Metal-free O–H/C–H difunctionalization of phenols by o-hydroxyarylsulfonium salts in water†

Dengfeng Chen, Qingyuan Feng, Yunqin Yang, Xu-Min Cai, Fei Wang and Shenlin Huang*

An environmentally benign method for C–H/O–H difunctionalization of phenols with sulfoxides under mild conditions has been developed. The reaction process is mediated by an electrophilic aromatic substitution and subsequent selective ary1 or alkyl migration, involving C–S and C–O bond formations with broad substrate scope.

Introduction

Carbon–heteroatom bond forming reactions are one of the most important tools used in pharmaceutical chemistry, medicinal chemistry, and material sciences. In particular, transition metal catalyzed C–O or C–S cross-couplings, have been widely used to construct important families of target molecules, aryl ethers, sulfides and sulfoxides. Traditionally, these reactions are carried out in organic solvents (e.g., THF, CH₃CN, DMSO, and DMF), which may cause potential health, safety, and waste disposal issues. Therefore, transition-metal-free C–O and C–S coupling reactions under greener conditions are desirable, especially in the pharmaceutical industry.

Herein, we report our efforts toward a novel environmentally benign O–H/C–H difunctionalization of phenols by o-hydroxyarylsulfonium salts in water (Scheme 1).

Our reaction design is detailed in Scheme 1. It is reasonable to hypothesize that sulfoxides may be activated using a sulfonylating agent like trifluoromethanesulfonic anhydride (Tf₂O), inspired by the Pummerer reaction. The activated sulfoxide A could be attacked by phenols at sulfur, giving rise to o-hydroxyarylsulfonium intermediates 3. Such intermediates might then undergo a Smiles-like rearrangement, thus affording versatile products o-(phenoxy)aryl sulfoxides, which could be readily converted to many important ligands and biologically active molecules (Scheme 1b). However, the following challenges in this strategy were anticipated: (1) the activated sulfoxide can be attacked by the phenolic hydroxyl group at the cationic sulfur, according to previous studies; (2) it may require one electron-withdrawing group (e.g., NO₂) to activate the migration of the aromatic ring in the Smiles rearrangement; (3) such rearrangement of sulfoxonium salts has been seldom reported.

Results and discussion

Our initial investigation began with 2-naphthol 1a and diphenyl sulfoxide 2a in the presence of Tf₂O in acetonitrile at 0 °C. To our delight, the new sulfonium salt 3a was isolated in 95% yield. Somewhat surprisingly, this type of o-hydroxyarylsulfonium salt has never been prepared by this electrophilic aromatic substitution approach. The efficiency of this process was briefly examined with various phenols and sulfoxides, as shown in Table 1. Naphthols with electron-withdrawing substituents (3b-3e)
solvents (CH$_3$CN, THF, and DMF). All surfactants including Triton X-100 and SDS were screened, as were organic solvents (CH$_3$CN, THF, and DMF). A decrease in yield (entry 5). No increase in yield was observed at higher temperature (entry 6). Other surfactants worked equally well as those with electron-donating groups (3f). In addition, both diaryl sulfoxides and alkyl aryl sulfoxides led to the corresponding products in excellent yields (3g, 3h, and 3j). Interestingly, 3e and 3g were isolated as zwitterions. Unfortunately, though not entirely unexpected, a poor yield was observed when 4-hydroxyacetophenone was treated with diphenyl sulfoxide 2a.

With isolated salt 3a in hand, we sought to determine its reactivity in a Smiles-like rearrangement, as a stepwise and general methodology to o-(phenoxy)naphthyl sulfide 4aa (Table 2). We first explored the choice of base under aqueous micellar conditions at 70 °C (entries 1–3), utilizing TPGS-750-M, a “benign-by-design” surfactant developed by Lipshutz. To our delight, in this medium, K$_3$PO$_4$ was identified to be the most effective base for this rearrangement (entry 4). Lowering the reaction temperature led to incomplete conversion and, therefore, a decreased yield (entry 5). No increase in yield was observed at higher temperature (entry 6). Other surfactants including Triton X-100 and SDS were screened, as were organic solvents (CH$_3$CN, THF, and DMF). All afforded inferior results (entries 7–11). A control reaction “on water” (i.e., in the absence of TPGS-750-M) was conducted and a significantly lower yield was observed (entry 12), confirming the importance of micellar catalysis in facilitating this transformation in aqueous media.

At this stage, we sought to develop a one-pot sequence. Unfortunately, synthesis of the sulfoxonium salts either in aqueous media or under solvent-free conditions was low yielding. Hence, sulfoxonium salts were prepared in situ and used directly for the rearrangement without chromatography. Gratifyingly, the desired sulfide 4aa was produced in 86% yield from the reaction of 2-naphthol 1a and diphenyl sulfoxide 2a (Table 3).

With the optimized conditions in hand, we proceeded to explore the substrate scope of phenols 1, as shown in Table 3. Naphthols with different substituents proceeded smoothly under the standard reaction conditions, leading to products in good to high yields (4aa–4fa). Importantly, these products (4ba–4ca) bearing Br and CN substitents could be potentially further functionalized. Unfortunately, naphthol 1g with an amide functional group gave the corresponding product 4ga in only 15% yield. Besides naphthols, the substrate scope was further expanded to phenol derivatives. Phenols 1h–1j containing electron-donating groups reacted smoothly with sulfoxides 2a and 2b generating the corresponding sulfides 4ha–4ja and 4ib (X-ray) in good yields. Phenols bearing electron- withdrawing groups showed lower reactivity, leading to products 4kb–4mb in moderate yields. Interestingly, for p-unsubstituted phenols 1j and 1l, the desired products 4ja and 4fb were obtained selectively.
The scope of sulfoxides was then evaluated in reactions with 2-naphthol 1a (Table 4). Adducts 4ab and 4ac were obtained in good yields from symmetrical diaryl sulfoxides 2b and 2c with different electronic properties. Furthermore, unsymmetrical diaryl sulfoxides 2d–2h were also investigated. Remarkably, the use of sulfoxide 2d, simultaneously bearing p-tolyl and phenyl residues resulted in phenyl-migrated product 4ad, while the p-tolyl-migrated isomer was not detected. A similar trend was observed for sulfoxides 2e–2h, and the more electron-deficient aryl groups were selectively migrated delivering the corresponding sulfides 4ae–4ah. These results suggest that the rearrangement takes place by ipso-attack of a negatively charged oxygen atom onto the more electron-deficient aryl group.

Besides diaryl sulfoxides, alkyl aryl sulfoxides also participated in this transformation, further expanding the range of participating substrates. Increasing the length of the alkyl chain slightly decreased the reaction efficiency, as demonstrated by products 4ai–4ak. In addition, benzyl phenyl sulfoxide 2l is also a competent reaction partner, providing 4al in 78% yield. Moreover, the aryl group could also be modified with different

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**Table 3** Scope of phenols

<table>
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<tr>
<th>Conditions:</th>
<th>Isolated yields from phenol 1a.</th>
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<tr>
<td>1 (0.2 mmol), 2 (0.22 mmol), Tf₂O (0.24 mmol), MeCN (0.1 M) at 0 °C for 3 h; K₂PO₃ (0.88 mmol), 2 wt% TPGS-750-M/H₂O (0.75 M) at 70 °C for 24 h.</td>
<td>Hydrolysis product (carboxylic acid) was also isolated in 34% yield.</td>
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**Table 4** Scope of sulfoxides

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<tr>
<th>See Table 3 for conditions.</th>
<th>Isolated yields from phenol 1a.</th>
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<tr>
<td>1a, 2a Ar = Ph; 2b Ar = 4-Cl-C₆H₄</td>
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</table>
electronic properties, and the reactions furnished the corresponding sulfides in good to high yields (4ak and 4am–4ar).

Importantly, there was no significant effect of substituents in the para, meta, or ortho positions. For example, p-bromophenyl methyl sulfoxide (2n), m-bromophenyl methyl sulfoxide (2o), and o-bromophenyl methyl sulfoxide (2p) all reacted uneventfully and gave methyl-migrated sulfides 4an–4ap in useful yields. Notably, p-cyanophenyl methyl sulfoxide (2r) afforded cyanophenyl-migrated product 4ar exclusively, whereas aryl methyl sulfoxides 2m–2q all provided methyl-migrated products 4am–4aq. These results suggest that stronger electron-withdrawing groups on the aryl moiety can suppress alkyl migration, leading to aryl migration instead.

To further explore the applicability of this approach, we tested this new transformation on estrone 1n containing a complex architecture. Accordingly, difunctionalization of estrone proceeded smoothly, affording 4ni or 4nb in 68% yield (Scheme 2a), demonstrating the mild and selective nature of this overall transformation. In addition, a formal synthesis of urokinase inhibitor 8 was accomplished efficiently as shown in Scheme 2b.

We next sought to prepare sulfoxides and sulfones in one-pot (Scheme 3). Starting from 2-naphthol 1a and diphenyl sulfoxide 2a, sulfonium salt formation and then rearrangement in water gave sulfoxide 4aa. Without isolation, the resulting sulfide could then be oxidized to sulfoxide 5aa and sulfone 6aa in good overall yields, respectively (Scheme 3a). Sulfone 6eg was also obtained in high yield under similar reaction conditions. The selectivity of the Smiles-like rearrangement was unambiguously confirmed by single crystal X-ray analysis of 6eg (Scheme 3b).

To understand whether the rearrangement step is intramolecular or intermolecular, a crossover reaction of naphthol 1a with diaryl sulfoxides 2b and 2c was conducted under the standard reaction conditions (Scheme 4). It was found that no cross-product was detected, which suggests that this aryl migration is intramolecular. Furthermore, 4ab was formed in 78% yield while 4ac was isolated in only 39% yield, indicating that sulfoxide 2b was more reactive than sulfoxide 2c.

Lastly, E Factors were calculated for the rearrangement under aqueous micellar conditions, to assess the level of waste generation. Initially, an E Factor of only 4 was obtained based on organic solvent used, as illustrated in Table 5. An E Factor of only 8.6, was realized even with water included in the calculation. Moreover, the aqueous medium containing TPGS-750-M can be recycled to generate a different sulfide 4am or 4ba efficiently. Since no additional water needs to be used in each cycle, the associated E Factors dropped significantly.
Conclusions

In conclusion, we have developed an unprecedented approach for C–H/O–H difunctionalization of phenols under mild conditions. The process is mediated by an electrophilic aromatic substitution and subsequent Smiles-like rearrangement, involving C–S and C–O bond formations. Notably, this rearrangement proceeded under aqueous micellar conditions, successfully addressing several environmental issues. Further studies on related rearrangements featuring multiple bond-formations in water are currently in progress in our laboratories.

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Notes and references


