Synthetic Photochemistry

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Visible-Light-Accelerated C–H Sulfinylation of Heteroarenes

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Abstract: *Heteroaromatic sulfoxides are a frequent structural motif in natural products, drugs, catalysts, and materials. We report a metal-free visible-light-accelerated synthesis of heteroaromatic sulfoxides from sulfinamides and peroxodisulfate. The reaction proceeds at room temperature with blue-light irradiation and allows the C–H sulfinylation of electron-rich heteroarenes, such as pyrroles and indoles. An electrophilic aromatic substitution mechanism is proposed based on the substrate scope, substitution selectivity, and competition experiments with different nucleophiles.*

The C–H acylation of aromatic compounds is an important transformation in organic synthesis, and a classic reaction for the synthesis of aromatic ketones is the electrophilic Friedel–Crafts acylation. The analogous sulfinylation reaction is, surprisingly, much less developed and explored despite the importance of aromatic sulfoxides, which are typical motifs in natural products,[1] drugs,[2] herbicides,[3] and performance materials.[4] Several proton-pump inhibitors containing sulfoxides (Figure 1) were among the worldwide most sold pharmaceuticals in 2011[5] and 2013.[6] Sulfoxides also find applications in organocatalysis,[7] and as ligands in transition-metal-catalyzed reactions.[8]

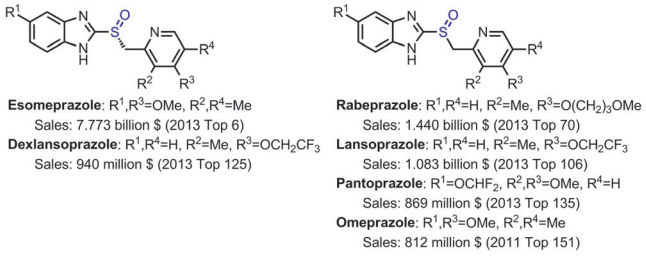
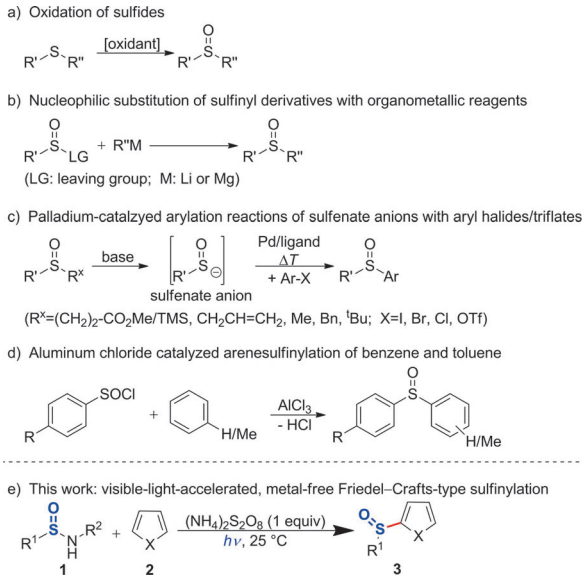


Figure 1. Best-selling sulfoxide drugs.

Several routes are described for the synthesis of aromatic sulfoxides. One is the oxidation of sulfides to yield sulfoxides (Scheme 1 a).[9] Another approach is the nucleophilic substitution of sulfinyl derivatives with organometallic reagents (Scheme 1 b).[10] However, the functional-group tolerance may be limited by the oxidizing agent or the reactivity of the organometallic species. In the last decade, many palladium-catalyzed arylation reactions of sulfenate anions[11] with



Scheme 1. Reactions for the preparation of sulfoxides.

aryl halides and triflates have been developed as an alternative strategy by the groups of Poli and Madec,[12] Walsh,[13] Nolan,[14] and Perrio (Scheme 1 c).[15] All of them require palladium (as the catalyst), ligands, bases, sulfenate anion precursors, aryl halides or triflates, and often high temperatures. A fourth approach involves classical electrophilic aromatic substitutions, for example, the aluminum chloride catalyzed arenesulfinylation of benzene and toluene with sulfinyl chlorides reported by Olah and Nishimura in 1974 (Scheme 1 d),[16] the Friedel–Crafts-type reaction of methyl sulfinates with electron-rich arenes using stoichiometric amounts of aluminum chloride,[17] and the synthesis of 3-arylsulfinylindoles from aryl sulfinic acids and indoles.[18]

For the synthesis of many drug motifs, a mild intermolecular sulfinylation of heteroarenes would be useful. Therefore, we developed a metal-free C–H sulfinylation of heteroarenes with sulfinamides and persulfate as a stoichiometric oxidant. The reaction is accelerated by irradiation with visible light (Scheme 1 e). Sulfinamides are more stable than sulfinyl chlorides and sulfinic acids, and are easy to handle and readily available.

The reaction conditions were optimized by irradiating a mixture of sulfinamide **1**, *N*-Me-pyrrole (**2a**, 20 equiv), and ammonium persulfate with visible light at room temperature. Different sulfinamides **1**, solvents, concentrations, amounts of oxidant and trapping reagent, and irradiation wavelengths were investigated (Table 1).

In a typical reaction mixture for the Friedel–Crafts-type sulfinylation, one equivalent of the sulfinamide **1a**, 20 equivalents of *N*-methyl pyrrole (**2a**), and one equivalent of

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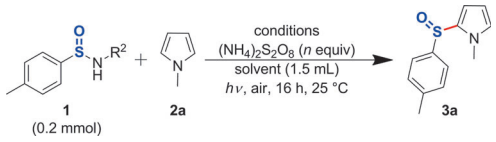
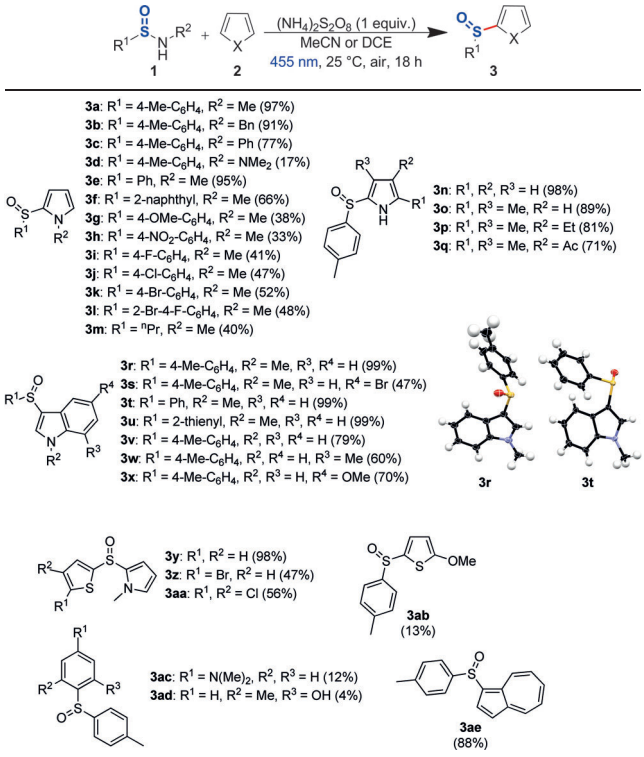
Table 1: Optimization of the reaction conditions.



Entry	Conditions	Yield [%][a]
1	**1a** (R^2 = ^{n}Bu), *n* = 1, MeCN, **455 nm**	56
2	**1a** (R^2 = ^{n}Bu), *n* = 1, MeCN, **no light**	13
3	**1a** (R^2 = ^{n}Bu), *n* = 1, MeCN, **no light, 55 °C**	27[b]
4	**1a** (R^2 = ^{n}Bu), **no oxidant**, MeCN, **455 nm**	–
5	**1a** (R^2 = ^{n}Bu), ***n* = 0.1**, MeCN, **455 nm**	7[b]
6	**1a** (R^2 = ^{n}Bu), *n* = 1, **no solvent**, **455 nm**	23
7	**1a** (R^2 = ^{n}Bu), *n* = 1, MeCN, **535 nm**	47
8	**1a** (R^2 = ^{n}Bu), *n* = 1, MeCN, **400 nm**	84
9	**1a** (R^2 = ^{n}Bu), *n* = 1, DCM **455 nm**	44
10	**1a (R^2 = ^{n}Bu), *n* = 1, DCE 455 nm**	**71**
11	**1b (R^2 = Ph), *n* = 1, MeCN, 455 nm**	**97**

[a] Determined by GC analysis with naphthalene as internal standard. [b] Yield of isolated product. DCM = dichloromethane, DCE = 1,2-dichloroethane.

Table 2: Substrate scope.[a]



[a] Yield of isolated product given in brackets.

ammonium persulfate in MeCN with blue-light irradiation were used to give **3a** in 56% yield (Table 1, entry 1). Without light, the yield decreases to 13% (Table 1, entry 2). The thermal decomposition of persulfate at 55 °C is less efficient than the acceleration by light and led to 27% product yield (Table 1, entry 3).[19] A control experiment without oxidant confirmed that persulfate is necessary for product formation (Table 1, entry 4), and furthermore, a stoichiometric amount is required (Table 1, entry 5).

Without solvent, the yield was still 23% (Table 1, entry 6). Green light (535 nm) accelerates the reaction as well (47% yield, Table 1, entry 7), but not as well as blue light. Irradiation at 400 nm is even more efficient (84%, Table 1, entry 8). The optimal solvent varies with the specific sulfinamide (see Table S1, entries 1–14 in the Supporting Information). Sulfinamide **1a** gives the highest product yields of 71% after 16 h (Table 1, entry 10) and 97% after 18 h in DCE (Table 2), whereas the yields in MeCN and DCM are lower (56% and 44% after 16 h, respectively, Table 1, entries 1 and 9). EtOH, DMF, and DMSO are not suitable solvents for the reaction (Table S1, entries 18–20 in the Supporting Information). However, sulfinamide **1b** gives a 97% product yield after 16 h in MeCN upon blue-light irradiation (Table 1, entry 11). The excess of the heteroarene **2a** can be reduced to 10 equivalents with a simultaneous increase of the overall concentration to 0.2 M and a prolonged reaction time of 19 h, yielding **3a** in 52% yield (Table S1, entry 15—compared to 56%, Table 1, entry 1). Only liquid sulfinamides like **1a** can be used at such high concentrations. Sulfinamide **1b** is solid and the yield drops dramatically at higher concentrations (12%, see Table S1, entry 17—compared to 97%, Table 1, entry 11). Applying *tert*-butyl hydroperoxide as the oxidant did not provide any product with or without blue-light irradiation (see Table S1, entries 22–25).[20]

The scope of the reaction was explored using the optimized reaction conditions (Table 1, entries 10 and 11): various sulfinamides **1**, heteroarenes **2** (3–20 equiv), one equivalent of ammonium persulfate, MeCN or DCE as the solvent, and blue-light irradiation for 18 h. The results are summarized in Table 2. Aromatic sulfinamides bearing electron-donating or electron-withdrawing substituents react to give moderate to excellent yields with pyrrole (**3a–3l**, **3n–3q** and **3y–3aa**) and indole (**3r–3x**) derivatives . Bromide and chloride substituents (**3j–3l**, **3s**, **3z** and **3aa**) are tolerated and allow potential further synthetic modifications of the coupling products. The molecular structures of compounds **3r** and **3t** were confirmed by single-crystal X-ray analysis (Table 2). 1-Methylindole and indole are exclusively sulfinylated at position 3 (**3r** and **3t**). The aliphatic *n*-propylsulfinamide (**1o**) reacts with *N*-methyl pyrrole to give the corresponding product **3m** in moderate yield. The reaction with a methoxy-substituted thiophene derivative **2n** (product **3ab**) and the benzene derivatives **2o** and **2p** (products **3ac**[21] and **3ad**) indicate the limits of the method towards decreasing nucleophilicity and increasing aromaticity of the arene component and give only small product yields. Azulene (**2q**) led to a high yield of 88% for **3ae** owing to its high nucleophilicity (N 6.66).[22]

Peroxodisulfate is strongly oxidizing with an oxidation potential of 1.86 V vs. SCE (in MeCN). Its photoinduced decomposition leads to sulfate radical anions, which are one-electron oxidants and hydrogen-atom abstraction agents.[19,23] Sulfinamide **1a** has an oxidation potential of 1.73 V vs. SCE (in MeCN, see Figure S1 in the Supporting Information) and is readily oxidized (see Scheme S1 in the Supporting Information). Hydrogen-atom abstraction from the radical cation $\mathbf{1}^{\bullet+}$ may give an electrophilic sulfinyl iminum ion that has

some structural features analogous to the Vilsmeier reagent.[19] Electrophilic aromatic substitution (S_EAr) with electron-rich arenes, such as pyrrole, and subsequent reduction and amine elimination[24] yields product **3**. The amine was detected in the crude reaction mixture before work up by GC/MS and TLC and was recovered during product isolation.

Experimental support for the proposed S_EAr mechanism is provided by the exclusive sulfinylation of indoles in position 3 (**3r** and **3t**, Table 2), which was confirmed by single-crystal X-ray analysis. In addition, the limitation of the arene scope to electron-rich heteroarenes indicates an electrophilic Friedel–Crafts-type mechanism: *N*-Me/Bn/Ph pyrrole (**2a**–**2c**), pyrrole (**2e**), 2,4-dimethylpyrrole (**2f**), 3-ethyl-2,4-dimethylpyrrole (**2g**), and even 3-acetyl-2,4-dimethylpyrrole (**2h**) give the expected products (**3a**–**3c** and **3e**–**3h**) in good yield. A radical mechanism is less likely, since the reaction proceeds in the presence of 2,2,6,6-tetramethyl-l-piperidinoxyl (TEMPO). Arenes **2**, which are not sufficiently nucleophilic result in the quantitative recovery of **1** from the reaction mixture. Mayr et al. have investigated the nucleophilicity (N) and electrophilicity (E) parameters of a large number of molecules thoroughly.[25] To support our S_EAr mechanism, we performed competition experiments with two nucleophiles and one electrophile (Scheme S3). Compound **2g** has a high nucleophilicity (N 11.63).[25b] If **2g** reacts with **1a** in the presence of the weaker nucleophiles **2a** (N 6.18)[26] or **2i** (N 6.9),[26] product **3p** is obtained exclusively in 79% and 78% yield, respectively, a comparable yield to the reaction without a second nucleophile (81%, Table 2). If two nucleophiles with similar nucleophilicity are present (**2a** and **2i**), both products are formed (see Scheme S3, **3a** (18%)/**3r** (72%) = 1:4).

The oxidation of *N*-methyl pyrrole (oxidation potential 1.20 V vs. SCE in MeCN)[27] by the sulfate radical anion is thermodynamically feasible and the resulting reactive intermediate could trigger an alternative reaction pathway (Scheme S2).[27,28] However, the competition experiments with different nucleophiles and the observed regioselectivity favor an electrophilic aromatic substitution mechanism.

The influence of light on the reaction was investigated by steady-state spectroscopy (see the Supporting Information). The starting materials **1a**, **2a**, and ammonium persulfate do not absorb visible light. The addition of peroxodisulfate to **1a** or **2a** also did not lead to any absorption in the visible region (Figures S2, S3). The clear reaction mixture of **1a** and **2a** does not absorb visible light either. Only after the addition of ammonium peroxodisulfate, the reaction mixture turns brown and absorbs over the whole visible region (Figures S4, S5). The formation of charge-transfer complexes is likely, but the exact molecular origin of the absorption remains unclear at present.

In summary, we report the facile sulfinylation of electron-rich heteroarenes using sulfinamides and peroxodisulfate at room temperature. The reaction is accelerated by irradiation with visible light, presumably through activation of the peroxodisulfate. Mechanistic investigations indicate a reaction involving electrophilic sulfinamide intermediates. The simple and mild reaction conditions recommend the method for the preparation of heteroaromatic sulfoxides, including precursors of bioactive compounds and drugs.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Friedel–Crafts reaction · metal-free conditions · sulfinylation · sulfoxide · visible light

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Communications

Synthetic Photochemistry

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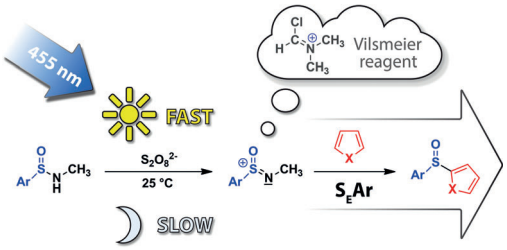
Visible-Light-Accelerated C–H Sulfinylation of Heteroarenes



Sulfoxides see the light: Sulfoxides were obtained from sulfinamides, electron-rich heteroarenes, and peroxodisulfate through visible-light-accelerated electrophilic aromatic substitution. The reaction proceeds at room temperature with blue-light irradiation and allows the C–H sulfinylation of electron-rich heteroarenes, such as pyrroles and indoles.