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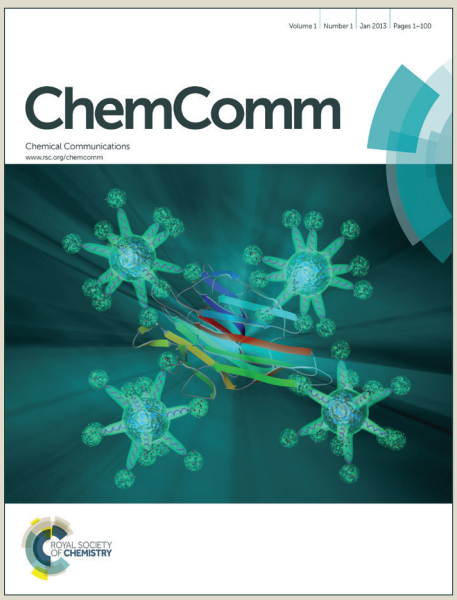

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ARTICLE TYPE

Direct and metal-free arylsulfonylation of alkynes with sulfonylhydrazides for the construction of 3-sulfonated coumarins†

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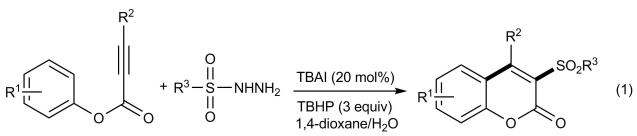
A novel and metal-free procedure has been developed for the construction of 3-sulfonated coumarins via the direct difunctionalization of alkynoates with sulfonylhydrazides. The present protocol, which simply utilizes TBAI as the catalyst and TBHP as the oxidant, provides a convenient and highly efficient approach to a series of sulfonated coumarins with high regioselectivity and good functional group tolerance.

As an extremely valuable functional group, sulfone functionality is widely used in organic chemistry and especially in medicinal chemistry.[1] The introduction of sulfone groups into organic framework strongly attracts synthetic pursuit of chemists because of their diverse synthetic applications and important biological properties.[2] On the other hand, the difunctionalization of alkynes has emerged as a fascinating and powerful tool for the construction of various valuable organic compounds due to its high efficiency in the cascade formation of carbon−carbon and carbon−heteroatom bonds.[3] Some useful difunctionalization reactions such as iodotrifluoromethylation,[4] aryloxygenation,[5] aryltrifluoromethylation[6] and arylphosphorylation,[7] have been reported. Nevertheless, up to date, only few strategies for the fabrication of sulfone-containing compounds have been developed via the difunctionalization of alkynes.[8-10] Recently, the halosulfonylations of alkynes with sulfonyl halides, sulfonyl hydrazides, or sulfinates leading to β-halo vinylsulfones have been reported by Nakamura[9a] and Li,[9b] and Jiang[9c], respectively. In 2013, Lei[10] described the oxysulfonylation of alkynes with sulfinic acids for the construction of β-ketosulfones in the presence of pyridine. It is still an attractive but challenging task to develop new, convenient, efficient, and especially, environmentally-benign methods to access other important sulfonated compounds through the direct difunctionalization of alkynes.

Coumarin represents an important class of structural scaffold widespread existed in various natural products, clinical pharmaceuticals, and biologically active compounds.[11] Many of them have been extensively recognized as the key subunits to design synthetic drug candidates in terms of their significantly pharmacological activities in the antitumor, antimalarial, anti-inflammatory, antibacterial, anti-HIV, antivirus, antiprotozoal, and antidiabetic fields.[12] Without a doubt, many promising pharmaceutical applications will lead to a great demand for the development of simple and efficient methods to construct structurally diverse substituted coumarins.

Herein, we report a new TBAI-catalyzed direct arylsulfonylation of alkynes with sulfonylhydrazides towards 3-sulfonated coumarins simply by using TBHP as the oxidant (eqn 1). Generally, 3-sulfonated coumarins were synthesized by the reaction of phenylsulfonylacetonitrile[13] or sulfonyl acetic acids[14] with salicyaldehyde and its derivatives. The oxidation of coumarinyl phenyl sulfide with hydrogen peroxide[15] and the three-component coupling of arynes, arylsulfonylacetonitrile and DMF[16] have also been developed. Nevertheless, most of the methods suffer from limitations such as tedious work-up procedures, harsh reaction conditions, or low yields. The present methodology provides a convenient and highly attractive approach to a variety of sulfonated coumarins in moderate to high yields under metal-free conditions. To the best of our knowledge, this is the first example of constructing sulfonated coumarins via the difunctionalization of alkynes.



(1)

Initially, the reaction between phenyl 3-phenylpropiolate **1a** and phenylsulfonohydrazide **2a** was carried out by using TBAI/TBHP system in CH_3CN at 80°C under air (Table 1, entry 1). Gratifyingly, the desired sulfonated coumarin **3a** was obtained in 67% yield. Further optimization of solvents demonstrated that 1,4-dioxane/H_2O (4:1) was the optimized reaction medium for the formation of product **3a** (Table 1, entries 1-12). Replacing TBAI with other catalysts such as TBAB, TBAF, I_2, NaI and KI did not improve the reaction efficiency (Table 1, entries 13-17). Next, the effects of various oxidants such as TBHP, DTBP, $K_2S_2O_8$, $(NH_4)_2S_2O_8$, H_2O_2 and O_2 were separately examined. Among the above oxidants tested, TBHP stood out to be the best choice, while others including DTBP, $(NH_4)_2S_2O_8$, H_2O_2, and O_2 were less effective (Table 1, entries 12, 19-22). When the reaction was conducted at room temperature, the desired product **3a** was

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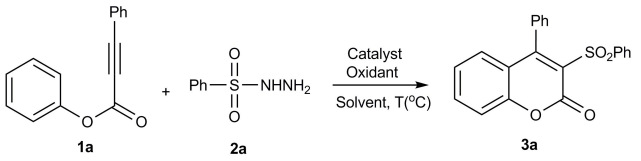
Table 1 Optimization of the reaction conditions[a]



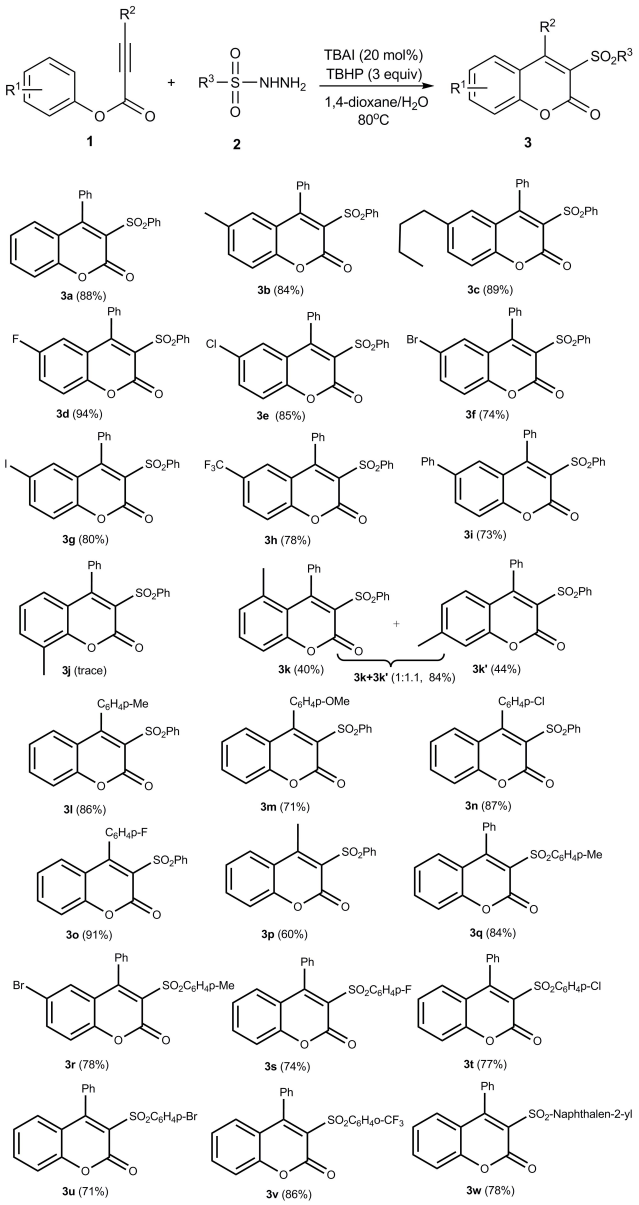
Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	TBAI	TBHP	CH_3CN	67
2	TBAI	TBHP	toluene	59
3	TBAI	TBHP	DMF	38
4	TBAI	TBHP	DMSO	trace
5	TBAI	TBHP	DME	70
6	TBAI	TBHP	1,4-dioxane	77
7	TBAI	TBHP	DCE	75
8	TBAI	TBHP	EtOH	41
9	TBAI	TBHP	H_2O	38
10	TBAI	TBHP	CH_3CN/H_2O (4/1)	70
11	TBAI	TBHP	DCE/H_2O (4/1)	85
12	TBAI	TBHP	1,4-dioxane/H_2O (4/1)	88
13	TBAB	TBHP	1,4-dioxane/H_2O (4/1)	40
14	TBAF	TBHP	1,4-dioxane/H_2O (4/1)	32
15	I_2	TBHP	1,4-dioxane/H_2O (4/1)	63
16	NaI	TBHP	1,4-dioxane/H_2O (4/1)	53
17	KI	TBHP	1,4-dioxane/H_2O (4/1)	27
18	TBAI	$K_2S_2O_8$	1,4-dioxane/H_2O (4/1)	75
19	TBAI	DTBP	1,4-dioxane/H_2O (4/1)	35
20	TBAI	$(NH_4)S_2O_8$	1,4-dioxane/H_2O (4/1)	49
21	TBAI	H_2O_2	1,4-dioxane/H_2O (4/1)	55
22	TBAI	O_2	1,4-dioxane/H_2O (4/1)	16
23	TBAI	TBHP	1,4-dioxane/H_2O (4/1)	39[c]
24	TBAI	TBHP	1,4-dioxane/H_2O (4/1)	66[d]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), catalyst (20 mol%), oxidant (3 equiv), solvent (2.5 mL), 80°C, 12 h, under air. n.r.= no reaction. TBHP: tert-Butyl hydroperoxide, 70% solution in water; TBAI=(n-Bu)$_4$NI; TBAB=(n-Bu)$_4$NBr; TEAF=(n-Bu)$_4$NF; DTBP: Di-tert-butyl peroxide; DCE: 1,2-dichloroethane; DME: 1,2-Dimethoxyethane.[b] Isolated yields based on **1a**.[c] 25°C [d] 60°C.

obtained in only 39% yield (Table 1, entry 23). With increasing of the reaction temperature the reaction efficiency was obviously improved, and the best yield was achieved when the reaction was performed at 80°C (Table 1, entries 12, 23-24).

With the optimized conditions in hand, the scope and generality of this reaction was investigated. As shown in Table 2, a series of sulfonated coumarins could be efficiently obtained by this new arylsulfonylation reaction. In general, aryl 3-phenylpropiolates with electron-donating or withdrawing groups on the phenoxy ring could be smoothly transformed into the desired products in moderate to good yields (**3a-3i**). The reaction was affected significantly by the steric effect. Only a trace amount of the desired product was detected with methyl group at the ortho-position of the phenoxy (**3j**). Substituent group at the meta-position of the phenoxy ring gave two regioselective products (**3k**/**3k'**). Furthermore, the effects of the substituent on the alkynyl were evaluated. Arylpropiolates bearing both electron donating and electron-withdrawing groups on the aromatic moieties could be compatible with this reaction to give the corresponding products in good yields (**3l-3o**). Notably, alkylpropiolate such as methylpropiolate was also tolerated to afford the desired product **3p** in 60% yield. In addition, the arylsulfonylation reaction could also proceed well by using various arylsulfonohydrazides leading to the desired products in good yields (**3q-3w**). Unfortunately, none of the desired product

Table 2 Results for metal-free arylsulfonylation of alkynes with sulfonylhydrazides[ab].

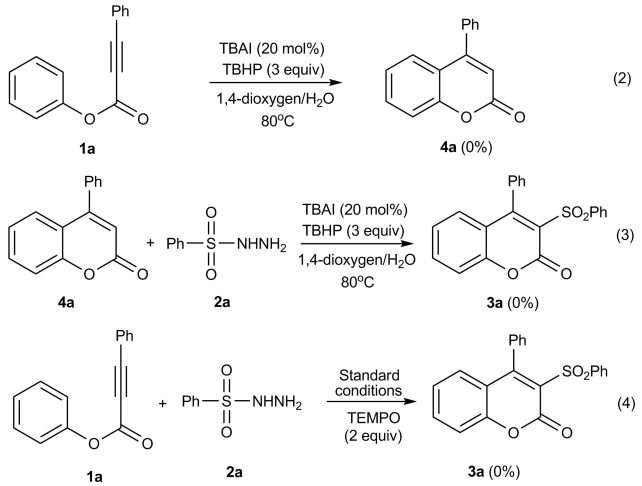


[a] Reaction conditions: **1** (0.25 mmol), **2** (0.75 mmol), TBAI (20 mol%), TBHP (3 equiv), 1,4-dioxane/H_2O (2.5 mL, 4/1), 80°C, 12-36 h. [b] Isolated yields based on **1**.

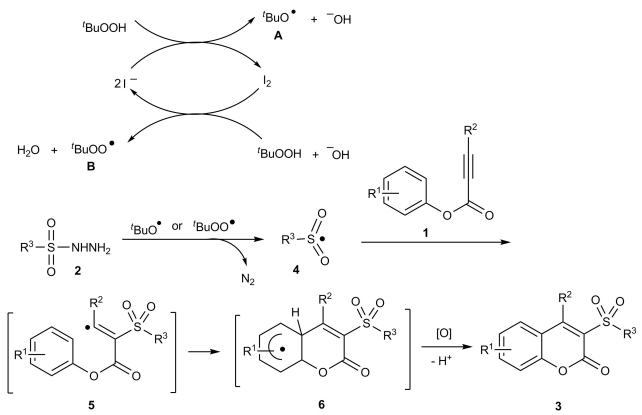
was obtained when alkyl sulfonylhydrazide such as methyl sulfonyl hydrazide was used as the substate.

In order to obtain further insights into this reaction, several control experiments were performed as shown in eqns. 2-4. When phenyl 3-phenylpropiolate **1a** was added independently under the tandard conditions, no conversion to coumarin **4a** was observed (eqn 2). Furthermore, the desired product **3a** was not obtained when the reaction of **2a** with preformed coumarin **4a** was conducted through the standard procedure (eqn 3). The above results indicated coumarin **4a** might not be the key intermediate in the present reaction system. Considering that sulfonyl radicals were easily generated from the TBAI/TBHP system,[17] so a radical pathway was supposed to be involved in the present

reaction. As shown in eqn 4, when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, a well-known radical scavenger) was added in this reaction system, the arylsulfonylation reaction was completely inhibited, thus suggesting the present reaction might involve a radical process.



On the basis of the above results and previous reports,[6,7,17-18] a tentative mechanism was proposed as shown in Scheme 1. Initially, TBHP was decomposed by iodide anion to give the tert-butoxyl **A** and tert-butylperoxy radical **B**. Subsequently, these radicals would abstract hydrogen atoms from sulfonylhydrazide **2** leading to the formation of sulfonyl radical **4** with the release of nitrogen. Next, the selective addition of sulfonyl radical **4** to alkynoate **1** gave the vinyl radical **5**. Intramolecular cyclization of vinyl radical **5** with an aryl ring generated the radical intermediate **6**. Finally, the oxidation of **6** produced the corresponding cyclohexadienyl cation, which underwent the deprotonation to yield the sulfonated oxindole **3**.



Scheme 1. Tentative mechanism.

In conclusion, we have developed a novel and metal-free procedure for the construction of sulfonated coumarins via direct arylsulfonylation of alkynes with sulfonylhydrazides simply by using TBAI/TBHP system. A series of biologically important sulfone-containing coumarins could be conveniently and efficiently obtained in good yields from readily-available starting materials with high regioselectivity and excellent functional group tolerance. This simple and metal-free reaction system is expected to extend the potential applications of functionalized coumarins in the synthetic and pharmaceutical chemistry.

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