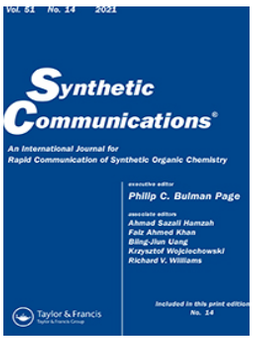

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An efficient approach to 3-thioether-functionalized 2,3-dihydrobenzofurans via a metal-free intramolecular radical cyclization/thiolation cascade reaction

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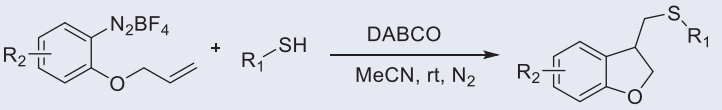
ABSTRACT

A diverse series of 3-thioether-functionalized 2,3-dihydrobenzofurans were prepared by an intramolecular radical cyclization/thiolation cascade reaction of alkenyl-tethered arenediazonium salts with thiophenols under transition-metal-free conditions. The mild and practical reaction conditions tolerated various functional groups and afforded the corresponding 2,3-dihydrobenzofurans in moderate to good yields.

GRAPHICAL ABSTRACT



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Cyclization; dihydrobenzofurans; diazonium salts; phenthiols

Introduction

The structural motifs of 2,3-Dihydrobenzofurans are important in a large number of natural products, bioactive molecules and pharmaceuticals (Fig. 1).[1] These compounds exhibit a wide range of important biological activities, such as antitubercular, antimalarial, anti-cancer, antinociceptive, anti-inflammatory, antifungal and antibacterial activities.[2] Owing to the significant importance of these structural motifs, enormous efforts have been devoted to developing transformations to synthesize the 2,3-dihydrobenzofurans[3] and considerable attention has been focused on the intramolecular cyclization using arenediazonium salts with olefins for the construction of the desired heterocycles.[4] For example, Correia and co-workers[5] reported the first intramolecular Heck reaction of *o*-(allyloxy) arenediazonium salts in the synthesis of dihydrobenzofuran acetic acid derivatives.

Meanwhile, Aryl diazonium salts are valuable precursors of highly active aryl radicals,[6] which can undergo Meerwein reactions with olefins,[7] in the presence of suitable reducing agents. Meijis and co-workers[8] developed the pioneering work on the rapid and regioselective cyclization in the *exo*-mode of aryl diazonium salts with

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ortho-substituents containing double bonds in the 5,6 positions relative to the radical center catalyzed by cooper salts, or with UV-light irradiation in the presence of Bu_3SnH. Then $FeSO_4$,[9] TBAI[10] were successfully employed as the reducing agents for the construction of the functionalized 2,3-dihydrobenzofurans. Wu and co-workers[11] disclosed an electrostatic interaction between the aryldiazonium salt with DABSO and the generated aryl radicals was also applied to the formation of 3-sulfonyl methyl 2,3-dihydrobenzofurans.[12] Polyzos and co-workers[13] described the annulative carbonylation of alkenyl-tethered arenediazonium salts mediated by visible-light photocatalysis in continuous flow.

Aromatic thioethers are present in numerous bioactive molecules, materials and fine chemicals.[14] Therefore, various synthetic procedures have been reported for the construction of aromatic thioethers.[15] Due to the biological importance of 2,3-dihydrobenzofurans and aromatic thioethers, there is an intense demand for the development of convenient pathways for the synthesis of thioether-functionalized 2,3-dihydrobenzofurans. Nakada and co-workers[16] disclosed a Pd-catalyzed carbothiolation for the construction of the desired 2,3-dihydrobenzofurans. It was found that the use of (IPr)Pd(allyl)Cl and a TIPS thioether was key to obtaining the alkyl aryl sulfides in high yield. Stimulated by this work, we embarked a program on radical cyclization/thiolation cascade reaction using arenediazonium salts and thiophenols as starting materials. One advantage over the existing method is that with the radical approach it should be possible to conduct under transition-metal-free conditions (Scheme 1).

Results and discussion

Initially, o-(allyloxy) benzenediazonium tetrafluoroborate **1a** and *p*-Toluenethiol **2a** were chosen as model substrates to explore and optimize the experimental conditions.

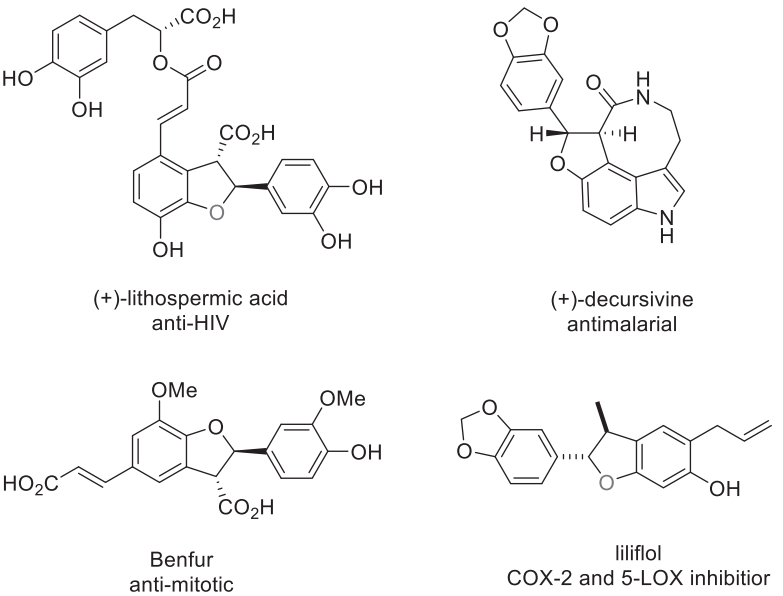
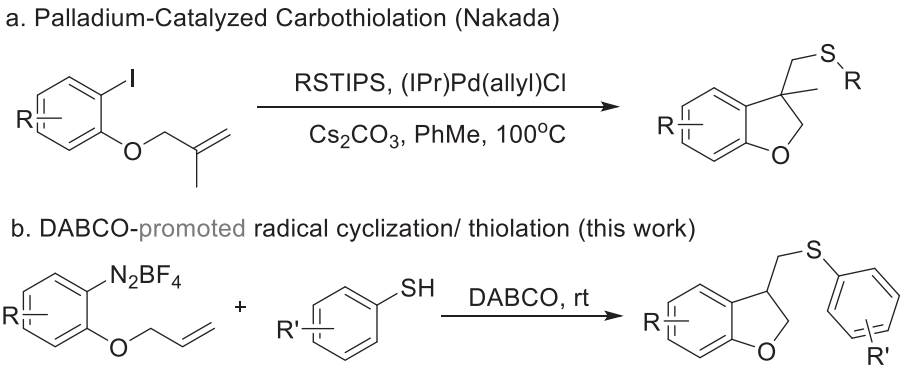


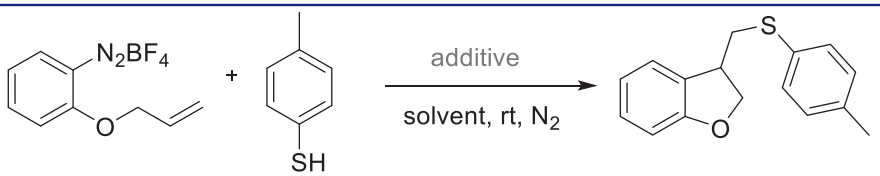
Figure 1. Representative natural products possessing a 2,3-dihydrobenzofuran core.

Initially, according to Studer's work,[10] TBAI was utilized as an additive and the reaction was performed at room temperature overnight under a nitrogen atmosphere (Table 1, entry 1). It was disappointing only a trace amount of the expected 3-thioether-functionalized 2,3-dihydrobenzofurans **3a** was detected and the corresponding diaryl disulfide was isolate as the main product. Then Et_3N was employed instead of TBAI and the desired product 3-((p-tolylthio)methyl)-2,3-dihydrobenzofuran **3a** was obtained in 56% yield (Table 1, entry 2). Encouraged by this result, a number of bases were subsequently studied to improve the reaction yields (Table 1, entries 3–7) and DABCO proved to be best with 79% yield. Decreasing the amount of DABCO from 1.5 equiv. to 1.0 equiv. gave an inferior result (Table 1, entry 8). A slight increase in yield was obtained when the amount of DABCO was increased to 2.0 equiv. or the temperature was raised to



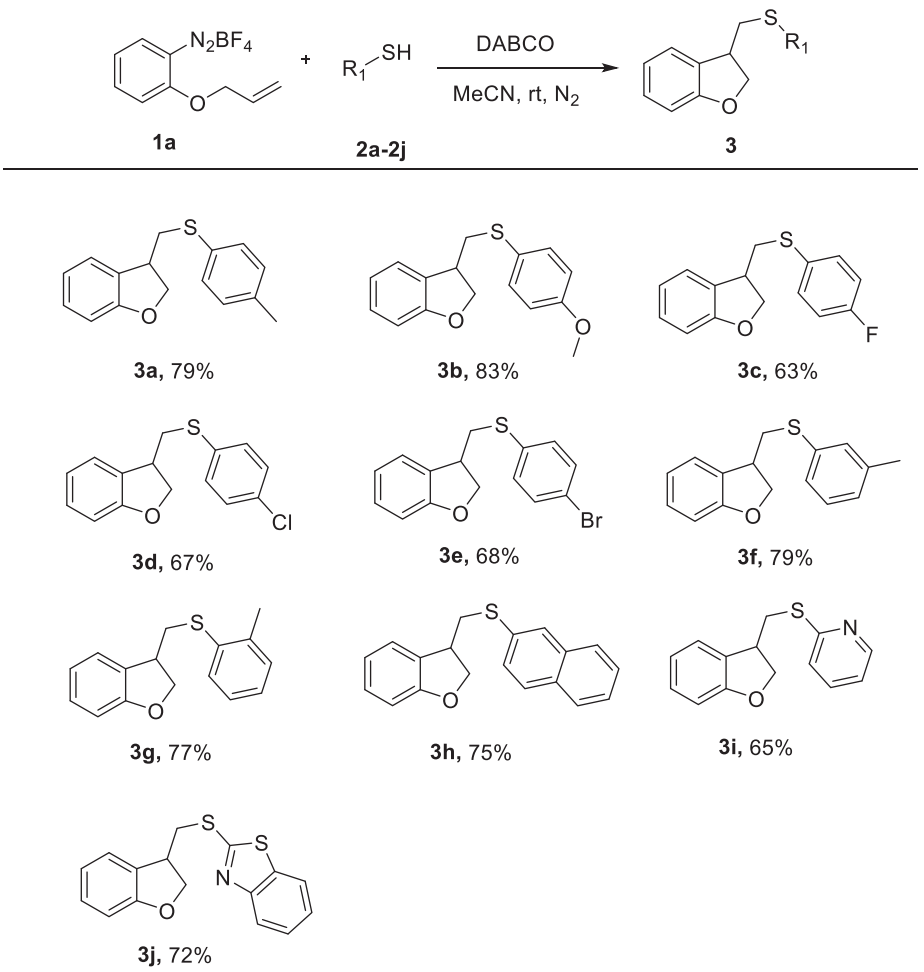
Scheme 1. (a, b) Strategies to 3-thioether-2,3-dihydrobenzofunans.

Table 1. Optimization of conditions.[a]



Entry	Additive (equiv.)	Solvent	Yield (%)[b]
1	TBAI (1.5)	MeCN	Trace
2	Et_3N (1.5)	MeCN	56
3	DBU (1.5)	MeCN	73
4	DABCO (1.5)	MeCN	79
5	Na_2CO_3 (1.5)	MeCN	21
6	NaOH (1.5)	MeCN	36
7	Cs_2CO_3 (1.5)	MeCN	30
8	DABCO (1.0)	MeCN	46
9	DABCO (2.0)	MeCN	80
10[c]	DABCO (1.5)	MeCN	82
11	DABCO (1.5)	DCE	67
12	DABCO (1.5)	DCM	70
13	DABCO (1.5)	MeOH	51
14	DABCO (1.5)	DMF	64
15[d]	DABCO (1.5)	MeCN	29

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol) and additive (0.3 mmol) in solvent (2.0 mL) at room temperature for 12 h under N_2; [b]isolated yield; [c]reaction was conducted at 40 °C; [d]reaction was conducted under air atmosphere.



Scheme 2. Scope of thiophenols. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol) and DABCO (0.3 mmol) in MeCN (2.0 mL) at room temperture for 12 h under N_2; isolated yield.

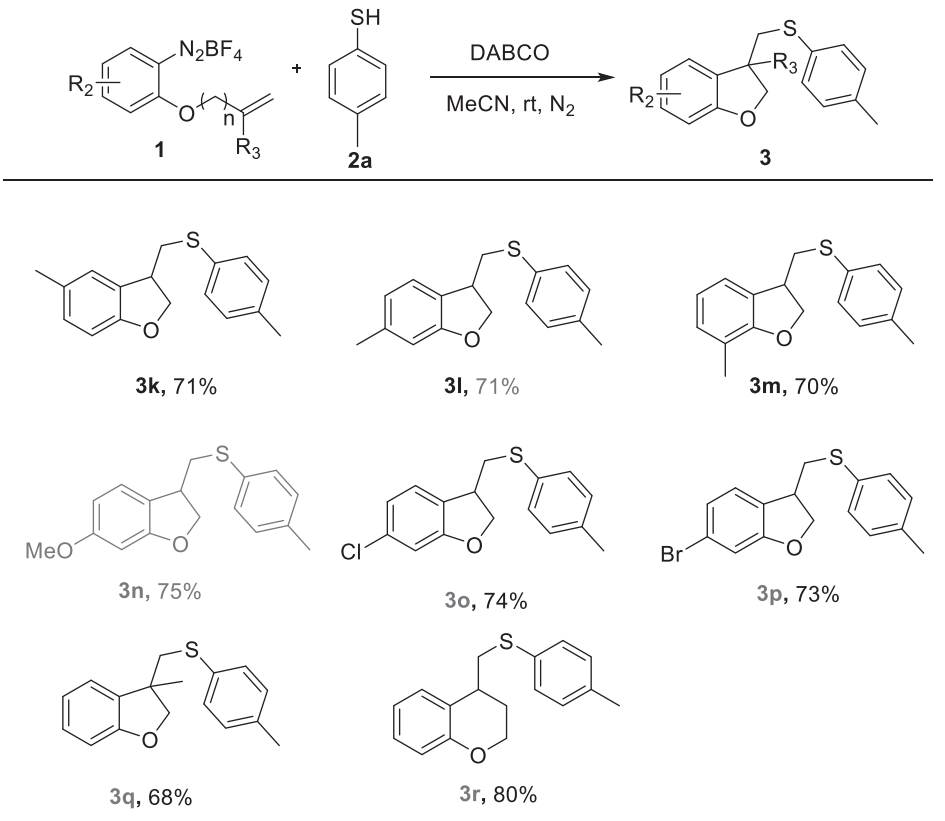
40 °C (Table 1, entries 9–10). However, given the economic and environmental factors, the radical cyclization/thiolation cascade reaction was conducted promoted by 1.5 equiv. DABCO at room temperature. Subsequently, to further explore this reaction, a variety of solvents were screened. Screening revealed that other solvents, such as DCE, DCM, MeOH and DMF, did not provide any better results than MeCN (Table 1, entries 11–14). Moreover, when the reaction was conducted in air, the yield of **3a** decreased dramatically.

After the establishment of the optimal reaction conditions, the scope of thiophenols for the DABCO-promoted intramolecular radical cyclization/thiolation cascade reaction was explored (Scheme 2). Initially, a range of *para*-substituted thiophenols were examined under the optimal conditions in order to study the electronic substituent effect. To our delight, it was observed that both electron-rich and electron-deficient thiophenols could react smoothly and afford the corresponding

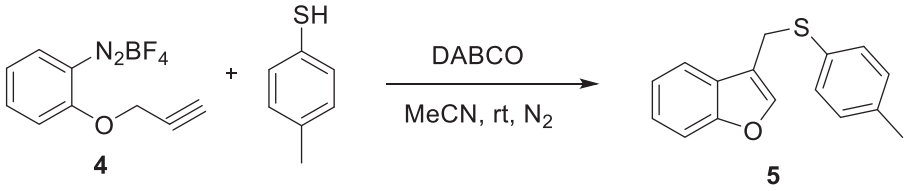
2,3-dihydrobenzofurans **3a–3e** in up to 83% yields, although the reactivity of the thiophenols with electron-donating groups was superior to that with electron-withdrawing groups.

The sterically hindered thiophenol (2-methylbenzenethiol **2g**) could also be used as starting materials for the preparation of 2,3-dihydrobenzofurans **3g** with satisfactory yield, indicating that steric effects had a slight effect on the yields of the intramolecular radical cyclization/thiolation cascade reaction (products **3a**, **3f** and **3g**). Besides, naphthalene-2-thiol was employed and gave product **3h** in 75% yield. To further demonstrated the generality of the reaction, the heteroaromatic thiols pyridine-2-thiol **2i** and benzo[d]thiazole-2-thiol **2j** were investigated and resulted the corresponding 2,3-dihydrobenzofunans **3i** and **3j** in 65% and 72% yields, respectively.

After the scope of thiophenols was examined, a series of arenediazonium tetrafluoroborate salts were investigated (Scheme 3). The electronic and steric variations in the aryl moiety of benzenediazonium tetrafluoroborates were also tested. Both donating and electron-withdrawing substituents afforded the desired radical cyclization/thiolation products in moderate to good yields (**3k–3p**). Remarkably, halogen atoms (Cl and Br groups) were found to be compatible with this transformation, affording 2,3-dihydrobenzofunans **3o** and **3p** in good yields, without the competing products between aryl halides with



Scheme 3. Scope of alkenyl-tethered arenediazonium salts. Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol) and DABCO (0.3 mmol) in MeCN (2.0 mL) at room temperature for 12 h under N_2; isolated yield.



Scheme 4. Construction of 3-thioether-benzofuran.

thiols being detected, thus enabling this methodology more useful for further transformations at the halogenated position. The use of *o*-methallyloxy benzenediazonium tetrafluoroborate **1q** furnished the 3-methyl-3-((*p*-tolylthio)methyl)-2,3-dihydrobenzofuran **3q** in 68% yield successfully, forming a quaternary C centers at the C3 position. Besides, 4-thioether-chromane **3r** could be realized by 6-*exo* cyclization of 1-butenyloxy-tethered arenediazonium tetrafluoroborate, in 80% yield.

To establish the scope of this transformation further, 2-propargyloxy substituted benzenediazonium tetrafluoroborate **4** was next investigated under optimal conditions. Gratifyingly, the expectative product 3-thioether-benzofunan **5** was obtained in 57% yield (Scheme 4).

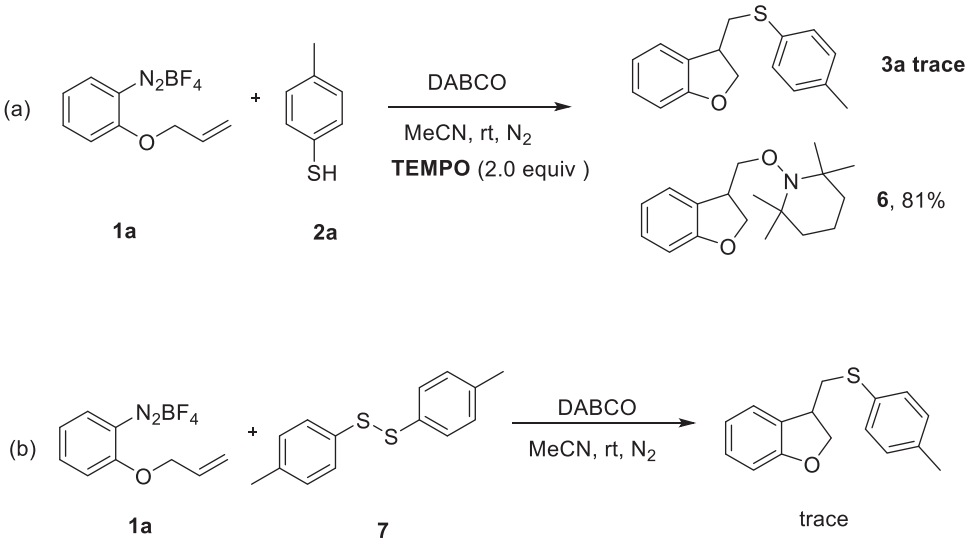
Control experiments were performed to understand the reaction mechanism. When TEMPO was added into the reaction system of *o*-(allyloxy) benzenediazonium tetrafluoroborate **1a** and *p*-toluenethiol **2a** under standard reaction conditions (Scheme 5a), the yield of product **3a** was dramatically decreased. In addition, the cyclized alkoxyamine **6** was obtained in 81% isolated yield[10b]. This result indicates that the reaction mechanism proceeded through a radical pathway. Then, the reaction employed 0.75 equiv. disulfide **7** as starting material was performed and the yield of the desired product **3a** decreased obviously, suggesting that the thiolate anion may play a crucial role in this reaction system (Scheme 5b).

Consequently, based on experimental observations and the literature[6a], a plausible mechanism for this DABCO-promoted intramolecular radical cyclization/thiolation cascade reaction was illustrated (Scheme 6). Initially, deprotonation of phenthiol **2** afforded the thiolate anion **A** using DABCO as organic base. Then a very rapid bimolecular reaction occurred between the diazonium cation **1** and the anion **A**, leading to the covalent intermediate diazo sulfide **B**. Thermal homolysis of intermediate **B** produced the aryl radical **C**, N_2 and sulfenyl radical **E**. The former conducted an intramolecular addition of the aromatic radical to the double bond in 5-*exo* mode rapidly and furnished the primary alkyl radical intermediate **D**, which would then react with sulfenyl radical **E** to form the desired 3-thioether-functionalized 2,3-dihydrobenzofurans **3**.

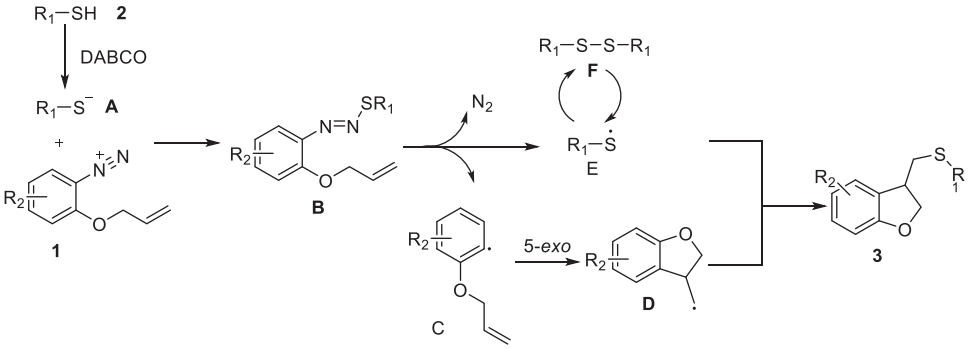
Experimental procedure

General procedure for the preparation of 3-thioether-functionalized 2,3-dihydrobenzofurans

In a flame-dried *Schlenk*-tube, *o*-allyloxy benzenediazonium tetrafluoroborate **1** (0.2 mmol), thiophenols **2** (0.3 mmol, 1.5 equiv.) and DABCO (0.3 mmol, 1.5 equiv.) in MeCN (2.0 mL) were reacted under nitrogen atmosphere. The mixture was stirred at room temperature for 12 h. Upon completion, the solvent was evaporated and the



Scheme 5. (a, b) Control experiments.



Scheme 6. Plausible mechanism.

residue was purified directly by preparative TLC using petrol ether as the eluent to give the corresponding product **3**.

3-((*p*-tolylthio)methyl)-2,3-dihydrobenzofuran (**3a**): colorless oil, 79% isolated yield, ^{1}H-NMR (400 MHz, Chloroform-*d*) δ 7.31 (d, $J = 8.0$ Hz, 2H), 7.25–7.21 (m, 1H), 7.18–7.06 (m, 3H), 6.85 (t, $J = 7.4$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 4.60 (t, $J = 9.0$ Hz, 1H), 4.43 (dd, $J = 9.2$, 5.6 Hz, 1H), 3.66–3.54 (m, 1H), 3.27 (dd, $J = 13.0$, 5.0 Hz, 1H), 2.95 (dd, $J = 13.0$, 9.7 Hz, 1H), 2.33 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.04, 136.92, 131.61, 130.84, 129.93, 129.24, 128.84, 124.55, 120.51, 109.82, 76.13, 41.66, 39.63, 21.07. HRMS (ESI) calcd for $C_{16}H_{17}OS^+$ ($M + H^+$): 257.0995, found: 257.0991.

Conclusion

In summary, a facile approach for 3-thioether-2,3-dihydrobenzofurans starting from *o*-(allyloxy) benzenediazonium salts and thiophenols promoted by DABCO was reported. The reaction proceeded via an intramolecular radical cyclization/thiolation cascade

reaction. The protocol displayed good functional group tolerance and afforded the desired products in moderate to good yields.

The material including full experimental detail, ^{1}H- and ^{13}C-NMR spectra can be found via the "Supplementary Content" section of this article's webpage.

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