Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Copper-catalyzed highly selective direct hydrosulfonylation of alkynes with arylsulfinic acids leading to vinyl sulfones†

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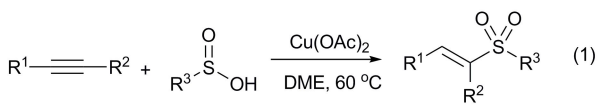
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A novel Cu-catalyzed direct hydrosulfonylation of alkynes with arylsulfinic acids for the synthesis of (*E*)-vinyl sulfones has been realized under mild conditions with 100% atom efficiency. The present protocol provides an attractive approach to various vinyl sulfones in good to excellent yields, with the advantages of operation simplicity, atom economy, and high stereo- and regioselectivities.

Transition-metal-catalyzed direct addition of H-heteroatom compounds to carbon-carbon unsaturated triple bond is one of the most straightforward and powerful tools for the construction of alkenyl heteroatom compounds because of its advantages in terms of synthetic efficiency and atom economy.[1] Over the past several decades, considerable efforts have been made in this area and some important alkenyl heteroatom compounds, such as phosphonates,[2] boronates,[3] selenides,[4] sulfides,[5] and nitrogen-[6] and oxygen-containing[7] products have been obtained via the catalytic addition reaction of alkynes. Nevertheless, there is still a great demand for the development of a new and selective catalytic system to offer other important alkenyl heteroatom compounds such as vinyl sulfones. Herein, we report a novel and efficient copper-catalyzed direct hydrosulfonylation of alkynes with arylsulfinic acids for the construction of vinyl sulfones in a one-pot procedure with 100% atom efficiency (eqn (1)).



(1)

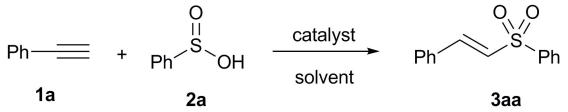
As an extremely valuable alkenyl heteroatom compounds, vinyl sulfones have attracted increasingly synthetic pursuit of chemists, since they can serve as key structural motifs of many biologically active compounds[8] and versatile building blocks for various organic transformations.[9] Generally, vinyl sulfones are prepared by Knoevenagel condensation of aromatic aldehydes with sulfonylacetic acids,[10] Wittig reaction,[11] Horner–Emmons reaction of carbonyl compounds with sulfonyl phosphoranes,[12] and β-elimination of selenosulfones or halosulfones,[13] in which the desired products were usually formed in a mixture of isomers. A number of alternative methods towards vinyl sulfones synthesis have also been developed such as the oxidation of vinyl sulfides with stoichiometric oxidants,[14] the cross-coupling of sulfinate salts with vinyl triflates, vinyl bromides, or alkenyl boronic acids with Cu or Pd catalysts,[15] the addition of $ArSO_2X$ (X = I, Cl, SePh, HgCl, ONO_2, etc.) to alkenes followed by β-elimination,[16] and the addition of $ArSO_2X$ (X = I, Cl, etc.), sodium sulfinates or 1,2-bis(phenylsulfonyl)ethane to alkynes.[17] However, most of these methods suffer from some limitations such as inaccessible starting materials, tedious procedures, relatively harsh reaction conditions, lack of atom economy, or the generation of large amounts of unwanted byproducts. Therefore, the development of mild, convenient, highly-selective and, especially, atom-economic, environmentally friendly, and resource efficient methods to afford vinyl sulfones is still highly desirable.

The present method of direct addition of arylsulfinic acids to alkynes is realized under mild conditions by employing simple and cheap copper salts as the catalyst, which provides a variety of vinyl sulfones in good to excellent yields and high regio- and stereoselectivity. To the best of our knowledge, this method is the first example of transition-metal-catalyzed direct synthesis of vinyl sulfones from simple and readily available materials with complete atom economy, and does not require the use of any ligand or additive.

Initially, the reaction of phenylacetylene **1a** with benzenesulfinic acid **2a** was performed to examine the catalytic activity of various transition metal complexes including Ru, Pd, Ag, Cu, Fe, Co, Ni, In and Zn salts in DME at 60°C under N_2. As shown in Table 1, among the above metal catalysts screened (entries 1-13), copper salts especially $Cu(OAc)_2$ was found to be the best catalyst for the formation of product **3aa**, other catalyst such as $Pd(OAc)_2$, $RuCl_3$, $In(OAc)_3$, $AgNO_3$, $NiCl_2$, $ZnBr_2$, $Co(OAc)_2$, or $FeBr_3$ did not or only sluggishly promoted this reaction. The screening of a range of solvents showed that the reaction performed in 1,2-Dimethoxyethane (DME) or THF was significantly better than those in 1,4-dioxane, toluene, DMSO, CH_3OH, CH_3CN and H_2O (entries 13-20). The desired product was obtained in only 42% yield under air atmosphere (entry 21). No conversion was observed when the reaction was performed at room temperature or in the absence of copper catalyst (entries 22-23).

Under the optimized conditions, the scope of the reaction of various alkynes with arylsulfinic acids was investigated and the results are shown in Table 2. In general, aromatic alkynes which have electron-donating or withdrawing groups on the aryl rings were suitable for this protocol, and the products were obtained in good to excellent yields. Various functionalities such as halogen, cyano, and alkynyl groups were tolerated in this process to afford

Table 1 Optimization of the reaction conditions[a]



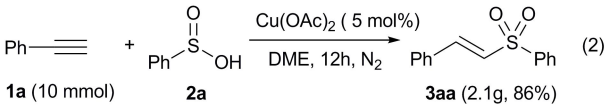
1a **2a** **3aa**

Entry	Catalyst	Solvent	Yield (%)[b]
1	$RuCl_3$	DME	0
2	$Pd(OAc)_2$	DME	0
3	$In(OAc)_3$	DME	0
4	$AgNO_3$	DME	0
5	$NiCl_2$	DME	trace
6	$ZnBr_2$	DME	trace
7	$Co(OAc)_2$	DME	trace
8	$FeBr_3$	DME	<10%
9	$CuBr_2$	DME	82
10	$CuCl_2$	DME	90
11	CuI	DME	50
12	$Cu(OTf)_2$	DME	75
13	**$Cu(OAc)_2$**	**DME**	**94**
14	$Cu(OAc)_2$	THF	92
15	$Cu(OAc)_2$	1,4-dioxane	65
16	$Cu(OAc)_2$	toluene	51
17	$Cu(OAc)_2$	DMSO	26
18	$Cu(OAc)_2$	CH_3OH	44
19	$Cu(OAc)_2$	CH_3CN	0
20	$Cu(OAc)_2$	H_2O	0
21	$Cu(OAc)_2$	DME	42[c]
22	$Cu(OAc)_2$	DME	0[d]
23	--	DME	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (5 mol %), solvent (3 mL), 60°C, N_2, 8h. [b] Isolated yields based on **1a**. [c] under air, [d] at room temperature.

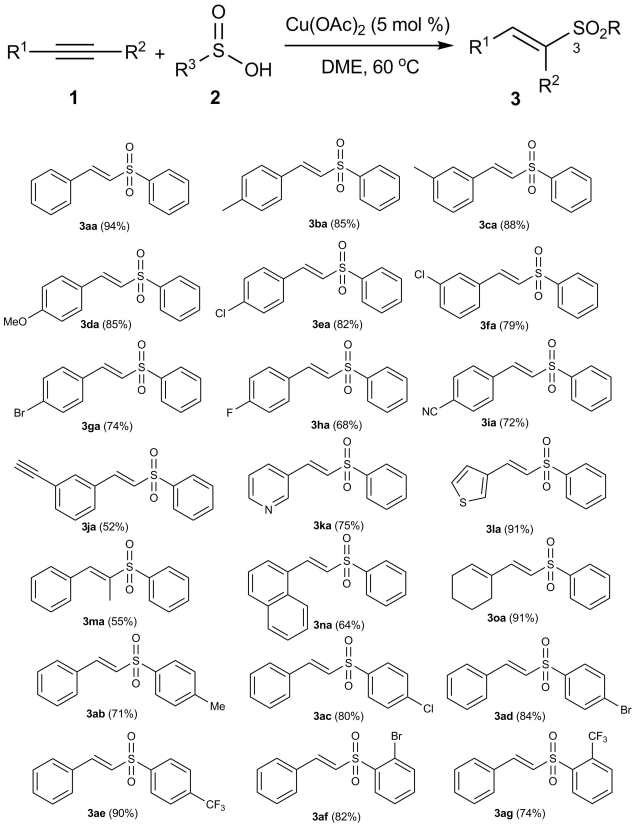
the corresponding products **3ea-3ja**, which could be employed for further transformations. Moreover, heteroaromatic alkynes such as 3-ethynylpyridine and 3-ethynylthiophene were also compatible with this reaction, providing the corresponding products (**3ka** and **3la**) in 75% and 91% yields, respectively. Notably, internal alkynes such as prop-1-ynylbenzene could also be used in the reaction to give the expected vinyl sulfone **3ma** in moderate yield. Meantime, 1-ethynylnaphthalene and 1-ethynylcyclohex-1-ene could be used in the reactions to give the expected products (**3na** and **3oa**) in 64% and 91% yields, respectively. Furthermore, the scope of a variety of arylsulfinic acids was examined. In addition to benzenesulfinic acid **2a**, a series of substituted arylsulfinic acids containing either electron-rich or electron-deficient groups were all suitable substrates, and generated the corresponding products in good yields (**3ab-3ae**). In addition, the sterically hindered substituted arylsulfinic acids such as 2-bromobenzenesulfinic acid and 2-(trifluoromethyl)benzenesulfinic acid were also tolerated in this reaction to afford the products in good yields (**3af** and **3ag**).

The feasibility of gram-scale reaction was investigated by using of the model reaction between **1a** and **2a**. It was found that this reaction could afford 2.1 g of **3aa** in 86% yield without any significant loss of its efficiency (eqn (2)). Therefore, this procedure could serve as a practical and efficient protocol to synthesize vinyl sulfones.



1a (10 mmol) **2a** **3aa** (2.1g, 86%)

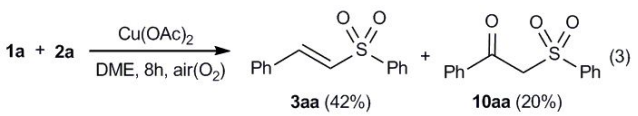
Table 2 Scope of the reaction of various alkynes with arylsulfinic acids [ab]



1 **2** **3**

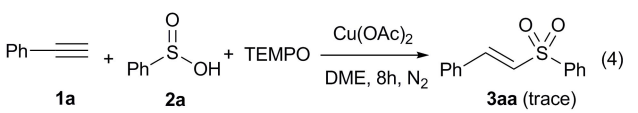
[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), $Cu(OAc)_2$ (5 mol %), DME (3 mL), 8h, N_2 (balloon). [b] Isolated yields based on **2**.

It is established that the oxidative addition of sulfinic acids to alkynes leading to β-keto sulfones proceeded via a radical process.[18a] When the reaction of **1a** and **2a** was performed in the copper catalytic system under air (dioxygen), in addition to the desired product **3aa**, the β-keto sulfone **10aa** was also obtained in 20% yield (eqn (3)). Therefore, a radical pathway was also supposed to be involved in this hydrosulfonylation reaction.



3aa (42%) **10aa** (20%)

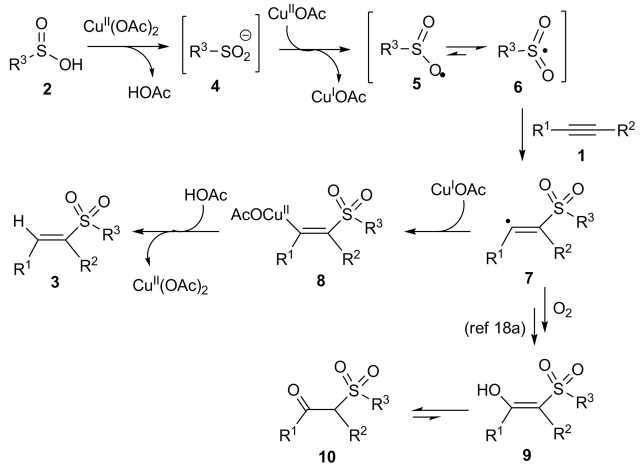
Furthermore, when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well known radical-capturing species) was added in the present reaction system, this hydrosulfonylation process was significantly inhibited (eqn (4)), indicating that this reaction might involve a radical process.



1a **2a** **3aa** (trace)

Based on the above information and previous studies,[17-19] we propose a postulated reaction pathway shown in Scheme 1. Firstly, the reaction of sulfinic acid **2** with $Cu(OAc)_2$ gave the sulfinyl anion **4**, which could be further oxidized by Cu^{II} via the single electron transfer (SET) process to afford an oxygen-

centered radical **5** resonating with sulfonyl radical **6**.[18] Subsequently, the selective addition of sulfonyl radical **6** to alkyne **1** would lead to the formation of reactive vinyl radical **7**, which interacted with Cu^{I} species to yield vinyl copper(II) complexes **8**. Finally, the protonation of **8** produced the desired product **3** and regenerated Cu(II) catalyst.[19] The side product **10** might be formed by the isomerization of intermediate **9**, which was generated from vinyl radical **7** in the presence of air (dioxygen) via the redox-transfer process.[18a]



Scheme 1. Postulated reaction pathway.

In conclusion, a novel and practical protocol of copper-catalyzed direct hydrosulfonylation of alkynes with arylsulfinic acids has been developed under mild conditions. It may possess some advantages of cheap catalysts, readily-available starting materials, operation simplicity, high atom economy and reaction selectivity, opening a new door towards the construction of vinyl sulfones. Studies of the detailed mechanism of this process and its application are ongoing.

This work was supported by the National Natural Science Foundation of China (No. 21302109, 21302110, and 21375075), the Taishan Scholar Foundation of Shandong Province, the Excellent Middle-Aged and Young Scientist Award Foundation of Shandong Province (BS2013YY019), and the Scientific Research Foundation of Qufu Normal University (BSQD 2012020).

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/b000000x/

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