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A radical cyclization cascade of 2-alkynylbenzonitriles with sodium arylsulfinates†

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A convenient radical cyclization cascade procedure for the construction of sulfonated indenones from 2-alkynylbenzonitriles and sodium arylsulfinates has been explored under mild reaction conditions. The present methodology offers a low-cost and operationally straightforward approach to synthesizing various sulfonated indenones in moderate to good yields by simple use of cheap sodium persulfate as an oxidant and environmentally benign water as a co-solvent.

Functionalized indenones are important structural scaffolds in a variety of synthetic drugs,[1] drug intermediates,[2] and natural products,[3] which display excellent biological and pharmaceutical activities.[4] There has been an ongoing interest in the development of simple, efficient methods for synthesizing indenone derivatives. Traditionally, methods for synthesizing indenones include intramolecular Friedel–Crafts reactions,[5] Grignard reactions,[6] and Heck–Larock cyclization reactions.[7] Generally, palladium[8] and rhodium[9] are selected as metal catalysts for the synthesis of indenones when the compounds such as 2-halobenzaldehydes, 2-haloacetophenones, 2-iodo-benzonitriles, and aroyl chlorides are used as substrates. Recently, the addition reactions to nitriles have been found to be efficient approaches for the construction of ketones.[10] These methods have made good progress in the synthesis of indenone derivatives. However, the development of simple and low-cost approaches to synthesizing functional indenones is still highly desirable.

Owing to its distinctive structure and electronic features, the sulfonyl group has been extensively exploited in pharmaceuticals, agrochemicals and bioactive compounds.[11] The common means for preparing sulfones including the oxidation of sulfides,[12] sulfonylation of arenes,[13] and transition metal catalyzed cross reactions are available.[14] These strategies can serve as promising approaches for the synthesis of some sulfone derivatives. However, examples of synthesizing sulfonated indenones by these means are scarce. Therefore, developing a simple and effective method of synthesizing sulfonated indenones is an important and difficult work, due to their importance in biology and medicinal chemistry.

The radical cascade annulation reaction to construct various heterocyclic frameworks is a well-established powerful strategy in the synthesis processes,[15] due to its simple operation and cost reduction. For example, Lei and co-workers described an electro-oxidative direct arylsulfonylation of ynones with sulfinic acids *via* a radical tandem cyclization strategy for the synthesis of sulfonated indenones.[16] Recently, radical addition–cyclizations of 2-alkynylbenzonitriles for the construction of indenones have become one of the most popular methods for chemists. For example, Jiang, Tu and co-workers reported the synthesis of 3-phosphinylated (Scheme 1a),[17] 3-alkylated (Scheme 1b)[18] and 3-sulfonylated indenones (Scheme 1c)[19] by using 2-alkynylbenzonitriles as substrates. Despite great progress, employment of expensive metal catalysts and requirement of organometallics or peroxides in these methods still stimulate chemists to develop more green and sustainable approaches. Besides, chemically stable and readily available sodium arylsulfinates have been widely utilized to obtain sulfone compounds through radical reactions.[20] According to these above reactions, herein we describe an efficient radical cascade annulation reaction for the selective synthesis of various 3-sulfonyl indenones through direct arylsulfonylation of 2-alkynylbenzonitriles with sodium arylsulfinates.

Initially, we utilized 2-(phenylethynyl)benzonitrile **1a** and sodium 4-methylbenzenesulfinate **2a** as the model substrates to optimize the reaction conditions and these results are summarized in Table 1. It was found that the desired product **3aa** was obtained in 36% yield when the reaction was performed in the presence of a $K_2S_2O_8$ oxidant (300 mol%) in CH_3CN/H_2O

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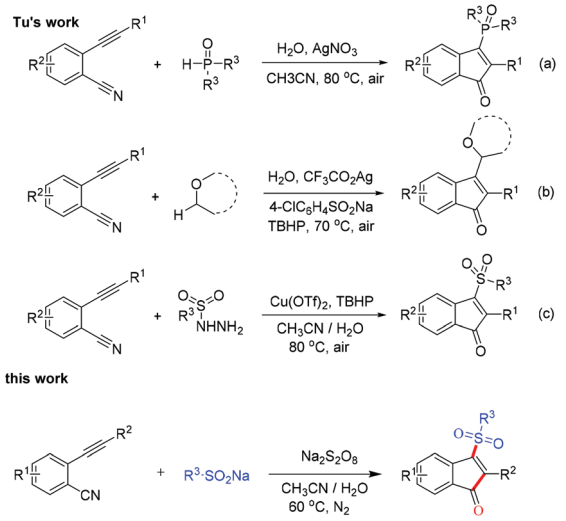
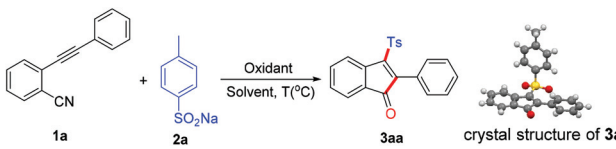


Scheme 1 Radical cascade cyclization synthesis of indenones by using 2-alkynylbenzonitriles.

Table 1 Optimization of reaction conditions[a]

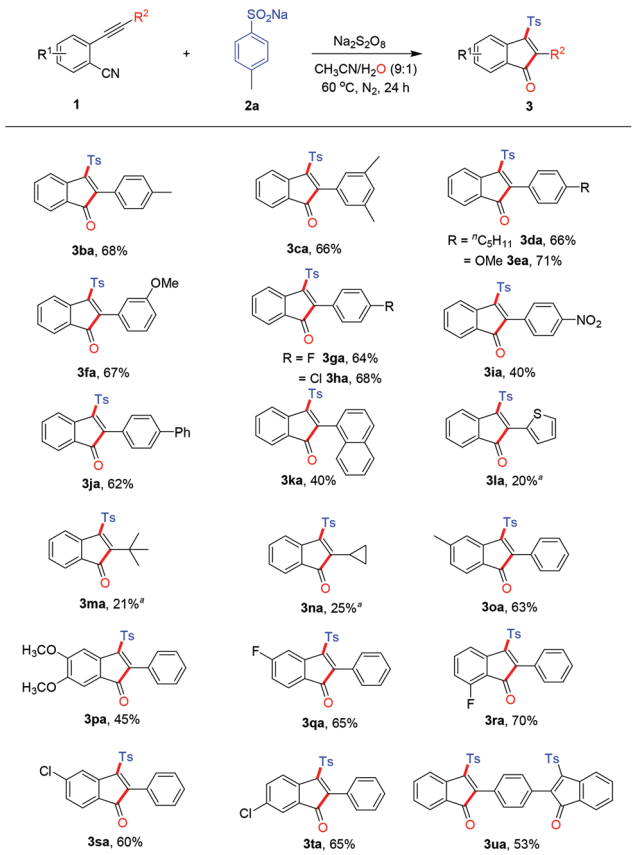


Entry	Oxidant	Solvent (v : v)	Yield[b] (%)
1	$K_2S_2O_8$	CH_3CN/H_2O (9 : 1)	36
2	$Na_2S_2O_8$	CH_3CN/H_2O (9 : 1)	67
3	$(NH_4)_2S_2O_8$	CH_3CN/H_2O (9 : 1)	21
4	Oxone	CH_3CN/H_2O (9 : 1)	Trace
5	$PhI(OAc)_2$	CH_3CN/H_2O (9 : 1)	n.r.
6	TBHP	CH_3CN/H_2O (9 : 1)	n.r.
7	DTBP	CH_3CN/H_2O (9 : 1)	n.r.
8	H_2O_2	CH_3CN/H_2O (9 : 1)	n.r.
9	$Na_2S_2O_8$	$DMSO/H_2O$ (9 : 1)	Trace
10	$Na_2S_2O_8$	DCM/H_2O (9 : 1)	15
11	$Na_2S_2O_8$	1,4-Dioxane/H_2O (9 : 1)	7
12	$Na_2S_2O_8$	DCE/H_2O (9 : 1)	Trace
13	$Na_2S_2O_8$	CH_3CN/H_2O (1 : 1)	24
14	$Na_2S_2O_8$	CH_3CN/H_2O (3 : 1)	48
15	$Na_2S_2O_8$	CH_3CN	36
16	$Na_2S_2O_8$	H_2O	Trace
17[c]	$Na_2S_2O_8$	CH_3CN/H_2O (9 : 1)	43
18[d]	$Na_2S_2O_8$	CH_3CN/H_2O (9 : 1)	32
19[e]	$Na_2S_2O_8$	CH_3CN/H_2O (9 : 1)	29
20[f]	$Na_2S_2O_8$	CH_3CN/H_2O (9 : 1)	55
21	—	CH_3CN/H_2O (9 : 1)	n.r.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.6 mmol), solvent (2 mL), at 60 °C for 24 h under a N_2 atmosphere. n.r. = no reaction. [b] Isolated yield. [c] $Na_2S_2O_8$ (0.40 mmol). [d] $Na_2S_2O_8$ (0.80 mmol). [e] At 40 °C. [f] At 80 °C.

(9 : 1) at 60 °C for 24 h under a N_2 atmosphere (entry 1). The structure of **3aa** was unambiguously established by X-ray crystallographic analysis (CCDC 1838957†). Encouraged by this result, we further optimized the reaction conditions by testing various oxidants. The investigation results showed that using $Na_2S_2O_8$ as an oxidant gave the best yield (67%), whereas other oxidants such as $(NH_4)_2S_2O_8$, oxone, $PhI(OAc)_2$, TBHP, DTBP, and H_2O_2 did not or only sluggishly promoted this reaction (Table 1, entries 3–8). Among a range of solvents tested, CH_3CN/H_2O (9/1) was found to be the best one (Table 1, entries 9–14). In contrast, the product **3aa** was isolated in low yield when the reaction was performed in the absence of H_2O or CH_3CN (Table 1, entries 15 and 16). In addition, changing the equivalents of $Na_2S_2O_8$ did not further improve the reaction either (Table 1, entries 17 and 18). It should be noted that running the reaction at either 40 or 80 °C gave inferior results, which demonstrates that temperature is important to the product yield (Table 1, entries 19 and 20). The control experiment showed that no reaction occurred in the absence of $Na_2S_2O_8$ (Table 1, entry 21).

With the optimized reaction conditions in hand, we evaluated the scope and the generality of the reaction in the next step (Scheme 2). First, we set out to explore the scope and the limitations of the reactions of various 2-alkynylbenzonitriles with sodium *p*-tolylsulfinate **2a** toward the formation of sulfonated indenones and the results are summarized in Scheme 2. Under the standard conditions, a broad range of **1** bearing electron-donating substituent groups including *p*-methyl,

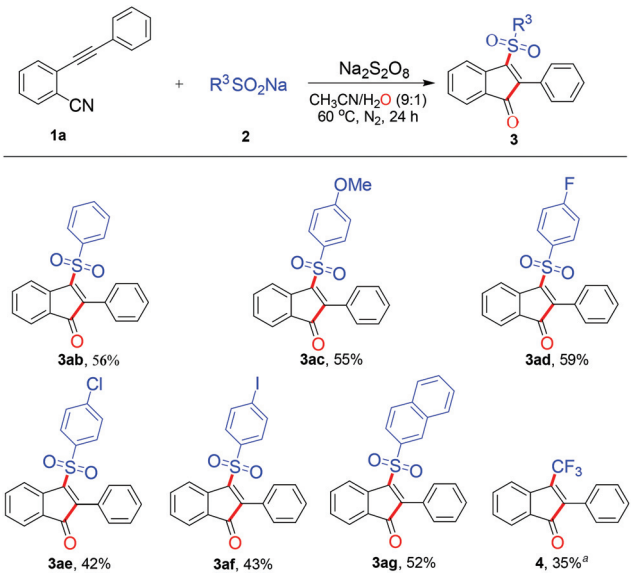


Scheme 2 Variation of 2-alkynylbenzonitriles. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Na_2S_2O_8$ (0.6 mol), $v(CH_3CN) : v(H_2O) = 9 : 1$ (total volume is 2 mL), 60 °C and 24 h under a N_2 atmosphere. Isolated yields. [a] At 100 °C for 36 h.

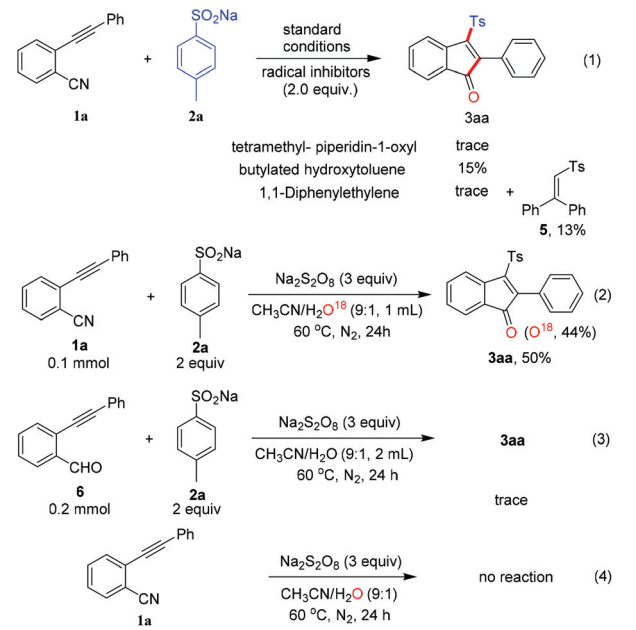
3,5-dimethyl, *n*-amyl, *p*-methoxy and *m*-methoxy groups on the arylalkynyl moiety all worked well, efficiently converting into the corresponding functionalized 3-sulfonylindenones **3ba–3fa** in good yields (66–71% yields). For example, the *p*-methoxy substituted substrate **2e** region-selectively formed 2-(4-methoxyphenyl)-3-tosyl-1*H*-inden-1-one **3ea** in 71% yield. Fluoro-substituted and chloro-substituted 2-alkynylbenzonitriles were tolerated well under the standard conditions, offering the corresponding products **3ga** and **3ha** in 64% and 68% yields, respectively. However, substrate **1i** with an electron-withdrawing NO_2 group displayed lower reactivity, giving **3ia** in 40% yield. The results showed that the electron-donating group substrates displayed higher reactivity than the electron-withdrawing group substrates. It is noteworthy that substrates **1j** and **1k** bearing diphenyl and naphthyl groups performed well under the standard conditions, giving the corresponding polycyclic aromatic hydrocarbon products **3ja** and **3ka** in 63% and 40% yields, respectively. Notably, heterocyclic and aliphatic alkynes have not been reported in previous articles due to their low reactivities. In our work, heterocyclic and aliphatic alkynes (**1l**, **1m** and **1n**) successfully underwent radical cascade cyclization to give **3la**, **3ma** and **3na**, albeit in low yields. Subsequently, our study focused on the substitution effect on the internal aryl ring of 2-alkynylbenzonitriles (products **3oa–3ta**). To our delight, the results showed that both electron-donating substituents including methyl (**1o**) and methoxy (**1p**) groups and electron-withdrawing substituents fluorine (**1q** and **1r**) and chlorine (**1s** and **1t**) could be smoothly transformed into the corresponding desired products in moderate to good yields under the optimized conditions. For example, methyl substituted substrate **1o** formed the desired product **3oa** in 63% yield. Fluoro-substituted products **3qa** and **3ra** were obtained in 65% and 70% yields, respectively. Finally, the symmetric substrate **1u** was compatible with the standard reaction conditions as well and gave the corresponding product **3ua** in 53% yield.

Next, the scope of sodium arylsulfinates was also explored under the standard reaction conditions (Scheme 3). To our delight, substrates **2b–2g**, bearing electron-donating or electron-deficient groups on the aryl ring, were compatible under the standard conditions. For example, substrate **2c** with a methoxy group was tolerated well under the standard conditions, affording **3ac** in 55% yield. Noticeably, the substrates bearing an electron-deficient halo group, including Cl and I on the aromatic ring, were well-tolerated under the reaction conditions, thereby providing an opportunity for additional modifications at the halogenated position (**3ae** and **3af**). Next, we investigated the reactivity of the substrate sodium naphthalene-2-sulfinate **2g**, affording the corresponding product **3ag** in 52% yield. However, sodium trifluoromethanesulfinate **2h** did not yield the corresponding product and formed compound **4**, which was consistent with the results reported by other chemists.[21]

To shed light on the possible mechanism of the reaction, several control experiments were carried out, as shown in Scheme 4. First, the addition of radical inhibitors tetramethyl-

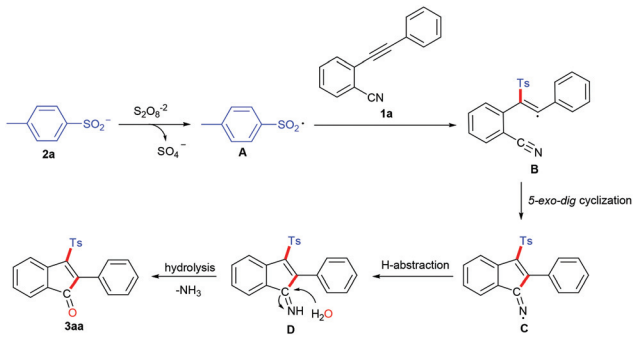


Scheme 3 Substrate scope of sodium sulfinates. Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Na_2S_2O_8$ (0.6 mol), v(CH_3CN) : v(H_2O) = 9 : 1 (total volume is 2 mL), 60 °C and 24 h under a N_2 atmosphere. Isolated yields. [a] At 100 °C with 36 h.



Scheme 4 Control experiments.

piperidin-1-oxyl, butylated hydroxytoluene and 1,1-diphenylethylene resulted in the inhibition of the reaction (eqn (1) in Scheme 4). Obviously, when the reaction of **1a** with **2a** was carried out in the presence of radical scavenger 1,1-diphenylethylene under standard reaction conditions, the formation of the desired products was totally suppressed and adduct **5** was obtained in 15% yield. The results suggest that the current reaction is likely to involve a TS radical and involves a radical process. The result of an ^{18}O-labeled experiment using $H_2{}^{18}O$



Scheme 5 Possible mechanism.

indicates that the reaction undergoes a hydrolysis process (eqn (2) in Scheme 4). Notably, compound **6** could not be converted into product **3aa**. The results imply that compound **6** is not the intermediate of this reaction (eqn (3) in Scheme 4). Moreover, when substrate **1a** reacted under optimal conditions in the absence of **2a**, no products were obtained (eqn (4) in Scheme 4). This result indicates that this radical tandem cyclization reaction is triggered by the benzenesulfonyl radical.

Based on the above control experiments and previous mechanistic studies,[20,22] a plausible mechanism is shown in Scheme 5. First, sodium benzenesulfinate **2a** is oxidized by $Na_2S_2O_8$ to generate benzenesulfonyl radical A.[20a,c,d] Then, intermolecular addition of **A** to **1a** offers the alkenyl radical intermediate **B**.[17–19,22] Intermediate **B** undergoes the 5-*exo-dig* cyclization reaction to give intermediate **C**, which abstracts a H-atom to produce unstable imine intermediate **D**. Finally, imine intermediate **D** is hydrolyzed by water to yield the desired product **3aa**.[17–19,22]

In summary, we have demonstrated an efficient protocol for the synthesis of sulfonated indenones *via* a radical cascade cyclization of 2-alkynylbenzonitriles with sodium arylsulfinates. This methodology allows one new C–C bond and C–S bond formation through the cleavage of one C–N bond. Furthermore, these synthetic 3-sulfonylindenones are ubiquitous structural units in a number of biologically active compounds; so the expansion of the synthetic application of this skeleton is currently under investigation in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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