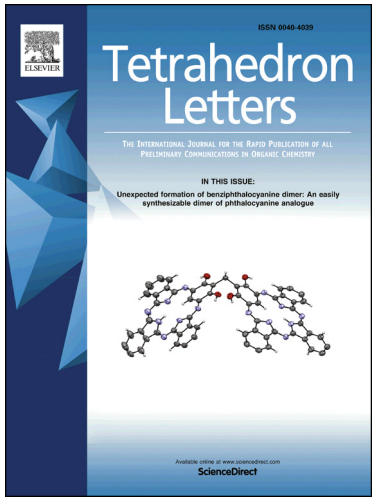

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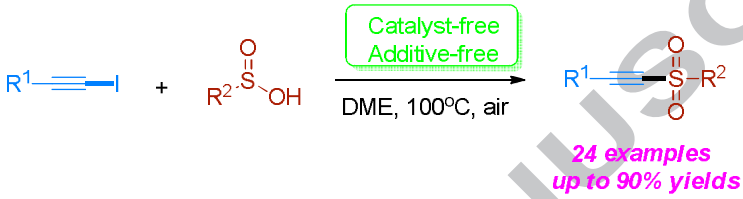

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Direct cross-coupling of aryl alkynyliodines with arylsulfinic acids leading to alkynyl sulfones under catalyst-free conditions

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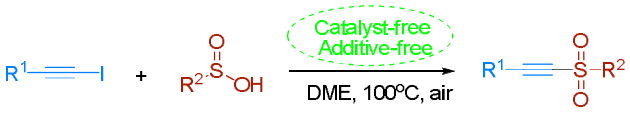
ABSTRACT

A facile and efficient one-pot method has been developed for the construction of alkynyl sulfones via direct cross-coupling reaction of aryl alkynyliodines and arylsulfinic acids. The present transformation could be accomplished under catalyst- and additive-free conditions, providing a series of alkynyl sulfones in moderate to good yields with favorable functional group tolerance.

Sulfone-containing compounds have shown various interesting biological activities and constitute primary components of clinical pharmaceuticals and drug candidates.[1] Furthermore, they can also serve as versatile building blocks in diverse range of synthetically useful transformations.[2] In particular, alkynyl sulfones are an important class of sulfone-containing molecules, which exhibit widespread applications in organic synthesis because sulfonyl group acts not only as an activator to enhance the reactivity of the triple bond but also as an easily removable protective motif.[3,4] In general, conventional methods for the synthesis of alkynylsulfones involve the oxidation of the alkynyl sulfides,[5] sulfonylation of alkynylsilanes,[6] and elimination reactions from β-keto sulfones,[7] α,β-unsaturated sulfones,[8] or 5-amino-4-isoxazolyl sulfones.[9] Alternative methods such as the sulfonylation reaction of alkynyl(aryl)iodonium salts by addition of arylsulfinate salts,[10] the coupling of alkynyl halides with copper sulfinates,[11] the addition of aryl sulfinates to ethynylbenzio-doxolone derivatives (R-EBX),[12] and the sulfonylation of arylacetylenic acids and arylacetylenes with sodium sulfinates[13] have also been developed. However, almost all of these methods might suffer from certain limitations such as the tedious work-up procedures, unstable or toxic starting materials, and complex reaction mixtures or low selectivity. Therefore, the development of direct and more efficient methods to access alkynyl sulfones in terms of operational simplicity, availability of starting materials and environmental sustainability is still in constant demand in the synthetic chemistry.

With our continued interest in the construction of sulfone-containing compounds,[14] herein, we wish to present a simple and efficient method for the construction of alkynyl sulfones through the direct cross-coupling of aryl alkynyliodines and arylsulfinic acids under catalyst- and additive-free conditions (Scheme 1).



Scheme 1. Direct cross-coupling of alkynyliodines with sulfinic acids to access alkynyl sulfones.

The initial exploration of this reaction was carried out using (iodoethynyl)benzene **1a** and 4-methylbenzenesulfinic acid **2a** as coupling partners to determine the optimal reaction conditions. When the model reaction was conducted in DME at room temperature under catalyst- and additive-free conditions, the desired product **3a** was isolated in 34% yield (Table 1, entry 1). To our delight, the reaction efficiency was significantly improved along with the increase of reaction temperature, and the highest yield (86%) was obtained when the reaction was carried out at 100°C (Table 1, entry 4). Then, the solvent effect was investigated. The reaction performed in DME gave higher yield than in other ether solvent such as THF or 1,4-dioxane (Table 1, entries 4, 7, 8). When reaction was conducted in DCE, CH_3CN or EtOH, the corresponding product **3a** was obtained in moderate yields (Table 1, entries 9-11). Nevertheless, low yields or none of the desired product was

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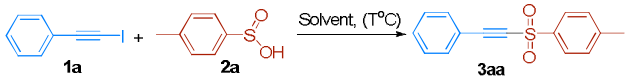
detected when toluene, DMF, or DMSO was used alone as the solvent (Table 1, entries 12-14). Also, the reaction efficiency was obviously low with the decreasing of **2a** loading (Table 1, entries 15 and 16). The highest yield was provided when the ratio of **1a**:**2a** is 1:2 (Table 1, entry 4). A further increase in the quantity of **2a** did not improve the reaction efficiency (Table 1, entry 17). As a consequence, the reaction conditions used in entry 4 were determined to be the optimized conditions.

Table 1. Optimization of reaction conditions[a]



Entry	T(°C)	Solvent	Yield (%)[b]
1	25	DME	34
2	60	DME	51
3	80	DME	65
4	**100**	**DME**	**86**
5	110	DME	82
6	120	DME	77
7	100	THF	56
8	100	1,4-dioxane	40
9	100	DCE	68
10	100	CH_3CN	59
11	100	EtOH	58
12	100	Toluene	17
13	100	DMF	Trace
14	100	DMSO	0
15	100	DME	56[c]
16	100	DME	61[d]
17	100	DME	85[e]

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), DME (2 mL), 100°C, 12h.

[b] Isolated yields based on **1a**.

[c] **1a** (0.1 mmol), **2a** (0.1 mmol).

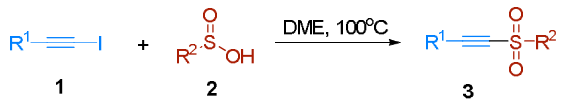
[d] **1a** (0.1 mmol), **2a** (0.15 mmol).

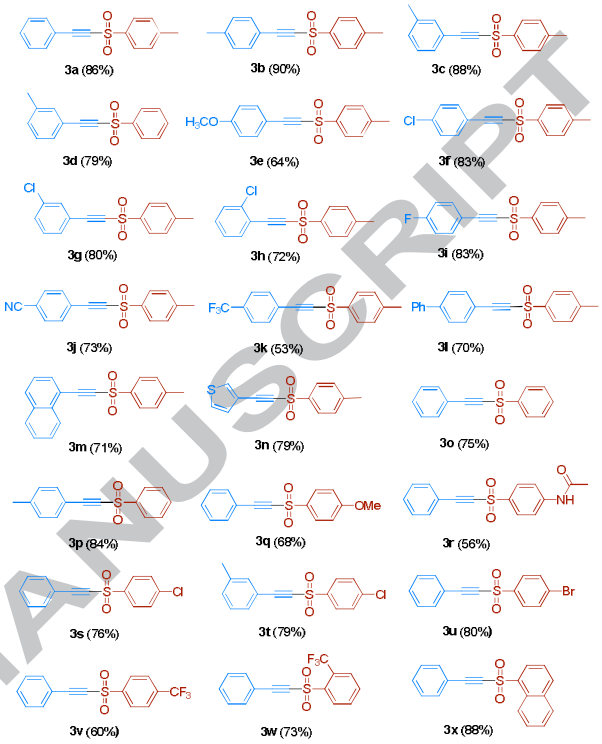
[e] **1a** (0.1 mmol), **2a** (0.3 mmol).

With the optimal reaction conditions in hand, the substrate scope of this coupling reaction was tested (Table 2). Generally, aromatic alkynyliodines with a wide range of aryl substituents including electron-rich substituents and electron-poor substituents all successfully delivered the desired products in satisfactory yields (**3b**-**3l**). In addition, 1-(iodoethynyl)naphthalene could undergo the transformation smoothly, furnishing its corresponding product (**3m**) in good yield. Remarkably, heteroaryl alkynyliodine such as 3-(iodoethynyl)thiophene was also suitable for this reaction, affording the desired product **3n** in 79% yield. Next, we also examined the scope of various sulfinic acids as the coupling partners. Both electron-donating (Me, OMe) and electron-withdrawing substituents (Cl, Br, CF_3) on the aryl groups of sulfinic acids were well tolerated in this process to give the desired products (**3q**-**3v**) in moderate to good yields. The *ortho* substituted sulfinic acids could also effectively react with (iodoethynyl)benzene leading to the product **3w** in good yield. Moreover, naphthalene-1-sulfinic acid was compatible with the standard conditions to provide the desired product **3x** in 88% yield.

Several control experiments were carried out to elucidate the possible reaction mechanism. Initially, none of the alkynyl sulfone **3a** was detected when the reaction of

Table 2. Catalyst-free cross-coupling of aryl alkynyliodines with arylsulfinic acids to access alkynyl sulfones[a,b]

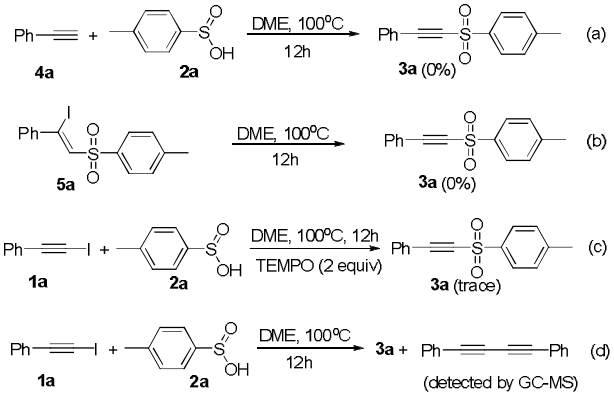




[a] Reaction conditions:**1** (0.1 mmol), **2** (0.2 mmol), DME (2 mL), 100°C, 12h.

[b] Isolated yields based on **1**.

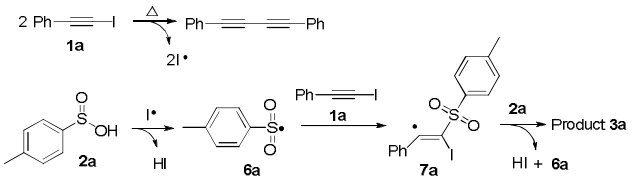
phenylacetylene **4a** with 4-methylbenzenesulfinic acid **2a** was conducted under the optimized conditions (Scheme 2 (a)). Furthermore, when the preformed β-iodovinyl sulfone **5a** was subjected separately under the standard conditions, the desired product **3a** was also not observed (Scheme 2 (b)). The above results suggested alkyne and β-iodovinyl sulfone should not be the key intermediates in the present reaction system. Next, the model reaction was significantly inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well known radical-capturing species, was added into reaction



Scheme 2. Preliminary mechanistic studies

system, indicating that the possible involvement of a radical process in the present transformation (Scheme 2, (c)). Moreover, in addition to product **3a**, the homocoupling diyne was also detected by GC-MS in the model reaction (see SI), which indicated an alkynyl and iodine radical might involve in this reaction system (Scheme 2, (d)).[15]

On the basis of these results, a possible reaction pathway for this coupling reaction was proposed as shown in Scheme 3. Firstly, sulfinic acid **2a** gave the sulfonyl radical **6a** with the help of iodine radical, which was generated in situ from homocoupling of alkynliodine. Then, the selective addition of sulfonyl radical **6a** to alkynyliodine **1a** would lead to formation of alkenyl radical **7a**. Finally, **7a** underwent β-fragmentation of an iodine radical that then abstracted a H-atom from the sulfinic acid **2a** to sustain the chain and produce the desired alkynyl sulfone **3a**. Nevertheless, another possible pathway involving the cross-coupling of sulfonyl radical with alkyne radical that generated in situ from alkynyliodine might also be involved in this reaction system.[15]



Scheme 3. Possible reaction pathway

In summary, we have successfully developed a convenient and efficient catalyst-free method for the construction of alkynyl sulfones through the direct cross-coupling of aryl alkynyliodines and arylsulfinic acids. The present protocol, which utilizes readily available starting materials, simple operation, and environmentally benign conditions, provides a highly attractive approach to various alkynyl sulfones in moderate to good yields. Preliminary mechanistic studies indicated that a radical process might be involved in the present reaction. Further investigation of the detailed reaction mechanism and synthetic application are ongoing in our lab.

Acknowledgements

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