NBS-Promoted Halosulfonylation of Terminal Alkynes: Highly Regio- and Stereoselective Synthesis of (E)-β-Halo Vinylsulfones

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NBS-Promoted Halosulfonylation of Terminal Alkynes: Highly Regio- and Stereoselective Synthesis of (E)-*β*-Halo Vinylsulfones

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An efficient NBS-promoted method for the synthesis of (E)-β-halo vinylsulfones has been developed. The present protocol went through an environmentally friendly metal-free process to achieve the halosulfonylation of terminal alkynes with high selectivity.

The development of green and efficient methods for the synthesis of privilege molecular skeletons is the central focus of modern organic chemistry and has been intensively pursued by the synthetic community.[1] Among them, the difunctionalization of alkynes, which involves the formation of two new vicinal chemical bonds, represents an important contribution to the functionalized alkenes.[2] The halosulfonylation of terminal alkynes has drawn considerable attention over the years, particularly in the development of atom economical and environmentally friendly reaction systems to provide β-halo vinylsulfone products.

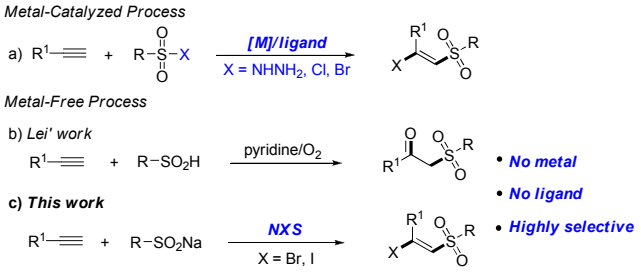
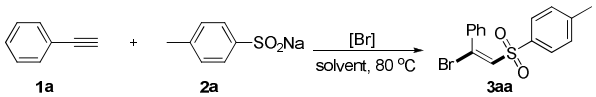


Figure 1. Difunctionalization of terminal alkyne.

On the other hand, *β*-halo vinylsulfones are well known to be an important class of compounds which are versatile building blocks and valuable intermediates in organic synthesis and medicinal chemistry.[3] For examples, as a core functional group in inhibitors of various enzymatic processes[4] and an important precursor in the synthesis of a series of useful biologically active molecules.[5] Due to its importance, various methods have been developed to construct this framework.[6] Generally, an overwhelming number of these alkyne difunctionalization transformations involve the transition metal-catalyzed (copper, iron, palladium, ruthenium *etc.*) addition of sulfonyl halogens to the terminal alkynes[6a-f] (Fig. 1a). Recently, Nakamura[6a] and Li, [6b] respectively, reported iron-catalyzed halosulfonylation of terminal alkynes using (p-Tol)$_3$P as ligand and TBHP as additives. Despite the synthetic efficiency, some of these metal-catalyzed methods often require air-sensitive and expensive ligands or additives, and produce large amounts of unwanted metal salt by-products, which makes them environmentally unfavourable and results in toxic metal residues in the products. Thus, the development of more efficient and environmentally friendly catalyst systems to achieve the halosulfonylation of terminal alkynes is still highly desirable. Very recently, Lei and coworkers reported an alkyne difunctionalization transformation via a novel metal-free process to form various *β*-keto sulfone products (Fig. 1b).[7] As our continuing interest in developing mild and efficient ways to the difunctionalization of C-C multiple bonds,[8] herein, we disclose a NXS-promoted halosulfonylation of terminal alkynes using commercially available sodium sulfinates as the sulfonyl precursor, affording (E)-*β*-bromo and iodo vinylsulfones with high selectivity (Fig. 1c). This environment friendly metal-free transformation has a broad substrate scope and may go through a radical addition process to the terminal alkynes with specific stereoselective.

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3aa

Entry	Catalyst	Solvent	Yield[b] (%)
1	NBS	DCE	53
2	NBS	DMF	trace
3	NBS	DMSO	trace
4	NBS	Toluene	88
5	TBAB	Toluene	n.d.
6	LiBr	Toluene	n.d.
7	-	Toluene	n.d.
8[c]	NBS	Toluene	85

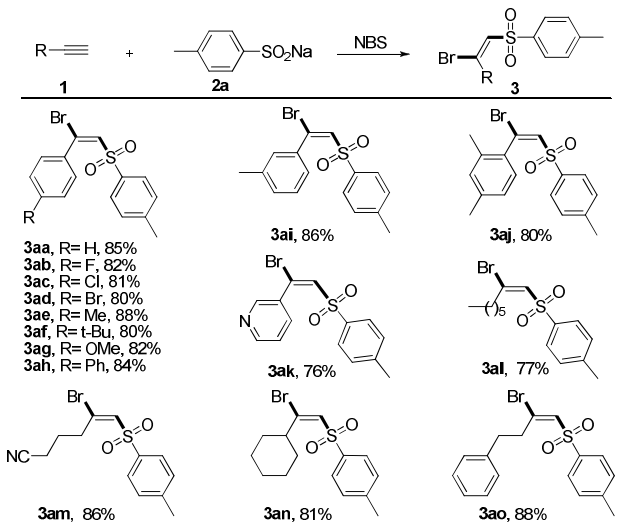
[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (0.5 mmol) in indicated solvent (2 mL) at 80 °C for 4 h. n.d. = not detected. [b] Determined by GC based on **1a**. [c] Performed under N_2.

Our initial investigations of this alkyne difunctionalization reaction focused on the addition of sodium sulfinate (**1a**) to

ethynylbenzene (**2a**) in the presence of NBS in 1,2-dichloroethane (DCE) at 80 °C. To our delight, the desired (E)-*β*-bromo vinylsulfones[9] was detected in 53% yield (Table 1, entry 1). The solvent played an important role to the success of the reaction. Polar solvents, such as DMF and DMSO were found to be totally inefficient for this transformation (entries 2-3). And non-polar solvent toluene was found to be the best solvent (entry 4). Other bromine sources LiBr, TBAB were also examined. However, no reaction occurred when using LiBr and TBAB instead of NBS (entries 5-6). This result indicated that NBS might be employed as not only bromine source, but also a trigger for this chemical process. In addition, this reaction was performed under N_2 atmosphere and has no much influence on the yield (entry 8). Thus, the optimal reaction conditions were **1a** (0.5 mmol), **2a** (0.5 mmol), NBS (0.5 mmol) in 2 mL toluene at 80 °C.

With the optimal reaction conditions in hand, we then examined the scope of this novel transformation (Table 2). Generally, various alkyl- and aryl-substituted terminal alkynes were found to be suitable reaction partner for this difunctionalization process. A series of *para*-substituted phenylacetylenes including some with electron-donating groups (Me, OMe, *t*-Bu, Ph) and some with electron-withdrawing groups (F, Cl, Br) were well tolerated and converted to the corresponding (E)-*β*-bromo vinylsulfones products **3aa**–**3ag** in good yields (80%–88%). It should be noted that these functional groups could be used for further modifications to achieve more complex structures. Then, different substituent positions were tested. *Ortho*- and *meta*- methyl substituted phenylacetylene proceeded smoothly to afford the desired products **3ah**–**3ai** in 83% and 85% yields, respectively. Notably, 3-ethynylpyridine also displayed the similar reactivity. Pleasingly, alkyl-substituted terminal acetylene can also be successfully transformed to the desired halosulfonylation products **3al**–**3ao** in good yields (70%–82%).

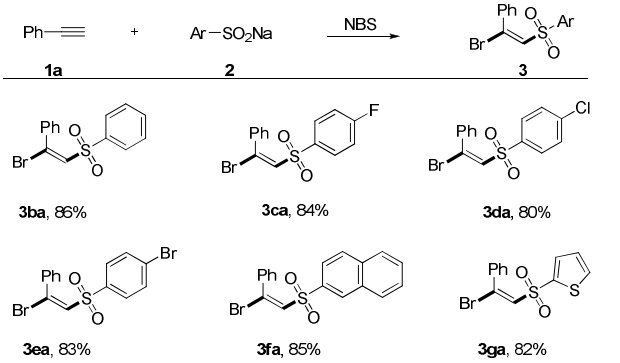
Table 2. Substrate scope of various terminal acetylenes [a, b]



[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.5 mmol), NBS (0.5 mmol) in toluene (2 mL) at 80 °C for 4 h. [b] Isolated yield.

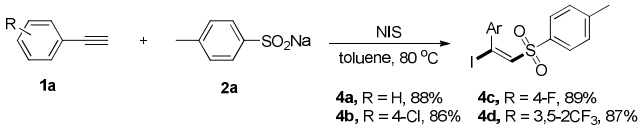
Then, the scope of the reaction with respect to the sodium sulfinates was also studied (Table 3). Different sodium benzenesulfinates bearing halogen substituents (F, Cl, Br) could react smoothly with ethynylbenzene (**1a**) to afford the halosulfonylation products **3ca**–**3ea** in good yields (70%–82%). It is worth mentioning that naphthalene and thiophene substituted sodium sulfinates were also suitable reaction partners for this novel transformation. However, our attempts to employ alkyl-substituted sodium sulfinates as the substrate turned out to be unfruitful, which might be caused by the instability of the alkyl-substituted sulfone radicals.

Table 3. Substrate scope of various sulfinate salts[a, b]



[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.5 mmol), NBS (0.5 mmol) in toluene (2 mL) at 80 °C for 4 h. [b] Isolated yield.

To further highlight the versatility of this alkyne difunctionalization strategy, we applied this method to the synthesis of (E)-*β*-iodo vinylsulfones and the expected products **4a**–**4d** were obtained in good yields by using NIS instead of NBS. However, NCS was found to be totally inefficient for this transformation.



The synthetic utility of this reaction was also studied. We tested the elegant cross-coupling[10] reactions using the newly formed (E)-*β*-halo vinylsulfones as the reaction partners (Fig. 2). The corresponding arylation, alkynylation products **5a** and **5b** were obtained in 89% and 90% yields, respectively, thus indicating that the vinyl sulfone moieties could be introduced easily to construct more complex molecules by using these products via the cross-coupling reactions.

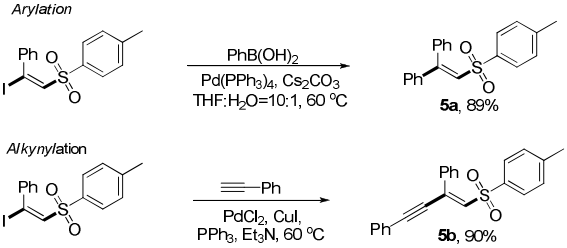


Figure 2. The synthetic utility of the (E)-*β*-halo vinylsulfones

To gain insight into the mechanism of the chemical process, several control experiments were conducted (Fig. 3). First, deuterated experiment was carried out to distinguish the hydrogen position of the terminal alkyne. As depicted in [eqn. (a)], deuterium product **3aa'** was obtained exclusively in 86% isolated yield and the deuterium atom (98% examined by ^{1}H NMR

spectroscopy) was still present. Next, when the radical scavengers, TEMPO and BHT, were employed in the reaction system, both could inhibit this halosulfonylation process, indicating that a radical pathway should be involved [eqn. (b)]. To find more direct evidence of the radical process, the styrene compounds were used to capture the sulfone radicals and the vinyl sulfone products **5a** and **5b** could be obtained in 86% and 80% yields, respectively. These observations suggested that the NBS-promoted alkyne halosulfonylation might go through a sulfone radical process. Furthermore, no sulfonyl bromide could be detected when **2a** was treated with NBS, thereby making this radical process different from the reported metal-promoted halosulfonylation processes[6a-f] [eqn. (d)].

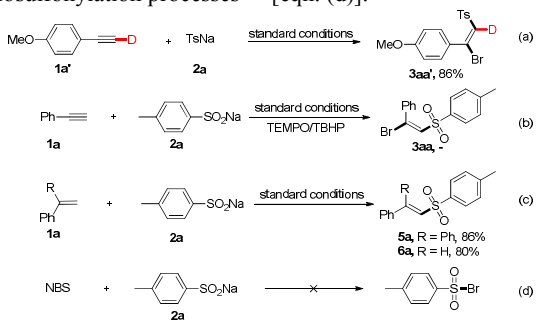
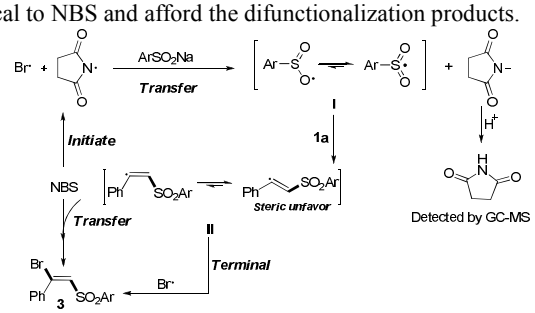


Figure 3. Control experiments

Based on the experimental results and previous reports,[6a-g] a plausible mechanism for this transformation is proposed in Scheme 1. The reaction was initially triggered by NBS to form the sulfone radical[11] which may go though the cracking of N-Br bond.[12] Subsequently, the radical addition of **I** to terminal alkyne formed the vinyl sulfone radical **II**,[6, 7] which would transfer the radical to NBS and afford the difunctionalization products.



Scheme 1 Possible reaction mechanism

In conclusion, an efficient NBS-promoted method for the synthesis of (E)-β-halo vinylsulfones has been developed. The present protocol went through an environmentally friendly metal-free process to achieve the halosulfonylation of terminal alkynes with high selectivity. NBS plays a dual role as both a trigger and bromine source in this chemical process. The mild reaction conditions, easily available starting materials and high selectivity make the present halosulfonylation protocol rather attractive and applicable. In addition, the resultant halo vinylsulfone products can be further modified efficiently, which may find their potential applications in organic synthesis and medicinal chemistry.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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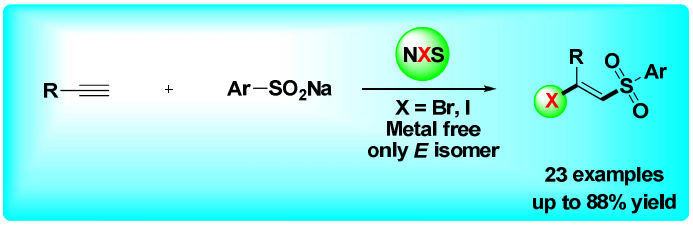

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