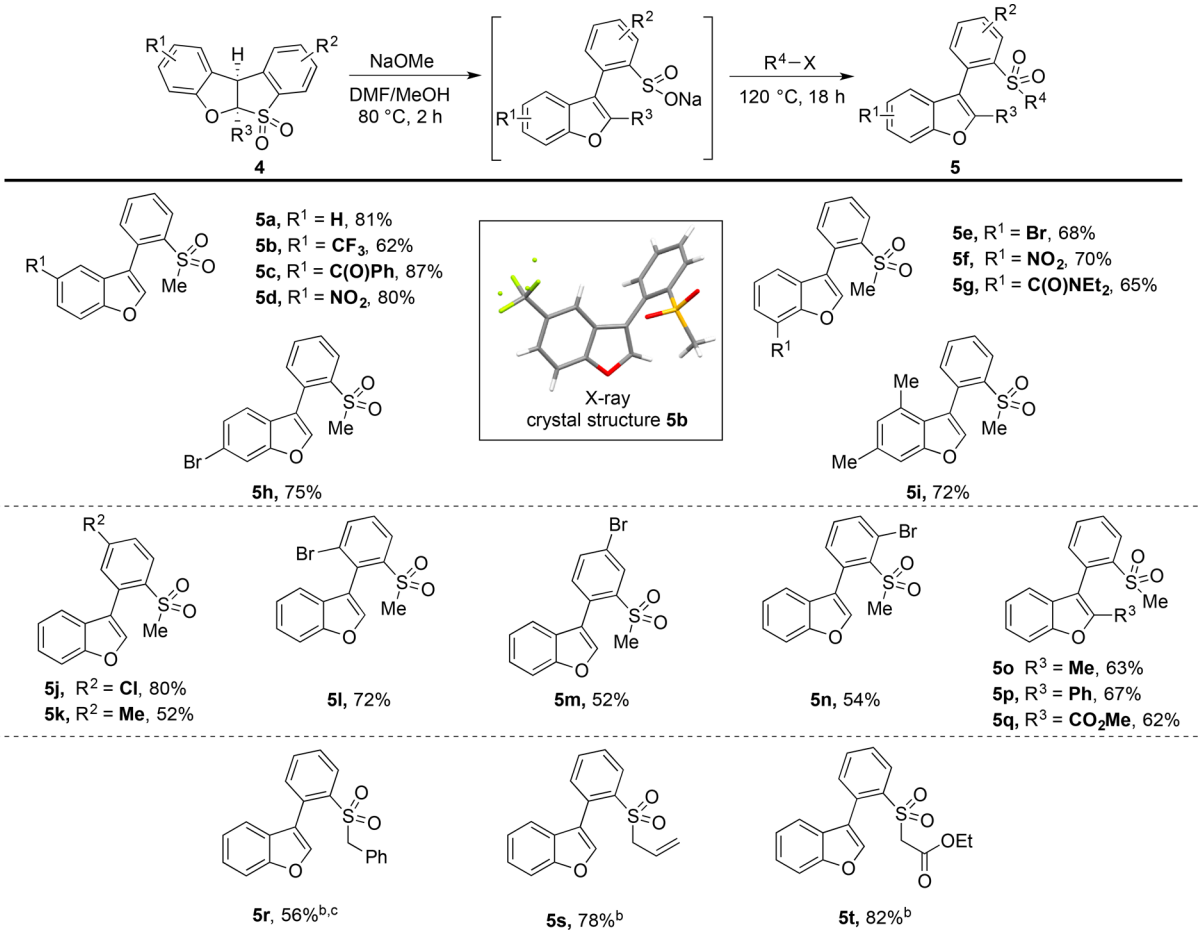
Scheme 4. Scope of the Transition Metal-Free Synthesis of Benzofurans[a]



[a]Reaction conditions: thioacetal *S,S*-dioxide **2** (1.0 equiv), NaOMe (1.5 equiv), MeI (1.5 equiv). [b]R^4–X (3.0 equiv). [c]^{t}BuOK used instead of NaOMe.

point of bond formation (**4a–g**). When *meta*-substituted phenols were used, a mixture of regioisomeric products was formed, although the major isomer (**4h**) could be isolated in 41% yield.[12] The least sterically crowded regioisomer was favored in this case. Phenols bearing electron-donating functional groups were poor substrates in this reaction; however, 3,5-dimethylphenol gave a respectable yield of the desired sulfone **4i**.

We also investigated the scope with respect to the benzothiophene *S*-oxide. As seen for the phenol substrates, a range of electron-donating and electron-withdrawing substituents were tolerated at each position (C4, C5, C6, and C7) of the benzothiophene *S*-oxide (**4j–n**). The use of C2-substituted benzothiophene *S*-oxides led to thioacetal *S,S*-dioxides bearing a quaternary carbon center (**4o–q**). The presence of electron-releasing methoxy groups on the benzene ring of the benzothiophene typically leads to less efficient arylation as the stability and electrophilicity of the activated *S*-oxide is reduced.[9a] In addition to halide substituents, we have previously shown that electron-withdrawing nitro groups are compatible with the arylation.[9a]

Having investigated the generality of the procedure we now looked to collapse these structures to form the desired benzofuran products **5**. We proposed that the C–S bond in the sulfone would be more susceptible to bond cleavage than the C–O bond upon treatment with base. Indeed, analysis of the bond lengths in the crystal structures of the thioacetal **3r** and thioacetal *S,S*-dioxide **4b** supported our hypothesis (Scheme 2). For example, the C–O and C–S bonds of the thioacetal **3r** are 1.458 and 1.799, respectively. Oxidation with *m*-CPBA resulted in the formation of thioacetal *S,S*-dioxide **4b**, which possesses a shorter C–O bond (1.421) and a longer C–S bond (1.847) compared to thioacetal **3r**.

The addition of NaOMe resulted in the formation of the desired C3-arylated benzofuran products (Scheme 4). The sulfinate products were converted in situ to the corresponding sulfones by treatment with MeI. Using these conditions, we transformed each of the sulfones (Scheme 3) to the corresponding benzofurans in good to very high yields. We were pleased to observe the formation of products bearing a halo group (**5e**, **5h**, **5j**, **5l–n**) as these would likely undergo competing reactions in more conventional approaches involving transition metal catalysts. Products **5o–q** revealed that the C2 substituent, which initially resides on the benzothiophene substrate, can be efficiently transferred to the benzofuran. This allowed access to C2,C3-disubstituted benzofurans from simple phenol starting materials. We also demonstrated that a range of electrophiles other than MeI could be used to quench the sulfinate upon completion of the base-mediated bond cleavage event (**5r–t**).

Based on previous reports, we have proposed a mechanism for the formation of the benzofuran products from

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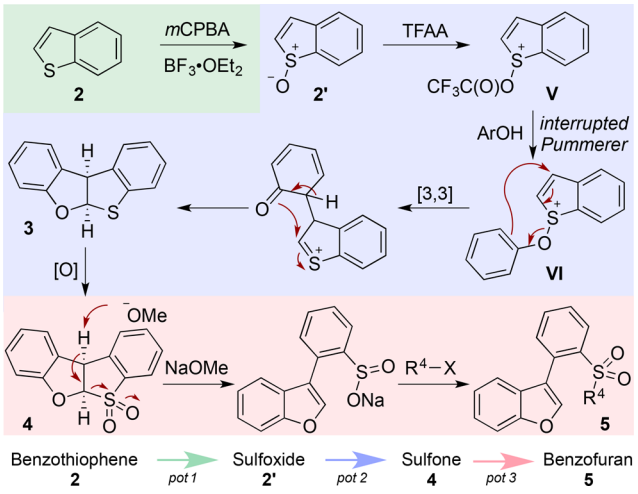
benzothiophenes and phenols (Scheme 5).[9] The process begins with oxidation of the benzothiophene **2** to the

Scheme 5. Mechanism for the Formation of Benzofurans from Phenols and Benzothiophenes[a]



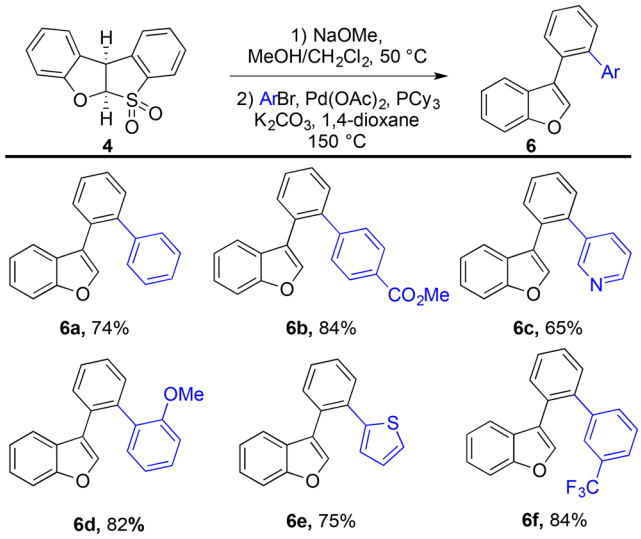
[a]Colors indicate one-pot processes.

benzothiophene *S*-oxide **2′**. The phenol is then captured by the activated sulfoxide **V** in an interrupted Pummerer-type process. The resultant aryloxysulfonium salt **VI** then undergoes spontaneous [3,3] sigmatropic rearrangement and cyclization to form the thioacetal intermediate **3**. Oxidation of the thioacetal provides sulfone **4** before addition of base gives access to the desired benzofuran product **5**.

Sulfinate salts are a class of versatile compounds that have recently found use as coupling partners in palladium-catalyzed cross-coupling reactions.[13] We therefore envisioned a subsequent desulfinative cross coupling of aryl halides with our sulfinate-containing benzofuran products. If successful, this would establish sulfoxides as a traceless activating group for C−H functionalization in this method. Thus, the intermediate aryl sulfinates, formed from treatment of the sulfones **4** with base, underwent desulfinative palladium-catalyzed cross-coupling in the same pot to provide the desired biphenyl benzofurans **6** (Scheme 6). This procedure gave good to very high yields for all substrates tested. A range of aryl bromides were applicable including electron-deficient (**6b**, **6f**), electron-rich (**6d**), and heteroaromatic bromides (**6c**, **6e**). In addition, *ortho*-, *meta*-, and *para*-substituted (**6b**, **6d**, **6f**) substrates all gave similarly high yields. The formation of **6d** was particularly impressive as it represents an efficient process for the cross-coupling of two sterically encumbered *ortho*-substituted reagents.[14] We believe this displays the potential for accessing a range of substituted benzofuran derivatives from benzothiophene *S*-oxides and phenols. Importantly, no trace of the sulfoxide group that is present in the starting material remained upon formation of the product.

We have reported on the synthesis of benzofurans from simple phenol starting materials. The reaction utilizes the unique reactivity of benzothiophene *S*-oxides to promote the C−H functionalization of phenols without the requirement for transition metal catalysts. The approach grants access to a variety of C3-arylated benzofurans that can also undergo further derivatization. In combination with our previous studies, we have shown that a common sulfoxide starting

Scheme 6. Scope of the Palladium-Catalyzed Desulfinative Coupling of Sulfones 4 with Aryl Bromides[a]



[a]Reaction conditions: thioacetal *S,S*-dioxide **4** (2.0 equiv), NaOMe (3.0 equiv), $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %) K_2CO_3 (1.5 equiv), ArBr (1.0 equiv).

material provides selective access to C3-arylated benzothiophenes or C3-arylated benzofurans through a divergent strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03267.

Experimental procedures, X-ray data, and NMR spectra (PDF)

Accession Codes

CCDC 1872998−1872999 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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