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Metal-Free Oxidative C(sp^3)−H Bond Thiolation of Ethers with Disulfides

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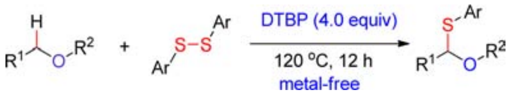
ABSTRACT



A novel method for the preparation of alkyl aryl sulfides through direct oxidation thiolation of commercial ethers with diaryl disulfides using di-*tert*-butyl peroxide (DTBP) as the oxidant without a metal catalyst was established. The C(sp^3)−H bond in various ethers was successfully converted into a C−S bond, and the corresponding sulfides were achieved with moderate to high yields.

C−H bond functionalization to form C−C and C−X (X = O, S, N, P, etc.) catalyzed by transition metals has attracted significant interest and has become an alternative to traditional Ullmann and other cross-coupling reactions during the past decades.[1] However, the direct thiolation of the C−H bond has gained less attention. In 2006, Yu et al.[2] first reported a C(sp^2)−H bond direct thiolation of the 2-aryl pyridine with aryl thiols catalyzed by a copper salt. Subsequently, Fukuzawa[3] and Cheng[4] also described the direct copper-catalyzed thiolation of the C(sp^2)−H bond with disulfides respectively. Recently, our group demonstrated a molecular-sieve-promoted TBHP-mediated thiolation of a C(sp^3)−H bond in the amide with disulfides.[5] Althouth the above progress has been made, the formation of C−S bonds through C−H functionalization under metal-free conditions also has been less explored.[6]

Transformation of an unactivated C(sp^3)−H bond into more usable compounds has attracted much attention.[7] In particular, great progress has been achieved in the functionalization of C−H bonds of ethers.[8] Li et al. reported the N-alkylation of azoles with ethers catalyzed by iron using TBHP as an oxidant in DCE at 80 °C.[9] Later, Reddy et al. demonstrated a novel C−O bond formation protocol in the reaction of ethers and β-ketoesters using Cu(OAc)$_2$ as the catalyst.[10] Very recently, Lei et al. observed a C−C bond formation reaction of arylboronic acids and cycloethers using DTBP as the oxidant catalyzed by nickel.[11] Moreover, the oxidative functionalization of C(sp^3)−H

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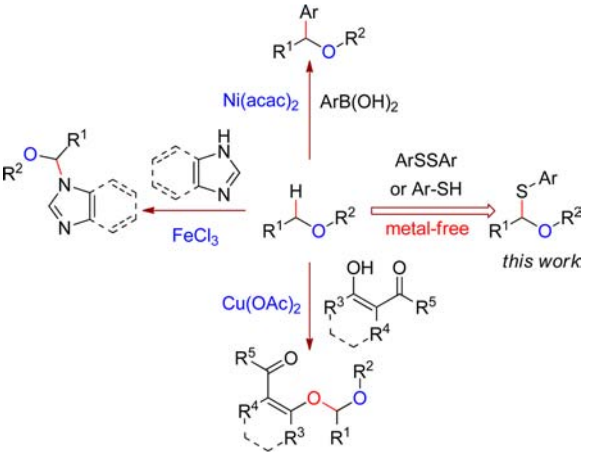
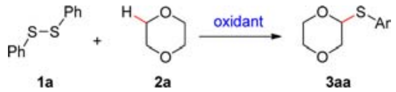
bonds adjacent to nitrogen atoms has also been demonstrated in recent years.[12] Moreover, to the best of our knowledge, no reports of metal-free oxidative C(sp^3)−H bond thiolation of ethers with disulfides or thiols are known and the discovery of an metal-free C−H transformation would be of great value.[13] Herein, we reported a novel protocol to construct α-arylthio ethers by using DTBP as an oxidant without the aid of a transition-metal catalyst (Scheme 1).

Scheme 1. C−X (X = C, N, O, S) Bond Formation via C(sp^3)−H Activation of Ethers



Our initial investigation focused on examining the coupling of diphenyldisulfide (**1a**, 0.5 mmol) with benzaldehyde (1.0 mmol) using 4 equiv of *tert*-butyl hydroperoxide (TBHP, 4.0 mmol) as an oxidant in 1,4-dioxane (2 mL) at 120 °C with stirring for 12 h. Surprisingly, the expected product *S*-phenyl benzothioate was not observed. Instead, we found that the diphenyldisulfide coupled with 1,4-dioxane directly, giving an unexpected alkyl aryl sulfide product of 2-(phenylthio)-1,4-dioxane (**3aa**) with 18% isolated yield (Table 1, entry 1). Given that alkyl aryl sulfides and its derivatives are valuable synthetic intermediates and important structural units found in numerous biological and pharmaceutically active compounds,[14] efforts were then made to improve the yield of this novel direct arylthiolation reaction. From a wide range of candidates, the DTBP was found to be particularly effective. Obviously the choice of oxidant was very important to the reaction according to the results of Table 1. Replacing TBHP with DTBP, the yield dramatically increased without the metal catalyst or other additives (Table 1, entry 2). But the formation of the desired product halted when the other oxidants, such as CAN, $NH_4S_2O_8$, $PhI(OAc)_2$, H_2O_2, NaClO, and DDQ, were added in this reaction (Table 1, entries 3−8). With respect to the amount of oxidant, 4 equiv of DTBP based on thiols (1 mmol of disulfides equivalent to 2 mmol of thiol) were found to be optimal, the model reaction was not completed with less than 4 equiv of DTBP (Table 1, entries 9−10), and no significant increase in yield of **3aa** was observed with more than 4 equiv of DTBP (Table 1, entries 11). The reaction yield was also affected by the reaction temperature: 67% yield at 100 °C (Table 1, entry 12) and 83% yield at 130 °C (Table 1, entry 13). Notably, the addition of some additives such as 4 Å MS (50 mg), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (10 mol %), and FeF_2 (10 mol %) suppressed the transformation slightly and the yield reduced (Table 1, entries 13−17).

Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant (equiv)	additive	solvent	yield (%) [b]
1	**TBHP (4.0)**	—	dioxane	18
2	**DTBP (4.0)**	—	dioxane	**85**
3	CAN (4.0)	—	dioxane	**N.D.**[c]
4	$NH_4S_2O_8$ (4.0)	—	dioxane	**N.D.**
5	$PhI(OAc)_2$ (4.0)	—	dioxane	**N.D.**
6	H_2O_2 (4.0)	—	dioxane	**N.D.**
7	NaClO (4.0)	—	dioxane	**N.D.**
8	DDQ (4.0)	—	dioxane	**N.D.**
9	DTBP (2.0)	—	dioxane	75
10	DTBP (3.0)	—	dioxane	80
11	DTBP (**6.0**)	—	dioxane	**84**
12	DTBP (4.0)	—	dioxane	67[d]
13	DTBP (4.0)	—	dioxane	83[e]
14	DTBP (4.0)	**MS**	dioxane	75
15	DTBP (4.0)	**$Pd(OAc)_2$**	dioxane	79
16	DTBP (4.0)	**$Cu(OAc)_2$**	dioxane	73
17	DTBP (4.0)	**FeF_2**	dioxane	71
18	DTBP (4.0)	—	PhCl	51[f]
19	DTBP (4.0)	—	PhH	68[f]
20	DTBP (4.0)	—	DCE	56[f]
21	DTBP (4.0)	—	CH_3CN	62 [f]
22	DTBP (4.0)	—	i-PrOH	N.D.[f]
23	DTBP (4.0)	—	DMSO	N.D.[f]
24	DTBP (4.0)	—	toluene	N.D.[f]
25	DTBP (4.0)	—	H_2O	**60**[g]
26	DTBP (4.0)	—	PhH	**63**[g]

[a] Reaction conditions: **1a** (0.5 mmol equal to 1.0 mmol thiophenol), **2a** (2 mL), heated at 120 °C for 12 h under different amounts of DTBP. [b] Isolated yield. [c] Not detected by GC-MS. [d] Reaction at 100 °C. [e] Reaction at 130 °C. [f] **1a** (0.5 mmol), **2a** (20.0 equiv), solvent (2 mL), heated at 120 °C for 12 h. [g] **1a** (0.5 mmol), **2a** (5.0 mmol), solvent (2 mL), heated at 120 °C for 12 h.

The effect of solvent on the model reaction was also examined. Moderate yields of the oxidative product **3aa** were obtained using chlorobenzene, benzene, CH_3CN, or DCE as a solvent; *i*-PrOH, DMSO, and toluene were not suitable for the reaction, which afforded no products (Table 1, entries 18−24). Gratifyingly, the reaction was also achieved with moderate yields in the presence of 5.0 equiv of

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2a using 2 mL of benzene or water as solvent (Table 1, entries 25−26). But it should be noted that an excess amount of dioxane as well as one of the substrate, was the most suitable reaction media for the model reaction.

Having identified the optimal reaction conditions, this approach was then applied to the coupling of 1,4-dioxane to a variety of diaryl disulfides, the results of which are shown in Scheme 2. In general, the electronic effects of the substituents on the aromatic ring of disulfides or thiols hardly influenced the reaction reactivity; both electron-rich and -deficient disulfides are reactive, giving desired products in good to excellent yields (entries 1−10). *Ortho*-substituted diaryl disulfides were all tolerated, but the steric effects of the disulfides had a slight impact on the yields (entries 6 and 11−14). In addition, the commonly used thiols such as 4-trifluoromethyl thiophenol, β-thionaphthaleneol, or thiophene-2-thiol, which surely would be oxidated into disulfides first, were also tested in this reaction, and the desired products were obtained with moderate to good yields without any differences when compared with disulfides (entries 7−9). Notably, the presence of the hydroxy on the phenyl ring of disulfides did not interfere with the C−H transformation process (entry 10). Disappointingly, the reaction did not work when disulfides containing a nitro or benzyl group was used as a substrate (entry 15).

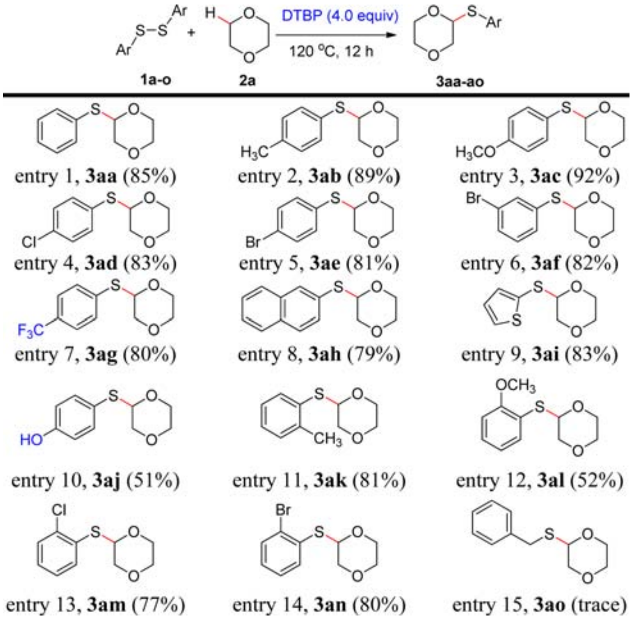
Subsequently, other target ethers were examined for to extend the application scope. As shown in Scheme 3, it was gratifying to find that a variety of ethers including cyclic and unsymmetrical linear ethers could couple with diverse disulfides with satisfactory yields. The C−H bond of tetrahydrofuran (THF), similar to 1,4-dioxane, was found to be highly effective with different kinds of disulfides or thiols, and the corresponding products were obtained in moderate to good yields (entries 1−5). The steric hindrance of disulfides has little influence on the yield of the reaction, and the reaction of 2,2′-dimethyl diphenyldisulfide with THF also proceeded well with a 81% yield (entry 6).

Surprisingly, methyl *tert*-butyl ether (MTBE), a very stable compound, which has only one CH$_3$ group adjacent to the oxygen atom and a large steric hindrance group, also led to the desired products with moderate yields (entries 7−12). Obviously, the sterically hindered effect of *tert*-butyl and the *ortho*-substituted disulfides effected the reaction; for example, it only resulted in a trace yield when the 2,2′-dimethoxy diphenyl disulfide reacted with MTBE, and we assumed that the trace yield was due to the large steric effects. Unfortunately, n-Bu$_2$O, Et$_2$O, and PhOCH$_3$ remained completely unreactive under the optimal reaction conditions.

Furthermore, under the optimal reaction conditions, this protocol could also be applied to the oxidative thiolation of the C(sp^3)−H bond adjacent to a nitrogen atom such as *N*,*N*-dimethylacetamide (DMA, entries 13−15). The disulfides bearing a strong electron-withdrawing group, such as p-CF$_3$, were also perfectly tolerated with DMA, offering the product with good yields.

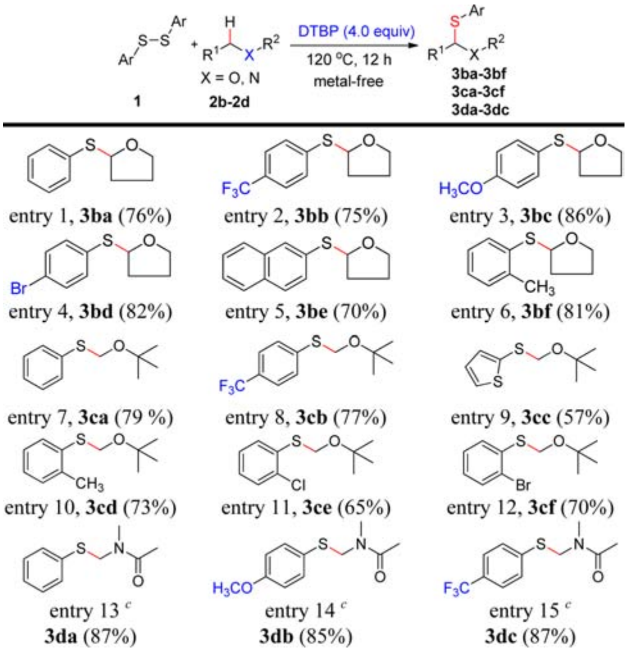
Lastly, in order to address the regioselectivity of the reaction, we explored a series of intramolecular competition reactions (Scheme 4). It was not the CH$_2$ group but the CH$_3$ group that tended to be thiolated when 1,2-dimethoxyethane (DME) reacted with 4,4′-dimethyl diphenyldisulfide. Although only the major regioisomer was isolated

Scheme 2. Thiolation of 1,4-Dioxane with Disulfides[a,b]



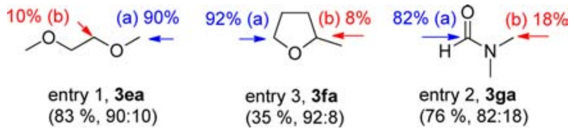
[a] Reaction were acrried out using **1** (0.5 mmol or thiols 1.0 mmol), **2a** (2 mL), DTBP (4 mmol) at 120 °C for 12 h. [b] Isolated yield based on **1**.

Scheme 3. Thiolation of Ethers and Amides[a,b]

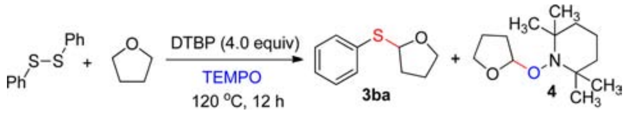


[a] Reactions were carried out using **1** (0.5 mmol, or thiols 1.0 mmol), **2** (2 mL), DTBP (4 mmol) at 120 °C for 12 h. [b] Isolated yield based on **1**. [c] **1** (0.5 mmol), DMA (2 mL), DTBP (4 mmol) at 120 °C for 6 h.

Scheme 4. Regioselectivity Studies of Thiolation



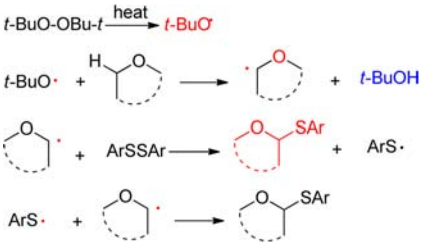
Scheme 5. Mechanism Studies of Thiolation



from the reaction mixture in 83% yield, a trace amount of another regioisomer was observed from crude NMR analysis and the ratio of the two regioisomers was 90%:10% (entry 1). We also found that the *para*-substitued diaryl disulfides embodied better regioselectivities than the *ortho*-substituted diaryl disulfides. 2-Methyltetrahydrofuran (2-methyl THF) showed low reactivity with good regioselectivity. The ratio of the two regioisomers was 92%:8%, and the main product yield was only 35% when 2-methyl THF reacted with diphenyl disulfide (entry 2). The reaction of *N*-dimethylformamide (DMF) with diphenyldisulfides led to two regioisomers with a ratio of 82%:18% (entry 3), and the two regioisomers were obtained with a 93% combined yield. It demonstrated that the regioselectivity toward the acyl C(sp^2)−H bond was superior to the C(sp^3)−H bond adjacent to nitrogen (see the Supporting Information).

To investigate the possible radical mechanism of the present transformation, a series of radical-trapping experiments were carried out. TEMPO, a radical-trapping reagent, was added into the reaction (Scheme 5). The formation of desired product **3ba** was suppressed, thus revealing that the initial steps of the transformation probably were caused by a radical process[9,11] (see the Supporting Information).

Scheme 6. A Plausible Reaction Mechanism



On the basis of the above results and previous publications,[8−11,13,15] a plausible catalytic mechanism was presented (Scheme 6). The DTBP decomposed to form *tert*-butoxyl radicals under heating conditions, the *tert*-butoxyl radical can abstract hydrogen from the ether to generate the corresponding alkoxy radical intermediate, and then the radical intermediate reacted with ArSSAr affording the product and the ArS$^\bullet$ free radical which would be trapped by another alkoxy radical.

In conclusion, this work described the first example of direct C−S bond formation via oxidative thiolation of commercial ethers under metal-free conditions. A high yielding, efficient, green methodology for the synthesis of alkyl aryl sulfide compounds was developed; moreover, this direct thiolation method is a new protocol for the construction of C−S bonds, which might be very valuable and attractive in sulfur chemistry and radical chemistry.

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Supporting Information Available. Experimental details, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.