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Synthesis of β-Hydroxysulfides from Thiophenols and Disulfides with *tert*-Butyl Hydroperoxide as the Oxidant and Reactant

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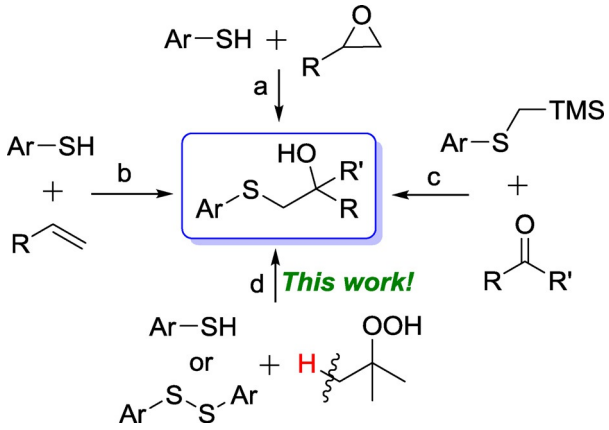
In this Communication, we developed a new procedure for the synthesis of β-hydroxysulfides from thiophenols or diaryl disulfides with TBHP as the oxidant. In the presence of zinc iodide or potassium iodide, with TBHP as the oxidant and pre-reactant, thiophenols and diaryl disulfides reacted with the methyl group of *t*BuOH smoothly and selectivity to give the corresponding 2-methyl-1-(arylthio)propan-2-ols as the terminal products in moderate to good yields.

tert-Butyl hydroperoxide (TBHP) is one of the most commonly used organic oxidants in organic chemistry. *tert*-Butanol, the expected product after oxidation reactions, is usually considered as waste. From the view point of sustainable development, it will be interesting if there is a procedure can use *tert*-butanol as the reactant when using TBHP as the oxidant.

On the other hand, sulfur-containing compounds hold numerous important applications in various areas and many pharmaceutical, agrochemical, and naturally occurring products contain at least one sulfur atom in their core structures.[1] Among the plentiful sulfurated chemicals, β-hydroxysulfides represent a class of compounds with high interest and importance. They have been found to exist in pharmaceuticals and natural products.[2] In synthetic chemistry, β-hydroxysulfides are excellent substrates for the synthesis of allylic alcohols,[3] benzoxathiepines,[4] benzotiazepines,[5] α-thioketones,[6] α-substituted α,β-unsaturated enones,[7] and β-hydroxysulfoxides.[8] These procedures have also been applied in the synthesis of natural products. Based on the importance of β-hydroxysulfides, many synthetic methodologies have been developed for their preparation. The most explored procedure is the reaction of thiophenols with epoxides, but the selectivity is problematic (Scheme 1 a).[9] Alternatively, procedures based on the reaction between alkenes and thiophenols (Scheme 1 b)[10] or phenylthiomethyltrimethylsilane and carbonyl compounds (Scheme 1 c) have also been developed.[11] However, drawbacks include the availability and stability of substrates as well as low yield; in addition, the selectivity issue still needs to be solved. Using this background information, we developed a new procedure for β-hydroxysulfide preparation. With thiophenols and disulfides as the substrates, using TBHP as the oxidant and it's by-product as the reaction partner, the desired β-hydroxysulfides were synthesized in moderate to good yields (Scheme 1 d). The C_{sp^3}–H bond in the methyl group of *tert*-butanol, which is the by-product of the TBHP oxidant, was smoothly and selectivity cleaved.



Scheme 1. Procedures for the preparation of β-hydroxysulfides.

In the optimized reaction system, toluene was found to be the most suitable solvent for this reaction. This surprised us, as the reaction of thiophenols with toluene, using TBHP as the oxidant, has previously been explored.[12] However, neither the reaction of thiophenol with the solvent nor the further oxidation of the product was observed in our system. ZnI_2 was found to be the best catalyst here; lower yields were obtained when CuI, I_2, or TBAI were tested. No product could be detected with MeCN, cyclohexane, or *i*PrOH as the reaction media. During the substrate testing, as shown in Table 1, moderate to good isolated yields were generally obtained. Good yields can be achieved with electron-donating substituted thiophenols. Interestingly, the methylthio substituent can be tolerated and gives the corresponding 2-methyl-1-[(4-(methylthio)phenylth-

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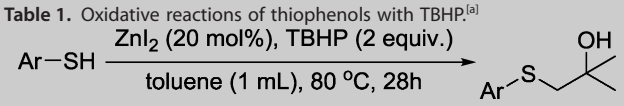
Table 1. Oxidative reactions of thiophenols with TBHP.[a]



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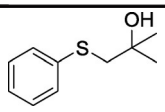
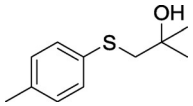
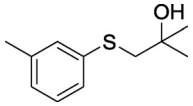
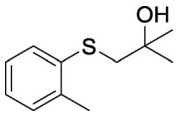
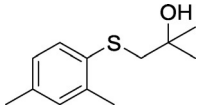
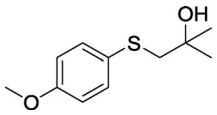
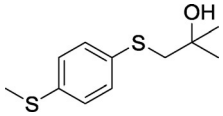
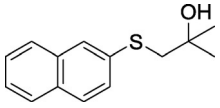
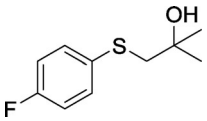
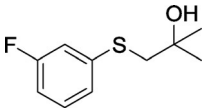
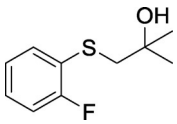
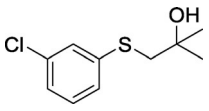
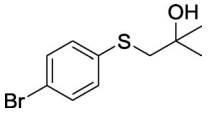
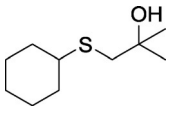
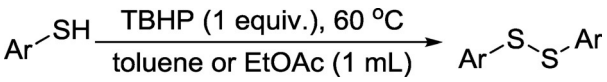
1		78
2		64
3		74
4		77
5		77
6		62
7		58
8		43
9		63
10		75
11		89
12		35
13		31
14		0

[a] ArSH (1 mmol), ZnI_2 (20 mol%), TBHP (2 equiv; 70% in water), toluene (1 mL), 80 °C, 28 h, argon. [b] Isolated yield.

io]propan-2-ol in 58% yield (Table 1, entry 7). Fluoro-substituted β-hydroxysulfoxides can be synthesized in 63–89% yields (Table 1, entries 9–11). Notably, chloro- and bromo-decorated products were obtained from the corresponding substrates under the same reaction conditions. These products are ready for further modification via cross-coupling methodologies (Table 1, entries 12 and 13). However, alkyl sulfide is not a suitable substrate here (Table 1, entry 14).

One main drawback of using thiophenols as substrates is their odor, which hampers their synthetic application. One solution for this problem is using the corresponding disulfides as the substrates, which can be produced from thiophenols and might also be the reaction intermediate. We found that diaryl disulfides can be produced in excellent yields by using TBHP as the oxidant with toluene or ethyl acetate as the solvent (Scheme 2).



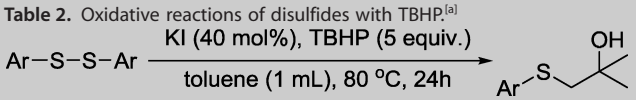
Scheme 2. Synthesis of disulfides from thiophenols.

Disulfides were then tested as substrates for this transformation. To our surprise, only a trace of the desired product could be detected when diphenyl disulfide was applied as the substrate under our former conditions. In our further optimization process, we found that I_2, MgI_2, and TBAI could all give the desired product, but in low yield. 76% of 2-methyl-1-(phenylthio)propan-2-ol can be achieved when KI is used as the promotor (Table 2, entry 1). Of the various solvents, toluene proved to be the best reaction media, rather than MeCN, *o*-xylene, 1,4-dioxane, THF, DCE, *t*BuOH, or *tert*-amyl alcohol. Next, various diaryl disulfides were tested with KI as the catalyst. Compared with thiophenols as starting materials, similar functional group generality was observed and even better yields were obtained in some cases. The yield of 1-[(4-bromophenyl)thio]-2-methylpropan-2-ol could be improved to 72% by using disulfide as the substrate (Table 1 entry 13 vs. Table 2 entry 15). The yields of chloro-substituted products were also increased (Table 2, entries 13 and 14). However, the nitro group could not be tolerated in either case, and no yield of the desired product was obtained.

Concerning the reaction mechanism, several control experiments were also performed. TEMPO (2 equiv) and BHT (2 equiv) were added to the reaction mixtures, and no desired product could be obtained in either case. Hence, we believe the reaction proceeded via a radical pathway. Based on our experimental results and knowledge, we propose that TBHP firstly reacted with the substrates and iodide to give *tert*-butyloxy and sulfur radicals. Then, the *tert*-butyloxy radical went through β-H transfer to give the corresponding methylene radical, which subsequently reacted with the sulfur radical to give the terminal product. To be clear, the methylene radical can also be formed through the radical exchange with thiol radical.

In conclusion, an interesting methodology for the synthesis of β-hydroxysulfoxides has been developed. With TBHP as the

Table 2. Oxidative reactions of disulfides with TBHP.[a]



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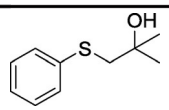
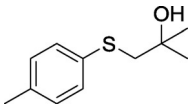
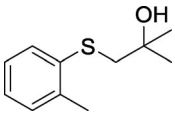
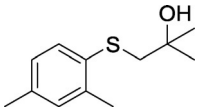
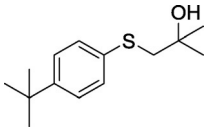
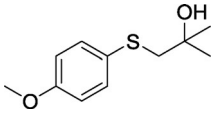
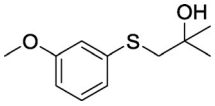
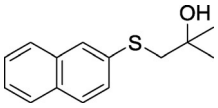
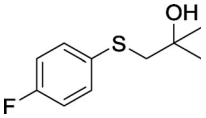
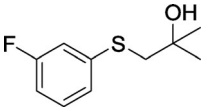
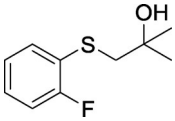
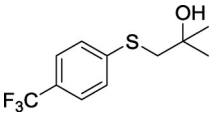
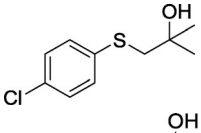
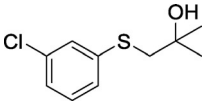
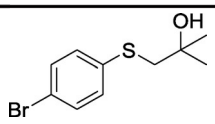
1		76
2		70
3		73
4		74
5		44
6		67
7		50
8		65
9		56
10		72
11		91
12		53
13		65
14		64
15		72

[a] ArSSAr (1 mmol), KI (40 mol%), TBHP (5 equiv; 70% in water), toluene (1 mL), 80 °C, 24 h, argon. [b] Isolated yield.

oxidant and reactant, 2-methyl-1-(arylthio)propan-2-ols were formed in moderate to good yields.

Experimental Section

General Procedure for Thiophenols

Thiophenol (1 mmol) and ZnI_2 (20 mol%) were added to a 15 mL tube equipped with a stirring bar. Then, the tube was flashed with argon and vacuum three times, and 1 mL of toluene and 2 equiv of TBHP (70% in water) were injected through a syringe. After that, the tube was closed and heated to 80 °C for 28 h. When the reaction was complete, the reaction mixture was cooled to room temperature. The reaction was quenched with distilled water and the solution was extracted with ethyl acetate. The crude product was purified by using column chromatography (ethyl acetate/pentane = 1:15).

General Procedure for Disulfides

1,2-Diphenyldisulfane (1 mmol) and KI (0.4 equiv) were added to a 25 mL Schlenk tube equipped with a stirring bar. Then, the tube was flashed with argon and vacuum three times, and 1 mL of toluene and 5 equiv of TBHP (70% in water) were injected through a syringe. After that, the tube was closed and heated to 80 °C for 24 h. When the reaction was complete, the reaction mixture was cooled to room temperature. The reaction was quenched with distilled water and the solution was extracted with ethyl acetate. The crude product was purified by using column chromatography (ethyl acetate/pentane = 1:15).

General Procedure for Disulfide Synthesis

A 15 mL tube equipped with a stirring bar, benzenethiol (1 mmol), EtOAc or toluene (1 mL), and TBHP (1 equiv; 70% in water) were added through the syringe. After that, the tube was closed and heated to 60 °C for 16 h. When the reaction was complete, the reaction mixture was cooled to room temperature. The reaction was quenched with distilled water and the solution was extracted with ethyl acetate. The crude product was purified by using column chromatography (pentane).

Acknowledgements

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Keywords: cascade process · C–H activation · green chemistry · oxidation · β-hydroxysulfides

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