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Novel Aerobic Oxidation of Primary Sulfones to Carboxylic Acids

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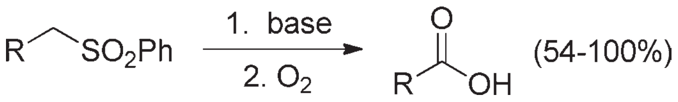
ABSTRACT



Primary alkyl aryl sulfones are converted to the corresponding carboxylic acids in fair to excellent yield through double deprotonation and exposure to atmospheric oxygen. The methodology allows for the convenient synthesis of ^{13}C labeled carboxylic acids.

Carboxylic acids are widely distributed in nature, and they find broad importance as food components,[1] pharmacophores,[2] and synthetic precursors.[3] As a consequence, the preparation of carboxylic acids occupies a place of particular importance in organic chemistry.[4] Conventional synthetic routes include the oxidation of primary alcohols[5] and aldehydes;[6] the hydrolysis of acyl derivatives, such as acyl halides,[7] anhydrides,[8] esters,[9] and amides;[10] and the addition of Grignard reagents[11] or transition metal complexes[12] to carbon dioxide. Despite the many existing methods, innovations continue to be reported, ranging from the aqueous aerobic oxidation of aldehydes[13] to electrocatalytic carboxylation of aliphatic halides.[14]

In our ongoing studies of sulfone-mediated furan synthesis, we require the conversion of the phenylsulfonylmethyl furan **1** to the corresponding furoic acid **2**. We originally envisioned using one of the literature methods for oxidizing the sulfonyl anion derived from **1** to introduce the desired carbonyl group. In the event, however, treatment of the anion of **1** with bis-(trimethylsilyl)peroxide,[15] *tert*-butyl trimethylsilylperoxide,[16] and chlorodimethoxyborane[17] resulted in disappointingly low conversions (< 10%). Other methods of oxidative desulfonylation have been

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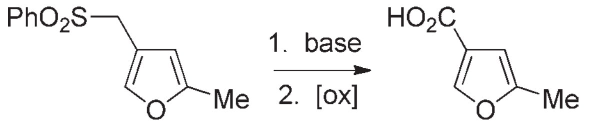
10.1021/ol200135m

Table 1. Oxidative Desulfonylation to Furoic Acid



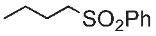
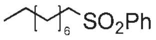
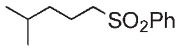
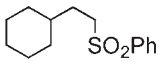
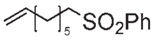
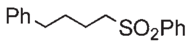
1 → **2**

entry	base[a]	oxidant	time (min)	yield[b]
1	1.0 *n*-BuLi	O_2	50	0[c]
2	2.5 *n*-BuLi	O_2	50	85
3	2.5 LiHMDS	O_2	50	88
4	2.5 NaHMDS	O_2	45	91
5	2.5 KHMDS	O_2	25	96
6	2.5 KHMDS	dry air	120	93

[a] 2.5 equiv. [b] Isolated yield. [c] Recovered starting material.

Table 2. Preparation of Primary Sulfones

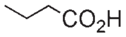
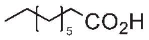
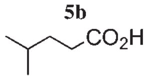
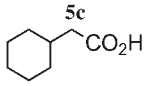
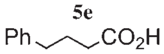
$$\underset{\mathbf{3}}{RCH_2Br} \xrightarrow[KH,\ THF]{PhSO_2CH_3} \underset{\mathbf{4}}{RCH_2CH_2SO_2Ph}$$

entry	electrophile	product	yield[a]
1	1-bromopropane	 **4a**	75(58)
2	1-bromooctane	 **4b**	83(60)
3	1-bromo-3-methylpropane	 **4c**	85(66)
4	(bromomethyl)-cyclohexane	 **4d**	54(28)
5	7-bromo-1-heptene	 **4e**	69(38)
6	1-bromo-3-phenyl-propane	 **4f**	54(44)

[a] Crude yield (isolated).

Table 3. Carboxylic Acids from Primary Sulfones

$$\underset{\mathbf{4}}{RCH_2SO_2Ph} \xrightarrow[THF]{2\ KHMDS} \xrightarrow{O_2} \underset{\mathbf{5}}{RCO_2H}$$

entry	sulfone	product	yield[a]
1	**4a**	 **5a**	67
2	**4b**	 **5b**	100
3	**4c**	 **5c**	54
4	**4d**	 **5d**	64
5	**4e**	 **5e**	100
6	**4f**	 **5f**	76
7	**4g**[b]	$Ph{-}CO_2H$ **5g**	61

[a] Isolated. [b] Benzyl phenyl sulfone (commercial material).

reported, using reagents such as MoOPh[18] and the Davis oxaziridine,[19] but it seemed prudent first to explore routes less constrained by toxicity and expense.

Toward this end, an earlier report by Horner and coworkers was particularly compelling, in which they observed the formation of benzoic acid from benzyl phenyl sulfone upon treatment with potassium *tert*-butoxide, a process in which the oxidant must have been atmospheric oxygen.[20] Curiously, however, this had not been developed into a preparative methodology. While, there are some examples of the aerobic oxidative desulfonylation of secondary sulfones to ketones,[21] the corresponding protocol for primary sulfones has been oddly absent in the literature.

Thus, we set about adapting Horner's conditions for our system. Initial attempts were not encouraging: treatment of furan **1** with 1 equiv of various bases (*n*-BuLi, KO*t*Bu, KHMDS) in THF and exposure to oxygen for up to 1 h led only to recovered starting material (Table 1, entry 1). This outcome was surprising, given the documented behavior of secondary sulfones under similar conditions (*vide supra*). Perhaps, however, the stability of the anion (primary and benzylic) prevented facile reaction with oxygen.

On this assumption, we considered the possibility of using the dianion of furan **1** for aerobic oxidation. Sulfonyl dianions are well established in the literature, and they are easily formed under conventional conditions.[22] To our delight, treatment of furan **1** with 2.5 equiv of *n*-butyllithium in THF at −78 °C, followed by sparging with oxygen for 50 min, led to the production of furoic acid **2** in very good yield (Table 1, entry 2). The oxidation exhibits a mild counterion effect, so that a progression from lithium to potassium leads to higher yields and shorter reaction times. Dry air can also be used as the oxidant, although the oxidation is predictably slower (entry 6).

Emboldened by this result, we launched an examination of the scope of this novel oxidative desulfonylation; thus

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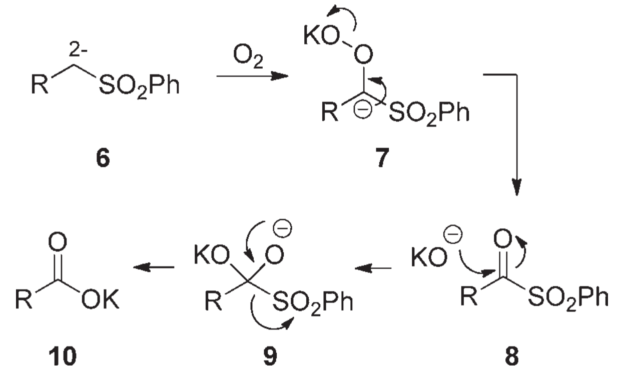
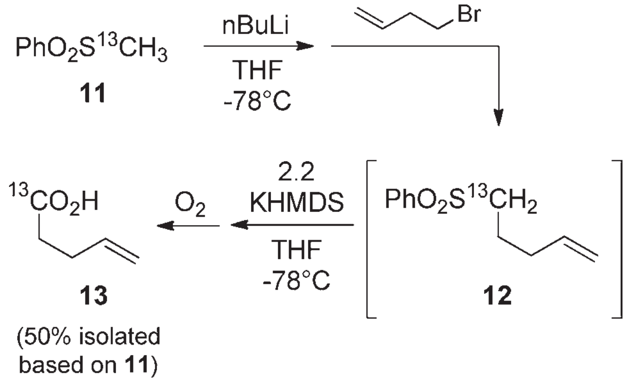
Scheme 1. Possible Mechanism for Oxidative Desulfonylation



Scheme 2. Synthesis of [^{13}C]-4-Pentenoic Acid



access to several primary sulfones was needed. Fortunately, there are many convenient methods to prepare primary sulfones from readily available starting materials, including the alkylation of methyl phenyl sulfone,[23] the reaction of alkyl halides with phenylsulfinate[24] or phenylsulfide,[25] and the conjugate addition onto vinyl sulfones. For this study, the methyl phenyl sulfone route was chosen (Table 2), although careful chromatographic separation was required to remove products of dialkylation.[26]

With the additional primary sulfones in hand, we subjected them to the oxidative desulfonylation conditions. Much to our satisfaction, all examples cleanly provided the corresponding carboxylic acids in fair to excellent yields (Table 3). To our knowledge, this represents the first such preparative aerobic oxidative desulfonylation of primary sulfones to their corresponding carboxylic acids, and thus represents a novel entry into this important class of compounds.

The mechanism of the desulfonylation is unknown, but a number of possibilities clearly exist. The formation of peroxides from organometallic reagents and oxygen is well-known,[27] so a reasonable first step might be the formation of the peroxide intermediate **7** (Scheme 1). Subsequent loss of a potassium-stabilized oxide moiety, followed by hydrolysis of the labile α-oxysulfone intermediate **8**,[28] would provide the carboxylate **10**.

In conclusion, a novel oxidative desulfonylation strategy is disclosed, in which primary sulfones are cleanly converted to carboxylic acids. Inasmuch as several robust routes to primary sulfones are available, the present work represents a new versatile route to carboxylic acids. In particular, the methyl phenyl sulfone methodology can be viewed as an alternative to the well-known cyanide route,[29] but with advantages with respect to acute toxicity. Furthermore, since ^{13}C-labeled methyl phenyl sulfone[30] is commercially available, useful carbonyl-labeled acids[31] can be accessed using this chemistry (Scheme 2). Further work is underway in this direction and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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