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Iron-catalyzed sulfonyl radical formations from sulfonylhydrazides and oxidative addition to alkenes†‡

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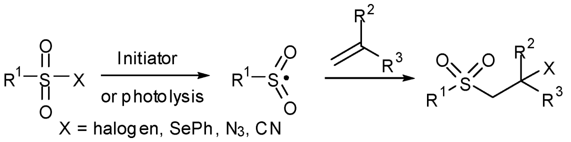
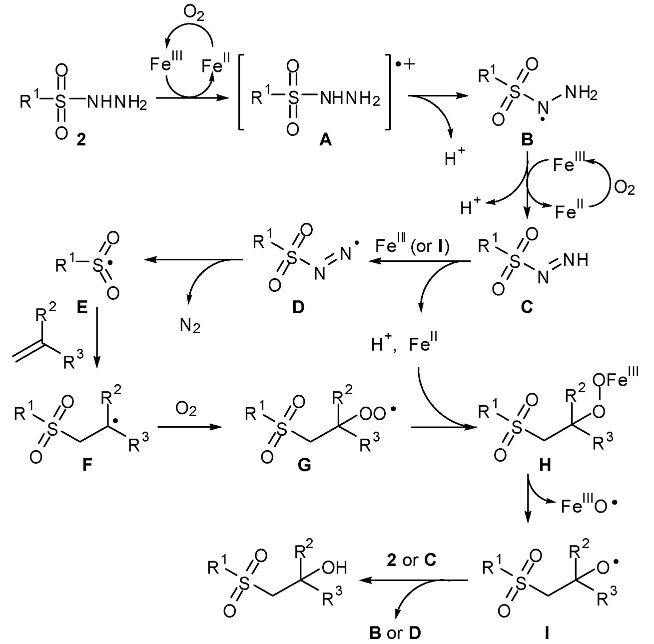
Generation of sulfonyl radicals from sulfonylhydrazides has been achieved in the presence of a non-toxic iron catalyst and oxygen. The intermolecular addition of resultant sulfonyl radicals to alkenes affords β-hydroxysulfone compounds.

Sulfone compounds are important materials because they include valuable biologically active compounds and useful building blocks in organic synthetic chemistry.[1,2] Sulfonyl radicals are useful intermediates for the synthesis of sulfone compounds. Various methods for the generation of sulfonyl radicals and the addition reaction to multiple bonds such as alkenes and alkynes have been extensively explored.[3] For instance, sulfonyl halides,[4] selenide,[5] cyanide[6] and azide[7] easily generate corresponding sulfonyl radicals by treatment of radical initiators or photolysis and they cause atom transfer radical additions to multiple bonds (Scheme 1). Sodium sulfinate derivatives also behave as a sulfonyl radical source in the presence of a stoichiometric amount of an oxidant such as manganese(III) and copper(II).[8] Recently, we reported iron-catalyzed mild oxidative additions of aryl or alkoxycarbonyl radicals to alkenes using hydrazine compounds as a precursor.[9] In these reactions, radical generation is initiated by iron/O_2-mediated oxidation of hydrazine compounds into diazenes compounds and subsequent additions of radicals generated from diazenes to alkenes followed by radical trapping by oxygen gives 2-arylperoxides and β-hydroxyesters. Herein, we wish to report iron-catalyzed formations of sulfonyl radicals and the intermolecular additions to alkenes using easily available sulfonylhydazides.[10] The proposed mechanism is similar to that of our previous study of iron-catalyzed radical reactions using carbazates.[9a] As shown in Scheme 2, it is presumed that generation of sulfonyl radicals **E** is initiated by oxidation of sulfonylhydrazides to give diazene **C** in the presence of an iron catalyst. Resultant sulfonyl radicals **E** would react with alkenes and molecular oxygen to give β-hydroxysulfone *via* intermediates **F**, **G**, **H** and **I**.



Scheme 1 Generations and reactions of sulfonyl radicals.



Scheme 2 Proposed mechanism of iron-catalyzed radical reactions using sulfonylhydrazides.

Treatment of α-methylstyrene (**1a**) with 1.5 equivalents of *p*-toluenesufonylhydrazide (**2a**) and a catalytic amount of iron(III) chloride ($FeCl_3$) (10 mol%) in heating THF under oxygen atmosphere gave β-hydroxysulfone compound **3a** in 31% yield (Table 1, Entry 1).[11] In this reaction condition, **2a** was exhausted in 3 h and the reaction stopped at this point.

When the amount of **2a** used was increased, significantly improved yield of product **3a** was observed (Entry 2). The change from oxygen to air did not modify the efficiency (Entry 3)§. A decrease of a loading iron catalyst resulted in lower yield of the product andprolonged reaction time (Entry 4). The use

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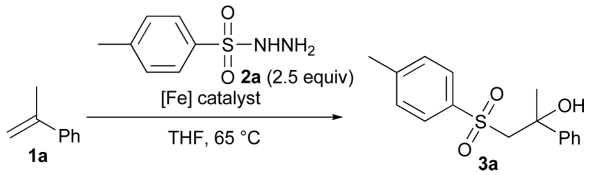
† This work is dedicated to the memory of Athel Beckwith, a teacher and scientist from whom we learned how to study chemistry by example. His pioneering advances in radical chemistry laid the foundation for much of the current radical clock methodology.

‡ Electronic supplementary information (ESI) available: Spectroscopic data of all new products. See DOI: 10.1039/c0ob01119c

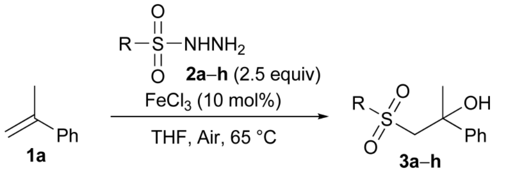
Table 1 Optimizations of *p*-toluenesulfonyl radical addition to **1a**[a]



Entry	[Fe] catalyst/mol (%)	Atmosphere	Time/h	Yield (%)[b]
1[c]	$FeCl_3$ (10 mol%)	O_2	3	31
2	$FeCl_3$ (10 mol%)	O_2	10	95
3	$FeCl_3$ (10 mol%)	Air	10	95
4	$FeCl_3$ (5 mol%)	Air	19	81
5	[Fe(Pc)] (10 mol%)	Air	19	91
6	Fe_2O_3 (10 mol%)	Air	31	41
7[d]	$FeCl_3$ (10 mol%)	Air	>24	16
8	None	Air	>24	24

[a] Reaction condition: **1a** (1.0 mmol), **2a** (2.5 mmol) and [Fe] (0.05 or 0.1 mmol) in THF (5 mL) [b] Isolated yield. [c] 1.5 equiv of **2a** (1.5 mmol) was used. [d] At room temperature.

Table 2 Reactions of various sulfonylhydrazides[a]



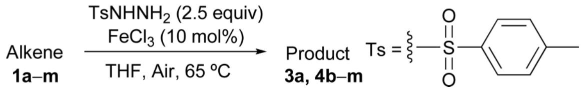
Entry	*R*		Time/h	Yield (%)[b]
1	$\text{4-MeC}_6\text{H}_4$	**a**	10	95
2	C_6H_5	**b**	11	89
3	$\text{4-BrC}_6\text{H}_4$	**c**	18	73
4	$\text{4-MeOC}_6\text{H}_4$	**d**	12	46
5	$\text{4-NO}_2\text{C}_6\text{H}_4$	**e**	12	71
6	$\text{4-CF}_3\text{C}_6\text{H}_4$	**f**	20	55
7	*c*-Hexyl	**g**	17	26
8	*n*-Octyl	**h**	24	73

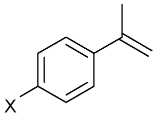
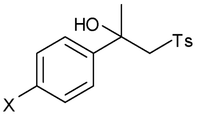
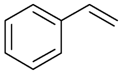
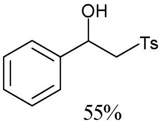
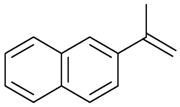
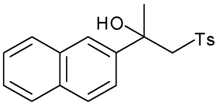
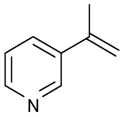
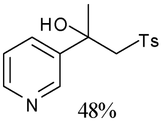
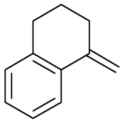
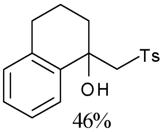
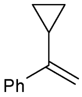
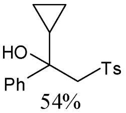
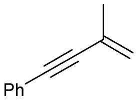
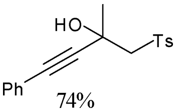
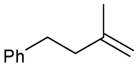
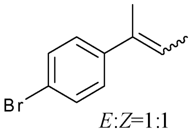
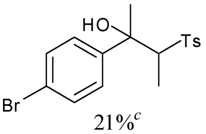
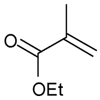
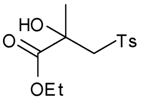
[a] Reaction condition: **1a** (1.0 mmol), **2a–h** (2.5 mmol) and $FeCl_3$ (0.1 mmol) in THF (5 mL) under air. [b] Isolated yield.

of iron phthalocyanine [Fe(Pc)] instead of $FeCl_3$ also gave β-hydroxysulfone compound **3a** in good yield (Entry 5), whereas iron(III) oxide (Fe_2O_3) was an ineffective catalyst (Entry 6). The reaction at room temperature or in the absence of an iron catalyst was very sluggish (Entries 7 and 8).

Next, reactions of various sulfonylhydrazides with α-methylstyrene (**1a**) were examined (Table 2). Although several arylsulfonylhydrazides were revealed to give corresponding β-hydroxysulfone compounds **3a–f** (Entries 1–6), the reactivity of arylsulfonylhydrazides **2d** and **2f** bearing *p*-methoxyphenyl or *p*-trifluoromethylphenyl was moderate and the reason is unclear (Entries 4 and 6). The reaction of cyclohexylsulfonylhydrazide (**2g**) gave the product in low yield (Entry 7). It is presumed this low yield was caused by competitive desulfonation of the resultant sulfonyl radical to generate a relatively stable cyclohexyl radical.[12] In support of this presumption, the reaction of n-octylsulfonylhydrazide (**2h**), which is expected to give a less stable normal alkyl radical by desulfonation, gave corresponding β-hydroxysulfone compound **3h** in good yield (Entry 8).

Table 3 Reactions of various alkenes



Entry	**1**		Time/h	Product[a]
	 X			 HO Ts X
1	X = H	**a**	10	95%
2	X = Br	**b**	14	73%
3[b]	X = OMe	**c**	19	62%
4	X = NO_2	**d**	13	80%
5[b]		**e**	6	 OH Ts 55%
6		**f**	12	 HO Ts 83%
7	 N	**g**	24	 HO Ts N 48%
8		**h**	16	 Ts OH 46%
9	 Ph	**i**	24	 HO Ph Ts 54%
10	 Ph	**j**	19	 HO Ts Ph 74%
11	 Ph	**k**	24	Not obtained
12	 Br *E*:*Z*=1:1	**l**	24	 HO Ts Br 21%[c]
13[d]	 O OEt	**m**	50	 HO O Ts OEt 55%

[a] Isolated yield. [b] 10 mol% of [Fe(Pc)] was used instead of $FeCl_3$. [c] Only one isomer was detected. [d] 20 mol% of [Fe(Pc)] was used instead of $FeCl_3$.

Finally, the scope of alkenes in the present reaction was examined (Table 3). Reactions of several α-methylstyrene derivatives bearing a *para*-substituted aromatic ring readily proceeded to give corresponding β-hydroxysulfone compounds **4b–d** in good yields (Entries 2–4). In the case of compound **1c**, $FeCl_3$ caused decomposition or polymerization of the electron-rich olefin, but it was found that the use of iron phthalocyanine catalyst afforded β-hydroxysulfone compound **4c** (Entry 3). The reaction of styrene (**1e**) afforded β-hydroxysulfone compound **4e** in moderate yield by the use of 10 mol% of [Fe(Pc)] catalyst (Entry 5). Other styrene derivatives **1f–i** underwent similar radical reactions to give corresponding β-hydroxysulfone compounds **4f–i** (Entries 6–9). In the case of alkene **1i**, ring opening reaction of the cyclopropyl group from a resultant radical intermediate was not observed. Enyne **1j** also showed good reactivity in the present reaction (Entry 10). Unfortunately, reaction of non-conjugated alkene **1k** did not afford a radical addition product (Entry 11). Since radical additions of sulfonyl radicals are known to be reversible,[13] the generation of a less stable radical from non-conjugated alkene **1k** might be an unfavourable factor in this reaction. The reaction of trisubstituted alkene **1l** was sluggish due to the steric effect (Entry 12). When ethyl methacrylate (**1m**) was treated with **2a** in the presence of 20 mol% of [Fe(Pc)] and air, addition of a sulfonyl radical took place to give β-hydroxysulfone compound **4m** (Entry 13).

In summary, we have developed a new method for the generation of sulfonyl radicals from sulfonylhydrazide and the synthesis of β-hydroxysulfone by the addition to alkenes. The reaction was shown to be catalysed by inexpensive and nontoxic iron compounds, and the experimental procedure is very simple and safe. The present reaction will provide new information on the chemistry of sulfonyl radicals.

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Notes and references

§ **Typical procedure:** A mixture of α-methylstyrene (**1a**) (118.2 mg, 1.0 mmol), *p*-toluenesulfonylhydrazide (**2a**) (465.6 mg, 2.5 mmol) and $FeCl_3$ (16.2 mg, 0.1 mmol) in THF (5 mL) was heated at 65 °C under air. After removal of solvent under reduced pressure, the residue was purified by silica gel chromatography (hexane–EtOAc, 3 : 1) to give **3a** (275.9 mg, 95%) as colourless crystals.

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