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ARTICLE TYPE

Chemistry Accepted Manuscript

Copper-catalyzed S-methylation of sulfonyl hydrazides with TBHP for the synthesis of methyl sulfones in water[†]

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Received (in XXX, XXX) Xth XXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX DOI: 10.1039/b000000x

A copper-catalyzed S-methylation of sulfonyl hydrazides with TBHP was efficiently developed, providing a variety of methyl sulfones with good to excellent yields. The reaction can be carried out in water smoothly without any ligand or additive under mild condition and this catalyst-in-water can be recycled for several times.

Indroduction

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The formation of C-S bonds has drawn much attention over the years in the chemical synthesis for their prevalence in many biologically active compounds as well as in organic materials.¹ As a type of these species, methyl sulfones have emerged as important synthetic targets in recent years due to their promising antibacterial, antifungal and antitumor activities and so on.² For example, MK-0524 was found to be the prostaglandin D₂ (DP) antagonist,³ and, additionally, Rofecoxib and Etoricoxib were identified as very effective and specific cyclooxygenase-2 inhibitors (Figure 1).⁴ Thus, substantial attention has been paid to approaches for acquiring methyl sulfones during the past several decades.



Figure 1. Structures of MK-0524, Rofecoxib and Etoricoxib.

Traditionally, known procedures to obtain methyl sulfones are mainly based on the oxidation of the corresponding sulfides,⁵ the electrophilic aromatic substitution of arenes,⁶ the coupling reaction of arylboronic acids,⁷ and the reaction of organomagnesium halides⁸ or organolithium compounds⁹ with sulfonate esters. However, with the desire of chemists to minimize synthetic steps and the amount of toxic waste in the formation of C-S bond, and, moreover, to find more selective and milder transformations, the concepts of green chemistry¹⁰ have witnessed explosive developments in the past few decades. As a consequence of the often green chemical character, significant improvements of the design and optimization of new oxidation reactions have been made recently. For instance, He *et al.* reported an iron-catalyzed selective oxidation of sulfides to sulfoxides with the polyethylene glycol/O₂ system (Figure 2a).¹¹

Subsequently, Yuan *et al.* utilized an atmospheric oxygen as the oxidant, developed a novel copper(I)-catalyzed synthesis of aryl methyl sulfones from aryl halides and easily available DMSO (Figure 2b).¹² Recently, an oxygenation reaction of thioether by using H_2O_2 under catalysis of a gigantic Zr_{24} -cluster-substituted polyoxometalate was reported by Yang *et al.* (Figure 2c).¹³ The studies mentioned above are usually focused on the employment of different catalysts or oxidants. However, methylation,¹⁴ known as a fundamental transformation in organic chemistry, has long been neglected as an importantly efficient strategy for the direct synthesis of methyl sulfones.



Figure 2. a) The iron-catalyzed selective oxidation of sulfides; b) the copper(I)-catalyzed synthesis of aryl methyl sulfones; c) the oxygenation reaction of thioether by H_2O_2 ; d) the copper-catalyzed S-methylation of sulfonyl hydrazides.

On the other hand, employing sulfonyl hydrazides as the sulfonyl precursor in the precense of *tert*-butyl hydroperoxide (TBHP) has been well developed in recent years.¹⁵ In this type of methodology, TBHP provides an efficient access toward forming

sulfonyl radicals which then performed with other building blocks. Howerver, the study on direct S-methylation of sulfonyl hydrazides with TBHP for the synthesis of methyl sulfones is rarely reported. With our ongoing interest in various in-water and on-water green chemical methodologies in organic synthesis,¹⁶ moreover, in view of the importance of methyl sulfones and the related scaffolds, we report herein a simple copper-catalyzed Smethylation of sulfonyl hydrazides, in which organic peroxide served as a methylating reagent, thus offering a new convenient pathway for the synthesis of various methyl sulfones (Figure 2d). In comparison with the previous reports on the construction of methyl sulfones, this new S-methylation can be carried out in water with the catalyst-in-water recycled several times without any ligand or additive, affording a much more environmentally benign and economical methodology.

Results and discussion

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Initially, 4-methylbenzenesulfonyl hydrazide (1a) was treated with Cu(OAc)₂ and di-tert-butyl peroxide (DTBP) in water at 120 °C for 12 h. No any product was observed. First of all, different peroxides were examined in the reaction (Scheme 1, entries 2 and 3). It was found that TBHP could perform well to afford the desired product 3a with a yield of 38%. Based on the previous reports about the activation of TBHP by iodine and copper,^{14g,17} we investigated different iodine and copper sources as catalysts. Iodine sources showed no catalytic activity (Scheme 1, entries 4 and 5), whereas product formation in moderate to excellent yields was observed when copper sources were employed in the reaction (Scheme 1, entries 6-10).

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	S NH2 H	Peroxide (2a), Catalyst H ₂ O (1 mL), T		
Entr.			3a	Violet(()) b
Enuy	Peroxide (2 equ)	Cataryst (20%)	T(*C)	
1	DTBP	Cu(OAc) ₂	120	n.d.
2	DCP	Cu(OAc) ₂	120	< 5%
3	TBHP	Cu(OAc) ₂	120	38%
4	TBHP	l ₂	120	n.d.
5	TBHP	NBu ₄ I	120	n.d.
6	TBHP	CuCl	120	65%
7	TBHP	CuBr	120	43%
8	TBHP	CuCl ₂ ·2H ₂ O	120	55%
9	TBHP	Cul ₂	120	51%
10	TBHP	Cu(OTf) ₂	120	88%
11	TBHP	Cu(OTf) ₂	140	87%
12	TBHP	Cu(OTf) ₂	80	61%
13	TBHP	Cu(OTf) ₂	25	46%
14	TBHP	Cu(OTf) ₂	120	73% ^c
15	TBHP	Cu(OTf) ₂	120	59% ^d

Reaction conditions: 1a (0.20 mmol), 2a (0.40 mmol), catalyst (20 mol %), solvent (1 mL), under N₂, 12 h. ^b Isolated yields based on 1a. ^c under air. ^d under O₂.





^a Reaction conditions: sulfonyl hydrazides (0.20 mmol), TBHP (0.40 mmol) and Cu(OTf)₂ (20 mol %) in 1 mL of H₂O, 120 °C, under N₂, 12 h. ^b Isolated yields based on sulfonyl hydrazides.

Screening of the temperature indicated 120 °C to be the optimal with the expected product 3a obtained in 88% yield under catalysis of Cu(OTf)₂. Rising the temperature had no effect on the yield while lowering the reaction temperature decreased the yields largely (Scheme 1, entries 11-13). When the reaction was subjected to air or oxygen atmosphere instead of nitrogen, a relatively lower yield was obtained (Scheme 1, entries 14 and 15). After investigation, the optimal reaction condition was decided as below. The reaction of 1a with 2a was carried out in water under nitrogen atmosphere at 120 °C in the presence of Cu(OTf)2.

With the optimal conditions established, we examined the scope of this S-methylation of sulfonyl hydrazides. The examples of the reactions between TBHP and sulfonyl hydrazides were presented in Scheme 2. We found that a series of substituted sulforyl hydrazides **1a** could be performed well in this reaction, affording the corresponding products with moderate to excellent yields. Electron-rich and electron-neutral aryl sulfonyl hydrazides were typically employed. In general, the substrates with electrondonating groups (R = Me, OMe) on the phenyl ring gave slightly

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higher yields than that bearing electron-withdrawing groups (R =I, CF₃, CN, NO₂). Interestingly, the reaction with some electrondeficient substituents such as phenyl halides substrated sulfonyl hydrazides (1f and 1g) could proceed smoothly. In particular, 4fluo-phenyl sulfonyl hydrazides, worked well in the reaction to afford the desired product with a high yield, indicating that the electron-deficient nature of the aryl halide favored the reaction. Sterically encumbered aryl sulfonyl hydrazides (2k-m) were also investigated and it was found that hidrance had a great negative influence on the reaction. For instance, ortho-nitro benzenesulfonylhydrazides furnished a trace amount of the corresponding product **3ma**. The α -naphthayl sulforyl hydrazides (**3qa**) was obtained with a lower yield (59%) than that (81%) of β -naphthayl sulforyl hydrazides (3pa) perhaps due to the hindrance of the α hydrogen atom close to the sulfonyl in the α -naphthayl sulfonyl hydrazides. On the other hand, disubstituted benzenesulfonylhydrazides can be also employed as the reaction substrates, affording the methyl sulfone product 3na and 3oa with good yields. It was also worth noting that when the aryl ring of the sulfonylhydrazide was replaced by the thiophene ring, the correponding thiolation product could be also obtained with a yield of 69%. In addition, we proved that this method was remarkably compatible with some aliphatic sulfonyl hydrazides (2s and 2t)

Scheme 3. Recycling catalyst-in-water system^a



 a Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), Cu(OTf)₂ (20 mol %), H₂O (1 mL), under N₂, 12 h. b Isolated yields based on **1a**.

Furthermore, the recycle of the catalyst-in-water was investigated. $Cu(OTf)_2$ catalyst was stable in air with good solubility in water but poor solubility in ethyl acetate. By virtue of this characteristic, catalyst-in-water could be recovered by a simple phase separation from the organic layer. The recovered catalyst-in-water could then be reused in the next round. As shown in Scheme 3, a slight loss of catalytic activity was observed after the six round, giving the corresponding methyl sulfones with a yield of 73%.

Encouraged by this green and sustainable synthesis, we then conducted the scale-up experiments to examine the synthetic utility. When 10 mmol of 4-methylphenyl-sulfonhydrazide **1a** was treated with 20 mmol of TBHP **2a**, the reaction also proceeded well to give the corresponding product **3aa** with a satisfactory yield of 72%, although extended reaction time was required (Scheme 4). The method could be used to prepare precursors of some important bioactive molecules, demonstrating a great potential in parmaceutical synthesis.



Scheme 4. The scale-up reaction: 1a (10 mmol) and 2a (20 mmol) and Cu(OTf)₂ (20 mol %) in 10 mL of H₂O, 120 °C, under N₂, 24 h. Product 3aa was isolated in 72% yeild.

Studies on the reaction mechanism

To get an insight into the mechanism of this S-methylation process, several controlled experiments were conducted. First, radical trapping experiment was conducted to elucidate whether the reaction involves radical species. When the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; 2 equiv) was employed under the standard conditions (Scheme 5a), the S-methylation process was completely shut off and no **3a** was detected. In addition, the TEMPO–CH₃ adduct **4** was detected by GC–MS, which indicates that a free radical process should be involved. On the other hand, the employment of **5** could afford **3ca** in 59% yield (Scheme 5b), suggesting that benzenesulfinic acid might be an intermediate in this reaction.





Scheme 5. Mechanistic investigations of the S-methylation process.



Scheme 6. The proposed mechanism for the reaction.

On the basis of the aforementioned experimental results and the previous reports,^{14g,16,17} a possible reaction pathway was proposed and depicted in scheme 6. Initially, thermally promoted homolytic cleavage of the radical initiator TBHP produces a *tert*butoxy radical 'BuO •, which converts to the methyl radical by releasing 1 equiv of acetone in the presence of Cu.^{17c,18} Subsequently, sulfonylhydrazides transform into major intermediate **6** which can isomerize to **7** to form copper intermediate **8** in the presence of the Cu(II). Finally, the methyl radical reduces the Cu(II) intermediate **8** to produce Smethylation compound **3a** and regenerate Cu(I), which is oxidized to Cu(II) for further reactions.

Conclusions

A copper-catalyzed S-methylation of sulfonyl hydrazides with TBHP was efficiently developed, affording a variety of methyl sulfones with good to excellent yields. This new S-methylation can be carried out in water under environmentally benign conditions without any ligand or additive. And the copper catalyst-in-water can be recovered by a simple phase separation and this catalyst in water can be recycled for several times without obvious loss of catalytic activity. Also, the by-products were nitrogen, acetone and water, no any pollution on the environment. What's more, the reaction has a broad scope of the reaction substrates, a variety of functional groups can perform well in the reaction conditions. Ongoing research including further mechanistic details, expanding the substrate scope and applications in organic synthesis are currently underway.

Experimental

A mixture of sulfonyl hydrazides (0.20 mmol), TBHP (0.40 mmol) and Cu(OTf)₂ (20 mol %) in water (1 mL) was put into a schlenk at 120 °C under magnetic stirring for 12 h under nitrogen. After the reaction was finished, the mixture was extracted with EtOAc (3×5 mL) and then the combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to give compound **3**.

Acknowledgements

We are grateful to the National Nature Science Foundation of China (21272222, 91213303, 21172205, J1030412).

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and characterization of products. See DOI: 10.1039/b000000x/
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In water Without any ligand or additive Catalyst-in-water system can be recycled

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