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ARTICLE TYPE

Direct difunctionalization of alkynes with sulfinic acids and molecular iodine: a simple and convenient approach to (*E*)-β-iodovinyl sulfones†

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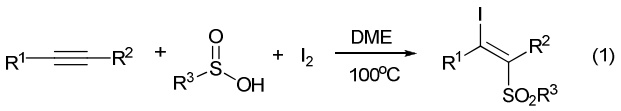
A simple and convenient approach for the construction of β-iodovinyl sulfones has been developed via direct difunctionalization of alkynes with sulfinic acids and molecular iodine. The present reaction provides a highly efficient approach to a diverse range of substituted (*E*)-β-iodovinyl sulfones in moderate to good yields with excellent stereo- and regio-selectivities but no need for any metal catalyst or additives.

As an important class of functionalized alkenes, β-halovinyl sulfones have drawn great attentions of chemists, since they can serve as not only key structural motifs of biologically active compounds and materials but also versatile building blocks for various organic transformations in synthetic chemistry.[1] In view of their importance, considerable efforts have been made to construct these frameworks.[2] From the synthetic standpoint, the direct difunctionalization of alkynes with sulfonyl halides represents one of most straightforward and useful tools for the construction of β-halovinyl sulfones because of its advantages in terms of synthetic efficiency and atom economy.[3] Through this route, both sulfone and halide functionalities can be introduced into the organic frameworks via the cascade C-S and C-Hal bond formation. In the past few decades, various β-bromovinyl and β-chlorovinyl sulfones have been effectively synthesized via the difunctionalization of alkynes.[2,3] Nevertheless, few examples for the construction of β-iodovinyl sulfones were reported owing to the instability of sulfonyl iodide.[4] In 2002, Nair and co-workers reported a cerium(IV) ammonium nitrate (CAN) mediated reaction of alkynes with aryl sulfinates leading to β-iodo vinyl sulfones in the presence of KI.[5] In 2010, Kuhakarn et al. described $PhI(OAc)_2$/KI-mediated reaction of alkynes with aryl sulfinates to give β-iodovinyl sulfones.[6] In 2013, Li reported a convenient procedure for the synthesis of (*E*)-β-iodovinyl sulfones through the TBHP mediated reaction of aryl acetylenes with sulfonylhydrazides and iodine.[7] Kuhakarn et al. reported iodine mediated iodosulfonation reaction of alkynes with sodium *p*-toluenesulfinate in the presence of 1.5 equiv of NaOAc.[8] Very recently, Taniguchi demonstrated a copper catalyzed iodosulfonylation of alkynes with aryl sulfinates and MI (M =K or Li).[9] Unfortunately, these established methods might suffer from some obvious limitations such as the low atom economy, the use of transition-metal catalyst, and stoichiometric amounts of bases, toxic or potentially dangerous oxidants. Therefore, the development of simple, efficient, atom-economic, and environmentally-benign method for the construction of β-iodovinyl sulfones still remains a highly desirable.

With our growing interest in developing new and more efficient ways for the construction of sulfone-containing organic compounds,[10] we herein report a simple and convenient approach for the synthesis of β-iodovinyl sulfones via the direct difunctionalization of alkynes with sulfinic acids and molecular iodine (eqn 1). The present reaction provides an efficient approach to various substituted β-iodovinyl sulfones in moderate to good yields with excellent stereo- and regio-selectivities making it unnecessary for any metal catalyst or additives.



(1)

Initially, the reaction among phenylacetylene **1a**, benzenesulfinic acid **2a**, and molecular iodine was investigated in DME (1,2-dimethoxyethane) at room temperature under air. To our delight, the desired product was obtained in 61% yield (Table 1, entry 1). Preliminary exploration found that higher yields up to 88% were obtained when the reaction temperature was raised further to 100°C (Table 1, entries 2-4). Among the solvents tested, apparently, DME was found to the most efficient reaction medium for this reaction (entry 4). 1,4-dioxane, DMA(1,1-dimethoxytrimethylamine), DCE (1,2-dichloroethane) and CH_3CN might also be effective (Table 1, entries 5-8). Nevertheless, lower yields were obtained when the reactions were performed separately in DMF, DMSO, toluene, and H_2O (Table 1, entries 9-12). The proportion of the substrates could also affect this transformation evidenced by the further optimization, showing that the optimal proportion of phenylacetylene, molecular iodine, and benzenesulfinic acid was 1:1:2 (Table 1, entries 4, 13-15).

Under the optimized conditions, the scope and limitations of the reactions of various alkynes with sulfinic acids were investigated and the results are shown in Table 2. Accordingly,

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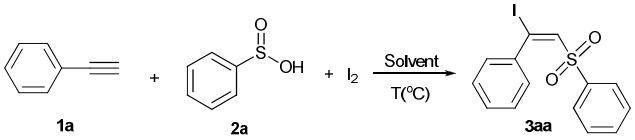
Table 1 Optimization of the reaction conditions[a]



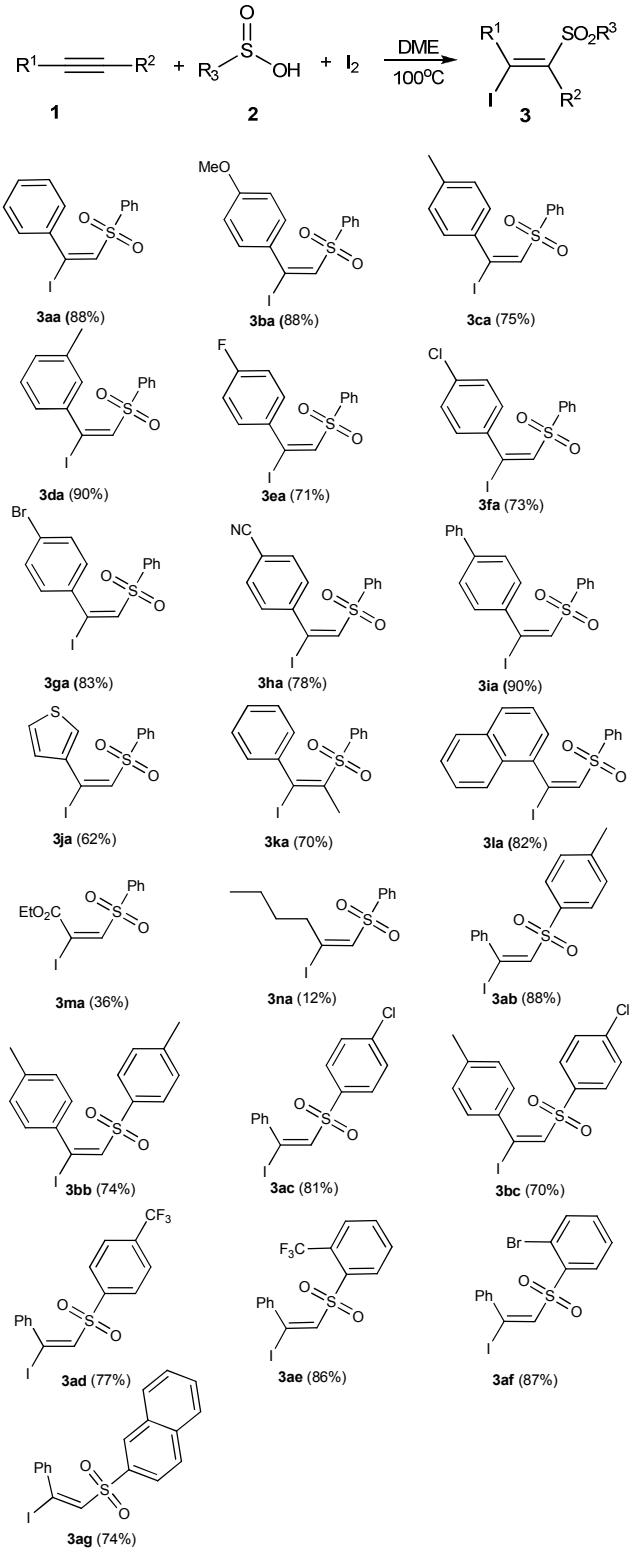
Entry	Solvent	T(°C)	Yield (%)[b]
1	DME	25	61
2	DME	60	72
3	DME	80	78
4	DME	100	88
5	1,4-dioxane	100	85
6	DMA	100	76
7	DCE	100	72
8	CH_3CN	100	71
9	DMF	100	52
10	DMSO	100	22
11	toluene	100	55
12	H_2O	100	38
13	DME	100	53[c]
14	DME	100	69[d]
15	DME	100	87[e]

[a] Reaction conditions: phenylacetylene **1a** (0.5 mmol), benzenesulfinic acid **2a** (1 mmol), I_2 (0.5 mmol), solvent (2 mL), 25-100°C, 12 h. [b] Isolated yields based on **1a**. [c] **1a** (0.5 mmol), **2a** (0.5 mmol); [d] **1a** (0.6 mmol), **2a** (0.5 mmol), [e] **1a** (0.5 mmol), **2a** (1.2 mmol).

alkynes bearing an electron-donating group (e.g., Me and OMe) or an electron-withdrawing group (e.g., F, Cl, Br and CN) are found to be tolerant in these transformations, and the corresponding products were obtained in good to excellent yields (**3aa**-**3ia**). It is noteworthy that this protocol could be tailored for heteroaromatic alkyne (e.g., 3-ethynylthiophene) and internal alkyne (e.g., prop-1-ynylbenzene) leading to the desired products in 62% and 70% yields, respectively (**3ja** and **3ka**). Also, 1-ethynylnaphthalene could be employed in the reaction to generate the desired product **3la** in high yield. Nevertheless, the corresponding products were obtained in relatively low yields when ethyl propiolate and 1-hexyne **1n** were used as the substrates (**3ma** and **3na**). In addition to benzenesulfinic acid, all substituted benzenesulfinic acids containing either electron-rich or electron- deficient groups were suitable for this reaction to furnish the corresponding products in good yields (**3ab**-**3bd**). Even the sterically-hindered substituted arylsulfinic acids (e.g., 2-(trifluoromethyl)benzenesulfinic acid and 2-bromobenzenesulfinic acid) and the bulky naphthalene-2-sulfinic acid could also work well to produce the β-iodovinyl sulfones (**3ae**-**3ag**) efficiently under the reaction conditions. Unfortunately, when alkylsulfinic acids such as methanesulfinic acid trifluoromethanesulfinic acid were used as the substrates, the corresponding products were not obtained.

Notably, the present reaction can be effectively scaled up to gram scale with the similar efficiency (2.96g, with 80% yield for the model reaction), suggesting that this simple protocol could be employed as a practical method to access β-iodovinyl sulfones. Furthermore, the synthetic utility of this reaction was also investigated. When the resulting β-iodovinyl sulfones were used to react with alkynes, the desired alkynylation products were obtained in high yields (eqn 2). Moreover, acetylenic sulfones are an important class of synthetic intermediate.[11] When stoichiometric amounts of K_2CO_3 was added into the present

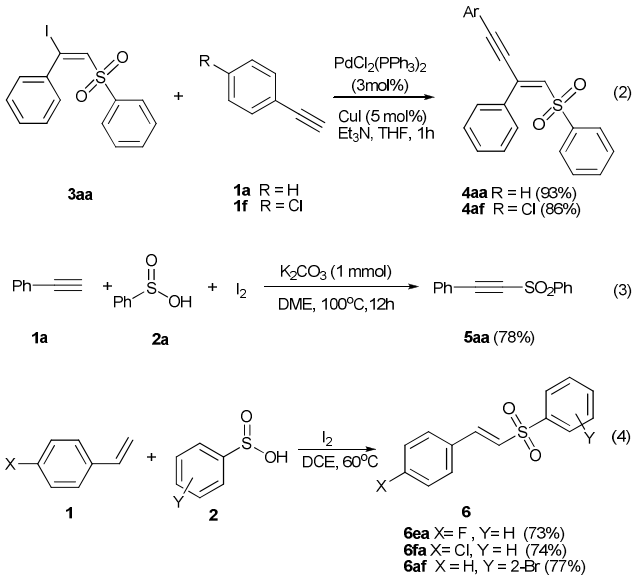
Table 2 Results for difunctionalization of alkynes with sulfinic acids and molecular iodine[ab,]



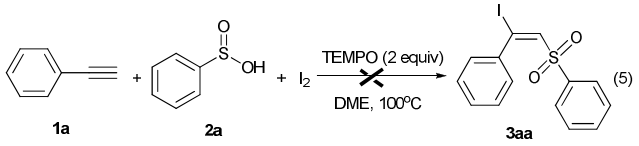
[a] Reaction conditions: alkynes **1** (0.5 mmol), sulfinic acids **2** (1 mmol), I_2 (0.5 mmol), DME (2 mL), 100°C, 12-24 h. [b] Isolated yields based on **1**.

model reaction system under the standard conditions, the corresponding acetylenic sulfone **5aa** was isolated in 78% yield

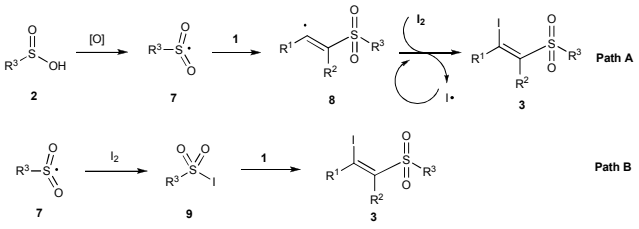
(eqn 3). Interestingly, when alkenes reacted with sulfinic acids and molecular iodine in DCE, the corresponding (*E*)-vinyl sulfones were obtained in good yields (eqn 4). Therefore, the developed reaction system can provide a simple, convenient, and metal-free synthetic method to access vinylsulfone structural motifs, which extensively exist in various nature products, biologically active compounds, and pharmaceuticals.[12]



It is known that sulfonyl radical species are easily generated from sulfinic acids under air.[10b-d,13] Therefore, a radical process might be presumably involved in the present reaction system. As shown in eqn (5), when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a well-known radical radical-capturing species, was added into this reaction system, the present reaction was completely inhibited as expected. It suggests that a radical pathway might be involved in this transformation.



Based the above experiments and referring to the previous studies,[4-10,13] the possible reaction pathways are proposed and demonstrated in Scheme 1. Firstly, the sulfonyl radical **4** was generated from sulfinic acids under air. Subsequently, the sulfonyl radical addition to alkyne **1** gives the alkenyl radical **5**, which further interacted with molecular iodine leading to



Scheme 1. Possible reaction pathway.

the formation of the desired β-iodovinyl sulfone **3** (Path A). Meanwhile, another pathway involving the direct iodosulfonylation of alkynes with sulfonyl iodides that generated in situ from molecular iodine and sulfinic acids might also be involved in the present reaction (Path B).[6,7]

In conclusion, we have developed a simple and efficient method for the synthesis of (*E*)-β-iodovinyl sulfones via the direct difunctionalization of alkynes with sulfinic acids and molecular iodine. The developed protocol provides an alternative and highly attractive route to various (*E*)-β-iodovinyl sulfones from the simple and readily available starting materials, and especially it avoids the use of any transition-metal catalyst, and stoichiometric amounts of bases, toxic or potentially dangerous oxidants. Such a new synthesis methodology for (*E*)-β-iodovinyl sulfones would find the potential applications in the fields of synthetic and pharmaceutical chemistry.

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