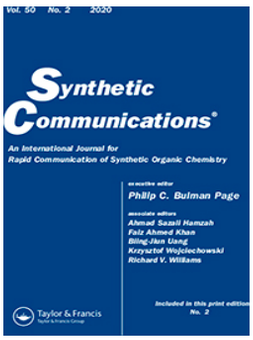

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Electrochemical decarboxylative sulfonylation of arylacetylenic acids with sodium arylsulfinates: Access to arylacetylenic sulfones

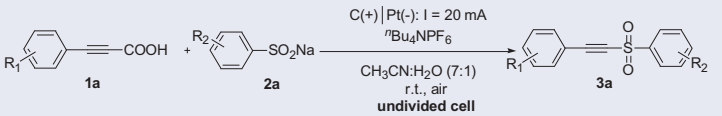
Qihao Zhong, Yongli Zhao, Shouri Sheng, and Junmin Chen

Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, China

ABSTRACT

An efficient decarboxylative sulfonylation of arylacetylenic acids with sodium arylsulfinates has been achieved by an electro-oxidative strategy. This novel protocol offers a simple, efficient, and green route to a series of arylacetylenic sulfones in moderate yields under metal-free and external oxidant-free conditions.

GRAPHICAL ABSTRACT



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Introduction

Sulfur-based compounds are ubiquitous in agrochemicals, bioactive products, pharmaceuticals, and functional materials.[1] Among different oxidative state of sulfur containing moleculars, organosulfone compounds have emerged as privileged building blocks in the area of pharmaceutical and agrochemical chemistry because of their impressive biological activities such as anti-HIV, anticancer, and antibacterial.[2] In particular, acetylenic sulfones are important synthetic building blocks and even subunits of a number of bioactive structures.[3] Numerous methods are available toward the synthesis of acetylenic sulfones, which could be summarized in four major methods: one is oxidation of the alkynyl sulfides.[4] The second approach is elimination reactions from β-keto sulfones or α,β-unsaturated sulfones.[5] The third method is the coupling of alkynyl halides with copper sulfinates.[6] Recently, some alternative methods were developed such as sulfonylation of arylacetylenic acids,[7] arylacetylenes,[8] alkynylsilanes[9] and alkynyl (aryl)iodonium salts[10] with sodium sulfinates as well as their alternatives such as sulfonyl hydrazides[11] under different catalyst systems. These routes are accompanied by

CONTACT Junmin Chen jxnuchenjm@163.com Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, China.

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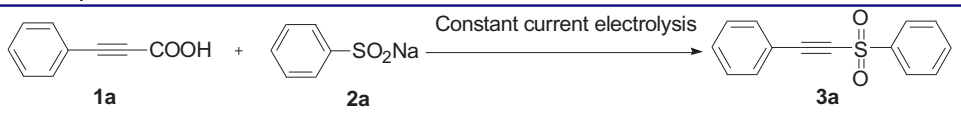
severe disadvantages such as harsh conditions, the necessity for several steps, elaborated precursors, and stoichiometric chemical oxidant. Furthermore, larger amounts of reagent waste, sophisticated synthetic conditions such as inert atmosphere as well as high-temperature, emerge as unfavorable aspects from the aforementioned approaches. Therefore, the development of a sustainable, nonhazardous and efficient method for the synthesis of acetylenic sulfones is consequently an important goal in organic chemistry.

In the past decade, electrochemistry has attracted continuous interest due to its inherently safe nature and access to extraordinary reaction pathways. Electro-organic chemistry can be seen as a green alternative to classical organic chemistry owing to the fact that it reverts solely to the electric current as an inexpensive and sustainable oxidizing or reducing agent, which minimizes the amount of waste dramatically.[12] Recently, sulfinates can be readily oxidized into the corresponding sulfonyl radicals and would be trapped by various electrophilic coupling partners under electrochemical conditions. For example, Wang and coworkers reported an electrochemical decarboxylative sulfonylation of cinnamic acids with sodium sulfinates to α,β-unsaturated phenyl sulfones by employing a constant current setup in undivided cells.[13] Furthermore, halide mediated oxidations of aryl sulfinates have also been developed in the preparations of oxindole and indenones.[14] However, the alkynylcarboxylic acid as coupling partner in electro-organic chemistry is not explored. Herein, we wish to present a novel metal-free and oxidant-free protocol for electrochemical decarboxylative sulfono functionalization using the reaction of arylacetylenic acids with sodium sulfinates, to provide a range of arylacetylenic sulfones molecules.

Results and discussion

The initial exploration of this reaction was carried out using 3-phenylpropiolic acid (**1a**) and sodium benzenesulfinate (**2a**) as coupling partners to determine the optimal reaction conditions and the results were summarized in Table 1. To our delight, when 3-phenylpropiolic acid (**1a**, 0.5 mmol) was treated with sodium benzenesulfinate (**2a**, 1.0 mmol) in a solution of $LiClO_4$ (1.0 mmol) in a solvent mixture CH_3CN/H_2O (7/1 mL), in a undivided cell with graphite rod (ϕ 6 mm) as an anode, Pt plate (10 mm× 10 mm) as a cathode under a constant current (20 mA). The corresponding acetylenic sulfone **3a** was obtained in a yield of 32% after the reaction proceeded at room temperature for 2 h (Table 1, entry 1). Other electrolytes, such as $^{n}Bu_4NClO_4$, $^{n}Bu_4NPF_6$, Et_4NPF_6, Et_4NOTs, $^{n}Bu_4NBF_4$ and $^{n}Bu_4NBr$, were screened (Table 1, entries 2–7), and it was found that $^{n}Bu_4NPF_6$was the most efficient electrolyte for this electrochemical reaction (Table 1, entry 3). Subsequently, other various mixture solvents, such as 1,4-dioxane/H_2O, DMF/H_2O, $^{i}PrOH/H_2O$, CH_3OH/H_2O, and THF/H_2O, were screened and found that these types of solvent mixtures were inefficient (Table 1, entries 8–12). Moreover, it was found that only a trace of the desired product **3a** was obtained by replacing the solvent mixture with a single solvent (CH_3CN or H_2O) (Table 1, entries 13 and 14). Next, the electrode materials were screened and it was noted that graphite as the working electrode and Pt plate as the counter electrode is the best. For example, when graphite or Pt plate was used as the working electrode and the counter electrode, respectively, only trace amount of **3a** was obtained (Table 1, entries 15 and

Table 1. Optimization of the reaction conditions.

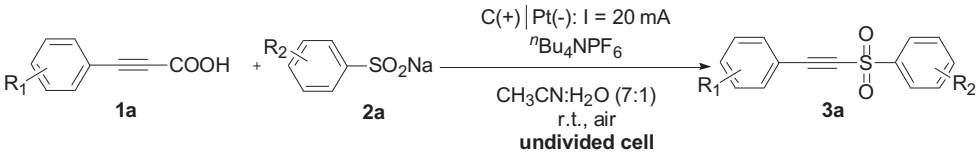


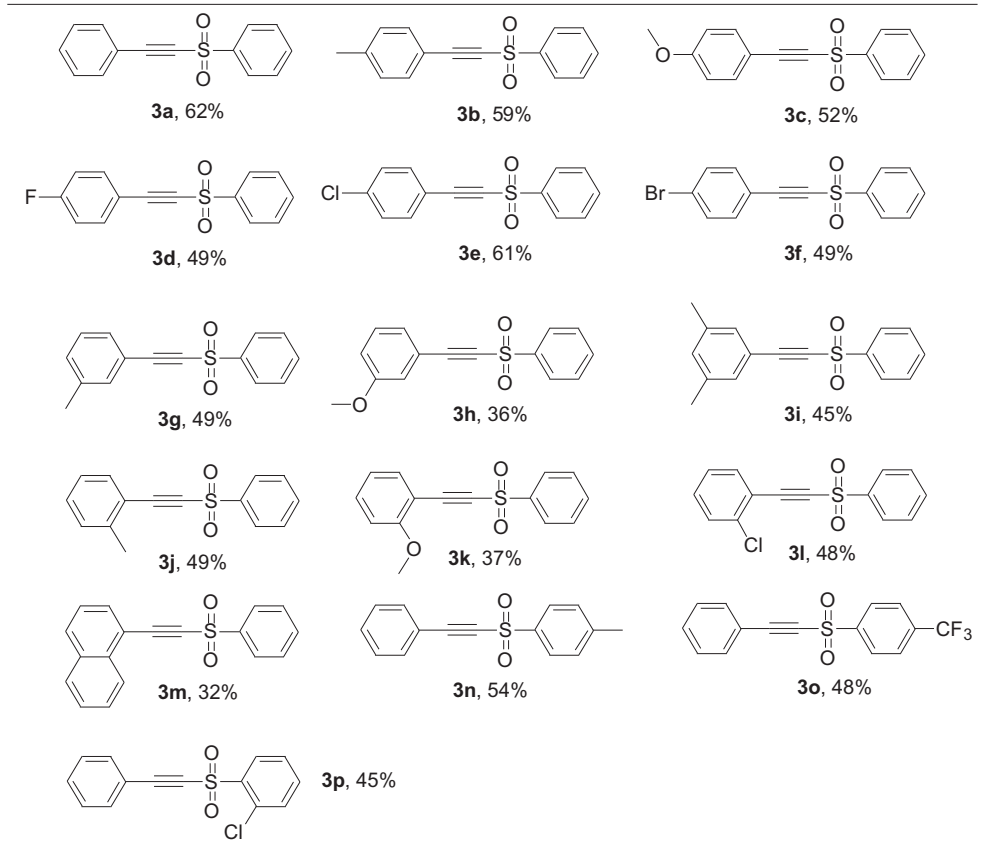
Entry[a]	Electrolyte	Electrode	Solvent	Yield (%)[b]
1	$LiClO_4$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	32
2	$^nBu_4NClO_4$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	27
3	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	61
4	Et_4NPF_6	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	53
5	Et_4NOTs	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	38
6	$^nBu_4NBF_4$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	36
7	$^nBu_4NBr$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	42
8	$^nBu_4NPF_6$	C(+)/Pt(−)	1,4-dioxane:H_2O (7:1)	15
9	$^nBu_4NPF_6$	C(+)/Pt(−)	DMF:H_2O (7:1)	13
10	$^nBu_4NPF_6$	C(+)/Pt(−)	^{i}PrOH:H_2O (7:1)	12
11	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3OH:H_2O (7:1)	Trace
12	$^nBu_4NPF_6$	C(+)/Pt(−)	THF:H_2O (7:1)	Trace
13	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN	Trace
14	$^nBu_4NPF_6$	C(+)/Pt(−)	H_2O	Trace
15	$^nBu_4NPF_6$	C(+)/C(−)	CH_3CN:H_2O (7:1)	Trace
16	$^nBu_4NPF_6$	Pt(+)/Pt(−)	CH_3CN:H_2O (7:1)	Trace
17	$^nBu_4NPF_6$	Pt (+)/C(−)	CH_3CN:H_2O (7:1)	37
18[c]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	18
19[d]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	34
20[e]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	56
21[f]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	43
22[g]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	38
23[h]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	53
24[i]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	35
25[j]	$^nBu_4NPF_6$	C(+)/Pt(−)	CH_3CN:H_2O (7:1)	0

[a]Reaction conditions: graphite rod (ϕ 6 mm) anode, Pt plate (10 mm× 10 mm) cathode, 1a (0.5 mmol), 2a (1.0 mmol), electrolyte (1 mmol), solvent (8 mL); The electrolysis was conducted in an undivided cell at a constant current (20 mA) at room temperatrure under air for 2 h. [b]Yields of the isolated products. [c]Electrolyte (0.5 mmol). [d]Electrolyte (1.5 mmol). [e]$T = 50\,^\circ$C. [f]0.1 mmol HOAc. [g]0.1 mmol NaOAc. [h]$I = 10$ mA. [i]$I = 30$ mA. [j]No current.

16). In addition, switching the electrodes resulted in only 37% yield (Table 1, entry 17). On the other hand, the amount of the supporting electrolyte such as $^nBu_4NPF_6$ was also investigated, a sharply reduced yield was obtained when decreasing or increasing the amount of $^nBu_4NPF_6$ (Table 1, entries 18 and 19). Then, the reaction temperature was investigated and it was found that increasing reaction temperature was detrimental, and a decreased yield was obtained (Table 1, entry 20). In order to further increasing the yield, some additives were investigated and it was found that a decreased yield was obtained when AcOH or NaOAc was added (Table 1, entries 21 and 22). Moreover, we investigated the current intensity; it was found that varying current such as 10 mA or 30 mA, led to a decrease of the product yield (Table 1, entries 23 and 24). Furthermore, no reaction occurred, with starting materials recovered, when the reaction was conducted without electricity (Table 1, entry 25). From the results described above, we conclude that the optimal reaction conditions call for the use of 2 equiv. of $^nBu_4NPF_6$ as the supporting electrolyte, and graphite as working electrode and Pt plate as the counter electrode. The reaction proceeds in a simple undivided cell using CH_3CN/H_2O (7/1 mL) as mixture solvents under a constant current (20 mA) at room temperatrure under air for 2 h.

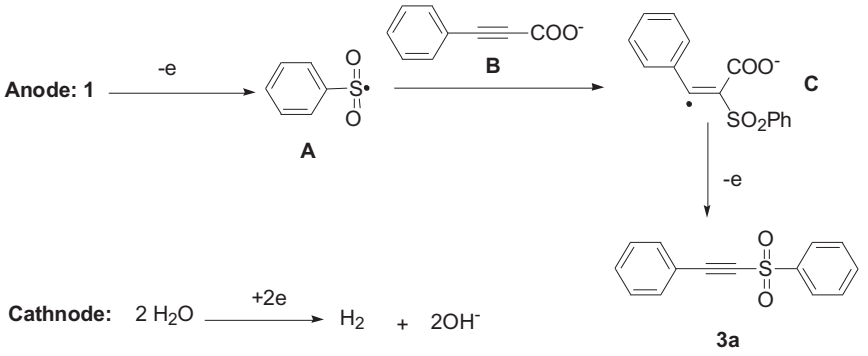
Table 2. Substrate scope for the decarboxylative sulfono functionalization.[a,b]





[a]Reaction conditions: graphite rod (ϕ 6 mm) anode, Pt plate (10 mm × 10 mm) cathode, **1** (0.5 mmol), **2** (1.0 mmol), ^{n}Bu$_4$NPF$_6$ (1.0 mmol), CH$_3$CN/H$_2$O = 7:1 (8 mL); the electrolysis was conducted in an undivided cell at a constant current (20 mA) at room temperature under air for 2 h. [b]Yield of isolated products.

With the optimal reaction conditions in hand, we next explored the generality and functional group compatibility of this transformation under the optimum reaction conditions, and the results are summarized in Tables 2. The reactions of sodium benzenesulfinate **2a** with 3-phenylpropiolic acid (**1a**) bearing electronically different groups on the *para* position (*p*-Me, *p*-MeO, *p*-F, *p*-Cl, *p*-Br) gave the corresponding products **3b − f** in good yields. It was worth to mention that halogen could be well tolerated under the electrochemical conditions and could thus provide a great opportunity for further transformation at the halide position. Arylacetylenic acids bearing substituents at the *meta* position (*m*-CH$_3$, and *m*-MeO) could also be converted to their corresponding acetylenic sulfones **3g** and **3h** in moderate yields (36-53% yields). Moreover, the substrates bearing multiple substituents, such as multiple methyl groups, could be



Scheme 1. Proposed mechanism.

applied to the reactions and gave the desired product **3i** in 45%. Additionally, arylacetylenic acids containing substituents at the *ortho* position (*o*-Me, *o*-MeO, *o*-Cl) were also effective substrates in this transformation and furnished the corresponding products **3j–l** in slightly low yields (39−49% yields). 3-(Naphthalen-1-yl)propiolic acid is also good substrate providing **3m** in 32% yields. Finally, the scope of sodium sulfinates was also investigated. For example, sodium benzenesulfinates bearing an electron-donating group such as *p*-Me (**2b**), and an electron-withdrawing group such as *p*-CF_3 (**2c**) could smoothly undergo decarboxylative sulfonylation and afforded the desired product in 54% and 48% yield, respectively. To our delight, the sterically congested substrate 2-chlorobenzene sulfinic acid sodium (**2d**) could proceed smoothly in this transformation and gave the corresponding products **3p** in 45% yields.

On the basis of previous similar literature,[13,14] a tentative mechanism for this electro-oxidative decarboxylative sulfonylation of arylacetylenic acids with sodium arylsulfinates is proposed in Scheme 1. Initially, sodium sulfinates produced a sulfonyl radical intermediate **A** on the anode via the single-electron transfer (SET) oxidation process. Subsequently, the attack of the a sulfonyl radical intermediate **A** onto arylacetylenic acid anion **B** generated radical intermediate **C**, which would be further oxidized to be decarboxylated and converted to the desired product **3a**.

Conclusion

In summary, we have disclosed an electrochemically decarboxylative sulfonylation of arylacetylenic acids with sodium benzenesulfinates. This protocol employs green and cheap electron as the oxidant, avoiding utilization of transition metals and external oxidant, thereby providing an environmentally benign method for synthesis of acetylenic sulfones. Further investigation into the mechanistic details and applications of this method are underway in our group.

Experimental

All reactions were carried out under air. Commercial reagent and compound were used without purification unless otherwise indicated. All products were characterized by ^{1}H NMR and ^{13}C NMR, using TMS as an internal reference (^{1}H NMR: 400 MHz, ^{13}C

NMR: 100 MHz) on Bruker 400 MHz spectrometers with $CDCl_3$ as the solvent. Flash chromatography was performed on silca gel (silca gel, 200-300 mesh). The substrates 1 were prepared according to literature.[15]

General procedure for the synthesis of arylacetylenic sulfones 3

A mixture of 3-phenylpropiolic acid **1** (0.5 mmol) and sodium benzenesulfinate **2** (1.0 mmol), $^{n}Bu_4PF_6$ (1.0 mmol), and CH_3CN/H_2O (7/1 mL) was added to an undivided cell. The cell was equipped with a graphite rod (ϕ 6 mm) as the anode with a platinum plate (10 mm × 10 mm) as the cathode. The reaction mixture was stirred and electrolyzed at a constant current of 20 mA under room temperature for 2 h. After electrolysis, the solvent was removed with a rotary evaporator. The solution was then added to 10 mL of water and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried with $MgSO_4$ and filtered. The solvent was removed with a rotary evaporator. The resulting mixture was purified by silica gel column chromatography to afford **3**.

Supporting Information (Characterization data, and copies of ^1H spectra for all of the products 3).

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