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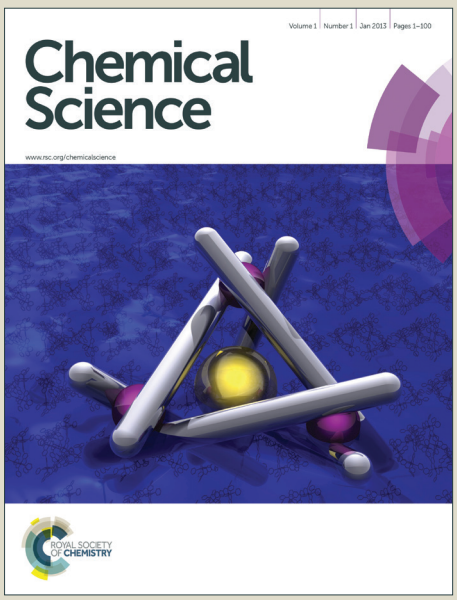

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ARTICLE TYPE

Catalytic and Direct Methyl Sulfonylation of Alkenes and Alkynes Using Methyl Sulfonyl Radical Generated from DMSO, Dioxygen and Copper System†

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This paper describes an efficient method to *β*-keto methyl sulfones and (*E*)-vinyl methyl sulfones using DMSO as the substrate. The methyl sulfonyl radical generated from DMSO in the presence of catalytic Cu(I) under O_2 atmosphere, was believed to be involved in this reaction. Isotopic labeling and $^{18}O_2$ experiments were performed to investigate the reaction mechanism.

Dimethyl sulfoxide (DMSO) has been used widely as solvent in organic synthesis due to its rather low cost, relative stability and low toxicity.[1] On the other hand, biologists have used DMSO as a hydroxyl radical scavenger to trap the highly reactive oxygen species present in biological system.[2] This is important since reactive oxygen species have been implicated to be the causative factors of many diseases. Detailed mechanistic studies have revealed that DMSO reacts with the OH radical present in the biological system to form methane, ethylene and methyl sulfonyl radical species.[3] We envisage that the methyl sulfonyl radical species generated from DMSO using this strategy may react with alkenes or alkynes to construct C-S bonds, generating interesting and synthetically useful methyl sulfones (Figure 1).

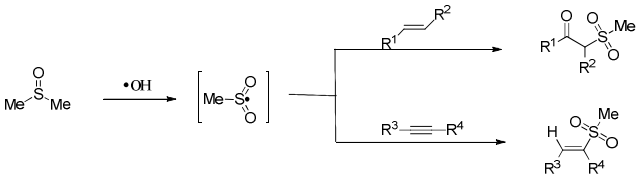
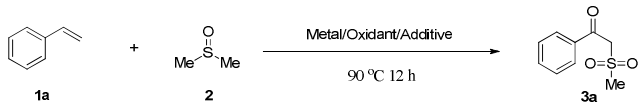


Figure 1. Functionalization of C-C unsaturated bonds.

It is important to note that sulfonyl radicals generated using various sulfonyl compounds have been well studied.[4] For example, sulfonyl halides,[5] selenides,[6] cyanides,[7] azides,[8] and sodium sulfinates,[9] etc have been found to be useful starting materials for the generation of the corresponding sulfonyl radicals. Recent work by Taniguchi has shown that sulfonyl radicals generated from the corresponding hydrazine compounds can be used to functionalize alkenes.[10] Furthermore, Lei has also shown that sulfonyl radicals generated from the corresponding sulfinic acids are useful for the oxidative difunctionalization of alkenes and alkynes.[11] However, as far as we know, there has been no report on the use of methyl sulfonyl radical generated from DMSO in organic synthesis.[12] Herein, we describe a novel method for the synthesis of *β*-keto methyl sulfones and (*E*)-vinyl methyl sulfones from alkenes and alkynes respectively using methyl sulfonyl radical generated from DMSO. This methyl sulfonation method is found to be highly chemo- and regio-selective.

As mentioned above, the hydroxyl radical has been shown to generate the methyl sulfonyl radical. It is well known that the highly reactive hydroxyl radical can be generated from hydrogen peroxide at thermal conditions *via* the well-known iron-catalyzed

Table 1. Optimization of reaction conditions for difunctionalization of alkenes.[a]



entry	solvent	catalyst	additive[f]	oxidant	yield[b]
1	DMSO	$FeCl_2$	D-1[d]	H_2O_2	15[c]
2	DMSO	CuBr	D-1[d]	H_2O_2	27[c]
3	DMSO	CuBr	D-1[d]	O_2	24[c]
4	DMSO	CuBr	D-2[e]	O_2	50
5	DMSO	CuBr	D-2	O_2	86(82[c])
6	DMSO	Cu_2O	D-2	O_2	54
7	DMSO	Cu(OTf).Benzene	D-2	O_2	77
8	DMSO	$Cu(OTf)_2$	D-2	O_2	36
9	DMSO	CuBr	D-3	O_2	80
10	DMSO	CuBr	D-4	O_2	64
11	DMSO	CuBr	D-2	air	73
12	DCE[g]	CuBr	D-2	O_2	5
13	DMSO	$CuBr_2/FeBr_3$[h]	-	O_2	-

[a]Conditions: 0.25 mmol **1a** and 10 mol% metal catalyst with 3.0 equiv additives were added to 1 mL **2** under oxidant (10.0 equiv H_2O_2 or 1 atm. O_2 balloon). [b]GC yields. [c]Isolated yields. [d]20 mol% additives. [e]1.5 equiv additives. [f]D-1: 1,10-phenanthroline; D-2: $HPO(OEt)_2$; D-3: $HPO(OMe)_2$; D-4: $HP(O^tBu)_2$. [g]5 mmol **2** in 1 mL DCE. [h]$CuBr_2$ (2.5 mol%), $FeBr_3$ (5 mol%).

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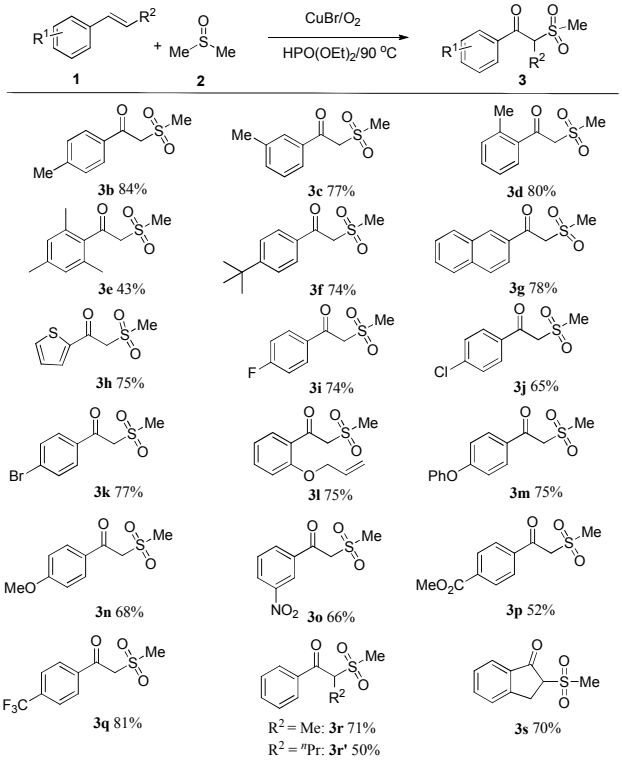
reactions.[3b,13] Thus, our initial exploration began by reacting styrene **1a** with DMSO (**2**) in presence of $FeCl_2$ and H_2O_2 catalytic system using 1,10-phenanthroline as the ligand at 90 °C (Table 1, entry 1). To our delight, the desired 2-(methylsulfonyl)-1-phenyl-ethanone **3a** could be obtained after 12 hours albeit in low yield (15%). The yield improved to 27% when CuBr was used instead of $FeCl_2$ (Table 1, entry 2). A more common oxidant such as O_2 was also effective in this reaction, furnishing the desired product in 24% yield (Table 1, entry 3). The yield improved dramatically when stoichiometric diethyl phosphite was employed as additive (Table 1, entries 4-5). Generally, copper catalysts with different counterions all promoted the reaction with fluctuating yields (see **SI**). Copper (I) showed more efficiency in the reaction condition compared to copper (II) catalysts (Table 1, entries 7-8). Simple substituents of phosphite like methyl, ethyl, led to more promising results compared to bulky ones (Table 1, entries 5 and 9-10). The reaction also proceeded well under air as oxidant with 73% yield (Table 1, entry 11). Attempts to use DCE as solvent was unsuccessful and trace amount of product was obtained (Table 1, entry 12). It is important to note that when we employed Ji's Cu/Fe catalytic system[14b] in the absence of triethylamine, the reaction was completely suppressed without phosphorylation or sulfonylation of alkene (Table 1, entry 13). No desired product was detected when the reaction was tested using Lei's reaction conditions (**1a** reacted with DMSO with pyridine under air atmosphere, see **SI**).

With the optimized reaction conditions in hand, we proceeded to survey the scope of the reaction (Table 2). Overall, the reaction tolerated a broad range of substituted aryl alkenes to give the corresponding *β*-keto methyl sulfones in good to excellent yields.

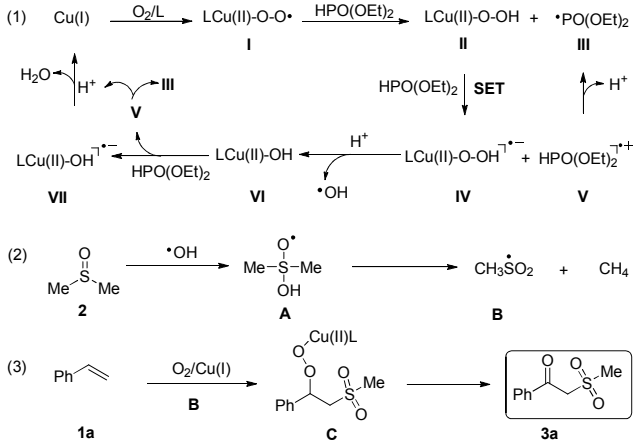
Table 2. Substrate scope for reaction of alkenes with DMSO.[a,b]



[a]Conditions: 0.25 mmol **1** and 10 mol% CuBr with 3.0 equiv $HPO(OEt)_2$ were stirred in 1 mL DMSO under 1 atm. O_2 balloon. [b]Isolated yields.

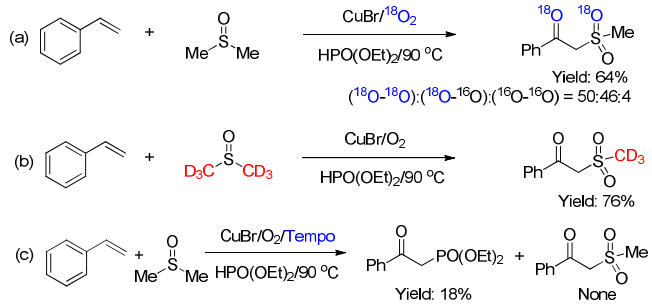
Ortho, *meta*- and *para*-substituted phenyl alkenes (**3b**–**3d**) worked well under our standard conditions affording the desired products in good to excellent yields (77–84%). Sterically hindered 2,4,6-trimethyl groups reduced the yield of the desired product (**3e**, 43%). On the other hand, 4-*t*-butyl group substituted phenyl alkene reacted well with DMSO affording product in good yield (**3f**). Naphthyl and heteroaryl substrates could also participate in the reaction (**3g**–**3h**), and a diverse of halogen substituents (F, Cl, Br) at the *para*-position of phenyl group could also be well tolerated (**3i**–**3k**). It is worth to note that the chloro, bromo, functionalities could be further functionalized in coupling reactions. When alkyl substituted alkenes were used as substrates, no reaction took place with recovery of starting material. This negative result encouraged us to study the chemo-selectivity of compound having both the alkyl and aryl substituted alkene moieties (**2l**). The result indicated that the alkyl substituted alkene moiety remained intact while the aryl substituted alkene reacted to afford the 1-(2-(allyloxy) phenyl)-2-(methylsulfonyl)ethanone (**3l**) in 75% yield. Examination of the electronic influence on the phenyl group revealed that both of electron-donating and electron-withdrawing groups gave promising results (**3m**–**3q**). Furthermore, internal and cyclic alkenes also proceeded efficiently to give the corresponding methyl sulfones in promising yields (**3r-3s**).

Although the mechanism is not fully understood, a possible reaction pathway was proposed for the styrene derivatives reacting with DMSO in $CuBr/O_2/HPO(OEt)_2$ conditions (Scheme 1). Initially, O_2 is activated by the copper catalyst to form copper complex-**I**.[14] A radical process takes place, forming the metal complex-**II** and phosphonic radical-**III**, respectively. One more equivalent phosphite as reductant takes part in the SET (Single Electron Transfer) process to give radical anion **IV** and cation **V**. While **V** probably changes to the phosphonic radical-**III** by deprotonation, copper (II) complex-**IV** generates the important hydroxyl radical and Cu(II)-OH-(**VI**) which may be further reduced by phosphite undergoing SET process to regenerate Cu(I). As reported,[3b] hydroxyl radical could react with DMSO to give several radical species, one of which is the methyl sulfonyl radical **B** from demethylation of dimethyl sulfinic acid radical **A**. Styrene is then attacked by radical specie **B** to form hydroperoxyl complex-**C**, which is then oxidized to give *β*-keto methyl sulfones.



Scheme 1. Proposed mechanism for difunctionalization of alkenes.

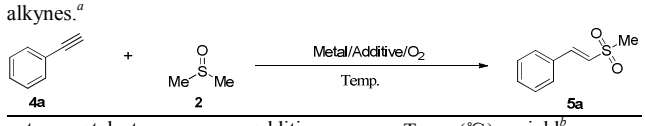
To further probe our proposed mechanism, the isotopic labeling experiments with $^{18}O_2$ and *d*-DMSO were performed. The results demonstrated that two additional oxygen present in the product originated from $^{18}O_2$ (Scheme 2 (a)) and demethylation of DMSO occurred smoothly (Scheme 2 (b)). Additionally, no product was detected when styrene was subjected with dimethyl sulfone under the same reaction conditions (see **SI**). This indicates that in the reaction system, active methyl sulfonyl ($MeSO_2$) radical species was involved rather than alkene reacting with dimethyl sulfone directly. D_2O exchange experiment was also performed. No D-labelled product was detected. Using radical scavenger reagent TEMPO, the desired reaction was completely suppressed and only a small amount of *β*-keto diethyl phosphonate was obtained (Scheme 2 (c)). Subjecting the *β*-keto diethyl phosphonate instead of the aryl alkene to our reaction conditions did not lead to the desired product, indicating that *β*-keto diethyl phosphonate is not the intermediate of this reaction. On the basis of these results, we may conclude that a DMSO/•OH radical process is most likely involved in our reaction system.



Scheme 2. Mechanistic studying.

Encouraged by these results, we explored the reaction with aryl alkynes under various conditions (Table 3). Initially, we employed the same reaction condition as alkenes and obtained (*E*)-(2-(methylsulfonyl)vinyl)benzene **5a** in moderate yield (Table 3, entry 1). Increasing the amount of phosphite D-2 resulted in slightly decreased yield while higher temperature gave a more positivie result (Table 3, entries 2-3). Dimetal-catalysts were screened however neither silver nor iron could improve the reaction (Table 3, entries 4-5). In addition to phosphite additive, we also examined organic base and acid but both of them surppr-essed the reaction (Table 3, entries 6-7). Finally we found that higher temperature and small amount of water were shown to improve the reaction efficiency compared to the reaction system for alkenes (Table 3, entry 8, also see **SI**).

Table 3. Optimization of reaction conditions for sulfonylation of alkynes.[a]

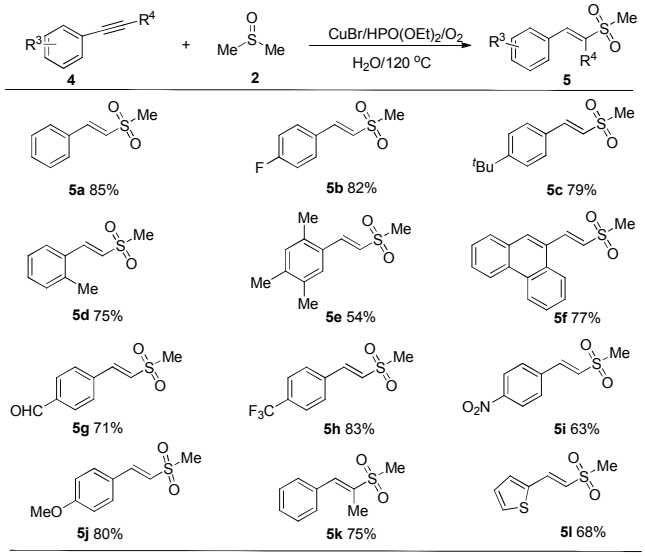


entry	catalyst	additive	Temp (℃)	yield[b]
1	CuBr	D-2	90	64
2	CuBr	D-2[c]	90	53
3	CuBr	D-2	120	75
4	CuBr+Ag(OTf)[d]	D-2	120	54
5	CuBr+$FeBr_2$[d]	D-2	120	-
6	CuBr	D-2 +TEA[e]	120	-
7	CuBr	D-2 +HOAc[e]	120	45
8	CuBr	D-2+ H_2O[f]	120	88(85[g])

[a]Conditions: 0.25 mmol **4a** and 10 mol% metal catalyst with 3.0 equiv D-2 were added to 1 mL DMSO under 1 atm. O_2 balloon. [b]GC yields. [c]4.0 equiv additives. [d]20 mol% catalysts. [e]3.0 equiv additives. [f]10.0 equiv additives. [g]Isolated yields.

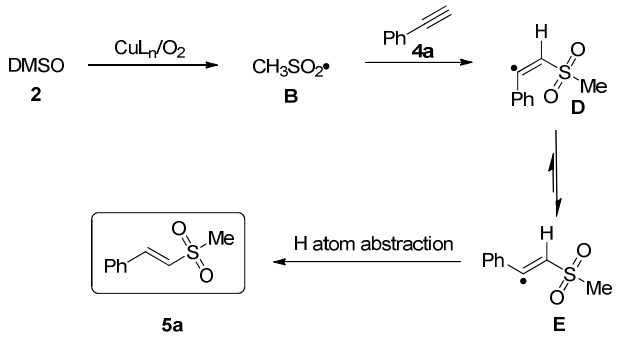
Further extension to other substrates revealed that all aryl alkynes reacted smoothly to afford desired vinyl methyl sulfones in good to excellent yields giving exclusively the *E* isomer (Table 4). *Ortho* and *para*-substituted phenyl moieties performed well in optimized condition irrespective of the halide (**5b**) or alkyl substitutions (**5c-5d**). Steric effect lowered the yield slightly when 1-ethynyl-2,4,5-trimethylbenzene (**4e**) was used as the substrate. Fused rings (**5f**) as well as heterocyclic compounds (**5l**) were also investigated and the corresponding vinyl methyl sulfones were obtained in good yields, 77% and 68%, respectively. The results showed that both electron-withdrawing (**5g-5i**) and electron-donating (**5j**) substitutions gave moderate to excellent yields (63%-83%). Notably, aldehyde, an useful functional group, could be well tolerated without oxidation to acid. Finally, internal alkynes also worked well to give (*E*)-(2-(methylsulfonyl)prop-1-en-1-yl)benzene in 75% yield (**5k**).

Table 4. Substrates scope for reaction of alkynes with DMSO.[a, b]



[a]Conditions: 0.25 mmol **4** and 10 mol% CuBr with 3.0 equiv $HPO(OEt)_2$ were stirred in 10 equiv H_2O and 1 mL DMSO under 1 atm. O_2 balloon. [b]Isolated yields.

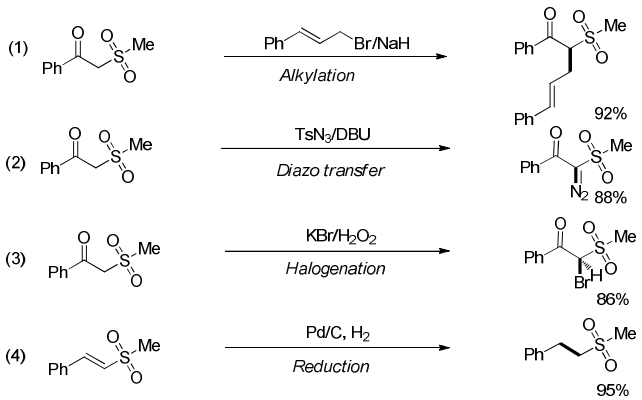
On the basis of these results, a reaction mechanism similar to the alkene system is proposed as depicted in Scheme 3. Similarly, methyl sulfonyl radical **B** was probably generated as shown in



Scheme 3. Proposed mechanism for methyl sulfonylation of alkynes.

Scheme 1, and reacted with the alkyne **4a** to form complex-**D**. Under thermal condition, the more stable intermediate **E** dominates. After hydrogen atom transfer, only *E* isomer **5a** was detected.

β-Keto and vinyl methyl sulfones are versatile synthetic intermediates that are widely applied for the synthesis of pharmaceuticals and natural products. For example, the *β*-keto methyl sulfone could be either alkylated with allyl bromide or diazo transferred with tosyl azide under suitable base conditions (Scheme 4, (1) and (2)).[15] It can also easily be halogenated in a radical process to afford 2-bromo-2-(methylsulfonyl)-1-phenyl-ethanone(Scheme 4, (3)), which is a key intermediate for the synthesis of biological active molecule 2-(methylsulfonyl)-3-phenyl-5,6-dihydroimidazo[2,1-b]thiazole.[16] The methyl sulfonyl group could be well tolerated in reduction condition to afford (2-(methylsulfonyl)ethyl)benzene in excellent yield from vinyl methyl sulfone (Scheme 4, (4)).



Scheme 4. Transformations of methyl sulfones.

In summary, a novel method for the synthesis of *β*-keto methyl sulfones and (*E*)-vinyl methyl sulfones was described. We demonstrated a new catalytic system that involves copper, oxygen and $HPO(OEt)_2$ to generate the hydroxyl radical *in situ* which initiates a cascade radical reaction. DMSO was activated in the reaction system to afford methyl sulfonyl radical that can functionalize both the aryl alkenes and alkynes. Isotopic labeling and $^{18}O_2$ experiments were performed to investigate the reaction mechanism. Further studies on the mechanism of this reaction as well as the application of this methyl sulfonyl radical for other transformations will be reported in due course.

Acknowledgement

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