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## Graphical Abstract

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A novel and metal-free method for the synthesis of β-bromo sulfones has been developed through direct difunctionalization of alkenes with sulfinic acids and NBS

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# Direct difunctionalization of alkenes with sulfinic acids and NBS leading to β-bromo sulfones

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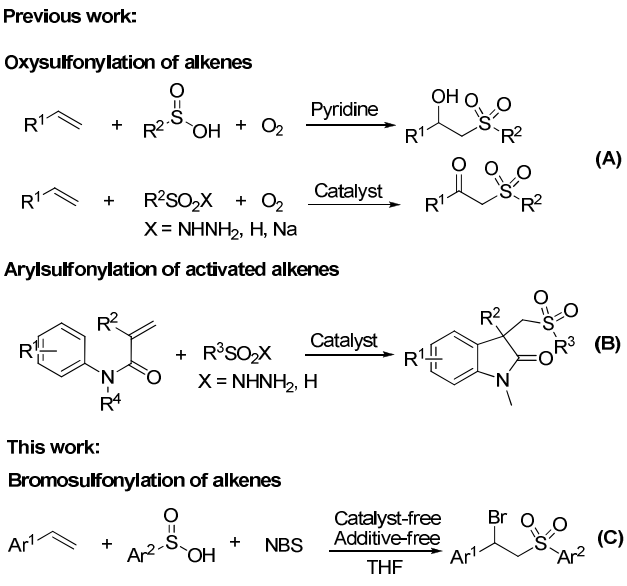
ABSTRACT

A new and metal-free method has been developed for the synthesis of β-bromo sulfones through the direct difunctionalization of alkenes with sulfinic acids and NBS. This protocol provides a simple, convenient, and efficient approach to various β-bromo sulfones in moderate to good yields with excellent selectivity, and especially does not require any catalyst or additive.



Sulfone groups are a very important class of functionalities, which extensively exist in various bioactive compounds, natural products, and organic functionalized materials.[1] Thus, the introduction of sulfone functionality into organic molecules to construct various organic sulfone compounds has drawn great interests of chemists.[2] On the other hand, the difunctionalization of alkenes, involving the formation of two new chemical bonds, has recently become a powerful and fascinating tool for the construction of various complex and highly valuable compounds in organic synthesis and medicinal chemistry.[3] Over the past several years, some important difunctionalization reactions such as diamination,[4] dioxygenation,[5] aminooxygenation,[6] and oxyphosphorylation[7] of alkenes have been effectively developed. Despite the significance of these reactions, difunctionalization of alkenes to simultaneously incorporate sulfone group and other different functional group remains a challenging but attractive target to pursue. In 2013, Lei's group[8] reported a novel oxysulfonylation of alkenes with dioxygen and sulfinic acids to access β-hydroxysulfones (Scheme 1, A). Very recently, metal-catalyzed procedures for the construction of β-ketosulfones via oxysulfonylation of alkenes have been described (Scheme 1, A).[9] Li,[10a] Jiao[10b] and our group[10c] also reported independently the arylsulfonylation of activated alkenes leading to sulfonated oxindoles (Scheme 1, B).

Herein, we wish to present a new and efficient synthesis method for the direct bromosulfonylation of alkenes with sulfinic acids and NBS to access β-bromo sulfones (Scheme 1, C).




**Scheme 1** Difunctionalization of alkenes to access sulfone-containing compounds.

Traditionally, β-bromo sulfones were synthesized by the bromination of bis(2-phenethyl)sulfone with N-bromosuccinimide in the presence of benzoyl peroxide,[11] the bromination of β-hydroxysulfones with phosphorus tribromide,[12]

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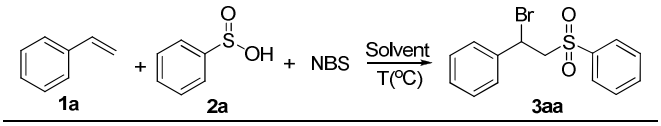
and the bromosulfonylation of alkenes with bromine and sulfinates or sulfonyl bromide.[13] Nevertheless, most of these methods might suffer from some limitations such as the use of stoichiometric amounts of potentially dangerous oxidants, unreadily-available starting materials, relatively harsh reaction conditions, and poor selectivity or low yields. Alternatively, the present methodology provides a simple and convenient approach to various β-bromo sulfones in moderate to good yields with excellent stereo- and regioselectivities under the toxic metal catalyst-free and additive-free conditions.

**Table 1**

Screening of the reaction conditions[a]




| Entry | Solvent | T(°C) | Yield (%)[b] |
|---|---|---|---|
| 1 | DCE | 80 | 79 |
| 2 | DME | 80 | 38 |
| 3 | 1,4-dioxane | 80 | 60 |
| 4 | THF | 80 | 83 |
| 5 | EtOAc | 80 | 70 |
| 6 | $CH_3CN$ | 80 | trace |
| 7 | toluene | 80 | trace |
| 8 | EtOH | 80 | trace |
| 9 | DMF | 80 | nr |
| 10 | DMSO | 80 | nr |
| 11 | $H_2O$ | 80 | nr |
| 12 | THF | 25 | 18 |
| 13 | THF | 60 | 33 |
| 14 | THF | 80 | 75[c] |
| 15 | THF | 80 | 71[d] |
| 16 | THF | 80 | 67[e] |

[a] Reaction conditions: styrene **1a** (0.6 mmol), benzenesulfinic acid **2a** (0.5 mmol), NBS (0.5 mmol), solvent (2 mL), 25-80°C, 10 h (sealed tube).

[b] Isolated yields based on **2a**.

[c] **1a** (0.5 mmol), **2a** (0.5 mmol), NBS (0.5 mmol).

[d] **1a** (0.5 mmol), **2a** (0.6 mmol), NBS (0.5 mmol).

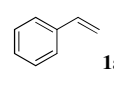
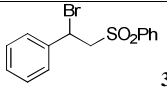
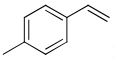
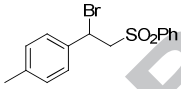
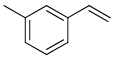
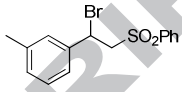
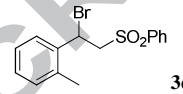
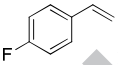
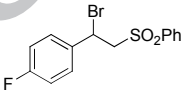
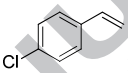
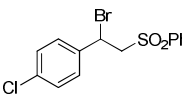
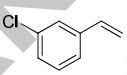
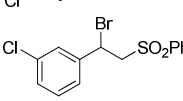
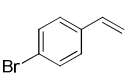
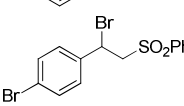
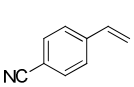
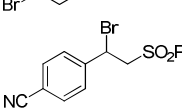
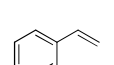
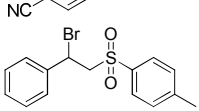
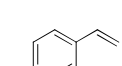
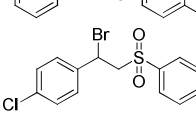
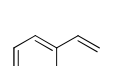
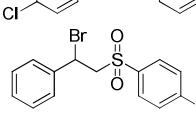
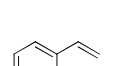
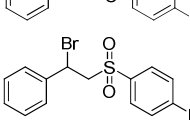
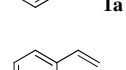
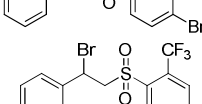
[e] **1a** (0.5 mmol), **2a** (0.5 mmol), NBS (0.6 mmol).

In an initial experiment, styrene **1a** and benzenesulfinic acid **2a**, were chosen as the model substrates to optimize the reaction conditions in the presence of NBS. Among the solvents examined, THF was found to be the most efficient reaction medium for this reaction (Table 1, entry 4). In contrast, only a trace amount of product **3aa** was detected when reaction was performed in $CH_3CN$, toluene, or EtOH (Table 1, entries 6-9). None of product was obtained in DMF, DMSO, or $H_2O$ (Table 1, entries 9-11). Further optimization of reaction temperature revealed that the best yield of **3aa** was obtained when reaction was conducted at 80°C and a lower reaction temperature led to a significantly lower yield of product (Table 1, entries 4, 12-13). The appropriate proportion of the styrene **1a**, benzenesulfinic acid **2a**, and NBS was 1.2:1:1 (Table 1, entries 14-16).

With the optimized reaction conditions in hand, we started to explore the scope and limitations of the reaction of alkenes with sulfinic acids and NBS. As demonstrated in Table 2, in general, aromatic alkenes bearing an electron-donating group or an electron-withdrawing group could react smoothly to give the corresponding products in good to excellent yields (**3aa**-**3ha**).

**Table 2**

Results for the reactions of alkenes with sulfinic acids and NBS[a]

| Entry | 1 | Time (h) | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** | 8 |  **3aa** | 83 |
| 2 |  **1b** | 8 |  **3ba** | 80 |
| 3 |  **1c** | 10 |  **3ca** | 79 |
| 4 |  **1d** | 8 |  **3da** | 73 |
| 5 |  **1e** | 10 |  **3ea** | 70 |
| 6 |  **1f** | 8 |  **3fa** | 73 |
| 7 |  **1g** | 10 |  **3ga** | 67 |
| 8 |  **1h** | 10 |  **3ha** | 66 |
| 9 |  **1i** | 10 |  **3ia** | trace |
| 10 |  **1a** | 10 |  **3ab** | 81 |
| 11 |  **1f** | 10 |  **3fb** | 75 |
| 12 |  **1a** | 10 |  **3ac** | 67 |
| 13 |  **1a** | 10 |  **3ad** | 74 |
| 14 |  **1a** | 12 |  **3ae** | 50 |

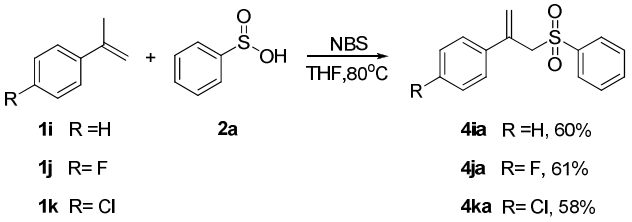
[a] Reaction conditions: alkenes **1** (0.6 mmol), sulfinic acids **2** (0.5 mmol), NBS (0.5 mmol), THF (2 mL), 80°C, 8-120 h (sealed tube).

[b] Isolated yields based on **2**.

Substrates bearing a methyl group in the para-, meta-, or ortho-position of the phenyl were subjected to the optimized reaction conditions (**1b–d**). The results showed that the reaction efficiency was not obviously affected by the steric hindrance. Moreover, halogen groups including F, Cl, and Br were compatible with this reaction leading to the products **3ea–3ha**, which could be employed for further transformations. Only a trace amount of desired product **3ia** was obtained when 4-vinylbenzonitrile was employed as substrate. Nevertheless, when

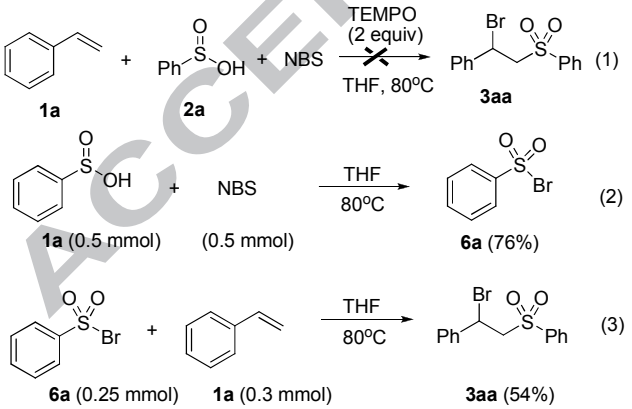
an aliphatic alkene such as 1-octene was used as the substrate, none of the desired product was obtained. In addition to benzenesulfinic acid, substituted benzenesulfinic acids containing either electron-rich or electron- deficient groups were all suitable for this reaction to generate the corresponding products in good yields (**3ab**-**3ad**). The sterically-hindered substituted arylsulfinic acids such as 2-(trifluoromethyl) benzenesulfinic acid could also be smoothly transformed to the desired β-bromo sulfone (**3ae**).

Interestingly, when α-methyl styrenes such as prop-1-en-2-ylbenzene **1i**, 1-fluoro-4-(prop-1-en-2-yl)benzene **1j**, and 1-chloro-4-(prop-1-en-2-yl)benzene **1k** were used as the substrates, the corresponding allylic sulfones **4ia-4ka** were obtained in good yields (Scheme 2). Therefore, this reaction system offers a useful and attractive strategy for the construction of allylic sulfone structural motifs, which are exceptionally valuable and versatile building blocks in synthetic and pharmaceutical chemistry.[14]



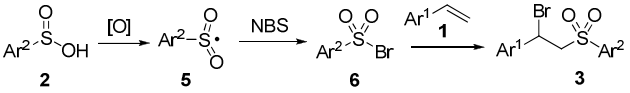

**Scheme 2** Method for the synthesis of allylic sulfones.

Considering that sulfonyl radicals were easily formed from sulfinic acids under air,[8,9d,10b,c,15] we supposed a radical pathway might be involved in this reaction system. As shown in Scheme 3 (Eq. 1), the model reaction was completely inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, a well-known radical scavenger) was added into the reaction system, suggesting that a radical pathway could be involved in the present transformation. Moreover, when the reaction of benzenesulfinic acid **2a** with NBS was conducted in the absence of styrene, benzenesulfonyl bromide **6a** was obtained in 76% yield (Scheme 3, Eq. 2). Furthermore, treatment of benzenesulfonyl bromide **6a** with styrene **1a** under the standard procedure led to the formation of desired product **3aa** (Scheme 3, Eq. 3). The above results indicated that sulfonyl bromide might be the critical intermediate in the present reaction system.




**Scheme 3** Investigation into the reaction mechanism

Although the detailed reaction mechanism is still unclear at the present stage, based on the above experiments and previous studies,[8-10,13,15] a possible reaction pathway is proposed as described in Scheme 4. Firstly, the sulfonyl radical **5** was generated from sulfinic acids **2** under air. Subsequently, sulfonyl radical **5** interacted with NBS to give sulfonyl bromide **6**. Finally, the addition of sulfonyl bromide **6** to alkene **1** would lead to the formation of the desired β-bromo sulfone **3**.




**Scheme 4** Postulated reaction pathway.

In conclusion, a novel and efficient method has been developed for the contruction of β-bromo sulfones through the direct difunctionalization of alkenes with sulfinic acids and NBS. This protocol, which utilizes simple and readily available starting materials and catalyst-free conditions, provides a convenient and highly attractive route to various β-bromo sulfones. Further studies on the scope and application of this reaction are underway.

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