Synthesis of Vinylic Sulfones in Aqueous Media

Jeffrey Goh, Manikantha Maraswami, and Teck-Peng Loh*

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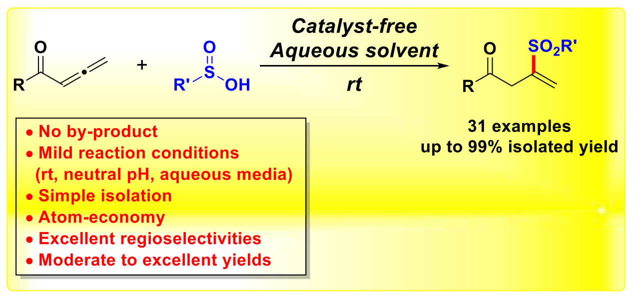
ABSTRACT: A green method for the sulfination of allenic carbonyl compounds to access a wide variety of vinylic sulfones is developed. This reaction works in aqueous media under very mild conditions. This reaction is atom economic. A wide variety of vinylic sulfones could be obtained in moderate to excellent yields with wide functional group tolerance. The efficiency of this method is demonstrated in some reactions where the desired products can be isolated by filtration.



The development of truly green and practical synthetic methods is of utmost importance in the chemical and pharmaceutical industries. The need to use metals and flammable toxic organic solvents both in the reactions as well as for workup and purification makes many of the organic reactions unsafe and environmentally unfriendly. Therefore, there has been much effort directed toward the development of new methods that work in water under very mild reaction conditions, are atom economic in nature, and avoid the use of metal or/and toxic flammable organic solvent. If successful, this metal-free approach can be employed for protein bioconjugation since metals are also known to destroy the tertiary structures of proteins. In this paper, we demonstrate the feasibility of this strategy with a green and practical synthesis of vinylic sulfones.

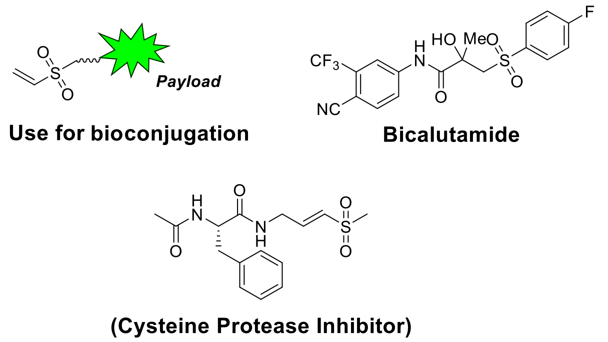


Figure 1. Applications of molecules containing the sulfone moiety.

Vinylic sulfones are chosen as the targets as they are important moieties featured widely in many biologically and pharmaceutically[1] active molecules (such as anticancer agents, cysteine protease inhibitors, antibacterial agents, and TSH receptor antagonists). They are useful building blocks in organic synthesis[2] and have also been widely used as linkers in protein[3] and material science (Figure 1). Traditionally, vinylic sulfones are synthesized via processes such as addition−elimination[4] and the Peterson reaction.[5] Other strategies including the use of acetylenic sulfones[6] and organometallic reagents[7] have also been reported. Jiang's group investigated the Cu(I)-catalyzed oxidative reaction of sulfonyl hydrazides[8] to couple with alkenes to form vinylic sulfones (Figure 2a). In addition, sulfonylation of carbon−carbon π bonds, such as alkenes and alkynes, have been extensively reported.[9] More recently, vinylic sulfones synthesized from allenes were also reported.[10] However, many of these methods suffer from various setbacks including the need to use toxic reagents/solvents, metal catalysts, and harsh reaction conditions and their poor atom-economy. For this reason, the establishment of coherent methodologies for the synthesis of these classes of compounds in a green manner is imperative. A well-developed green synthetic methodology to synthesize vinylic sulfones can potentially supplement or replace existing strategies, thereby reducing chemical waste and offering an alternative approach to access this crucial class of compounds.

In our group, we have developed a number of metal-free water-based green synthetic methods. These methods include the Mukaiyama−aldol C−C bond formation reaction involving reactive aldehdyes,[11] C−S bond formation involving cysteine bioconjugation with allenic amides[12] and $C-SO_2R$/C-phosphorus reactions[13] with reactive allylic alcohols. More recently, we have successfully employed 2*H*-azirines as a linker

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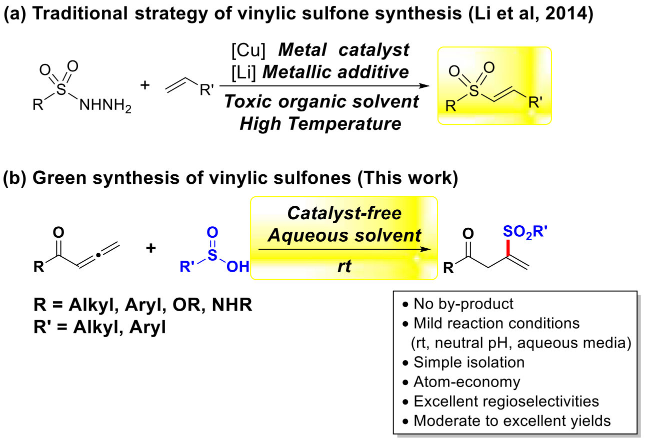
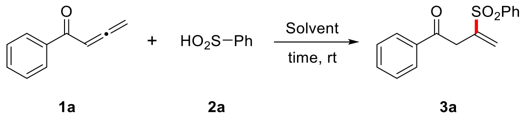


Figure 2. Vinylic sulfone synthesis

for disulfide bionconjugation under biocompatible conditions.[14] In this investigation, we envision a highly efficient atom-economical cross-coupling between electron-deficient allenic carbonyl compounds and sulfinic acids for the construction of the carbon−sulfur bond to afford the desired vinylic sulfones (Figure 2b).

1-Phenylbuta-2,3-dien-1-one (**1a**) and benzene sulfinic acid (**2a**) were chosen as model substrates for the cross-coupling reaction (Table 1). The reaction was initially screened using a variety of nonpolar organic solvents (refer to the SI), resulting in poor yields of the desired product **3a**. The yield of **3a** was improved when polar aprotic solvents were employed (refer to the SI). Inspired by this result, we started to screen polar protic solvents and observed that the yields were increased dramatically (Table 1, entries 5−7). The yield of **3a** can be improved by employing EtOH as a cosolvent along with H_2O as a 1:1 mixture (Table 1, entry 9), affording the product in 99% yield. It is important to note that the reaction conducted in either water or buffer pH 7 (Table 1, entries 6 and 7) afforded the desired vinylic sulfone in comparable yields. These results suggest the possibilities of using this method for bioconjugation with biomolecules such as proteins. We also found that continuous and intense stirring to ensure interaction between the organic substrates are useful; this observation is also in line with other reported "in water" or "on water" reactions.[15−19]

Table 1. Optimization of the Sulfa-Michael Reaction Conditions[a]

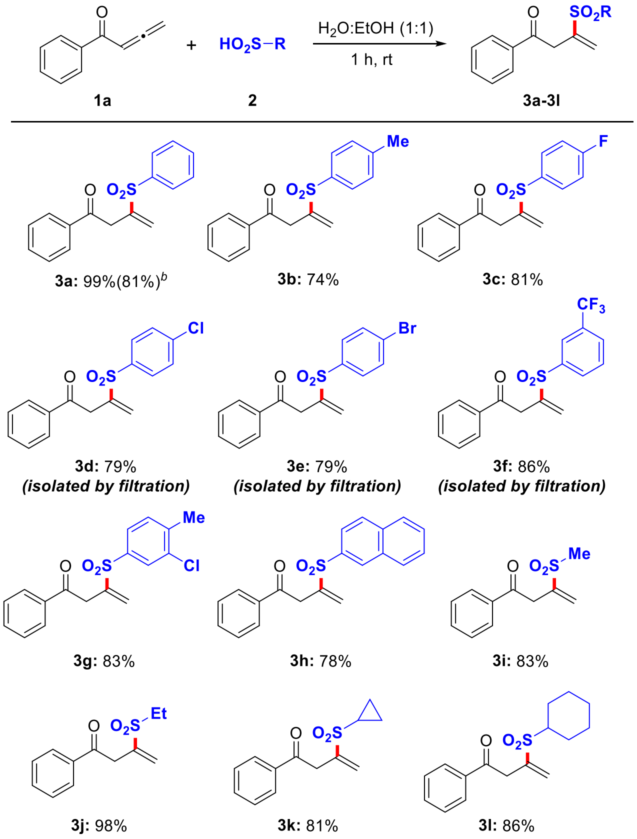


entry	solvent	time (h)	conv[b] (%)	yield[b] (%)
1	PhMe	12	100	13
2	Et_2O	12	100	7
3	cyclohexane	12	100	18
4	1,2-DCE	12	100	30
5	EtOH	12	100	75
6	H_2O	12	100	76
7	PBS buffer (pH 7.0)	12	100	75
8[c]	H_2O:EtOH	1	91	58
9	H_2O:EtOH	1	100	98(99)[d]
10[e]	H_2O:EtOH	1	100	98

[a] Experimental conditions: **1a** (0.15 mmol) and **2a** (0.23 mmol) in the specified solvent (1 mL) at room temperature. [b] Conversions and yields were determined by ^1H NMR using CH_2I_2 as the internal standard. [c] 1.0 equiv of **2a** was used. [d] Isolated yield. [e] 2.0 equiv of **2a** was used.

With the optimized reaction conditions in hand, the substrate scope of the sulfinic acids was investigated in an ethanol/water solvent system. A variety of aryl and alkyl sulfinic acids were investigated under this protocol as shown in Scheme 1. Aryl sulfinic acids bearing electron-donating groups (**3b−3h**) reacted smoothly to afford the corresponding vinylic sulfones in good yields. Even an electron-deficient sulfinic acid (**3f**) worked well under these conditions. More interestingly, vinylic sulfones **3d−3f** can be easily isolated by a simple filtration in this transformation. In addition, aliphatic sulfinic acids (**3i−3l**) also undergo this transformation to give the vinylic sulfones in good to excellent yields.

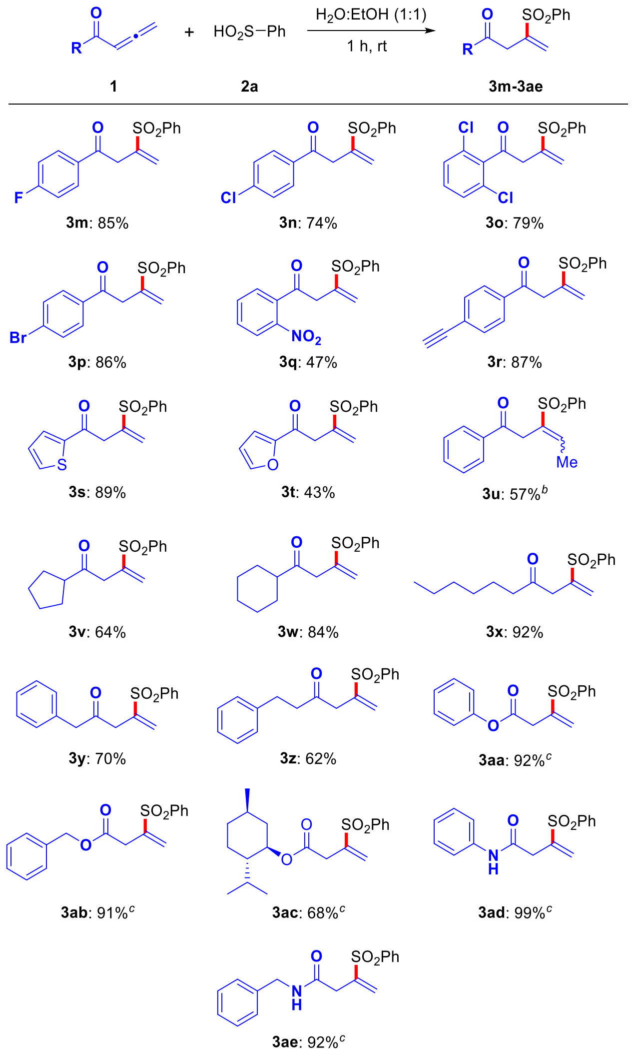
Scheme 1. Substrate Scope of the Sulfinic Acids[a]



[a] Experimental conditions: **1a** (0.15 mmol) and **2** (0.23 mmol) in H_2O/EtOH (1:1) (1 mL) at room temperature for 1 h. Isolated yields. [b] Gram-scale reaction

Subsequently, the substrate scope of the electron-deficient allenes was explored. As depicted in Scheme 2, it is evident that a wide diversity of allenic carbonyl compounds (allenic ketones/esters/amides) undergo a smooth transformation to afford the desired vinylic sulfones in modest to excellent yields. Aryl rings bearing electron-donating groups (**3m−3p**) reacted smoothly under these conditions to give the corresponding products in good yields. However, the yield of **3q** is significantly diminished when the aryl ring bears an electron-withdrawing nitro substituent. Heterocylic allenic ketones (**3s**

Scheme 2. Substrate Scope of the Allenes[a]

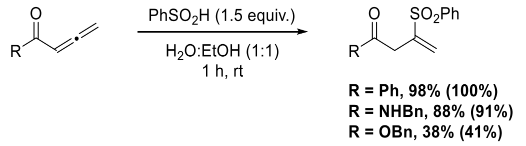


[a]Experimental conditions: **1** (0.15 mmol) and **2a** (0.23 mmol) in H_2O/EtOH (1:1) (1 mL) at room temperature for 1 h. Isolated yields. [b]Reaction was stirred for 72 h. [c]Reaction was stirred overnight.

and 3t) also worked well under this protocol. Even aliphatic allenic ketones (**3v**−**3z**) reacted with ease to give the vinylic sulfones in modest to good yields. Allenic esters and amides (**3aa**−**3ae**), which are inherently less reactive than the ketone variants, also provided the vinylic sulfones in excellent to near quantitative yields. The menthol (**3ac**) allene derivative also reacted smoothly under these conditions to afford the corresponding vinylic sulfone in 68% yield.

Thereafter, we carried out a competitive study between the three electron-deficient allene variants (i.e., allenic ketone/amide/ester). The reactions were carried out under the same conditions and stopped in 1 h. The yields were determined using NMR analyses (based on CH_2I_2 as the internal standard). Based on our initial investigation, it is conclusive that the allenic ketone is the most reactive under the reaction conditions; the starting material was fully converted to afford the corresponding vinylic sulfone with a ^{1}H NMR yield of 98%. Under the same conditions, the allenic amide provided a conversion of 91% with an NMR yield of 88%, whereas the allenic ester was found to be the least reactive under this protocol; only 41% of the substrate was converted, obtaining a modest yield of 38% of the desired product. To our surprise, it was observed that the allenic amide was more reactive than allenic ester. We postulated that the increased reactivity of allenic amides as compared to allenic esters is due to the result of hydrogen bonding with the aqueous based medium. On the basis of the results of the competitive study (Scheme 3), the reactivity of the different allenic carbonyl species are as follows: allenic ketones are the most reactive followed by allenic amides and, finally, allenic esters. This is evident based on the longer reaction time required for allenic esters as compared to allenic ketones or amides (Scheme 3).

Scheme 3. Competitive Study between Various Allenes[a,b]



[a]Experimental conditions: **1** (0.15 mmol) and **2a** (0.23 mmol) in H_2O/EtOH (1:1, 1 mL) at room temperature for 1 h. [b]Conversions and yields were determined by ^{1}H NMR using CH_2I_2 as the internal standard.

In order to demonstrate the versatility of this protocol, a handful of synthetic transformations (Figure 3) of the obtained products was evaluated. Interestingly, benzyl amine displaced the sulfonyl group under the optimized conditions to give enaminone **4** in 80% yield. Functionalization of vinylic sulfone **3a** by a Zn/CuI-mediated Michael reaction[20] with *tert*-butyl iodide gave the corresponding alkylated sulfone **5** in 66% yield. Vinylic sulfone **3a** can also undergo protection of the ketone with 1,2-bis(trimethylsiloxy)ethane to afford the protected vinylic sulfone **6** in 32% yield.[21] Treating vinylic sulfone **3ab**

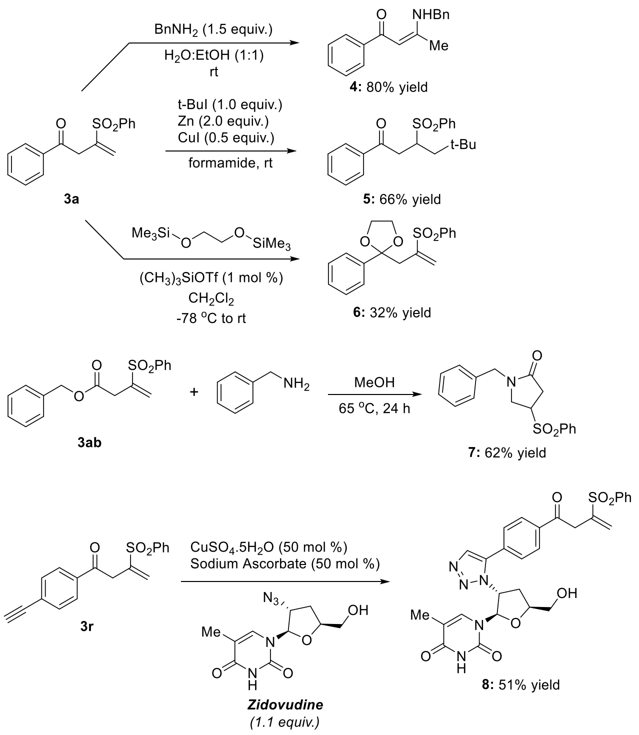


Figure 3. Synthetic transformations and functionalization of vinylic sulfones.

with benzylamine afforded γ-lactam **7** in 62% yield.[22] Vinylic sulfone **3r** can conveniently participate in a click reaction[23] with the antiviral drug, Zidovudine,[24] affording the corresponding compound **8** in 51% yield.

The feasibility of this synthetic protocol can be demonstrated by isolating solid products obtained after a reaction, in some cases, by a simple filtration without the need for extraction and column chromatography (Figure 4). It is noteworthy to highlight that the reaction also proceeds with 1.0 equiv of sulfinic acid (Table 1, entry 8). We postulated that water plays two important roles in this reaction. First, water enhances the rate of the reaction via the hydrophobic effect.[25] In addition, water could also possibly activate[13a] the sulfinic acid as described by Loh's group.

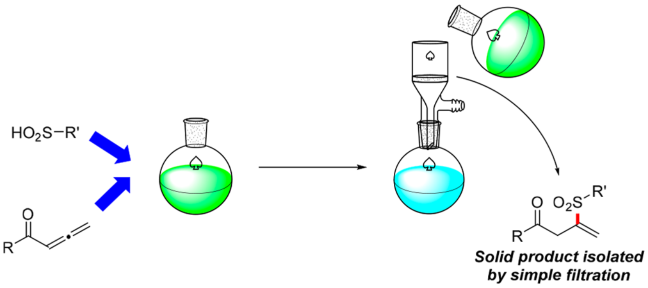
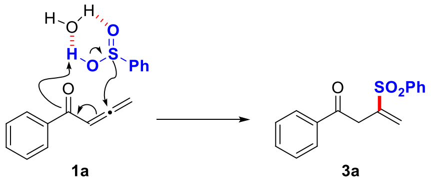


Figure 4. Simplicity of reaction demonstrated by filtration to obtain solid products.

The proposed mechanism of the sulfination is depicted in Scheme 4 below. Nucleophilic attack by the sulfinic acid selectively on the β-position via a Michael reaction afforded the enol tautomer, which readily tautomerizes to give the vinylic sulfone product. It is important to note that this reaction works under neutral pH 7 conditions, showing that the reactions may even work without the need to add excess sulfinic acid (Table 1, entries 7 and 8).

Scheme 4. Proposed Mechanism



In summary, we have developed an efficient method to effect vinylic sulfination of allenic carbonyl compounds in an environmentally friendly manner. Remarkably, the reaction can be performed in water/ethanol solvent mixture under metal-free conditions where solid vinylic sulfones can be isolated without chromatography. In this protocol, an excess amount of sulfinic acid improves the yield of the reaction. With this newfound protocol, we have increased the reactions in the toolbox of green synthetic methods developed by our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04257.

Experimental procedures, screening reaction conditions, analytical data for all new compounds, and NMR spectra of products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Teck-Peng Loh − *Institute of Advanced Synthesis (IAS) and Yangtze River Delta Research Institute, Northwestern Polytechnical University (NPU), Xi'an 710072, China; Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371;* orcid.org/0000-0002-2936-337X; Email: teckpeng@ntu.edu.sg

Authors

Jeffrey Goh − *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371*

Manikantha Maraswami − *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.0c04257

Notes

The authors declare no competing financial interest.

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