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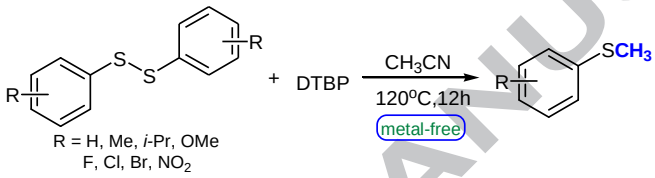

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ABSTRACT

An efficient approach for S-methylation of diaryl disulfides with di-*tert*-butyl peroxide under metal-free and neutral conditions was established. The present protocol shows good functional group tolerance to afford aryl methyl sulfides in moderate to good yields.

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Sulfur-containing molecules are of great value in biology, pharmaceutical chemistry and material science.[1] As one of these species, aryl methyl sulfides is not only a prevalent structural motif in bioactive natural products and therapeutic agents,[2] but also serves as versatile synthetic intermediates that can be converted into sulfoxides or sulfones[3] and thiols or arenes.[4] In addition, they are conveniently employed to the formation of C-C,[5] C-N[6] or C-B[7] bonds and the carbothiolation of terminal alkynes[8] via C-S bond cleavage. Although significant progress has been achieved in the C(aryl)-S cross-coupling of thiols and aryl halides or pseudohalides catalyzed by transition metals such as palladium,[9] nickel[10] and copper[11] complexes, the strategy is not suitable for the synthesis of aryl methyl sulfides presumably due to the low boiling point of methanethiol. In fact, typical approaches to aryl methyl sulfides involve the coupling reaction of aryl halides with dimethyldisulfide,[12] the reduction of methyl sulfoxides,[13] and the directed or heteroatom-facilitated lithiation of aromatic C-H bonds followed by electrophilic substitution with dimethyldisulfide.[14] Very recently, a simple and environmentally friendly synthetic route to aryl methyl sulfides, catalyzed by eosin Y and induced by visible light from arenediazonium salts and dimethyldisulfide has been explored under metal-free and mild reaction conditions.[15] Notably, DMSO has also emerged as a readily accessible and promising methylthiolation surrogate for this transformation in recent years, and except for using aryl halides[16] and aryl carboxylic acids[17] as substrates, direct methylthiolation via aromatic C-H bond with DMSO has been preferable.[18] Despite these impressive advances, generally, several or one of the items involving catalytic or stoichiometric amount of transition metal salt, an appropriate additive, toxic and effluvial methylthiolation reagent or limited substrates, and harsh reaction conditions was required in the aforementioned instances.

Recently, organic peroxides appeared as the oxidants in the cross-dehydrogenative coupling (CDC) reactions for C-C, C-O or C-N bonds formation[19] and C(sp^3)-H bond thiolation of ethers or cycloalkanes with disulfides,[20] in which they might play the role as H-acceptors to activate C-H bonds. Besides, the in situ-formed methyl radicals originated from various peroxides have also been effectively employed in the direct methylation of amides, carboxylic acids, arenes, activated alkenes, 1,3-dicarbonyl compounds and pyrimidinones or pyridinones.[21]

Hence, considering the extensive use of aryl methyl sulfides and the urgent striving for the environmentally benign synthetic procedures, we herein describe a transition-metal-free S-methylation of diaryl disulfides by using peroxide as the methyl source under neutral conditions, which might offer an alternative pathway for the synthesis of various aryl methyl sulfides.

Inspired by the previous report about *N*-methylation of amides and *O*-methylation of carboxylic acids via the activation of dicumyl peroxide (DCP) in the presence of CuCl in chlorobenzene,[21b] we attempted the combination of diphenyl disulfide (0.5 mmol) and DCP (2.5 mmol) with CuCl as catalyst and 1,2-dichloroethane (DCE) as reaction medium under a nitrogen atmosphere. To our delight, phenyl methyl sulfide was obtained in 48% yield at 120 °C for 12 hours (Table1, entry 1). And $FeCl_2$ was also suitable for the reaction, albeit generating a somewhat low yield (entry 2). Surprisingly, a control experiment revealed that CuCl or $FeCl_2$ was not crucial for this transformation (entry 3), namely, catalyst was not a prerequisite for the generation of the methyl group from DCP under the above conditions. When the reaction was subjected to air, a slightly low yield was obtained (entry 4). Encouraged by this result, further optimization of the reaction conditions was investigated and

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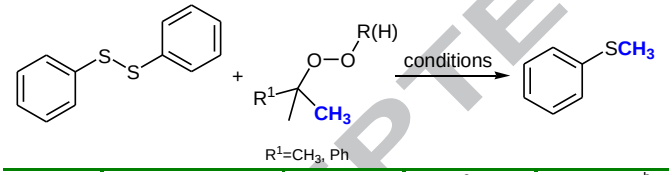
the results were summarized in Table 1. First, some other organic peroxides were screened for this transformation, such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP) and *tert*-butyl peroxybenzoate (TBPB) (entries 5-7). It was found that TBHP was nearly ineffective and DTBP was the promising reagent for this methylation. Next, the effect of solvent was examined. Transformation proceeded in chlorobenzene, benzene or CH_2Cl_2 afforded the methylating product in approximate yields (entries 9-11), whereas almost no desired product was observed when using DMSO or DMF as solvents (entries 12, 13). And acetonitrile (CH_3CN) was the best choice, furnishing in 65% yield (entry 8). Meanwhile, the effect of reaction temperature was tested. At 100 °C diphenyl disulfide could be successfully methylated with DTBP to afford a fair yield of desired product, however, a further decrease of the temperature to 80 °C resulted in no reaction (entries 14, 15). And the ideal temperature for the reaction was found to be 120 °C, that is, decomposition of peroxides requires a relatively high temperature, although further elevating the temperature did not give any significant improvement (entry 8), which is consistent with the previous results.[20a,b] With respect to the ratio of diphenyl disulfide and DTBP, it was concluded that reducing the amount of DTBP resulted in low efficiency (entries 8,17,18), and the similar yield was observed when 6.0 or 8.0 equiv. amount of DTBP based on diphenyl disulfide was devoted (entries 19, 20). Further extension of the reaction time to 24 hours afforded a comparable yield with 12 hours at the same temperature (entry 21). So, it was obvious that the optimal condition for S-methylation of diphenyl disulfide was using DTBP as the methylation reagent and CH_3CN as solvent at 120 ^oC for 12 h under an atmosphere of nitrogen.

Table 1 Optimization of reaction conditions[a]

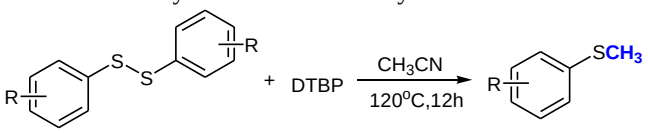


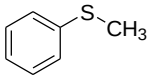
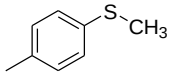
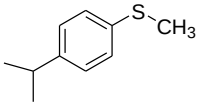
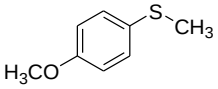
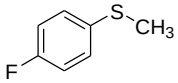
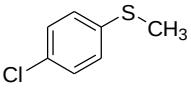
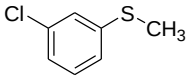
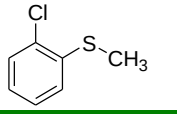
Entry	Peroxide	Solvent	T(^oC)	Yield(%)[b]
1[c]	DCP	DCE	120	48
2[d]	DCP	DCE	120	40
3	DCP	DCE	120	47
4[e]	DCP	DCE	120	44
5	TBHP	DCE	120	/
6	DTBP	DCE	120	60
7	TBPB	DCE	120	48
8	DTBP	CH_3CN	120	65
9	DTBP	PhCl	120	42
10	DTBP	PhH	120	40
11	DTBP	CH_2Cl_2	120	48
12	DTBP	DMSO	120	/
13	DTBP	DMF	120	/
14	DTBP	CH_3CN	80	<5
15	DTBP	CH_3CN	100	40
16	DTBP	CH_3CN	140	65
17	DTBP(3eq.)	CH_3CN	120	50
18	DTBP(4eq.)	CH_3CN	120	58
19	DTBP(6eq.)	CH_3CN	120	70
20	DTBP(8eq.)	CH_3CN	120	70
21[f]	DTBP(6eq.)	CH_3CN	120	71

[a] Reaction conditions: diphenyl disulfide (0.5 mmol), peroxide (2.5 mmol), solvent (2.0 mL), N_2, 12 h.
[b] Isolated yield. [c] CuCl. [d] $FeCl_2$. [e] in air. [f] 24 h.

With the optimized reaction conditions, the generatlity of this S-methylation of diayl disulfides was evaluated. As shown in Table 2, a variety of diayl disulfides was subjected to the reaction, and the corresponding products were obtained in 58-82% yields. Specifically, diaryl disulfides with electron-donating groups such as methyl and *i*-propyl could afford the corresponding S-methylation products in satisfactory yields (Table 2, entries 1-3). However, diaryl disulfide with strong electron-donating substituent such as methoxy group generated the desired S-methylation product in a slightly lower yield (entry 4). Meanwhile, diaryl disulfides possessing halogen groups were also available for the reaction. Notably, in these cases, the expected products were obtained in good yields while keeping fluoro, chloro and bromo functional groups intact, which might have potential use in fluorine chemistry or could offer an opportunity for further functionalization at the substituted positions (entries 5-10). Diaryl disulfides with electron-withdrawing substituent such as nitro group were good coupling partners, generating the anticipated products in 82%, 78% and 60% respectively (entries 11-13). Obviously, compared with *para*- and *meta*-substituted diaryl disulfides, a substrate with an *ortho*-substituent could also proceed smoothly, albeit generating the desired product in a lower yield probably due to steric hindrance (entries 9,13). Interestingly, heterocyclic disulfides such as 2,2'-dithiodipyridine and 2,2′-dithiobis(benzothiazole) were also suitable substrates in this methylation process, affording the corresponding S-methylation products in 65% and 62% (entries 14, 15).

Table 2 S-Methylation of various diaryl disulfides[a, 22]



Entry	R	Product	Yield(%)[b]
1	H		70
2	*p*-CH_3		68
3	*p*-*i*-Pr		65
4	*p*-CH_3O		60
5	*p*-F		78
6	*p*-Cl		80
7	*m*-Cl		72
8	*o*-Cl		58

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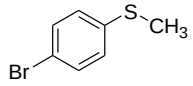
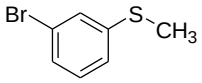
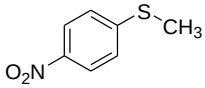
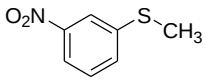
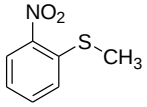
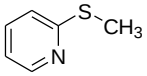
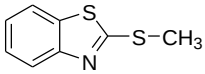
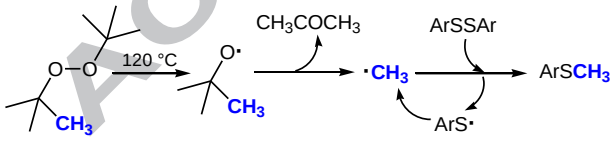
9	*p*-Br		71
10	*m*-Br		67
11	*p*-NO_2		82
12	*m*-NO_2		78
13	*o*-NO_2		60
14[c]	2-pyridyl		65
15[c]	benzothiazole		62

[a] Reaction conditions: diaryl disulfides (0.5 mmol), DTBP (3.0 mmol), CH_3CN (2.0 mL), 120 °C, 12 h.
[b] Isolated yield.
[c] Heterocyclic disulfide.

To investigate the reaction mechanism, the radical-trap experiment was performed. When stoichiometric amount of the radical-trapping reagent, 2,2,6,6-tetramethylpiperidine-N-oxide (TEMPO, 4 equiv. based on diphenyl disulfide) was added to the reaction mixture under exactly the same reaction conditions, the formation of target product was nearly suppressed and at the same time, the TEMPO-CH_3 adduct was detected by GC-MS, which suggested that a radical pathway may be involved in the S-methylation process. Based on the aforementioned results and the related publications,[21] a plausible reaction pathway for the reaction was proposed in Scheme 1. Initially, DTBP decomposed to form *tert*-butoxyl radicals under heating conditions, and thermal β-methyl elimination led to generate ketone and a methyl radical, then the radical intermediate reacted with ArSSAr affording the product and the ArS· free radical which would be trapped by another methyl radical.



Scheme 1 Plausible reaction pathway

In summary, the S-methylation of diaryl disulfide by using peroxide as the methylating reagent under metal-free and neutral conditions has been developed. This work represents a facile and environmentally friendly pathway for possible complement to the traditional synthesis of aryl methyl sulfides.

Acknowledgments
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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.xxx.

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22. General procedure

Diaryl disulfide (0.5 mmol), DTBP (3.0 mmol) and CH_3CN (2.0 mL) were taken in a 25 mL Schlenk round-bottomed flask. The reaction mixture was stirred at 120 °C for 12 hours under a nitrogen atmosphere. After cooling to room temperature, the product was diluted with H_2O (5 mL) and extracted with EtOAc (4×10 mL). The extracts were combined and washed by brine (3×10 mL), dried over $MgSO_4$, filtered, and evaporated, and purified by chromatography on silica gel to obtain the desired products with ethyl acetate/hexane (v/v=1:30 ~ 1:100). The products were characterized by their spectral and analytical data and compared with those of the known compounds (See supporting information).

Typical data for representative compound:

4-isopropylthioanisole (Table 2, entry 3)

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.19 (d, J = 8.4Hz, 2 H), 7.15-7.12 (d, J = 8.4 Hz, 2 H), 2.87-2.83 (m, 1 H), 2.44 (s, 3 H), 1.22 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.1, 135.2, 127.3, 127.0, 33.7, 24.0, 16.4. GC-MS (EI, m/z): 166 [M+]

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Highlights

- Metal-free one-pot protocol for the synthesis of aryl methyl sulfides was established.
- Reaction proceeds through radical mechanism.
- Various aryl methyl sulfides were obtained in moderate to good yields under neutral conditions.

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