Aerobic oxysulfonylation of alkynes in aqueous media: highly selective access to β-keto sulfones

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ABSTRACT

The first application of inexpensive commercially available sulfinate salts to produce β-keto sulfones directly from alkynes via aerobic oxysulfonylation has been developed. It is a highly selective (undesired Glaser–Hay homo-coupling and ATRA process totally suppressed) general method of functionalization of alkynes on water at room temperature involving $FeCl_3/K_2S_2O_8$ catalyzed formation of sulfonyl radicals from sulfinate salts.

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The transformation of alkynes is a method fundamental to organic synthesis. Besides the early examples of hydration of alkynes to ketones[1] and addition reactions,[2] various novel transition-metal catalyzed reactions of alkynes were developed which enriched the basic alkyne chemistry. These reactions also resulted in many methods of industrial importance, viz. Pd-catalyzed Wacker-type oxidation,[3] click reactions,[4] and Sonogashira coupling.[5] Consequently, great advances have been made in this field to exploit the prominent potential of alkynes. In particular, the transition-metal catalyzed functionalization of terminal alkynes has blossomed significantly during the last decade.[6] However, only rare examples of transition-metal catalyzed aerobic oxidation of terminal alkynes have been reported.[7,8] The area is extraordinarily challenging and finding new reactions to broaden it is of great importance.

Dioxygen, as an oxygen source and oxidant, is an attractive reagent in organic synthesis which efficiently complies with the green chemistry principles.[7] Recently, it has been used in a number of transition-metal catalyzed aerobic oxidative radical reactions of alkenes to achieve important functionalizations but terminal alkynes have seldom been used in this way.[7–9] The limited number of reports with alkynes may be attributed to two main obstacles. Firstly, it is the well known undesired Glaser–Hay homo-coupling of terminal alkynes which can hardly be avoided and secondly, it is the preferential atom transfer radical addition (ATRA) process over

oxygen capture by the in situ generated vinyl radical intermediate which leads to alkenes in the reaction. Thus, these alkyne-based reactions are usually not selective generating concurrently a number of undesired by-products. In the light of above mentioned difficulties, developing a highly selective aerobic oxidation reaction of terminal alkynes in which both the homo-coupling and ATRA are totally suppressed is certainly desired. For overcoming these limitations and in continuation of our work on simple starting materials,[10] especially alkynes,[10g] we report herein a highly efficient aerobic oxysulfonylation protocol for the synthesis of β-keto sulfones directly from alkynes using dioxygen and arenesulfinates in aqueous media.

β-Keto sulfones[11] are valuable compounds in organic synthesis and pharmaceutical industry. A number of methods have been reported for their synthesis but β-keto sulfones have rarely been obtained from alkynes.[12] To the best of our knowledge, there is only one example where β-keto sulfones have been prepared from alkynes using aerobic oxidative radical reaction.[9e] All the previous reports suffer severely from limitations like extremely low yields in most cases, long reaction time, elevated temperatures, and incompatibility with green chemistry principles. Consequently, we report herein an efficient synthesis of β-keto sulfones by aerobic oxysulfonylation of alkynes on water at room temperature (Scheme 1). Besides being catalytic, our protocol involves the use of cost-effective and environmentally benign catalyst system ($FeCl_3/K_2S_2O_8$) and solvent (water). Moreover, arenesulfinates have never been used as sulfonyl radical precursors for ensuing oxygen capture in conjunction with alkynes.

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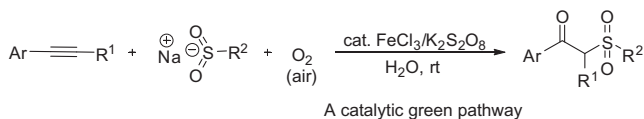
Scheme 1. Aerobic oxysulfonylation of alkynes.

Scheme 2. Model reaction under $AgNO_3/K_2S_2O_8$ catalysis in aqueous media.

Recently, we have communicated our work on the synthesis of β-keto sulfones from alkenes and arenesulfinates via aerobic oxysulfonylation using $AgNO_3/K_2S_2O_8$ catalytic system[10i] and also under transition metal-free conditions.[10j] Our previous findings led us to investigate the more challenging reaction of alkynes with sulfinate salts under the same reaction conditions. Our initial trial with phenylacetylene (**1a**) and sodium *p*-toluenesulfinate (**2a**) in the presence of 20 mol % of $AgNO_3$ and 20 mol % of $K_2S_2O_8$ in DMF at room temperature for 18 h delivered a complex mixture containing 18% of β-keto sulfone **3a** (Table 1, entry 1). Our reaction with alkenes also worked well under aqueous conditions, so the next trial was performed in aqueous media which fetched better results (entry 2). On using water as a solvent, β-keto sulfone **3a** was produced in 27% yield. The homo-coupled product of **1a** and a regioisomeric mixture of vinyl sulfones were formed in 20% and 24% yield, respectively along with other side products (Scheme 2). The expected Glaser–Hay homo-coupling and ATRA process were seriously interfering with our reaction conditions.

We further tried the reaction using other metal salts in aqueous media. Copper salts worsen the situation as the side reactions were facilitated considerably in their presence (entries 3 and 4). Most delightfully, a dramatic change in the TLC pattern was observed on using $FeCl_3$ as a catalyst. The side reactions were totally suppressed (reason not very clear) and the yield of β-keto sulfone **3a** rose to 92% (entry 5). Motivated by the results, we tried other iron salts but $FeCl_3$ produced the best yield (entries 5–7) as well as accelerated the reaction appreciably. The reaction could be
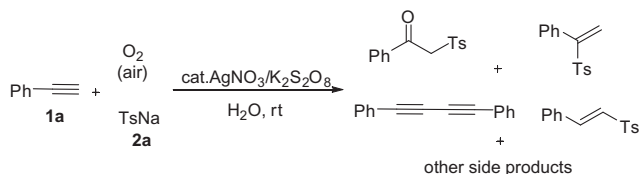
completed in 7 h in the presence of $FeCl_3/K_2S_2O_8$ catalyst system (entry 8). Evaluation of $(NH_4)_2S_2O_8$, TBHP, DTBP, pyridine, and Et_3N as additives in the oxysulfonylation protocol showed that persulfate salts outperformed the other additives; $(NH_4)_2S_2O_8$ producing a slight drop in yield as compared to $K_2S_2O_8$ (entries 5, 9–13). In the absence of any additive, the yield of β-keto sulfone **3a** was decreased (entry 14). Also, in the absence of any metal catalyst the reaction became very sluggish (entry 15). The reaction did not improve in the presence of other solvents (entries 16–21). The exceptional lower yields in less polar solvents may be due to insolubility of the reagent/catalyst in them.

With the best catalyst system chosen, we next tried to optimize the catalyst/additive loading and the substrate-reagent ratio. After extensive investigation, we established that the maximum yield of **3a** (92%) was obtained on using 1.0 equiv of **1a** and 1.5 equiv of **2a** in the presence of 20 mol % each of $FeCl_3$ and $K_2S_2O_8$.

Once we decided the best set of conditions for our reaction, we moved onto the substrate-scope of the reaction. The reaction was tried with various alkynes **1** and sodium arenesulfinates **2** (Table 2). As evident from the table, aryl alkynes proved to be excellent substrates for the aerobic oxysulfonylation. Both electron-rich (R = Me or OMe) and electron-poor (R = Br, Cl, F or CN) aryl alkynes were oxysulfonylated with sulfinate salts **2a** (R = Me) and **2b** (R = H) in good yields (**3a–o**). Not much change in the yield of products **3e–i** was observed with the variation of positions (*o*-, *m*-, and *p*-)

Table 1
Optimization of metal salt, additive, and solvent[a]

Entry	Solvent	Metal salt (20 mol %)	Additive (20 mol %)	Yield[b] (%)
1	DMF	$AgNO_3$	$K_2S_2O_8$	18
2	Water	$AgNO_3$	$K_2S_2O_8$	27
3	Water	CuCl	$K_2S_2O_8$	12
4	Water	$Cu(OAc)_2$	$K_2S_2O_8$	15
5	Water	$FeCl_3$	$K_2S_2O_8$	92
6	Water	Fe_2O_3	$K_2S_2O_8$	43
7	Water	[Fe(Pc)]	$K_2S_2O_8$	81
8	Water	$FeCl_3$	$K_2S_2O_8$	92[c]
9	Water	$FeCl_3$	$(NH_4)_2S_2O_8$	84
10	Water	$FeCl_3$	TBHP	73
11	Water	$FeCl_3$	DTBP	79
12	Water	$FeCl_3$	Pyridine	70
13	Water	$FeCl_3$	Et_3N	71
14	Water	$FeCl_3$	—	65
15	Water	—	$K_2S_2O_8$	17
16	DMF	$FeCl_3$	$K_2S_2O_8$	83
17	DMSO	$FeCl_3$	$K_2S_2O_8$	75
18	EtOH	$FeCl_3$	$K_2S_2O_8$	70
19	CH_3CN	$FeCl_3$	$K_2S_2O_8$	55
20	DCM	$FeCl_3$	$K_2S_2O_8$	22
21	Dioxane	$FeCl_3$	$K_2S_2O_8$	23

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.40 mmol), catalyst, additive, and solvent (3 mL) in a flask open to air.[14]
[b] Yield of isolated and purified product **3a**.
[c] Reaction time 7 h.

Table 2
Substrate scope of the reaction[a]

Entry	Ar	R^1	R^2	Product	Time (h)	Yield[b] (%)
1	Ph	H	4-MeC_6H_4	**3a**	7	92
2	4-MeC_6H_4	H	4-MeC_6H_4	**3b**	9	85
3	4-BrC_6H_4	H	4-MeC_6H_4	**3c**	8	88
4	Ph	H	Ph	**3d**	7	94
5	3-MeC_6H_4	H	Ph	**3e**	8	82
6	2-MeC_6H_4	H	Ph	**3f**	9	79
7	4-MeC_6H_4	H	Ph	**3g**	8	86
8	4-MeOC_6H_4	H	Ph	**3h**	6	93
9	2-MeOC_6H_4	H	Ph	**3i**	7	81
10	4-IC_6H_4	H	Ph	**3j**	9	68
11	4-BrC_6H_4	H	Ph	**3k**	7	90
12	4-ClC_6H_4	H	Ph	**3l**	8	79
13	4-FC_6H_4	H	Ph	**3m**	8	72
14	4-CNC_6H_4	H	Ph	**3n**	9	65
15	4-PhC_6H_4	H	Ph	**3o**	8	70
16	2-naphthyl	H	Ph	**3p**	7	73
17	2-thienyl	H	Ph	**3q**	8	77
18	Ph	Me	Ph	**3r**	9	56
19	Ph	H	4-MeOC_6H_4	**3s**	6	93
20	Ph	H	4-BrC_6H_4	**3t**	7	82
21	Ph	H	4-ClC_6H_4	**3u**	7	87
22	Ph	H	4-FC_6H_4	**3v**	8	84
23	Ph	H	2-naphthyl	**3w**	8	89

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.375 mmol), $FeCl_3$ (20 mol %), $K_2S_2O_8$ (20 mol %), and water (3 mL) in a flask open to air.[14]
[b] Yield of isolated and purified product **3** and reaction time is given.