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Synthesis of Aryl Sulfides: Metal-Free C−H Sulfenylation of Electron-Rich Arenes

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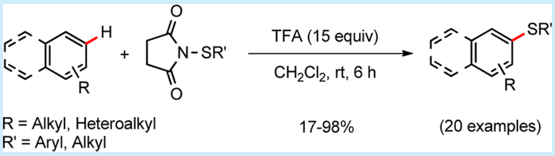
Supporting Information

ABSTRACT: A simple, efficient, and practical metal-free C−H sulfenylation of substituted electron-rich arenes has been developed. This method is highly regioselective, and the corresponding aryl sulfides were obtained in moderate to excellent yields from stable and readily accessible *N*-(alkylthio)- and *N*-(arylthio)succinimides at room temperature in the presence of TFA.



Aryl sulfides are important building blocks in organic synthesis and can be used in material science as well as in the pharmaceutical industry.[1] For example, these scaffolds are found in bioactive natural products such as lissoclibadin 6, an antimicrobial agent,[2] and in bioactive non-natural compounds such as AZD4407, a 5-lipoxygenase inhibitor,[3] or KRP-203, an immunomodulator (Figure 1).[4]

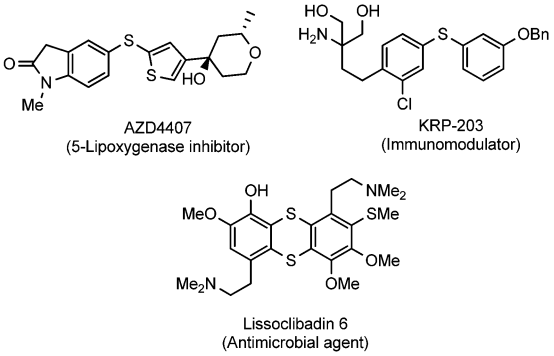


Figure 1. Representative examples of biologically active compounds incorporating an aryl sulfide moiety.

One of the most powerful reactions to introduce a sulfenyl group on an arene is the cross-coupling of thiols or disulfides with aryl halides or pseudohalides, catalyzed by transition metals[1b,5] such as palladium,[6] copper,[7] cobalt,[8] indium,[9] nickel,[10] iron,[11] rhodium,[12] and gold.[13] In addition, aryl sulfides were also prepared by using cross-couplings of arylmagnesium halides[14] or arylboronic acid derivatives[15] with arylsulfur reagents in the presence of suitable catalysts. In the past few years, the development of mild and selective methods for the direct functionalization of C−H bonds has received great attention from organic chemists. Therefore, various methods of direct C−H thiolation, employing an appropriate sulfenylating reagent, have been developed to produce aryl sulfides including copper-mediated alkylthiolation of 2-phenylpyridine with dimethyl disulfide[16] or dimethyl sulfoxide[17] under oxidative conditions. A copper-catalyzed arylthiolation of acidic C−H bonds of heterocycles such as benzoxazoles, benzothiazoles, and indoles has also been achieved with diaryl disulfides or aryl thiols.[18] Recently, the direct arylthiolation of nonacidic arenes was reported with transition-metal catalysts (Fe,[19a] Pd,[19b] or Cu[19c]) using diaryl disulfides[19a,c] or arylsulfonyl cyanides[19b] as sulfenylating reagents. In addition, the C−H sulfenylation of electron-rich arenes was realized under metal-free conditions[20] using aryl thiols or diaryl disulfides in the presence of an oxidizing agent.[21] Recently, Daugulis et al. reported a Cu(II)-catalyzed directed thioetherification of aromatics by C−H activation utilizing a 8-acetamidoquinoline moiety as a chelating group.[22] This bidentate directing group was also used by Shi et al. to perform a nickel-catalyzed sulfenylation of sp^2 and sp^3 C−H bonds.[23] 2-Pyridine, 2-pyrimidine, pyrazole, and oxime ether were also reported as directing groups in rhodium-catalyzed C−H thiolation of arenes with aryl and alkyl disulfides.[24] In the past few years, electrophilic sulfenylating reagents, such as *N*-thiosuccinimides, *N*-thiophthalimides, or trifluoromethanesulfenamides, were utilized to perform the arylthiolation and the trifluoromethylthiolation of (hetero)aromatic C−H bonds. For example, the direct trifluoromethylthiolation of *N*-heteroarenes and aromatics was achieved using *N*-[(trifluoromethyl)thio]phthalimide[25a] and *N*-methyl-*N*-tosyltrifluoromethanesulfenamide[25b] under metal-free and acidic conditions, respectively. Very recently, palladium-catalyzed and Lewis acid catalyzed C−H sulfenylation of unactivated arenes[26a] and phenols[26b] was realized with *N*-(arylthio)succinimides as sulfenylating reagents. Despite some advantages, these established methods suffer from the use of prefunctionalized reagents, harsh reaction conditions, or toxic metal salts as catalysts. As a consequence, the development of efficient and attractive protocols for the formation of C_{Ar}−S bonds, avoiding aryl halides, organometallic reagents, or transition-

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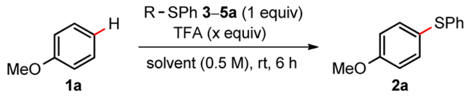
metal catalysts, is of great interest from a viewpoint of atom economy and waste treatment of halide salts and metals. Herein, we report an efficient metal-free regioselective C−H sulfenylation of electron-rich arenes from *N*-(arylthio)-succinimides using trifluoroacetic acid (TFA) at room temperature.

The direct phenylthiolation of anisole **1a** was chosen as a model reaction, and various electrophilic sulfenylating reagents, **3**−**5a**, were employed in the presence of TFA (Table 1). By using diphenyl disulfide **3** in neat TFA (30 equiv) at room temperature, the expected sulfide **2a** was not observed (Table 1, entry 1). On the contrary, when **1a** was treated with *S*-phenyl benzenethiosulfonate **4**, compound **2a** was obtained in 39% yield (Table 1, entry 2), and the yield was increased to 85% by using 1 equiv of *N*-(phenylthio)-succinimide **5a** in neat TFA (Table 1, entry 3). The best yield in **2a** was obtained when anisole was treated with **5a** in the presence of 15 equiv of TFA in CH_2Cl_2 (97%) (Table 1, entry 4). We have to point out that when the reaction was performed with 10 and 5 equiv of TFA, the yield of **2a** decreased slightly (91% and 87% respectively, Table 1, entries 5 and 6). It is worth noting that sulfide **2a** was not formed when a stoichiometric amount of TFA was used (Table 1, entry 7). From the optimization studies, the following conditions were chosen to study the scope of the reaction: arene **1** (1 equiv), *N*-(thio)succinimide **5** (1 equiv), TFA (15 equiv), CH_2Cl_2 (0.5 M) at rt for 6 h.

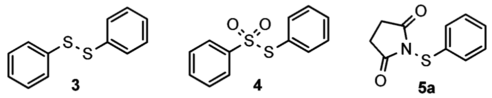
To test the general scope of the arylthiolation, various arenes were subjected to the optimized conditions (Scheme

Table 1. Evaluation of Reaction Conditions



entry	R-SPh	TFA (equiv)	solvent	yield[a] (%)
1	**3**	30	TFA	0
2	**4**	30	TFA	39
3	**5a**	30	TFA	85
4	**5a**	15	CH_2Cl_2	97 (76)[b]
5	**5a**	10	CH_2Cl_2	91
6	**5a**	5	CH_2Cl_2	87
7	**5a**	1	CH_2Cl_2	0

[a]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]Isolated yield given in parentheses. Difference between the isolated and the NMR yields may be due to an overestimation of the NMR yield as well as a loss during the workup/purification process.



Scheme 1. Metal-Free Phenylsulfenylation of Arenes: Scope and Limitation

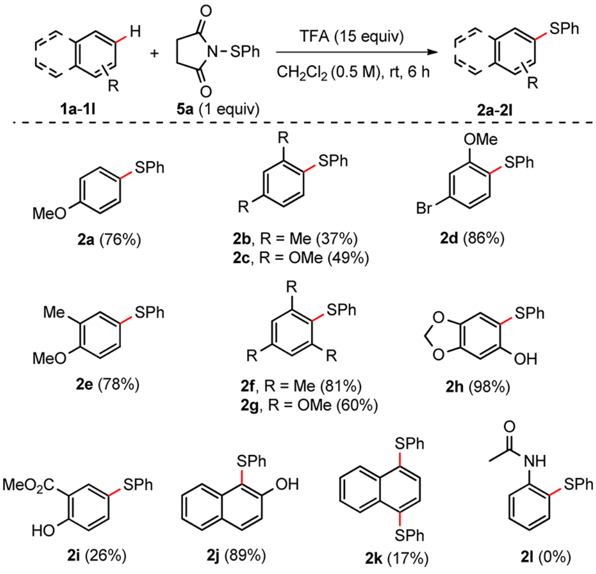
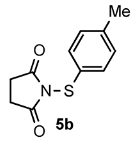
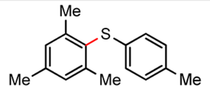
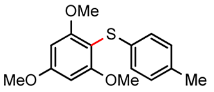
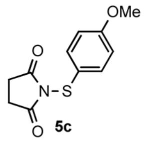
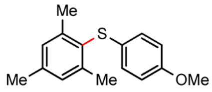
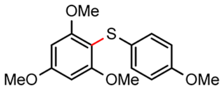
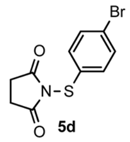
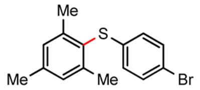
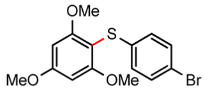
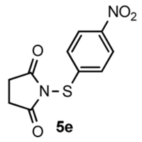
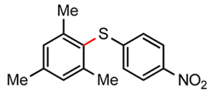
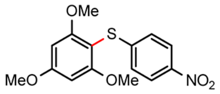
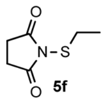
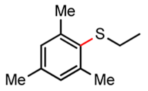
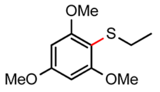


Table 2. Metal-Free Aryl(alkyl)sulfenylation of Arenes: Scope and Limitation

entry	*N*-(thio)succinimide **5**	product **2**	yield (%)
1	 **5b**	 **2m**	91
2		 **2n**	65
3	 **5c**	 **2o**	87
4		 **2p**	61
5	 **5d**	 **2q**	96
6		 **2r**	71
7	 **5e**	 **2s**	0
8		 **2t**	47
9	 **5f**	 **2u**	41
10		 **2v**	71

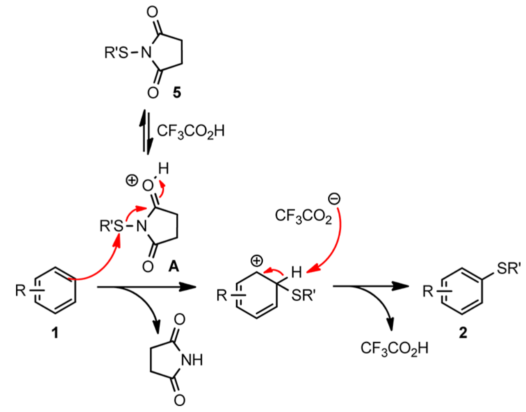
1). The sulfenylation of substituted arenes was regioselective in accord with Holleman's rules.[27] The arylthiolation of anisole **1a** provided the corresponding methoxyphenyl sulfide **2a** in 76% yield. When the arenes were substituted with two electron-donating groups in a relative *meta* position, the yields in the corresponding sulfenylated arenes **2b** and **2c** were obtained in modest yields, 37% and 49%, respectively.[28] 3-Bromoanisole **1d** gave *o*-(phenylthio)anisole **2d** with a good yield of 86%. When anisole was substituted by a methyl group at the *ortho* position as in **1e**, the corresponding sulfenylated compound **2e** was isolated in 78% yield. The arylthiolation of arenes enriched by three electron-donating groups afforded the thiolated products **2f**, **2g**, and **2h** in 81%, 60%, and 98% yield, respectively. In the case of phenol **1i**, the presence of an electron-withdrawing group at the *ortho* position is detrimental to the yield, as the sulfenylated arene **2i** was isolated in a low yield of 26%. Interestingly, 2-naphthol **1j** was sulfenylated at the C1 position leading to diaryl sulfide **2j** in high isolated yield (89%). However, naphthalene furnished the corresponding diarylthiolated compound **2k** in a poor yield of 17%. We have to point out that no product was formed when acetanilide **2l** was subjected to the optimized conditions.

In addition to the sulfenylation of electron-rich arenes with **5a**, we have examined the reactivity of various *N*-(arylthio)-succinimides **5b**−**5f** using mesitylene **1f** and 1,3,5-trimethoxybenzene **1g** as the substrates (Table 2). When *N*-(tolylthio)-succinimide **5b** was used, sulfenylated arenes **2m** and **2n** were obtained in 91% and 65% yield, respectively (Table 2, entries 1 and 2). Both electron-donating, such as a methoxy, and moderate electron-withdrawing groups, such as a bromine, on the arylthio moiety were tolerated and afforded the corresponding diaryl sulfides (**2o**, **2p** and **2q**, **2r**) in good yields (Table 2, entries 3−6). Furthermore, when a strong electron-withdrawing group was present on the arylthio moiety, such as a nitro group (**5e**), mesitylene **1f** did not react under the optimized conditions (Table 2, entry 7), but on the contrary, 1,3,5-trimethoxybenzene **1g** afforded the corresponding sulfenylated derivative **2t** in a moderate yield (47%) (Table 2, entry 8). The low yields obtained for the diaryl sulfides **2s** and **2t** could be explained by the short lifetime of the *N*-(arylthio)succinimide **5e** under strong acidic conditions. The reaction was also performed with *N*-(ethylthio)succinimide **5f**, which led to aryl alkyl sulfides **2u** and **2v** in 41% and 71%, respectively (Table 2, entries 9 and 10).

To rationalize the observed results, a mechanism can be proposed for this metal-free C−H sulfenylation induced by TFA. When arenes **1** are treated with an *N*-(arylthio)- or *N*-(alkylthio)succinimide **5** in the presence of TFA, the succinimide moiety is protonated, generating an electrophilic thio intermediate **A** which can undergo a nucleophilic attack of the electron-rich arene to produce the expected sulfenylated product **2** and succinimide as the byproduct (Scheme 2).

In summary, we have demonstrated that TFA can promote direct C−H sulfenylation of electron-rich arenes using readily available *N*-(arylthio)- and *N*-(alkylthio)succinimides as sulfenylating reagents. This metal-free reaction is highly regioselective, affording sulfenylated arenes in moderate to excellent yields. In the future, the developed method will be utilized in the synthesis of biologically active compounds incorporating the diaryl sulfide moiety.

Scheme 2. Possible Mechanism for the Sulfenylation of Arenes



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01889.

Experimental procedures, characterization, and ^{1}H and ^{13}C NMR spectra of isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(28) The modest yields obtained for **2b** and **2c** could be due to the formation of bis-sulfenylated arenes (observed by GC/MS analysis of the crude reaction mixture) among other compounds. The corresponding C2-sulfenylated arenes were only detected in trace amounts by GC/MS.