Heteroatom Chemistry
Volume 13, Number 5, 2002

Efficient Electrophilic and Nucleophilic Epoxidations Utilizing a Sulfonylperoxy Radical and Peroxysulfate Species

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Received 22 June 2001; revised 5 April 2002

ABSTRACT: *Reaction of superoxide anion radical ($O_2^{-\cdot}$) with o-nitrobenzenesulfonyl chloride yields a o-nitrobenzenesulfonyl peroxy radical with strong oxidizing ability, which is capable of oxidizing aryl methylene moieties to aryl ketones and relatively electron-rich alkenes regioselectively to epoxides. The oxidizing species is tentatively attributed to the o-nitrobenzenesulfonyl peroxy radical of structure* **1**. *Tetrabutylammonium peroxydisulfate ($(TBA)_2S_2O_8$,* **2***) was prepared by the reaction of tetrabutylammonium hydrogen sulfate with potassium peroxydisulfate. The epoxidation of enals and enones, such as α,β-unsaturated aldehydes or ketones, was efficiently achieved with* **2** *in the presence of hydrogen peroxide and base in acetonitrile or in methanol at 25°C. A base-sensitive substrate, such as cinnamaldehyde, could be successfully epoxidized under mild reaction conditions and in short reaction time.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:431–436, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10078

INTRODUCTION

Intensive research interests [1] in the physical properties and chemical reactivities of the superoxide ion have stimulated the development of organic syntheses using the superoxide anion as a key reagent. Only a few studies of the oxidation of sulfur compounds, such as thiols [2], thiouracils [3], disulfides [4], and sulfur halides [5], have been reported.

Earlier, a peroxysulfonate intermediate was postulated by Berger [6] to be the key reagent in alkaline autoxidation of thiols to sulfonates. The superoxide anion radical ($O_2^{-\cdot}$) displays three basic modes of operation, a base, an anion, and a radical, but in general, it is a very weak oxidizing agent. In order to increase the usefulness of $O_2^{-\cdot}$, it has been examined in reactions with various substrates such as disulfides, sulfinyl chlorides, and sulfonyl chlorides. *o*-Nitrobenzenesulfonyl chloride was found to be the most interesting and useful substrate, and it was reacted with $O_2^{-\cdot}$ in MeCN at ca. −30°C to form the *o*-nitrobenzenesulfonyl peroxy radical **1**, which is stable enough for use in organic syntheses at low temperatures [7] (Scheme 1).

The epoxidation of electron-deficient olefins such as α,β-unsaturated ketones or aldehydes has been an important target for the functionalizations of ketones or aldehydes in organic synthesis. In contrast to the electrophilic epoxidation of alkenes, generally epoxidation of electron-deficient olefins requires the use of a nucleophilic oxidant employed under the alkaline condition. A number of epoxidations of electron-deficient olefins have been developed using *tert*-butyl peroxide [8], hydrogen peroxide [9],

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Dedicated to Prof. Shigeru Oae on the occasion of this memorial symposium.

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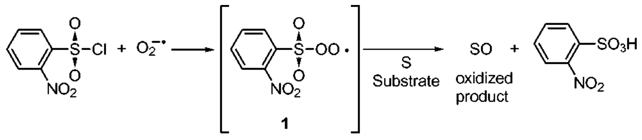
Contract grant sponsor: KOSEF.
Contract grant number: R03-2001-00033.
Contract grant sponsor: School of Molecular Science of MOE.

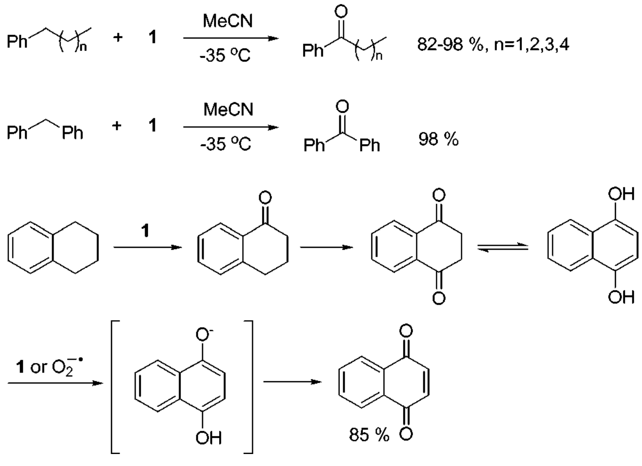


SCHEME 1

peroxide-ammonium fluoride [10], sodium perborate [11], or dioxirane [12] under strong alkaline conditions. However, in general, the known methods for the epoxidations require a relatively long reaction time and the yields are varied depending upon the substrates and reaction conditions. We have been interested in the epoxidation of electron-deficient olefins, such as α,β-unsaturated ketones, utilizing a peroxysulfonate. In our earlier work [13], attempts to epoxidize the electron-deficient double bond by use of a sulfonyl peroxy intermediate under alkaline conditions failed. Now, the sulfonyl peroxy intermediate **1** turned out to be a sulfonyl peroxy radical, which showed a strong electrophilic oxidizing ability to epoxidize a double bond of a chain or ring compound regioselectively.

RESULTS AND DISCUSSION

Benzylic methylene moieties were oxidized by **1** to give ketones in high yields under mild conditions [14] (Scheme 2). In order to confirm the radical character of **1** and to extend its utility, oxidations of arylacetic acids have been achieved to give the corresponding ketones or aldehydes and alcohols (see Scheme 3) [15]. Competitive decarboxylation reactions between phenylacetic acid and *p*-substituted phenyl acetic acids were carried out. The ratios of rate constants for the oxidative decarboxylation of various substituted phenylacetates relative to phenylacetate were found to decrease with decreasing electron density at the benzylic carbon. Radical **1** shows an electrophilic oxidation ability toward arylacetic acids that can be correlated by the Hammett's equation, Hammett's ρ^+ value being -0.408 ($\gamma = 0.9996$) [15].



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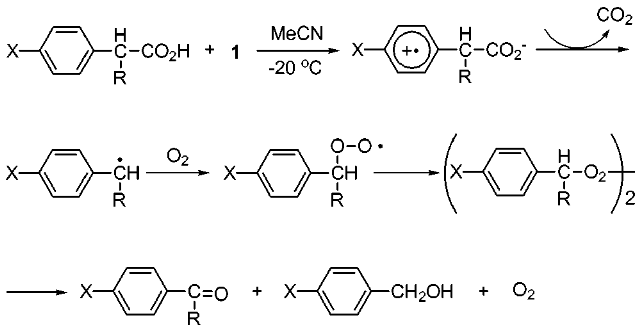
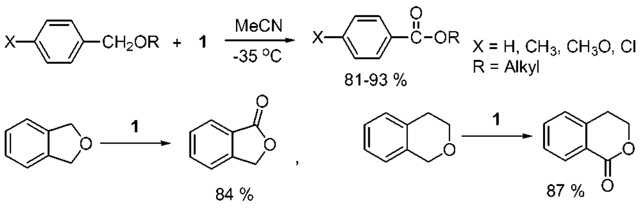


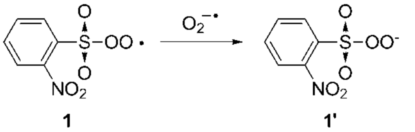
SCHEME 3

The α-C—H bonds of benzylic ethers, in various substrates having benzylic ether groups, were also found to be oxidized by **1**, and gave the corresponding benzylic esters in good yields [16] (Scheme 4). These reactions can be rationalized by invoking the radical process with **1**. In order to measure the effects of p-substituents on the oxidation of benzylic ethers, competitive oxidations of p-substituted benzylic propyl ethers with **1** were carried out. The results could be correlated by Hammett's equation using σ^+ rather than σ constants of substituents in the aromatic ring and with a value of $\rho^+ = -0.57$ ($r = 0.99$). This ρ^+ value indicates that **1** is an electrophilic species and the value of ρ^+ is comparable to the ρ^+ (-0.65) for benzylic hydrogen abstraction from dibenzylic ethers by the benzoyloxyl radicals [17].

It may be possible that the intermediate **1** is converted to the anion **1**′ by a one-electron transfer from $O_2^{-\cdot}$ under alkaline conditions (Scheme 5). Thus, if **1**′ exists, nucleophilic epoxidations of α,β-unsaturated carbonyl compounds with **1**′ would be expected. However, electrophilic epoxidations on



SCHEME 4



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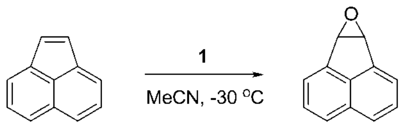


SCHEME 7

the other double bonds of L-carvone, and α- and β-ionone occurred as shown in Scheme 6. From these results it appears that, the sulfonylperoxy radical intermediate **1**, and not the anion type **1**′, is involved in these reactions.

Highly strained acenaphthalene was smoothly epoxidized in quantitative yields at −30°C in acetonitrile by the use of **1** (Scheme 7). Acenaphthalene oxide is known to be unstable under acidic conditions, but more stable under basic conditions [18]. Thus, acenaphthalene oxide could be isolated in higher yield by the use of **1** as the oxidant than that obtained by other known methods [19], perhaps because of the stability of the product under basic conditions. Here, the sulfonyl peroxy intermediate is likely to be more of the character of a radical rather than an anion.

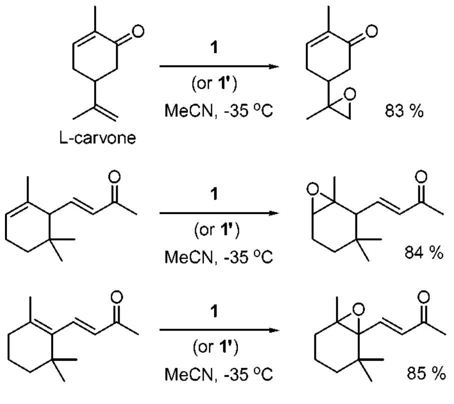
When cis-stilbene was reacted with **1** at −30°C in MeCN, a mixture of trans- (70%) and cis-oxide (30%) was obtained (Scheme 8). If the peroxy intermediate **1** is anionic, stereospecific epoxidation of cis-stilbene to cis-epoxide may occur.

Arene oxides and their subsequent metabolites have been implicated as the intermediates which are responsible for the carcinogenicity and mutagenicity of polyaromatic hydrocarbons, and there has been a considerable interest both in the related chemical reactions and in understanding how they are formed physiologically. Polyaromatic compounds, such as phenanthrene and pyrene, which are inert to superoxide itself, were readily oxidized to the corresponding K-region arene oxides by treatment with **1**. Anthracene was oxidized to anthraquinone under the same conditions. It is interesting that various arenes were readily oxidized to their oxides under mild conditions. Such arene oxides are important metabolites formed in vivo from processes catalyzed by monooxygenase [20, Y. H. Kim, K. S. Kim, and B. C. Jung, unpublished data.] (Scheme 9).

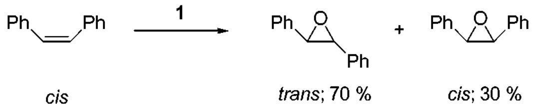
Metabolic degradation of polyaromatic hydrocarbons is believed to be caused by oxidation by a certain activated oxygen, namely by an enzyme present in all aerobic organisms and also soil bacteria [20]. 2-Methylnaphthalene is oxidized to phthalic acid, together with other unidentified products by **1** under mild conditions (Y. H. Kim, K. S. Kim, and B. C. Jung, unpublished data.) (Scheme 10). The oxidation is considered to be initiated via epoxidation of an aromatic ring, followed by fragmentations to carbonyl compound. It is intriguing that the aromatic ring can be readily destroyed at low temperature because destruction of the aromatic ring usually requires a high energy process under drastic conditions.

Biomimetic oxidation of triacetylated inosine to triacetylated xanthosine was carried out with **1**. The oxidation appears to be initiated via the formation of an aziridine, followed by conversion into the monooxygenated product (Scheme 11).

In our earlier work [21] we reported that various α,β-unsaturated ketones reacted with **2** in the presence of H_2O_2 and NaOH in CH_3CN at 25°C to give the corresponding epoxides in excellent yields. The yields of epoxidation were generally varied depending on the reaction conditions as shown in Table 1. The best solvent used is acetonitrile or methanol (entries 4, 8, and 9 in Table 1) which may be attributed to the increase of the solubility of base in the polar solvents. Among a variety of bases, better results were obtained by the use of sodium hydroxide (95% in acetonitrile, entry 4, and 98% in methanol,



SCHEME 6



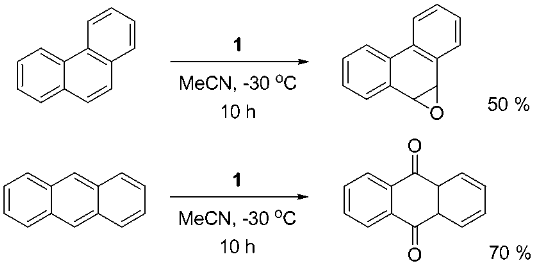
SCHEME 8

TABLE 1 Ketones Under Various Conditions

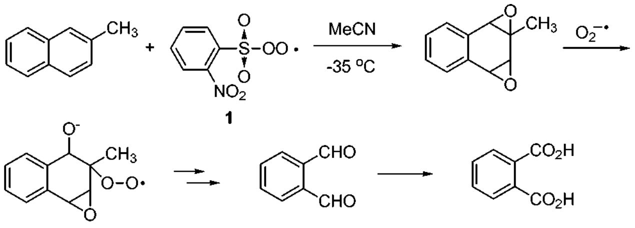
$$\mathbf{4a} \xrightarrow[\text{solvent}]{2/H_2O_2/\text{Base}} \mathbf{5a}$$

Entry	*2/H_2O_2 (equiv)*	*Base (equiv)*	*Solvent*	*Time (min)*	*Yield[a] (%)*
1	1/1	K_2CO_3 (1)	CH_3CN	60	50
2	1/–	NaOH (1)	CH_3CN	60	Trace
3	–/1	NaOH (1)	CH_3CN	60	30
4	1/1	NaOH (1)	CH_3CN	30	95
5	1/1	NaOH (1)	Benzene	60	10
6	1/1	NaOH (1)	CH_2Cl_2	60	65
7	1/1	NaOH (1)	$CHCl_3$	60	73
8	1/1	NaOH (1)	MeOH	5	98
9	0.5/0.5	NaOH (0.5)	MeOH	10	90

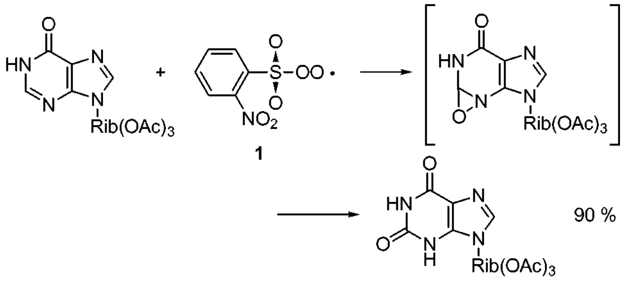
[a] Isolated yield.



SCHEME 9



SCHEME 10



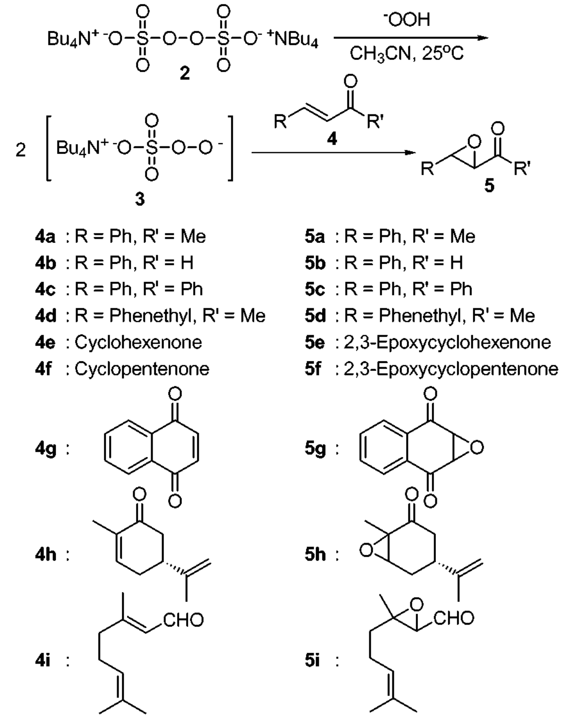
SCHEME 11

entry 8). When potassium carbonate was used as a base, the yield was low (50% in acetonitrile, entry 1). An equimolar amount of H_2O_2 and NaOH in the absence of **2** resulted in a low yield under the same conditions (30%, entry 3). In the absence of H_2O_2, trace amount of epoxide was isolated (entry 2). When 0.5 equiv of each **2**, H_2O_2, and NaOH (entry 9) were used, the epoxide was obtained in about 90% yield. This result indicates that 0.5 equiv of each **2** and HOO^- form a stoichiometric amount of **3** with respect to the substrate, as shown in Scheme 12.

The epoxidation of various electron-deficient olefins was carried out in acetonitrile solvent using 1 equiv each of **2** and H_2O_2 in the presence of 1 equiv of NaOH at 25°C. Cyclic enones and a chain double bond of an α,β-unsaturated carbonyl group can be smoothly epoxidized. The results obtained are shown in Table 2.

Concerning the epoxidation mechanism, the epoxidations appears to be initiated by the formation of peroxysulfate anion **3** by the attack of HOO^- on **2**. The 1,4-addition of **3** to α,β-unsaturated ketones or aldehydes may produce the epoxide products, together with tetrabutylammonium sulfate **6**, as shown in Scheme 13.

Tetrabutylammonium sulfate **6** was actually isolated in 80% yield. There are two competitive routes for the epoxidation of an enone: one is epoxidation by **3** and the other one is epoxidation by HOO^-. The main epoxidaion route by **3** can be rationalized by the following results. Equivalent amounts of **2**, H_2O_2, and NaOH gave the best yields (entry 4, 8, and 9 in Table 1). Equivalent amounts of H_2O_2 and NaOH in the absence of **2** resulted in a low yield (entry 3 in Table 1) under the same reaction conditions. The peroxydisulfate **2** without using H_2O_2 afforded a trace amount of epoxide (entry 2 in Table 1). The



SCHEME 12

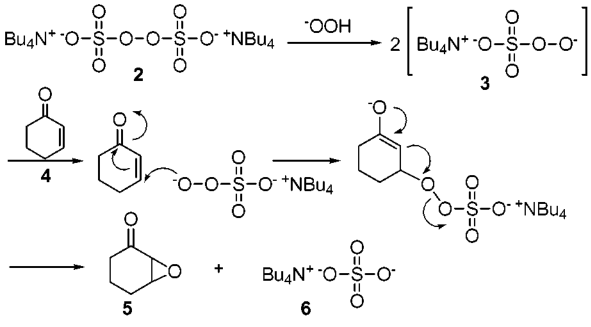
stronger nucleophilicity of HOO^- over HO^- may be the reason for the formation of **3** more easily. Such a peroxysulfate **3** has neither been isolated nor confirmed. However, judging from the above results, the new epoxidation should involve such a tetrabutylammonium peroxysulfate **3**, which shows a strong nucleophilic oxidizing ability.

In conclusion, *o*-nitrobenzenesulfonylperoxy radical, intermediate **1**, which shows strong oxidizing ability, oxidized benzyl ethers to the corresponding benzyl esters in situ at −35°C in acetonitrile in excellent yields, and relatively electron rich alkenes were regioselectively epoxidized in good yields. However, cyclic and acyclic α,β-unsaturated ketones were smoothly oxidized to the corresponding epoxides by nucleophilic epoxidations with tetrabutylammonium peroxysulfate anion **3**. Furthermore, acetal, ketal, and thioether moieties have been found to be inert to **2** in the furanylation and pyranylation of alcohols [22] and in the oxidation of alcohols. The present epoxidation may provide a practically efficient method for epoxidations of electron-deficient carbonyl compounds under mild conditions containing various functional groups.

TABLE 2 Epoxidation of α,β-Unsaturated Carbonyl Compounds in Acetonitrile at 25°C[a]

Entry	*Substrate*	*Time (min)*	*Product*	*Yield[b] (%)*
1	**4a**	30	**5a**	95
2	**4d**	150	**5d**	88
3	**4e**	30	**5e**	95
4	**4f**	30	**5f**	85
5	**4g**	30	**5g**	95
6	**4h**	120	**5h**	92

[a] The ratio of **2**:**4**: H_2O_2/NaOH = 1:1:1:1.
[b] Isolated yield.



SCHEME 13 Possible mechanism for epoxidation.

EXPERIMENTAL

Electrophilic Epoxydation with **1**

In a general procedure, a solution of 2-nitrobenzenesulfonyl chloride (220 mg, 1 mmol) and L-carvone (90 mg, 0.6 mmol; 2 ml CH_3CN) was added to a heterogeneous solution of potassium superoxide (222 mg, 3 mmol; 1 ml CH_3CN) at ca. −35°C maintained under a dry argon atmosphere. After having been stirred for ca. 4 h at ca. −35°C, the reaction mixture was concentrated and then extracted with $CHCl_3$; concentration of the $CHCl_3$ layer gave highly pure epoxide (78 mg, 87%). Further purification by preparative TLC afforded pure epoxide (74.8 mg, 83%).

Nucleophilic Epoxidation with **2**

The following experimental procedure is representative. 2-Cyclohexen-1-one (98 mg, 1 mmol) was dissolved in anhydrous acetonitrile (1 ml). The solution of **2** (667 mg, 1 mmol) and sodium hydroxide (40 mg, 1 mmol) in anhydrous acetonitrile (4 ml) was added and then hydrogen peroxide (50% w/w, 0.052 ml, 1 mmol) was slowly added to the reaction mixture. After having been stirred for 0.5 h at 25°C with monitoring of the reaction by TLC, the reaction mixture was extracted with methylene chloride (30 ml × 3), washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a crude product which was purified by a flash column chromatography (silica gel 230–400 mesh, 20 × 2 cm, eluent; EtOAc/*n*-Hexane = 1:5, 95%).

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