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S-Arylation of thiols with masked *o*-benzoquinones: synthesis of alkyl aryl/diaryl sulfides†

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A novel, efficient, and metal-free C–S bond formation of masked *o*-benzoquinones with thiols is reported. This protocol involves the synthesis of unsymmetrical alkyl aryl/diaryl sulfides in excellent yields under mild and catalyst-free conditions.

Over the last several years organosulfur chemistry has received significant relevance in organic synthesis due to the role of sulfur in both environmental and biological fields.[1] Among all the sulfur compounds, aryl sulfides and their derivatives have broad applications in organic synthesis, the pharmaceutical industry as well as in materials science.[2] The diaryl sulfide unit is an integral part of many drugs which are employed for inflammatory, malarial, Parkinson's, Alzheimer's, cancer, and HIV diseases (Fig. 1).[3]

Conventionally these diaryl sulfides can be synthesized by the cross-coupling of aryl halides with thiophenols. Traditional methods for the synthesis of these compounds require harsh conditions involving elevated temperatures (>200 °C) and high boiling polar solvents such as DMF, HMPA, quinoline or *N*,*N*-dimethylacetamide and also require strong reducing agents like $LiAlH_4$ and DIBAL-H for the reduction of sulfoxides and sulfones.[4] When compared to the catalytic formation of C–O and C–N bonds, the formation of a C–S bond remains scarce because sulfur readily undergoes oxidative S–S bond formation leading to disulfide by-products and also has a great tendency to coordinate with metals which deactivates the metal catalysts.[5] To overcome these problems, several methods were reported for the cross-coupling of aryl halides and thiophenols which were catalyzed by transition metals such as palladium,[6] nickel,[7] cobalt,[8] iron,[9] copper or copper-based enzyme laccase[10] and related metals.[11] Chan–Lam type *S*-arylation of thiols with boronic acids is an another alternative.[12] Recently Lee *et al.* reported an *N*-chlorosuccinimide promoted one-pot approach for the synthesis of aryl sulfides through the cross-coupling between thiols and Grignard reagents.[13] However, there are still some limitations in the cross-coupling of aryl halides with thiophenols. Pd catalysts are air sensitive, Cu promoted reactions require the usual stoichiometric amount of copper salts, high temperature, and long reaction time whereas Co, Ni catalysts are associated with toxicity and also all these reactions require expensive ligands. Moreover metal contamination is a serious issue in the pharmaceutical industry. For this purpose environmentally-friendly, inexpensive, mild, and efficient protocols are still desirable in this area.

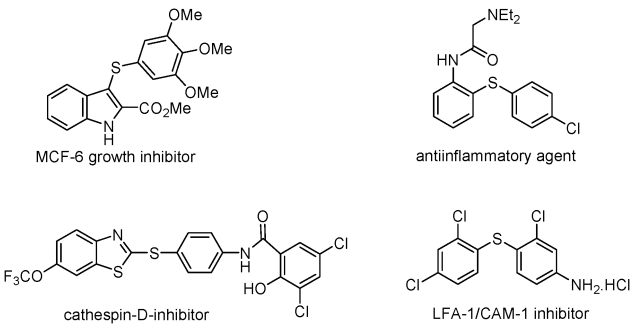

Fig. 1 Some of the diaryl sulfide containing biologically active molecules.

Dearomatization of phenols is an important event in the field of biosynthesis which involves the synthesis of many natural products. *o*-Benzoquinone monoketals commonly called masked *o*-benzoquinones (MOBs) are versatile intermediates in the synthesis of many natural products,[14] which can be easily obtained by the oxidation of 2-methoxyphenols in methanol using hypervalent iodine reagents such as diacetoxyiodobenzene (DIB). These linearly conjugated dienes can easily undergo the Diels–Alder reaction with various dienophiles, self-dimerization in the absence of external reactants and conjugate addition with nucleophiles.[15] Naphthoquinone monoketals belong to a

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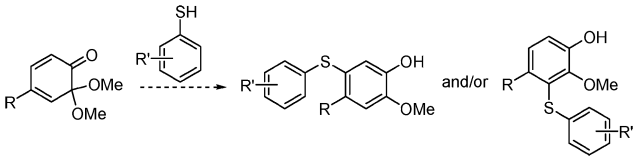


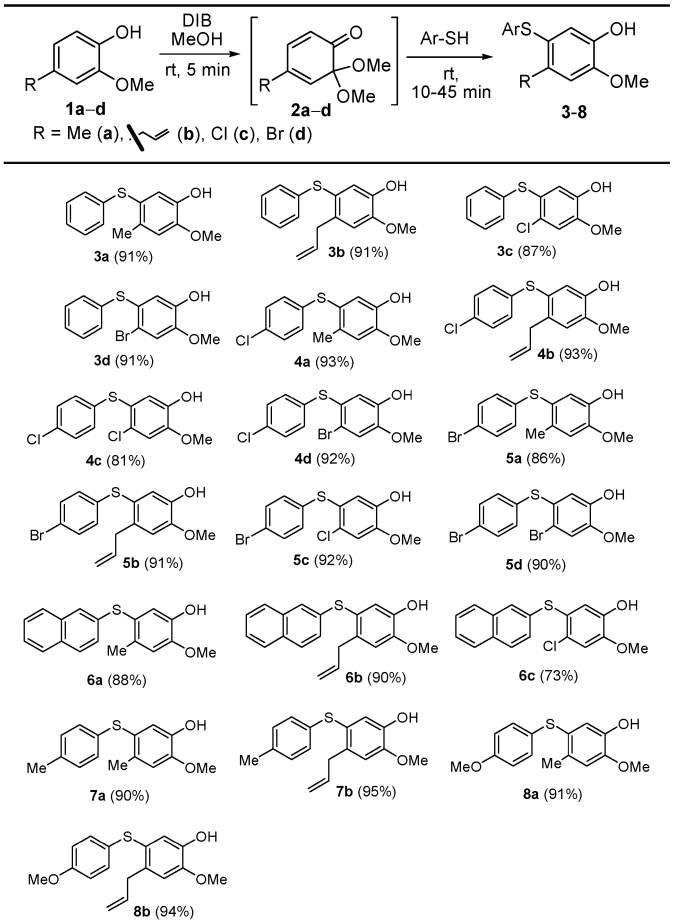
Scheme 1 Working hypothesis.

promising class of compounds which are an integral part of several antibiotics such as angucyclines or angucyclinones.[16] These naphthoquinone monoketals can be obtained by the oxidation of β-naphthols in methanol using DIB. Recently, we reported a Lewis acid mediated *anti*-Michael addition reaction for the synthesis of unsymmetrical oxygenated biaryls by adding the electron-rich arenes to these electron deficient MOBs.[17a] To further exploit the reactivity of MOBs,[17] we were interested to add some of the non-carbon nucleophiles such as thiols to these MOBs. In continuation of our green protocols for the formation of carbon and hetero atom bonds,[18] herein, we report the catalyst-free, eco-friendly method for the construction of the C–S bond to synthesise unsymmetrical alkyl aryl/diaryl sulfides. This protocol involves the oxidative dearomatization of 2-methoxyphenols/β-naphthols into quinone monoketals and subsequent conjugate addition with thiols. The working hypothesis for the addition of thiophenols to MOBs is depicted in Scheme 1.

In an initial experiment, 1 equiv. of DIB was added to a solution of creosol (**1a**) in dry methanol and stirred at room temperature for 5 min to generate the corresponding MOB (**2a**). To the *in situ* generated MOB, 1 equiv. of thiophenol was added. As expected the unsymmetrical diaryl sulfide was obtained in 91% yield in 15 min. This reaction proceeds through Michael addition of nucleophilic thiophenol to electrophilic MOB **2a** followed by prototropic shift leading to the formation of unsymmetrical diaryl sulfide **3a**. To probe the scope of the reaction, we have tested a series of thiophenols and all the reactions underwent cleanly to furnish diaryl sulfides in excellent yields 84–93%. Similarly the same reaction was performed with eugenol (**1b**), 4-chloro- and 4-bromo-guaiacols (**1c** and **1d**) and thioarenols under similar conditions. In the case of eugenol (**1b**) the reactions reached completion in 20 min to afford the unsymmetrical diaryl sulfides in excellent yields (90–95%) whereas in the case of 4-chloro- and 4-bromo-guaiacols (**1c** and **1d**) the reactions reached completion in 45 min, and the corresponding diaryl sulfides obtained in very high to excellent yields ranging from 73–92% which are shown in Table 1. The structure of the products was confirmed by ^{1}H and ^{13}C NMR. The protons corresponding to 2-methoxyphenols appear as singlets in ^{1}H NMR which indicates that there is no *ortho*-coupling. This supported the observation that the thiophenol attacks at position 3 of MOB instead of position 5. The structure of **7a** was further confirmed by single crystal X-ray analysis (Fig. 2).[19]

As evident from the above reactions the *S*-arylation of thiophenols *via* Michael addition to MOBs is facile. To ensure that the current protocol is compatible with aliphatic thiols, we performed the reactions of 2-methoxyphenols **1a** and **1b** with benzyl thiol and ester functionalized thiols. In the case of

Table 1 Synthesis of diaryl sulfides from MOBs and thiophenols



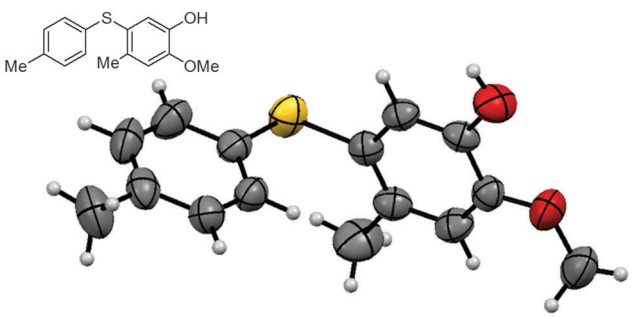


Fig. 2 ORTEP plot of **7a**.

benzyl thiol the reactions reached completion in 15–20 min whereas in the case of ester functionalized thiols, the reactions reached completion in 2 h and the corresponding alkyl aryl thiols were obtained in very high yields (Table 2).

At this juncture, we turned our attention to the addition of thiols to naphthoquinone monoketals **2e** and **2f** derived from the oxidation of β-naphthols in methanol using 2.2 equiv. of DIB. In this experiment, 1 equiv. of thioarenol/alkyl thiol was added to a solution of naphthoquinone monoketal in methanol and stirred the reaction mixture at room temperature for 2.5–3 h (6 h in the case of functionalized thiols). In all the reactions,

Table 2 Synthesis of aryl sulfides from MOBs and thiols

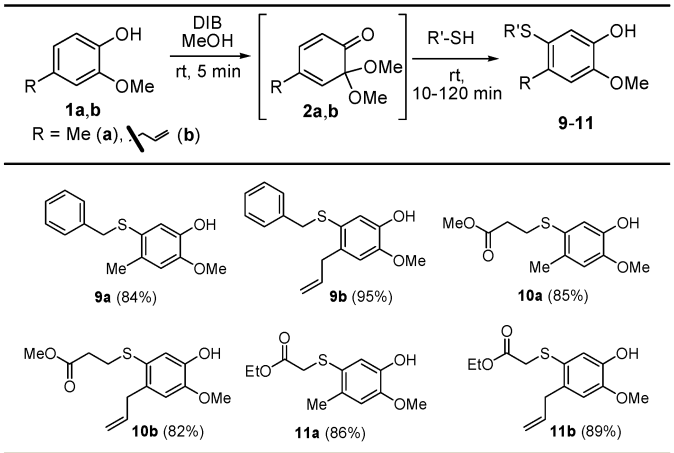
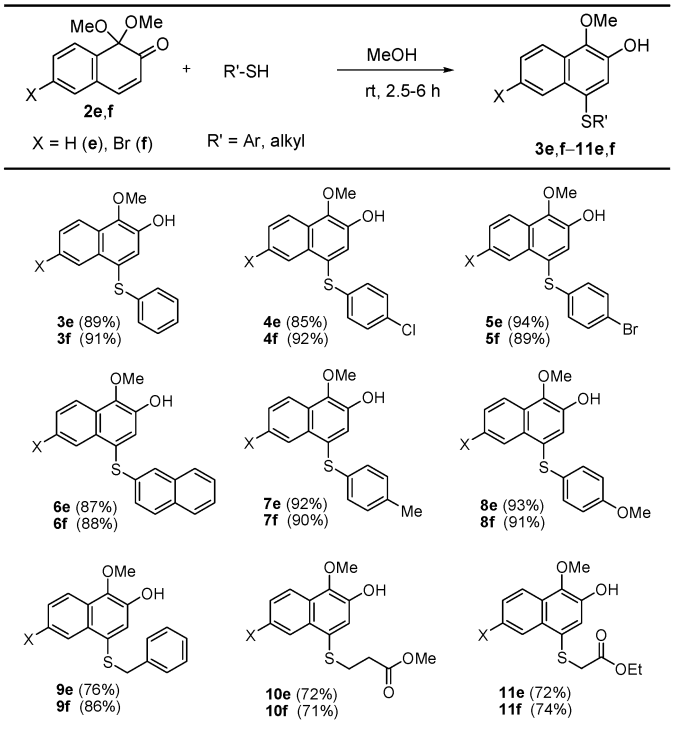


Table 3 Reactions of naphthoquinones with thiols



the naphthoquinone monoketals were transferred into the corresponding diaryl/alkyl aryl sulfides in high to excellent yields ranging from 78–94% (Table 3).

In order to understand the observed regiochemistry in the attack of thiols on MOBs, the condensed Fukui functions have been evaluated for MOBs. These calculations have been done at the B3LYP/6-31G* level of theory using the Gaussian09 program. In Fukui's frontier molecular orbital theory, the relative nucleophilicity or electrophilicity at different sites of the molecule is interpreted in terms of the highest occupied molecular orbital (HOMO) or lowest unoccupied molecular orbital (LUMO) electron density.[20] If HOMO electron density is more at a particular site of a molecule an electrophilic attack will take place at that position. Similarly, largest Fukui function

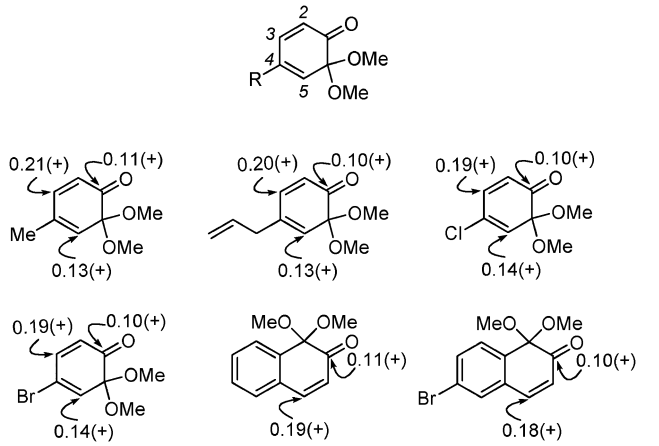


Fig. 3 Fukui functions for nucleophilic attack on MOBs.

of the LUMO indicates the preferred site for a nucleophilic attack in the molecule.

In MOBs **2a–d** three electrophilic sites (C-1, C-3, C-5) and in naphthalenones **2e** and **2f**, two electrophilic sites (C-1, C-3) are available on which nucleophiles may attack. From the analysis of electrophilic Fukui functions for MOBs **2a–d** and naphthoquinone monoketals **2e** and **2f**, the C-3 position has larger electrophilic activation (f_k^+ = 0.18–0.21) (Fig. 3) on which nucleophilic attack takes place. Thus the calculated Fukui functions support the experimentally observed regioselectivity from the attack of nucleophiles (thiol) on the C-3 position of MOBs studied.

In summary, we have developed a rapid method for the synthesis of aryl sulfides through the reaction of *in situ* generated masked *o*-benzoquinones with thiols under aerobic and catalyst-free conditions. The significant features of the reactions are short reaction times, high yields, operational simplicity, and the absence of toxic/expensive reagents.

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