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Recent studies on organic synthesis mediated by radical species of peroxysulfur compounds*

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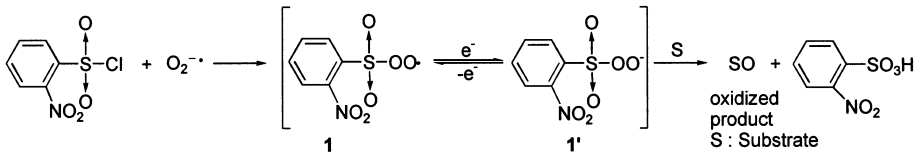
Abstract: Reaction of superoxide ion ($O_2^{-\cdot}$) with *o*-nitrobenzenesulfonyl chloride yields a material with strong oxidizing ability, capable of oxidizing benzylic methylenes to the aryl ketones, benzylic ethers to benzoic esters, hydrazones to ketones, and electron deficient alkenes regioselectively to epoxides. The oxidizing species is tentatively assigned the *o*-nitrobenzenesulfonyl peroxy radical structure **1**. Tetrabutylammonium hydrogen sulfate, on treatment with potassium persulfate under phase transfer conditions, gives tetrabutyl ammonium peroxydisulfate **2**, a new oxidizing agent capable of oxidizing primary and secondary alcohols to the corresponding aldehydes and ketones in almost quantitative yields in aprotic solvents under anhydrous conditions; **2** is evidently a source of tetrabutylammonium sulfate radical **3**. Further reactions include formation of the tetrahydropyranyl or tetrahydrofuranyl ether derivatives on reaction with alcohols, regioselective iodinations of anisyl derivatives, and α,β-unsaturated ketones or esters, nucleophilic epoxidations of α,β-unsaturated ketones, and an interesting addition of the 1,3-dioxolanyl group to electron deficient alkenes, including a conversion of 1-nitrocyclohexene into a masked α-formylcyclohexanone.

Superoxide anion radical ($O_2^{-\bullet}$) reacts as a base, an anion, and a radical, but in general is a very weak oxidizing agent. In an attempt to activate $O_2^{-\bullet}$, we have examined the reaction of such substrates as disulfides, sulfinyl chlorides and sulfonyl chlorides. *o*-Nitrobenzenesulfonyl chloride was found to be the best activator, specifically when reacted with $O_2^{-\bullet}$ in MeCN at −30 °C to form a species probably having the structure **1**, which is stable enough for organic syntheses at low temperature (Scheme 1) [1].



Scheme 1

In connection with the metabolic oxidation of thioamide drugs, $O_2^{-\bullet}$ was previously shown to react with thioamides or thioureas in MeCN under reflux for a long reaction time giving the corresponding amides or ureas (up to 85%) [2]. The sulfonylperoxy radical intermediate **1** shows much stronger oxidizing ability giving excellent yields of amides or ureas at −35 °C in the same reactions (Scheme 2) [3].

Benzylic methylene moieties have been found to be oxidized with **1** to ketones in high yields under mild conditions (Scheme 3) [4].

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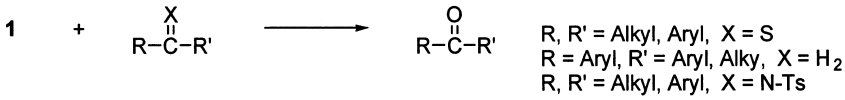
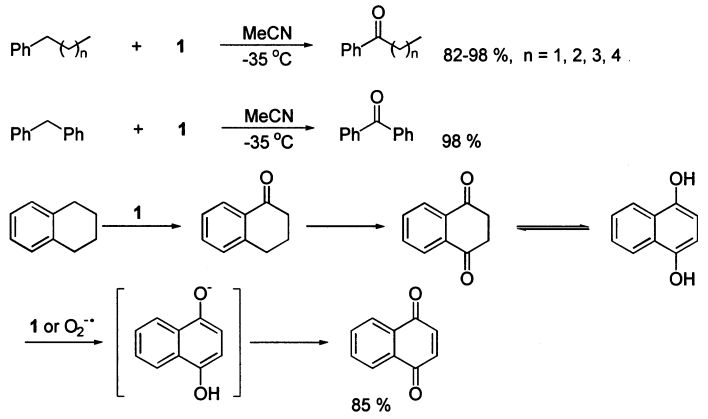
†*Corresponding author.*

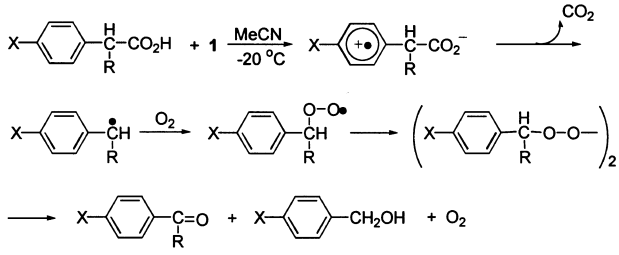


Scheme 2



Scheme 3

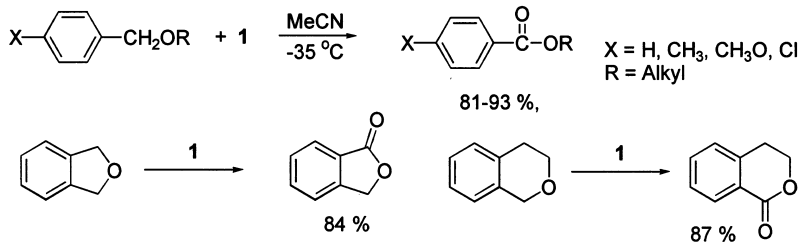
In order to confirm the radical character of **1** and to extend the utility of **1**, oxidations of arylacetic acids have been achieved to give the corresponding ketones or aldehydes, and alcohols as shown in Scheme 4 [5]. Competitive decarboxylation reactions between phenylacetic acid and *p*-substituted phenyl acids were carried out. The ratio of the rate constants for the oxidative decarboxylation of various substituted phenylacetates relative to phenylacetate was found to decrease with decreasing electron density at the benzylic carbon. Compound **1** shows an electrophilic oxidation ability toward arylacetic acids, giving a Hammett ρ^+ value of -0.408 ($y = 0.9996$) [5].



Scheme 4

A number of substrates having benzylic ether moiety were reacted with **1** to afford the corresponding benzylic esters in good yields [6]. These reactions can be explained by the radical process with **1** (Scheme 5).

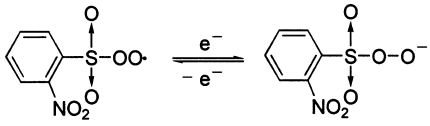
In order to see the effects of *p*-substituted groups for the oxidation of a series of benzylic ethers, competitive oxidation of *p*-substituted benzylic propyl ethers with **1** were carried out. The Hammett



Scheme 5

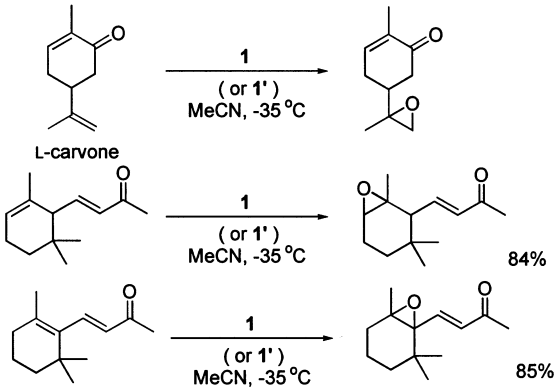
correlation plot for the oxidation of these benzyl propyl ethers showed a better correlation of relative rate factors with the σ^+ rather than the σ constants of substituents in the aromatic ring and afforded the reaction constant $\rho^+ = -0.57$ ($r = 0.99$). This ρ^+ value shows **1** to be an electrophilic species and appears to be comparable to $\rho^+ = -0.65$ [7] for benzylic hydrogen abstraction from dibenzyl ethers by the benzoyloxyl radical.

It may be also possible for **1** to convert to the anion **1′** by one electron transfer from $O_2^{-\bullet}$ in the presence of excess of $O_2^{-\bullet}$ under alkaline conditions (Scheme 6).



Scheme 6

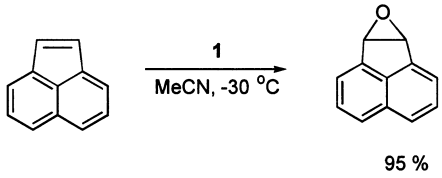
Thus if **1′** exists, nucleophilic epoxidations of α,β-unsaturated carbonyl compounds with **1′** are expected. However electrophilic epoxidations on other double bonds of L-carvone, α- and β-ionone occurred as shown in Scheme 7.



Scheme 7

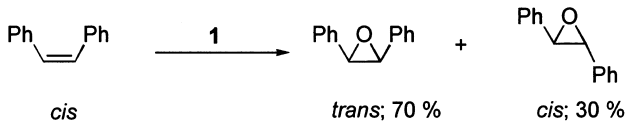
From these results, it is more likely that the sulfonylperoxy radical intermediate **1** is involved rather than the anion **1′**.

Highly strained acenaphthylene was smoothly epoxidized in quantitative yields at −30 °C in acetonitrile. Acenaphthylene oxide is known to be unstable under acidic conditions, but more stable under basic conditions [8]. Thus, acenaphthylene oxide could be isolated in higher yields than those obtained from known methods [9], perhaps because of the stability of the product under basic conditions. The sulfonyl peroxy intermediate is likely to have radical rather than anion character (Scheme 8).



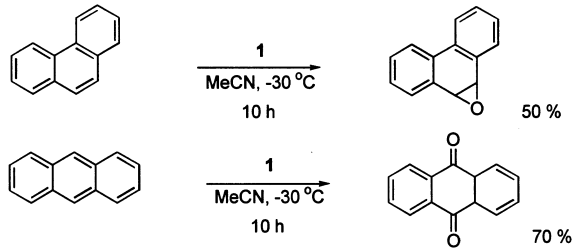
Scheme 8

When *cis*-stilbene was reacted with **1** at −30 °C in MeCN, a mixture of *trans*- (70%) and *cis*-oxide (30%) was obtained. Epoxidation with the peroxy anion **1′** would probably be expected to be stereospecific (Scheme 9).



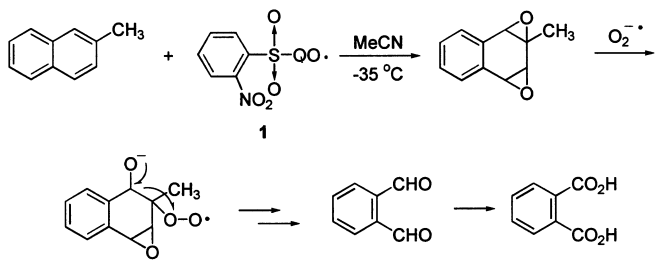
Scheme 9

Arene oxides and their subsequent metabolites have been implicated as the intermediates which are responsible for the carcinogenicity and mutagenicity of polyaromatic hydrocarbons. 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 treating with **1**. Anthracene was oxidized to anthraquinone under same conditions. It is interesting that various arenes were readily oxidized to their oxides under mild conditions. Such arene oxides are important metabolite formed *in vivo* from processes catalyzed by monooxygenase (Scheme 10) [10,11].



Scheme 10

Metabolic degradation of polyaromatic hydrocarbons is believed to involve oxidation with an activated oxygen species by an enzyme in all aerobic organisms and also soil bacteria [10]. 2-Methylnaphthalene is oxidized to phthalic acid together with other unidentified products by **1** under mild conditions [11]. The oxidation is considered to be initiated via epoxidation of an aromatic ring, followed by fragmentations to the carbonyl compound. It is intriguing that the aromatic ring can be readily destroyed at low temperature because destruction of the aromatic ring usually requires high energy under drastic conditions (Scheme 11).

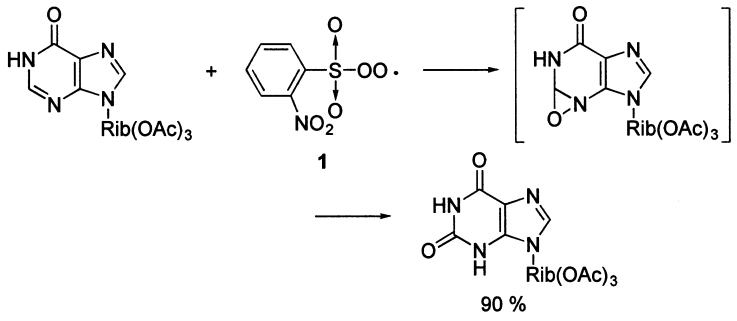


Scheme 11

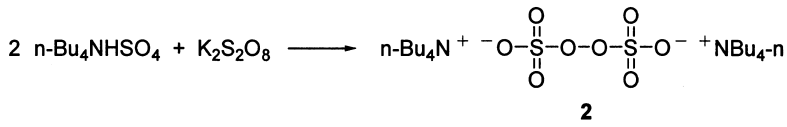
Biomimetic oxidation of triacetylated inosine to triacetylated xanthosine was examined with **1**, and the oxidation appears to be initiated via the formation of an oxaziridine, followed by conversion into the monooxygenated product (Scheme 12).

Recently, tetrabutylammonium peroxydisulfate **2** has been successfully prepared by the reaction of tetrabutylammonium sulfonic acid with potassium peroxydisulfate (95%, m.p. 119–120 °C) (Scheme 13) [1].

Metal peroxydisulfates and ammonium peroxydisulfate are soluble only in aqueous media. However,



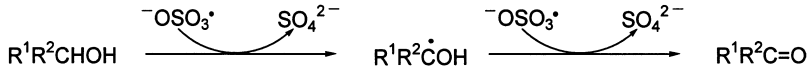
Scheme 12



Scheme 13

tetrabutylammonium peroxydisulfate **2** is soluble in aprotic solvents such as chloroform, dichloromethane, acetonitrile, dichloroethane and acetone. Thus, it turned out to be an excellent source for the formation of sulfate ion radical ($^{\bullet}OSO_3^-$) under anhydrous conditions.

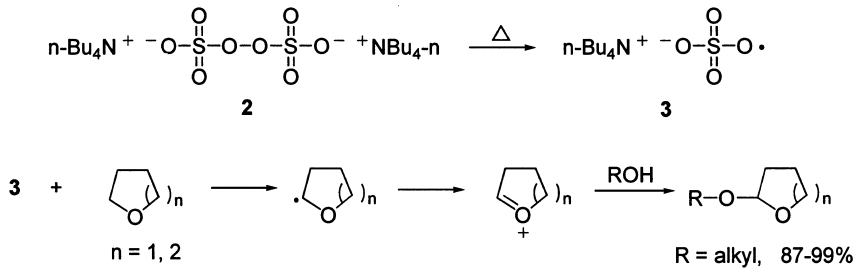
Under these conditions, primary or secondary alcohols are oxidized to aldehydes or ketones (87–99%) in the presence of alkenes and pyridyl functionalities without reacting with these groups [12]. Under anhydrous conditions, side reactions due to hydroxyl or perhydroxyl-radical species can be avoided (Scheme 14).



Scheme 14

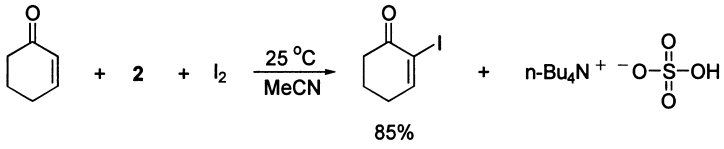
Both tetrahydrofuranyl ethers and tetrahydropyranyl ethers are utilized for the protection of alcohols. However, it has been a problem to prepare tetrahydrofuranyl ethers by tetrahydrofuranylation of alcohols in mineral acid conditions because the ethers are sensitive and hydrolyzed under acidic conditions. Recently, it was found that various alcohols containing functional moieties are readily tetrahydrofuranylated or tetrahydropyranylated in excellent yields by the reaction of tetrabutylammonium peroxydisulfate with tetrahydrofuran or tetrahydropyran as a solvent [13,14].

This reaction is carried out without using an acid catalyst under mild conditions. The reaction appears to be initiated by the formation of the sulfate anion radical, and then the tetrahydrofuranyl radical, followed by addition of alcohol to the oxonium intermediate (Scheme 15).



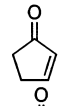
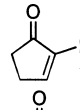
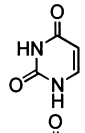
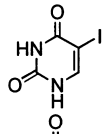
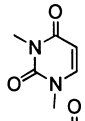
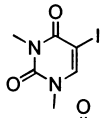
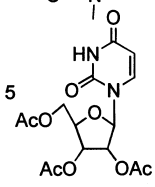
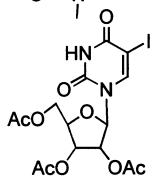
Scheme 15

Regioselective iodinations on α-position of electron deficient olefins have been found by using **2** with I_2. As an example, α-iodination of cyclohexenone with I_2 is shown in Scheme 16 and Table 1 [15].



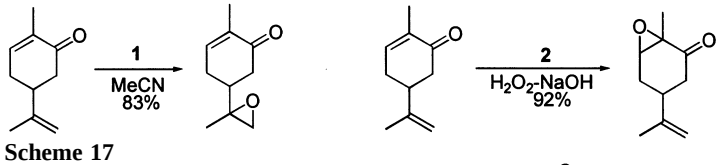
Scheme 16

Table 1 Iodination of cyclic α,β-unsaturated olefins

Run	Reactant	2 (eq.) / I_2 (eq.)	Temp(°C)	Time (h)	Product	Yield[a] (%)
1		1.0 / 1.0	r.t.	5		85
2		1.0 / 1.0	r.t.	3.5		83
3		1.0 / 1.0	r.t.	1		72
4		1.0 / 1.0	r.t.	3.5		75
5		1.0 / 1.0	r.t.	12		82

a: Isolated Yields.

In contrast to the electrophilic epoxidation of alkenes with **1**, **2** cleaves to tetrabutylammonium peroxysulfate **4** in the presence of hydrogen peroxide and NaOH; **4** has been found to be a practical oxidizing agent for the epoxidations of α,β-unsaturated ketones as a nucleophilic reagent (Scheme 17, Table 2) [16]. The peroxydisulfate ($TBA_2S_2O_8$, **2**) may convert to tetrabutylammonium peroxysulfate **4** by attack of HOO^- followed by 1,4-addition to the α,β-unsaturated ketone to produce the epoxide product together with tetrabutylammoniurn sulfate **5** as shown in Fig. 1 [16].



Scheme 17

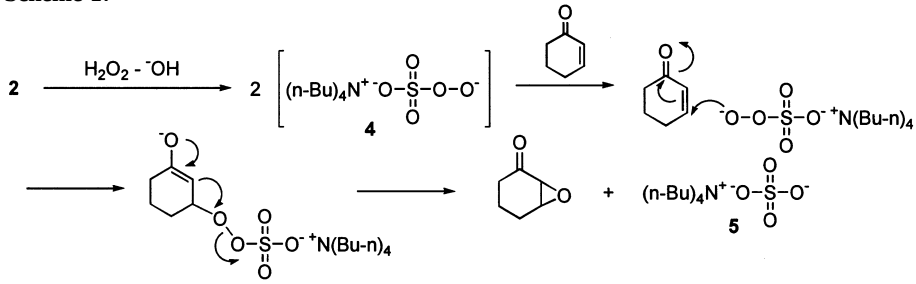
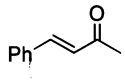
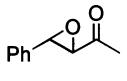
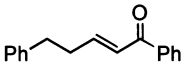
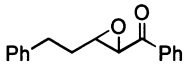
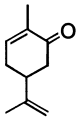
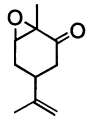
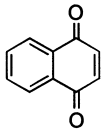
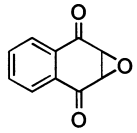
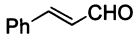
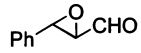


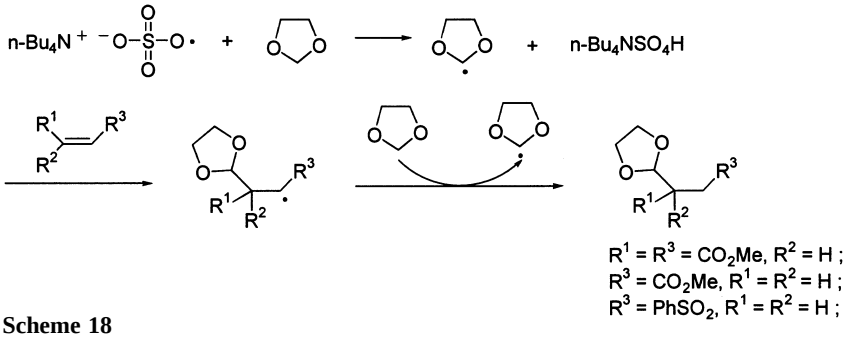
Fig. 1 Epoxidation of α,β-unsaturated ketones with **2**-H_2O_2-$^-$OH.

Table 2 Epoxidation of α,β-unsaturated ketones in methanol

Run	Substrate	**2** (eq.)	H_2O_2 (eq.)	Base (eq.)	Time(h)	Product	Yield[a] (%)
1		1	1	K_2CO_3 (1)	1		50
2		1	none	NaOH (1)	1		trace
3		none	1	NaOH (1)	1		30
4		1	1	NaOH (1)	0.2		95
5		1	1	NaOH (1)	2.0		98
6		0.5	0.5	NaOH (0.5)	0.1		90
7		1	1	NaOH (1)	0.1		95
8		1	1	NaOH (1)	1		92
9		1	1	NaOH (1)	0.2		95
10		1	1	NaOH (1)	0.4		90

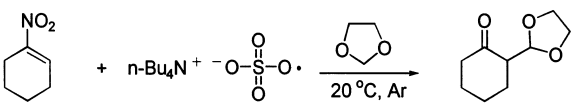
a: Isolated Yields

A novel masked formylation at the β-position of alkenes through 1,4-addition using the 1,3-dioxolanyl radical has been observed. Cyclic α,β-unsaturated ketones and esters, and sulfonyl alkenes react with **2** in 1,3-dioxolane as the reagent and solvent to afford the corresponding 1,3-dioxolanyl adducts in excellent yields [17]. The reaction is effective in introducing a formyl function at the β-position of cyclic pentenone, hexenone or heptenone. In this reaction, 1,2-addition products are not formed. This reaction appears to proceed through the 1,4-addition of 1,3-dioxolanyl radical to the electron deficient β-carbon adjacent to the carbonyl group as shown in Scheme 18.



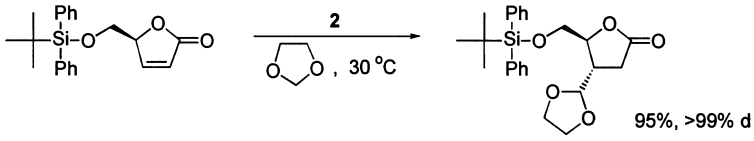
Scheme 18

It is possible to introduce the formyl group at the α-position of a cyclohexanone by the reaction of 1-nitrocyclohexene with **2** in 1,3-dioxolane (Scheme 19).



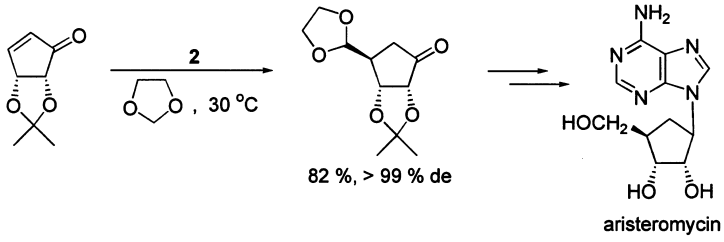
Scheme 19

When a chiral lactone was reacted with 1,3-dioxolane in the presence of **2**, extremely high diastereoselective β-masked formylation was obtained (Scheme 20) [18].



Scheme 20

This reaction can be utilized for the total synthesis of the natural product, aristeromycin (Scheme 21) [19].



Scheme 21

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