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Electrochemical Induced Regio- and Stereoselective Difunctionalization of Alkynes: The Synthesis of (*E*)-β-Iodovinyl Sulfones

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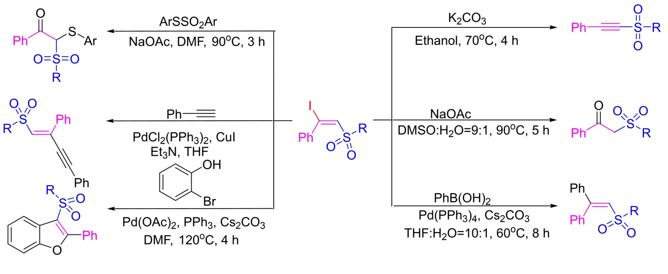
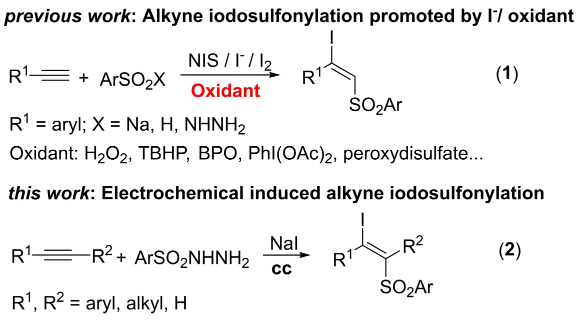
An efficient, green, and oxidant-free electrochemical method for alkyne difunctionalization was described. Using undivided electrochemical cell for iodosulfonylation of alkynes with commercially available iodide radical (NaI), arylsulfonyl radical ($ArSO_2NHNH_2$) sources, a variety of (*E*)-β-iodovinyl sulfones were obtained in one-pot with wide substrate scope, excellent regio- and stereoselectivity under mild and ecofriendly conditions.



Scheme 1. Application of β-iodovinyl sulfones.



Scheme 2. Strategies for the synthesis of β-iodovinyl sulfones.

Introduction

Alkyne iodosulfonylation is a powerful strategy for synthesizing β-iodovinyl sulfone compounds that are interesting for rapid construction of diverse functional groups in biologically active molecules (Scheme 1).[1] Typically, the direct difunctionalization of alkynes could provide a straightforward method for achieving scaffold diversity in organic transformations, which involves the formation of two new vicinal chemical bonds.[2] In this context, the choice of suitable iodine and sulfonyl sources for the formation of C–I/C–S bonds is the key factor in achieving these molecular skeleton. Traditional strategies for the synthesis of β-iodovinyl sulfone often proceed via a reaction between terminal alkyne and sulfinate (or sulfonyl hydrazide) promoted by iodide source, such as NIS, I^- or I_2, which requires stoichiometric chemical oxidant or high reaction temperature (Scheme 2, eq 1).[1d,3] Obviously, the use of sacrificial reagent inevitably leads to decreased atom economy of the overall chemical transformation, and not accord with the increased environmental requirements.

Notably, Organic electrochemistry provide new opportunities for the construction of C–X bonds via the replacement of common reagents by electricity.[4] Recent advances have shown that electric current can be used to induce reduction and oxidation reactions, and difunctionalization of alkenes can be achieved through electrochemical anodic oxidation in the absence of oxidizing agents.[5,6] Inspired by the above elegant works, we envisioned that whether the alkyne iodosulfonylation can be achieved under sustainable electrochemical oxidative conditions.

Results and Discussion

We thus started to explore the practicability of the proposed route as shown in Scheme 2, eq 2. Initially, p-toluenesulfonyhydrazide (**1a**) and phenylacetylene (**2a**) were chosen as the model substrates in an undivided cell equipped with a pair of platinum-plate electrodes (10 mm × 10 mm × 0.1 mm) in the presence of iodine source. As shown in Table 1, after extensive experiments, we identified that the optimized conditions comprised the use of chloroform ($CHCl_3$) and water (v/v 1/1) as cosolvent, NaI (1.4 equiv) as iodine source and electrolyte under a constant current (40 mA). The expected product **3a** was obtained in an optimal 88% yield along with nitrogen and hydrogen as major byproducts after the reaction proceeded at ambient temperature for 5 h (Table 1, entry 1). Other iodine sources, such as *n*-Bu_4NI and NaI, were also examined and the

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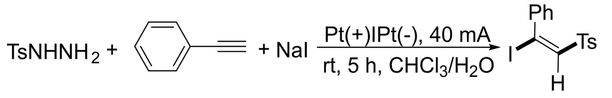
Table 1. Optimization of reaction condition.[a]

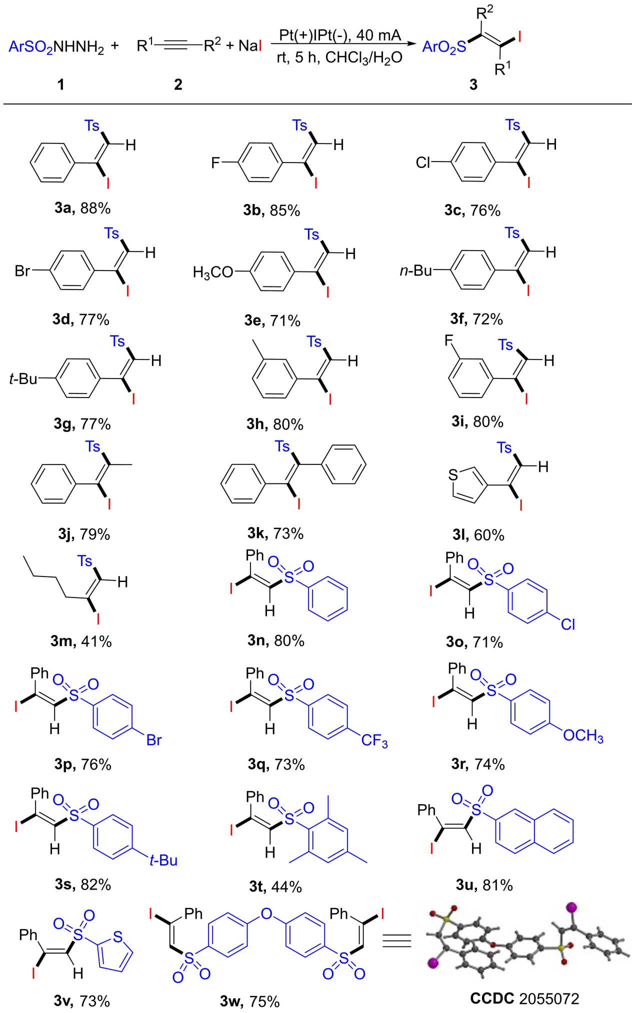


1a **2a** **3a**

Entry	Variation from the stand conditions	Yield [%][b]
1	None	88
2	KI instead of NaI	81
3	Bu_4NI instead of NaI	87
4	MeCN instead of $CHCl_3$	24
5	THF instead of $CHCl_3$	39
6	20 mA instead of 40 mA	30
7	60 mA instead of 40 mA	65
8	2.8 equiv. of NaI was used	63
9	2.8 equiv. of 1a was used	73
10	3 h instead of 5 h	9
11	8 h instead of 5 h	12
12	No electric current	N.D.

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.7 mmol), NaI (0.7 mmol), $CHCl_3/H_2O = 1:1$ (3 mL); Pt (10 mm×10 mm×0.1 mm) anode and cathode, undivided cell, rt, 5 h; [b] Isolated yield.

Table 2. Scope of alkynes and arylsulfonohydrazides.[a]



3a, 88% **3b**, 85% **3c**, 76% **3d**, 77% **3e**, 71% **3f**, 72% **3g**, 77% **3h**, 80% **3i**, 80% **3j**, 79% **3k**, 73% **3l**, 60% **3m**, 41% **3n**, 80% **3o**, 71% **3p**, 76% **3q**, 73% **3r**, 74% **3s**, 82% **3t**, 44% **3u**, 81% **3v**, 73% **3w**, 75%

[a] Reaction conditions: for entries **3a-3v**, **1** (0.5 mmol), **2** (0.7 mmol), NaI (0.7 mmol), $CHCl_3/H_2O = 1:1$ (3 mL); Pt (10 mm×10 mm×0.1 mm) anode and cathode, undivided cell, rt, 5 h; for entry **3w**, **1** (0.5 mmol), **2** (1.4 mmol), NaI (1.4 mmol), $CHCl_3/H_2O$ = 1:1 (3 mL), Pt (10 mm × 10 mm × 0.1 mm) anode and cathode, undivided cell, rt, 5 h.

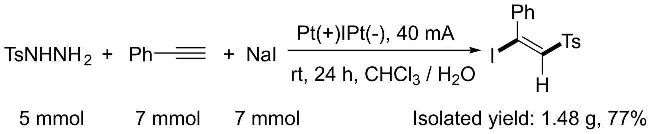
results indicated that all iodine salts could conduct this reaction smoothly (Table 1, entries 2–3). Replacement of $CHCl_3$ with other solvents (MeCN or THF) gave inferior results (entries 4–5). Alteration of the electric current, reaction time and the ratio of terminal alkyne **2a** and NaI did not enhance the coupling efficiency (entries 6–11). Control experiment showed that without constant current no desired product **3a** was detected (Table 1, entry 12), indicating the electric current is crucial to this transformation.

With the optimal reaction conditions in hand, the substrate scope of the reaction with regard to arylsulfonohydrazide **1** and alkynes **2** was explored, and the results are summarized in Table 2. Generally, the para- and meta- substituted aromatic terminal alkynes bearing electron-donating (n-butyl, tert-butyl, methoxyl or methyl) or electron-withdrawing groups (fluor-, chloro- or bromo-) on the benzene ring readily coupled with p-toluenesulfonylhydrazide **1a** and NaI under the constant current, affording the desired products **3a-3i** in 71–88% yields. As for the sterically hindered substrates, such as internal alkyne **2j** and **2k**, the steric hindrance did not significantly affect the reaction efficiency, high regioselective (*E*)-β-iodovinyl sulfones **3j** and **3k** were obtained in 79 and 73% yields, respectively. Furthermore, the heterocyclic compound 3-ethynylthiophene **2l** was successfully employed, providing the corresponding iodosulfonylation product **3l** in 60% yield and excellent stereoselectivity. It should be noted that the aliphatic terminal alkyne **1m**, which showed lower reactivity in difunctionalization reactions, was also suitable for the reaction, leading to the desired product **3m** in 41% yield.

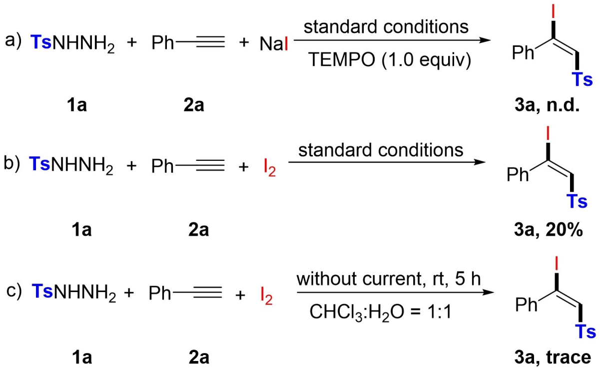
Next, we explored the compatibility of the sulfonyl reagents. Substituted arylsulfonohydrazides with Br-, Cl-, CF_3-, CH_3O- and *t*-Bu- groups reacted with **2a** to provide products **3n-3s** in 71–82% yields regardless of their different electronic properties (Table 2, **3n-3s**). Unfortunately, the steric hindrance had a negative influence on the reaction. For instance, β-iodovinyl sulfone **3t** was isolated in only 44% yield due to the ortho-substituted steric effect of 2,4,6-trimethylbenzenesulfonyl hydrazide (Table 2, **3t**). Besides, introducing heteroaryl and polycyclic aromatic substituents into sulfonyl hydrazides also gave the coupling products **3u** and **3v** in moderate yields. Notably, the bis-coupling product **3w** from bis-substituted arylsulfonohydrazides **1w** was obtained in 75% yield (Table 2, **3w**). As only E isomer of **3w** was obtained by X-ray diffraction analysis (CCDC No. 2055072), the regio- and stereoselectivity of the reaction was unambiguously confirmed.

With the aim of evaluating the scalability of the reaction, further study was conducted on a gram scale and the result revealed that the electrolytic model reaction could be performed with 77% yield under slightly modified reaction conditions (Scheme 3).

To shine light on the reaction mechanism, some control experiments were performed. As shown in Scheme 4, desired



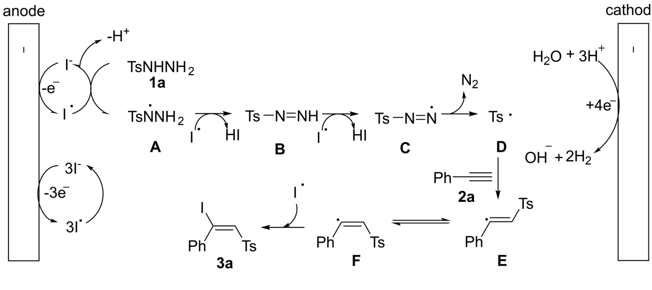
Scheme 3. Electrochemical gram-scale synthesis of (*E*)-β-iodovinyl sulfone.



Scheme 4. Mechanistic studies.

product **3a** was not detected under the standard condition when 1.0 equiv. of radical-trapping reagent, 2,2,6,6-tetramethylpiperidinooxy (TEMPO), was added into the system (Scheme 4a), which indicated that the reaction might proceed via a radical pathway. In addition, using stoichiometric amount of I_2 as the iodine source greatly decreased the reaction efficiency (20% yield, Scheme 4b) and no iodosulfonylation occurred in the absence of current (Scheme 4c). These results illustrated that iodine radical was likely to be involved in the reaction process and the electric current played a critical role in this difunctionalization.

Based on the mechanistic studies and preceding literature,[7] a plausible radical-based pathway is presented for the electrochemical synthesis of (*E*)-β-iodovinyl sulfones **3a**. As shown in Scheme 5, the active catalytic species, iodine radical, was generated via the oxidation of iodine ions in the anodic electrode and then reacted with arylsulfonyl hydrazide **1a** to achieve the radical intermediate A, which further oxidated by iodine radical in two steps to afford arylsulfonyl radical D, accompanied by the loss of molecular HI and N_2. In the meantime, the molecular HI further underwent oxidation to regenerate the iodide radical and release of H^+. Next, radical coupling occurred between arylsulfonyl radical D and alkyne **2a** to produce radical intermediate E, which is easily captured by iodine radical to afford the target product **3a**. At the cathode, reduction took place to H^+, providing molecular H_2 to fulfill the electrochemical cycle.



Scheme 5. Proposed mechanism.

Conclusions

In conclusion, we developed an efficient electrochemical iodosulfonylation of alkynes under oxidant-free condition. This protocol features a broad substrate scope, chemical oxidant free, excellent regio- and stereoselectivity and gram-scale synthesis. Further detailed mechanistic studies and applications based on this efficient transformation are underway in our laboratory.

Experimental Section

Typical procedure for synthesis of (*E*)-β-iodovinyl sulfones. Compound **1**, sulfonylhydrazide (0.5 mmol), compound **2**, alkyne (0.7 mmol), NaI (0.7 mmol) and $CHCl_3/H_2O$ (3 mL, v/v = 1:1) were charged into a 20 mL glass tube without exclusion of air. The tube was equipped with platinum plates (10 mm × 10 mm × 0.1 mm) as both the anode and cathode. The constant current (40 mA) electrolysis was carried out for 5 hours at room temperature. Then, saturated sodium thiosulfate solution was added to quench the reaction and the mixture was extracted with ethyl acetate (5.0 mL × 3). The organic phases were combined and dried with anhydrous $MgSO_4$, purified by silica gel column chromatography (ether/ethyl acetate as eluent) to afford the corresponding product **3**. The identity and purity of products were confirmed by ^1H, ^{13}C, HRMS and X-ray single crystal diffractometer spectroscopic analysis.

Deposition Number 2055072 (for **3w**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Electrochemically catalyzed · Difunctionalization · Iodosulfonylation · Regioselectivity · Stereoselectivity

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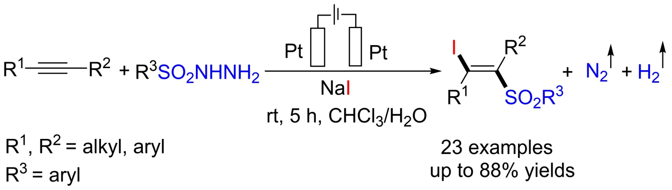

An efficient method for electrochemical iodosulfonylation of alkynes was developed under oxidant-free condition. This procedure affords valuable β-iodovinyl sulfones with broad substrate scope, excellent regio- and stereoselectivity. Moreover, this facile protocol can be applied to gram-scale synthesis of (*E*)-β-iodovinyl sulfone.

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Electrochemical Induced Regio- and Stereoselective Difunctionalization of Alkynes: The Synthesis of (*E*)-β-Iodovinyl Sulfones