RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 13191

Received 21st December 2013
Accepted 26th February 2014

DOI: 10.1039/c3ra47863g

www.rsc.org/advances

Molecular-iodine-catalyzed aerobic oxidative synthesis of β-hydroxy sulfones from alkenes†

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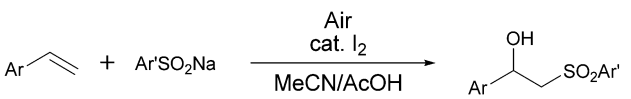
The synthesis of β-hydroxy sulfones from alkenes and sodium sulfinates under aerobic oxidative conditions was achieved in the presence of a catalytic amount of molecular iodine. Molecular oxygen in air serves as the terminal oxidant and the catalytic amount of molecular iodine acts as the sulfonyl radical initiator and peroxide reductant.

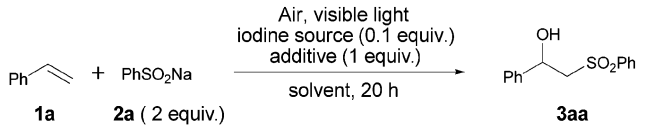
Sulfur-containing compounds have been used in numerous applications including as medicines, agrochemicals, dyes, and semiconductors. Thus, construction of the C–S bond is important, and many C–S-bond-forming reactions have been developed to date.[1] In particular, β-hydroxy sulfones are not only one of the most important structural motifs in bioactive compounds[2] but also key reaction intermediates in organic synthesis.[3] In general, β-hydroxy sulfones are prepared *via* the nucleophilic addition of sulfinates to epoxides,[4] the reduction of β-oxosulfones,[5] or the hydroxylation of α,β-unsaturated sulfones.[6] In addition, the oxysulfonylation of alkenes, which are easy to handle and inexpensive substrates, using sulfonyl chloride or sulfonylhydrazide as sulfone sources has been reported.[7]



Scheme 1 Aerobic oxidative synthesis of β-hydroxy sulfones from alkenes using a catalytic amount of molecular iodine.

On the other hand, we have developed various oxidation methods using catalytic iodine sources and molecular oxygen as the terminal oxidant under visible light irradiation.[8] Molecular

Table 1 Optimization of reaction conditions for the aerobic oxidative synthesis of β-hydroxy sulfones[a]



1a **2a** (2 equiv.) **3aa**

Entry	Iodine source	Additive	Solvent (mL)	**3aa**[b] (%)
1	I_2	—	MeCN (1)	13
2	I_2	Et_3N	MeCN (1)	0
3	I_2	K_2CO_3	MeCN (1)	2
4	I_2	AcOH	MeCN (1)	38
5	I_2	$TsOH \cdot H_2O$	MeCN (1)	59
6	I_2	TFA	MeCN (1)	66
7	I_2	—	Hexane/AcOH (1/0.25)	60
8	I_2	—	$CHCl_3$/AcOH (1/0.25)	70
9	I_2	—	EtOAc/AcOH (1/0.25)	72
10	I_2	—	THF/AcOH (1/0.25)	77
11	I_2	—	MeOH/AcOH (1/0.25)	79
12	I_2	—	AcOH (1.25)	56
13	I_2	—	MeCN/AcOH (1/0.25)	85
14	NIS	—	MeCN/AcOH (1/0.25)	65
15	NaI	—	MeCN/AcOH (1/0.25)	70
16	MgI_2	—	MeCN/AcOH (1/0.25)	60
17	CaI_2	—	MeCN/AcOH (1/0.25)	74
18	Cl_4	—	MeCN/AcOH (1/0.25)	60
19	I_2	—	MeCN/AcOH (1/0.4)	91
20[c]	I_2	—	MeCN/AcOH (1/0.4)	67
21[d]	I_2	—	MeCN/AcOH (1/0.4)	88 (93)
22[d]	—	—	MeCN/AcOH (1/0.4)	0
23[d,e]	I_2	—	MeCN/AcOH (1/0.4)	37

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2 equiv.), iodine source (0.1 equiv.) and additive (1 equiv.) in solvent was stirred and irradiated externally with a fluorescent lamp for 20 h. [b] ^1H NMR yields. Number in parenthesis is isolated yield. [c] The reaction was carried out in the dark. [d] The reaction was carried out without positive irradiation from fluorescent lamp. [e] The reaction was carried out under argon.

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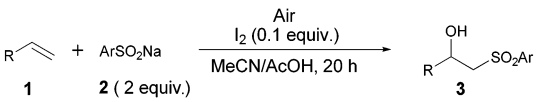
† Electronic supplementary information (ESI) available: General procedure: a solution of styrene (**1a**, 0.3 mmol), sodium benzenesulfinate (**2a**, 2 equiv.) and iodine (0.1 equiv.) in MeCN/AcOH (1 mL/0.4 mL) in a pyrex test tube was stirred under air for 20 h. The reaction mixture was washed with aq. $Na_2S_2O_3$ and concentrated *in vacuo*. Purification of the crude product by a silica gel column (hexane : EtOAc = 3 : 1) provided 1-phenyl-2-(phenylsulfonyl)ethanol (**3aa**) (R_f = 0.29, 73.2 mg, 93%). See DOI: 10.1039/c3ra47863g

oxygen is photosynthesized by plants and is an effective oxidant with atom efficiency higher than that of other oxidants such as toxic heavy metals and complex organic reagents. Through our study of aerobic photo-oxidation with iodine sources, we discovered the oxysulfonylation of alkenes. During the course of our present study, Lei and co-workers reported impressive results for the aerobic oxysulfonylation of alkenes using sulfinic acids.[9] However, this reaction requires sulfinic acids, which are air sensitive, as well as a stoichiometric amount of triphenylphosphine as the reductant. Herein, we report the synthesis of β-hydroxy sulfones from alkenes and sodium sulfinates, which are readily available and easily handled, using a catalytic amount of molecular iodine and molecular oxygen from air (Scheme 1).

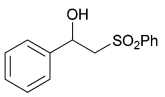
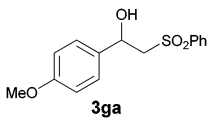
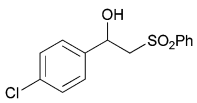
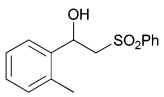
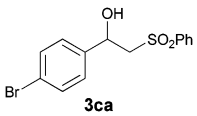
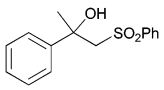
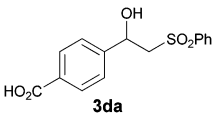
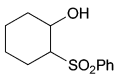
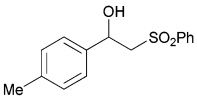
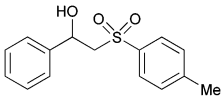
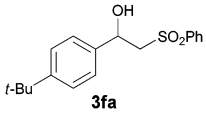
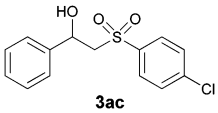
Table 1 shows the results of the optimization of the reaction conditions. Styrene (**1a**) was chosen as the test substrate and reacted with sodium benzenesulfinate (**2a**) in the model reaction. When iodine was used as the catalyst and acetonitrile as the solvent under visible light irradiation conditions, hydroxy sulfone (**3aa**) was obtained in low yield (entry 1). Addition of protic acids, such as acetic acid, *p*-toluenesulfonic acid, and trifluoroacetic acid, provided increased yields of **3aa** (entries 2–6). Thus, the solvent and iodine source were investigated using acetic acid as a cosolvent (entries 7–19), and the highest yield of **3aa** was obtained using MeCN/AcOH (1 mL/0.4 mL) as the solvent and I_2 as the catalyst (entry 19). Next, the necessity of visible light irradiation was examined, and the reaction was found to be depressed in the dark (entry 20). On the other hand, the reaction proceeded in high yield, even without positive irradiation of visible light (entry 21). In addition, without an iodine source and molecular oxygen, lower yields were obtained (entries 22 and 23).

Next, the scope and limitations of the reaction of various alkenes (**1**) and aryl sulfinates (**2**) under the optimized reaction conditions were investigated, and the results are presented in Table 2. In general, β-hydroxy sulfones were obtained in good to high yields, regardless of the electron-donating or -withdrawing group on the aromatic ring of the styrene substrate (entries 1–7).

Table 2 Scope and limitations for the aerobic oxidative synthesis of β-hydroxy sulfones[a]



1 2 (2 equiv.) 3

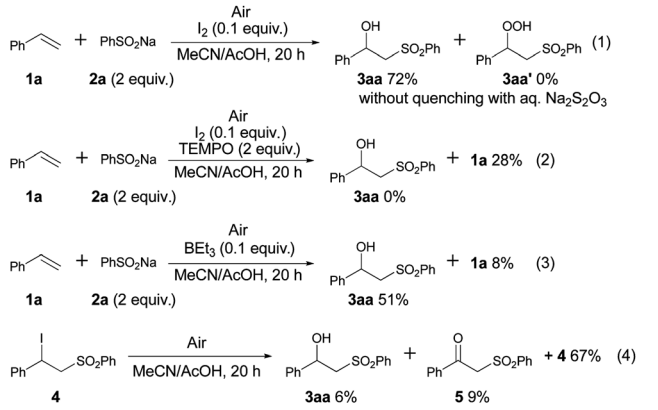
Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **3aa**	93 (79)[c]	7	 **3ga**	61[d]
2	 **3ba**	80	8	 **3ha**	94
3	 **3ca**	72	9	 **3ia**	79[e]
4	 **3da**	87	10	 **3ja**	0[f]
5	 **3ea**	86	11	 **3ab**	91
6	 **3fa**	93	12	 **3ac**	93

[a] Reaction conditions: **1** (0.3 mmol), **2** (2 equiv.), and I_2 (0.1 equiv.) in MeCN/AcOH (1 mL/0.4 mL) was stirred for 20 h. [b] Isolated yields. [c] Styrene (**1a**: 10 mmol, 1.04 g), $PhSO_2Na$ (**2a**: 2 equiv.), I_2 (0.1 equiv.), MeCN/AcOH (30 mL/14 mL) was stirred for 72 h. [d] The reaction was carried out for 72 h. [e] The reaction was carried out for 48 h. [f] *trans*-(2-Iodocyclohexyl)sulfonylbenzene (22%) was obtained.

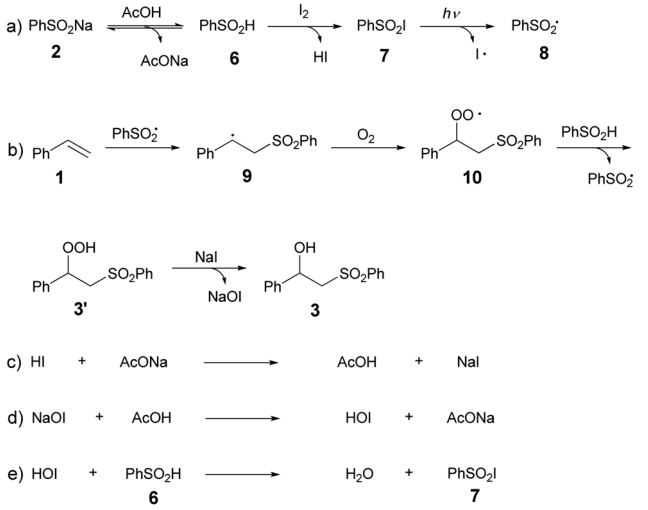
In addition, a gram-scale reaction was carried out under the optimized conditions, and the desired product was obtained in good yield (entry 1). A longer reaction time was required for the reaction of 4-methoxystyrene (1 g) because light absorption was interrupted by **3ga**, which is less soluble in the solvent (entry 7). Furthermore, sterically hindered *o*-methylstyrene and a disubstituted styrene were good substrates (entries 8 and 9) for the reaction. On the other hand, cyclohexene was a poor substrate, and *trans*-(2-iodocyclohexyl)sulfonylbenzene was obtained in just 22% yield (entry 10). Finally, sulfinates other than sodium benzenesulfinate, including sodium 4-methylbenzenesulfinate and sodium 4-chlorobenzenesulfinate, were suitable and provided the desired products in high yields (entries 11 and 12).

To resolve the reaction mechanism, several control experiments were then examined. Without quenching with aq. $Na_2S_2O_3$, β-hydroxy sulfone **3aa** was detected in 72% yield, and no β-hydroperoxysulfone **3aa′** was detected in the ^{1}H NMR spectrum (Scheme 2, eqn (1)). When 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added as a radical scavenger, however, the reaction did not proceed (Scheme 2, eqn (2)). On the other hand, when triethylborane instead of iodine was used as radical initiator, the reaction proceed (Scheme 2, eqn (3)). These results indicating that a radical mechanism is involved. The β-iodo sulfone **4** was eliminated as a possible intermediate when its reaction under the optimized conditions resulted in its recovery (67% yield) and the formation of **3aa** and **5** in low yield (Scheme 2, eqn (4)).[10]

A plausible reaction path for this oxidation, postulated on the basis of all of the above mentioned results, is presented in Scheme 3. A sulfone radical is generated from sodium sulfinate and molecular iodine *via* sulfonyl iodide 7 upon exposure to light in the presence of acetic acid.[10] This sulfone radical adds to the substrate **1** to give benzyl radical species **9**, which traps molecular oxygen and is converted to peroxy radical **10** and then hydroperoxide **3′**. Hydroperoxide **3′** is subsequently reduced to the β-hydroxy sulfone **3** by an iodide species, such as sodium iodide, and the hypoiodite is regenerated. Hypoiodite also serves as sulfone radical initiator *via* sulfonyl iodide 7.



Scheme 2 Results of the mechanistic study of the aerobic oxidative synthesis of β-hydroxy sulfones.



Scheme 3 Proposed reaction pathway for the aerobic oxidative synthesis of β-hydroxy sulfones.

Conclusions

In conclusion, we reported the synthesis of β-hydroxy sulfones from alkenes using molecular oxygen and molecular iodine. This novel reaction is interesting because it uses a catalytic amount of molecular iodine and molecular oxygen from the air as the terminal oxidant without light irradiation.

Notes and references

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