A Regioselective Catalyst- and Additive-Free Synthesis of β-Keto Sulfones from Aryl Acetylenes and Sodium Arenesulfinates

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Abstract: A facile and regioselective procedure for the preparation of β-keto sulfones has been developed through a simple reaction of aryl acetylenes and sodium arenesulfinates in nitroethane as a solvent at 50 °C. The procedure is catalyst- and additive-free and shows a wide range of functional-group tolerance. In this system the formation of new C–O and C–S bonds occurs in a one-pot procedure.

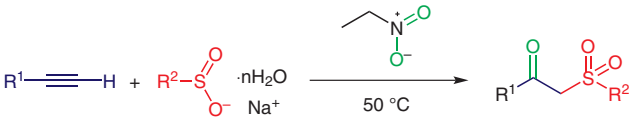
Key words: β-keto sulfone, aryl acetylene, sodium arene sulfinates, vinyl nitronic ester, sulfone, sulfinates salt

Catalyst- and/or additive-free protocols can provide economical and environmental benign routes for the synthesis of key organic intermediates.[1] Sulfones are versatile intermediates for organic transformations involving carbon–carbon bond formations such as the Julia olefination.[2] Amongst the different derivatives of sulfones, β-keto sulfones are increasingly drawing interest due to their synthetic utility as precursors in Michael[3] and Knoevenagel reactions,[4] in the synthesis of disubstituted acetylenes,[5] allenes,[6] vinyl sulfones,[7] polyfunctionalized 4*H*-pyrans,[3,8] ketones,[9] epoxy sulfones,[10] and optically active β-hydroxysulfones.[11] In addition, some of these derivatives also show fungicidal activity.[12]

General protocols for the synthesis of β-keto sulfones include oxidation of β-keto sulfides or β-hydroxy sulfones,[13] alkylation of metallic arenesulfinates,[14] acylation of α-sulfonyl carbanions,[15] ruthenium(II) complex catalyzed reaction of sulfonyl chlorides with silyl enol ethers,[16] $SnCl_2$-catalyzed reaction of diazo sulfones with aldehydes,[17] free-radical rearrangement of enol sulfonates,[18] AIBN-catalyzed reaction of polystyrene-supported arene seleno sulfonates[19] with aryl acetylenes and from ketones using sodium arenesulfinates with the PhI(OH)OTs/TBAB system.[20] However, most of these methods have one or more drawbacks in terms of functional-group tolerance, presence of side reactions, and need for strict reaction conditions or complicated procedures.

Recently, Xi et al. reported an attractive method for the preparation of β-keto sulfones by acid-catalyzed reaction of sulfonyl chloride with aryl acetylenes at 50 °C in aqueous THF.[21] However, the presence of acid and use of sulfonyl chloride leads to a system of poor functional-group tolerance. To obviate the use of acid and sulfonyl chloride it appeared to be beneficial to obtain β-keto sulfones directly from alkynes and sodium arenesulfinates, as use of sodium arenesulfinates can provide weakly basic reaction conditions, and hence be suitable for the preparation of β-keto sulfones containing amine and other acid-sensitive moieties.

Herein we report an efficient one-pot catalyst- and additive-free procedure for the synthesis of β-keto sulfones via the reaction of sodium arenesulfinates with aryl acetylenes (Scheme 1). To the best of our knowledge, this has not been reported so far. In this system the formation of new C–O and C–S bonds occurs with the regioselective addition of the sulfonyl moiety at the terminal carbon of the acetylene. In addition reaction conditions are mild, and the procedure is insensitive to moisture.



Scheme 1 Synthesis of β-keto sulfones with aryl acetylenes and sodium arenesulfinates

We have recently developed the highly efficient methods for β-sulfonation of α,β-enones and direct sulfonylation of alcohols using sodium arene sulfinates as sulfonylating agents employing $FeCl_3$/TMSCl as catalyst.[22] In continuation of this work, we investigated the preparation of β-keto sulfones directly from sodium arenesulfinates and aryl acetylenes. Initially, we examined the reaction between phenylacetylene and sodium benzenesulfinate as a model system using various solvents at different temperatures to obtain the desired product 1-phenyl-2-(phenylsulfonyl)ethanone (**1a**, Table 1).

The best conditions were found using nitroethane as solvent at 50 °C, with 1.0 equivalent of phenylacetylene and 1.5 equivalents of sodium benzenesulfinate resulting in 52% isolated yield of the desired product (Table 1, entry 3). Reactions with other solvents such as water and nitromethane (Table 1, entries 1 and 2) provided comparatively lower yields of **1a**. However, with DMF, DMSO, CH_2Cl_2, toluene, THF, MeOH, and PEG 400 no product was formed (Table 1, entries 4–10). To study the influ-

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Table 1 Optimization of Reaction Conditions with Phenylacetylene and Sodium Benzenesulfinate[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	H_2O	50	48	18
2	$MeNO_2$	50	48	25
3	$EtNO_2$	50	48	52
4	DMF	50	48	0
5	DMSO	50	48	0
6	CH_2Cl_2	50	48	0
7	toluene	50	48	0
8	THF	50	48	0
9	MeOH	50	48	0
10	PEG 400	50	48	0
11	$EtNO_2$	25	48	35
12	$EtNO_2$	40	48	42
13	$EtNO_2$	60	48	38
14	$EtNO_2$	70	48	22
15	$EtNO_2$	80	48	0

[a] Reaction conditions: phenylacetylene (1.0 mmol), sodium benzenesulfinate (1.5 mmol), and solvent (5 mL).
[b] Yield of isolated products.

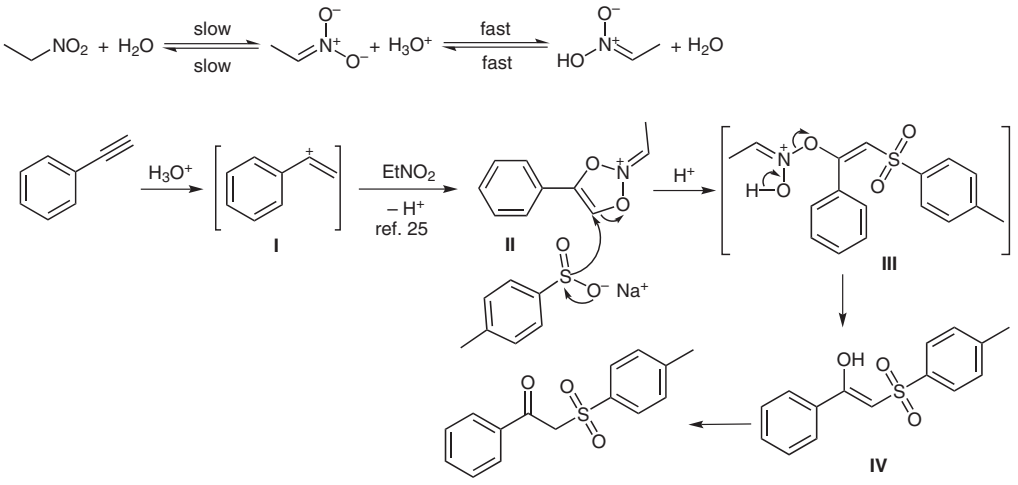
ence of temperature on the reaction, experiments were carried out with the model substrates in nitroethane in the range 25–80 °C. As can be seen (Table 1, entries 11–15), conversion was highly sensitive to temperature change, being highest at 50 °C. Furthermore, an excellent regioselective addition of the sulfonyl group at the terminal carbon of acetylene was observed resulting in **1a** as the exclusive product of the reaction.

As the yield of **1a**, obtained under the optimized reaction conditions (Table 1, entry 3) after screening various solvents at different temperatures, was moderate, attempts at further optimization were carried out. Unfortunately, adding various catalysts and/or additives such as iron(III) chloride, ceric ammonium nitrate, $PhI(OAc)_2$, and cat. H_2SO_4 led to no further enhancement in yield of **1a**.

To explore the scope and the limitations of this reaction, various structurally diverse aryl acetylenes and sodium arenesulfinates were examined under the optimized reaction conditions (Table 1, entry 3), and the results are shown in Table 2.

The results in Table 2 demonstrate that the reaction proceeds smoothly using various aryl acetylenes and sodium arenesulfinates to afford β-keto sulfones in moderate to good yields. It was found that electron-donating groups, such as methyl (**2b** and **2c**, Table 2, entries 3–5) and methoxy (**2e**, Table 2, entries 8 and 9), on the aryl acetylene resulted in the desired product being obtained in good yield. However, in the case of electron-poor aryl acetylenes such as **2d** (Table 2, entries 6 and 7) low yields were observed. Sodium *p*-toluenesulfinate (**3b**), with an electron-donating methyl substituent on the aryl ring provides better yields of β-keto sulfones compared to sodium benzenesulfinate (**3a**), indicating that the addition of the arylsulfonyl moiety to the terminal carbon of the acetylene is nucleophilic in nature. It is noteworthy that an aryl acetylene with a halide substituent **2d** (Table 2, entries 6 and 7) was well tolerated using this protocol; hence giving potential for further functionalization of the aryl ring.

The C–H acidity of nitroalkanes and their prototropy to give nitronic acids is well known.[23] Moreover, the electrophilic addition of C–H acids such as nitroalkanes to acetylenic systems, vinyl nitronic ester intermediates, and their subsequent rearrangement to α-substituted ketones are also well established.[24,25] Based on these observations, a plausible mechanism is shown in Scheme 2. Protonation of the terminal carbon of the acetylene will generate a vinyl cationic species **I** which can react with nitroethane leading to the formation of vinyl nitronic ester **II**.[25] The intermediacy of **II** was supported by mass spectrometric analysis of the reaction mixture after six hours, showing a



Scheme 2 A plausible mechanism for the synthesis of β-keto sulfone

peak at *m/z* = 333 $[M + 1]^+$. Nucleophilic addition of sulfonyl anion on **II** generates an intermediate **III** which on nitrosoethane elimination and protonation forms enol **IV** which subsequently tautomerizes to the more stable keto form.

In conclusion, we have developed a new catalyst- and additive-free protocol for the synthesis of β-keto sulfones using various aryl acetylenes and sodium arenesulfinates affording moderate to good yields of the desired products. The addition of the sulfonyl group occurs exclusively at the terminal carbon of the acetylenes. The notable advantages of this methodology over the existing procedures are simplicity of operation, mild conditions, inexpensive reagents, and high functional-group tolerance.

Table 2 Reaction of Sodium Arenesulfinates with Aryl Acetylenes in Nitroethane at 50 °C[a]

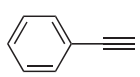
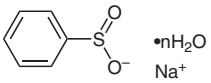
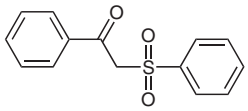
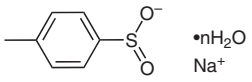
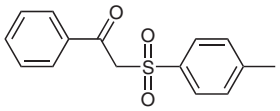
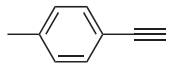
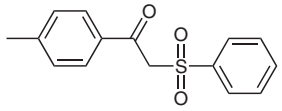
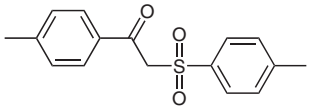
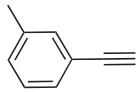
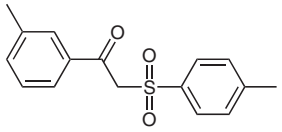
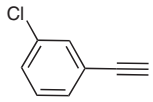
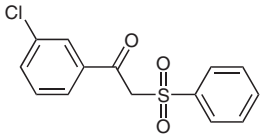
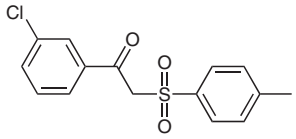
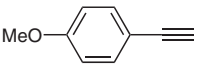
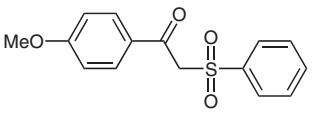
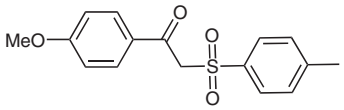
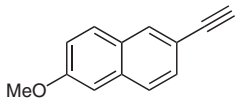
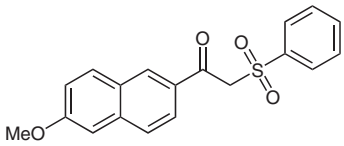
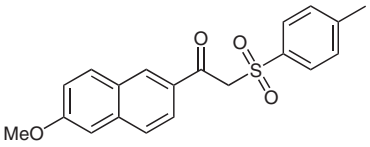
Entry	Aryl acetylene	Sodium arene sulfinate	Product	Time (h)	Yield (%)[b]
1	 **2a**	 **3a**	 **1a**	48	52
2	**2a**	 **3b**	 **1b**	48	57
3	 **2b**	**3a**	 **1c**	48	51
4	**2b**	**3b**	 **1d**	48	50
5	 **2c**	**3b**	 **1e**	48	57
6	 **2d**	**3a**	 **1f**	48	39
7	**2d**	**3b**	 **1g**	48	41
8	 **2e**	**3a**	 **1h**	48	49

Table 2 Reaction of Sodium Arenesulfinates with Aryl Acetylenes in Nitroethane at 50 °C[a] (continued)

Entry	Aryl acetylene	Sodium arene sulfinate	Product	Time (h)	Yield (%)[b]
9	**2e**	**3b**	 **1i**	48	51
10	 **2f**	**3a**	 **1j**	48	46
11	**2f**	**3b**	 **1k**	48	49

[a] Reaction conditions: aryl acetylene (1.0 mmol), sodium arene sulfinate (1.5 mmol), and $EtNO_2$ (5 mL) at 50 °C.
[b] Yield of isolated products.

Typical Experimental Procedure

A mixture of aryl acetylene (1 mmol) and sodium arene sulfinate (1.5 mmol) in $EtNO_2$ (5 mL) was heated at 50 °C for 48 h. The cooled mixture was partitioned between EtOAc and H_2O, the organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography, eluted with hexane–acetone to afford the pure product.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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