

Selective Oxidation of Sulfides to Sulfoxides with Molecular Oxygen Catalyzed by *N*-Hydroxyphthalimide (NHPI) in the Presence of Alcohols

Takahiro Iwahama, Satoshi Sakaguchi, and Yasutaka Ishii*

Department of Applied Chemistry, Faculty of Engineering

& High Technology Research Center, Kansai University, Suita, Osaka 564-8680, Japan

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Abstract: Aerobic oxidation of various sulfides using *N*-hydroxyphthalimide (NHPI) in the presence of alcohols was examined. For instance, the oxidation of diphenyl sulfide in the presence of cyclohexanol and a catalytic amount of NHPI in benzonitrile gave diphenyl sulfoxide in 88 % yield along with a small amount of diphenyl sulfone (7 %). The actual oxidant in this oxidation is considered to be an α -hydroxy hydroperoxide generated by the autoxidation of alcohol assisted by the NHPI which serves as the radical catalyst.

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Selective oxidation of sulfides to sulfoxides is a very important reaction in organic synthesis, since they are used as precursors of sulfur-stabilized carbanions and the Pummerer reaction.¹ Hence, numerous oxidizing reagents have been developed for this purpose.² Among them, molecular oxygen is the most attractive oxidant from the economical and environmental points of view. However, the direct introduction of molecular oxygen to sulfides is difficult, because the ground state of molecular oxygen is the inert triplet. Therefore, methods combined with molecular oxygen and reducing reagents such as H₂ or aldehydes are often used for oxygenation reactions of organic compounds.³ There have been several works on the oxidation of sulfides to sulfoxides with molecular oxygen.⁴

In preceding papers, we reported that *N*-hydroxyphthalimide (NHPI), which serves as the radical catalyst, promotes the aerobic oxidations of alkanes and alcohols in the presence or absence of a transition metal under mild conditions.⁵ The NHPI-catalyzed oxidation of alkanes has been found to proceed *via* a radical process involving the homolytic cleavage of a carbon-hydrogen bond of substrates and the addition of dioxygen to the resulting alkyl radicals giving hydroperoxides which are eventually converted into an alcohol or ketone.^{5c} If the resulting hydroperoxides can oxidize organic substrates, this method provides a new synthetic tool of oxygen-containing compounds from various substrates.

In this paper, we demonstrate the selective oxidation of sulfides to sulfoxides as an approach for the utilization of hydroperoxides formed *in situ* from alcohols under the influence of O₂ and NHPI (Scheme 1).

The oxidation of diphenyl sulfide (**1**) with molecular oxygen (1 atm) in the presence of an

Scheme 1

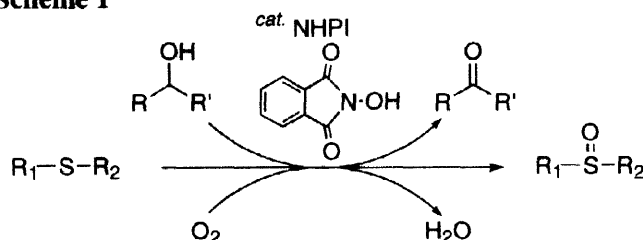


Table 1. Oxidation of Diphenyl Sulfide (1) with Molecular Oxygen Catalyzed by NHPI in the Presence of Various Alcohols^a

Run	Alcohol	Time (h)	Conv. (%)	Yield (%) ^b	
				sulfoxide (2)	sulfone (3)
1	—	16	no reaction		
2	cyclohexanol (4)	16	90	88	7
3 ^c	4	24	31	>99	n.d.
4 ^d	4	12	98	80	14
5 ^e	4	18	84	90	5
6 ^{d,f}	4	20	90	91	4
7	2-octanol	16	84	86	6
8	benzyl alcohol	16	91	78	13
9 ^d	1-phenylethanol	16	72	96	1
10	2-propanol	16	37	95	trace

^a **1** (2 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol%) and alcohol (10 mmol) in benzonitrile (1 mL) at 80 °C. ^b Selectivity based on **1** reacted. ^c Reaction was carried out at 70 °C. ^d Reaction was carried out at 90 °C. ^e **4** (3 eq.) was used. ^f Co(OAc)₂ (0.2 mol%) was added.

alcohol was chosen as a model reaction and carried out under several reaction conditions (Table 1). The oxidation of **1** under a dioxygen atmosphere in the presence of a catalytic amount of NHPI (10 mol%) and 5 equiv of cyclohexanol (**4**) in benzonitrile at 80 °C for 16 h gave diphenyl sulfoxide (**2**) and diphenyl sulfone (**3**) in 88 % and 7 % yield, respectively, at 90 % conversion (run 2). In this reaction, 33 % (3.3 mmol) of alcohol **4** was consumed and 2.7 mmol of cyclohexanone (**5**) was obtained (82 % selectivity). However, the oxidation of **1** at 70 °C proceeded slowly to form **2** in low conversion, although the **2** was only formed without formation of **3** (run 3). Although the quantity of alcohol used was reduced from 5 to 3 equiv, the result was almost the same as that obtained by the use of 5 equiv (run 5). No reaction took place in the absence of alcohol (run 1).

In a previous paper, we reported that the aerobic oxidation of various alcohols was enhanced in the presence of a small amount of Co(OAc)₂.^{3b} Thus, the oxidation of **1** in the presence of Co(OAc)₂ (0.2 mol%) was carried out. It is interesting to note that **1** was oxidized to **2** in high yield even at 70 °C (run 6).

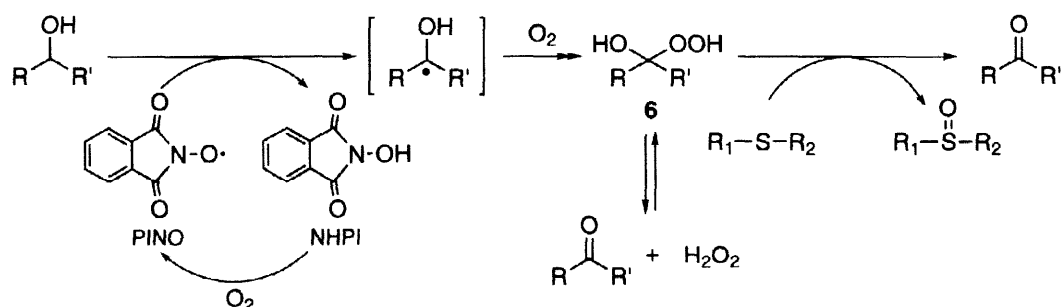
On the other hand, 2-octanol and benzyl alcohol could be used in place of **4** (runs 7 and 8). The oxidation of **1** using 1-phenylethanol proceeded even at 70 °C to give **2** in higher selectivity (run 9). However, 2-propanol afforded **2** in an unsatisfactory conversion (run 10). These results may be attributed to the ease of abstraction for the α-hydrogen of alcohols employed.

Table 2. Oxidation of Various Sulfides to Sulfoxides with Molecular Oxygen (1 atm) Catalyzed by NHPI in the Presence of Cyclohexanol (4) ^a

Run	R ₁ -S-R ₂		Conv. (%)	Yield (%) ^b	Run	R ₁ -S-R ₂		Conv. (%)	Yield (%) ^b
1	R ₁ = Ph	R ₂ = Me	99	86	5	R ₁ = 4-NO ₂ Ph	R ₂ = Me	<5	trace
2	R ₁ = 4-ClPh	R ₂ = Me	88	92	6	R ₁ = Ph	R ₂ = Et	51	83
3	R ₁ = 4-MePh	R ₂ = Me	24	94	7 ^d	thianthrene		86	87
4 ^c	R ₁ = 4-MePh	R ₂ = Me	87	96	8	R ₁ = R ₂ = <i>t</i> -Butyl		15	60

^a Substrate (2 mmol) was allowed to react under dioxygen (1 atm) in the presence of NHPI (10 mol%) and **4** (5 eq.) in benzonitrile (1 mL) at 90 °C for 12 h. ^b Selectivity based on substrate reacted. ^c Reaction was carried out at 80 °C for 24 h in the presence of 1-phenylethanol instead of **4**. ^d Reaction was carried out at 80 °C for 12 h.

Scheme 2



On the basis of these results, the aerobic oxidation of various sulfides assisted by NHPI was examined in the presence of cyclohexanol **4** under selected reaction conditions (Table 2). Thioanisol derivatives were converted into the corresponding sulfoxides in good yields except for 4-nitrophenyl methyl sulfide (runs 1-5). Similar results were also obtained in the oxidation of ethyl phenyl sulfide and thianthrene (runs 6 and 7). However, the oxidation of aliphatic sulfide such as di-*tert*-butyl sulfide led to sulfoxide in lower conversion under these conditions (run 8).

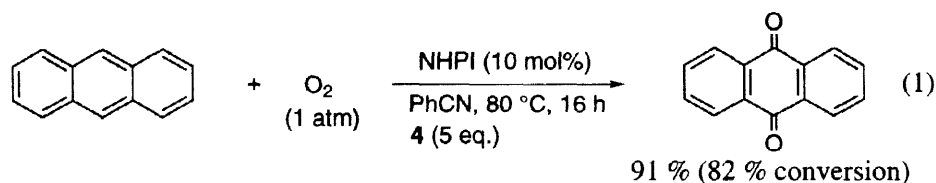
The outline of the present oxidation of sulfides is illustrated as Scheme 2. The first step is the abstraction of an α -hydrogen atom from the alcohol by phthalimide *N*-oxyl (PINO) generated from NHPI and dioxygen followed by the formation of α -hydroxy hydroperoxide (**6**). The resulting **6** may be in equilibrium with H₂O₂ and ketone, because the ketone reacts with H₂O₂ to reach an equilibrium with **6** in solution.⁶ However, we believe that the actual oxidizing reagent of sulfides to sulfoxides is not H₂O₂ but hydroperoxide **6**, since the oxidation of **1** with H₂O₂ in the presence of cyclohexanone **5** at 80 °C for 3 h gave **2** in 89 % yield (86 % conversion), while the same oxidation of **1** in the absence of **5** led to **2** in lower conversion (32 %) (Table 3).⁷

Table 3. Oxidation of 1 with H₂O₂ in the Presence of Cyclohexanone (5) ^a

Run	5	Conv. (%)	Yield (%) ^b	
			2	3
1 ^c	0.5 eq.	86	89	4
2	—	32	93	n.d.

^a **1** (2 mmol) was allowed to react with H₂O₂ (1 eq.) in benzonitrile (2 mL) at 80 °C for 3 h. ^b Selectivity based on reacted **1**. ^c **5** was recovered in 78 % yield.

In conclusion, we have found the NHPI-catalyzed selective oxidation of sulfides to sulfoxides by molecular oxygen in the presence of an alcohol such as cyclohexanol. By using this method, it is possible for a variety of organic compounds other than sulfides to be oxidized. For example, anthracene has been found to be converted into anthraquinone in good yield (eq. 1). Further investigations to extend the present system to the oxidation of various substrates are in progress.



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- Although it is known that benzonitrile reacts with H₂O₂ under basic conditions to generate peroxycarboximidic acid which serves as a good oxidizing agent, such an amide was not detected in the present NHPI-catalyzed oxidation.