

COMMUNICATIONS

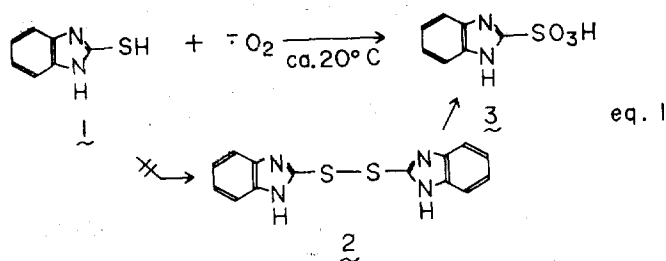
LETTERS

Direct Oxidation of Benzimidazole-2-thiol to the Benzimidazole-2-sulfonic Acid with Superoxide Ion

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Although biological reactions on superoxide anion (O_2^-) have been intensively studied over the past two decades since the discovery in 1969 that O_2^- is a respiratory intermediate in aerobic organisms¹, little work has yet appeared on the reactivities of O_2^- with simple organic compounds². There is a only short statement concerning the oxidation of alkyl³ or aryl thiols⁴ to the disulfides with O_2^- without any detailed experimental data. Chemical oxidations of thiols to their sulfinic or sulfonic acids have been generally known to need strong oxidation conditions such as boiling nitric acid⁵, potassium permanganate⁶, Caro's acid (KHSO_5)⁷, alkaline autooxidation⁸ or hydrogen peroxide in the presence of alkaline⁹. While, enzymic oxidations of the cystein to the corresponding sulfinic acid have been well known to occur readily *in vivo*¹⁰ and *in vitro*¹¹.

We have now found that benzimidazole-2-thiol was readily oxidized to its sulfonic acid with O_2^- generated from KO_2 in various aprotic solvents such as dimethyl sulfoxide, tetrahydrofuran or acetonitrile under mild conditions in good yields.



A typical procedure is as follows. A solution of benzimidazole-2-thiol (150 mg, 1 mmol, anhydrous DMSO: 1.0 ml) was slowly added into the suspension of potassium superoxide (KO_2 : 296 mg, 4 mmol, anhydrous DMSO: 2.0 ml) at 20 °C. The reaction mixture was stirred at 20 °C for 1–2 h and then quenched into a cold water (1.0 ml) containing. The complete reaction was confirmed by thin layer chromatography silica gel, $R_f(1)=0.63$, $R_f(3)=0.0$ in acetone. The solution was acidified to pH=1 with 1*N* HCl solution to give white crystals. When acetone (10.0 ml) was added to the solution white crystals appeared. The filtration gave a white solid (228 mg, 99%), which was recrystallized from water–acetone (1:1 v/v) to give white needle crystals. The product was identified as the sulfonic acid by comparison its ¹H NMR and IR spectra with those of the authentic sample. The results obtained are summarized in Table 1.

The oxidations of thiols to the corresponding disulfides by an electron transfer have been well discussed.¹² However in the oxidation of (1) with O_2^- , no formation of disulfide (2) was detected.

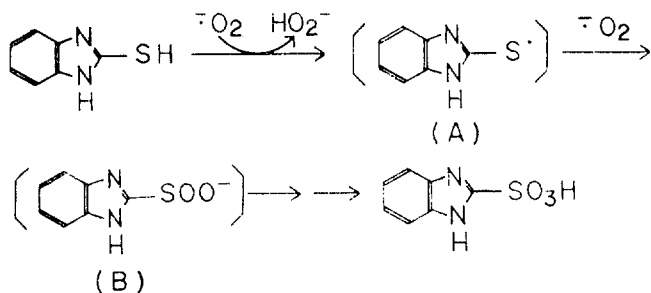
The oxidation of (1) appears to be initiated by the formation of a thyl radical (A) by an hydrogen abstraction and then to form a peroxy sulfenate (B)¹³ with O_2^- as shown below.

Though the intermediate (B) has never been isolated, it has been demonstrated to be an intermediate of oxidizing reagent in the alkaline autooxidation,¹⁴ or in the oxidation of disulfides and thiolsulfenates with KO_2 ¹⁵.

TABLE 1: The Reactions of Benzimidazole-2-Thiol and Its Disulfide with KO_2 in Various Solvents

Run	Substrate	Solvents	Reaction time(h)	Reaction temp(°C)	Sulfonic acid, yield(%) ^a	Other product(%)
1	1	DMSO	2	20	99	Me_2SO_2 (35)
2	1	THF	2	20	98	
3	1	CH_3CN	12	20	81	
4	2	DMSO	24	20	Traceable ^b	
5	2	DMSO	24	50	Small ^b amount	

^a Isolated yield; ^b Starting material (2) was almost quantitatively recovered; ^c Identified by comparison its ¹H NMR spectrum and GC with those of authentic sample.



Actually, dimethyl sulfone¹⁶ was isolated as an oxidation product of dimethyl sulfoxide when the oxidation of **1** with O_2^- was carried out in dimethyl sulfoxide, which was used as an activated oxygen trapping reagent (Run 1). Presumably, dimethyl sulfoxide was oxidized to the sulfone with an intermediate of the peroxysulfinate (B).

It is noteworthy that the oxidation of the thiol (**1**) to the sulfonic acid (**3**) is much faster than that of the disulfide (**2**) (Runs 1 and 4), which suggests that the oxidation of (**1**) may not involve to form an intermediate of the disulfide (**3**) (eq. 1).

Referendes and Notes

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- (13) Peroxysulfenate (B) will be oxidized further to a peroxysulfinate (RS(O)O^-) or peroxysulfonate (RS(O)OO^-), which is an unstable oxidizing intermediate.
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- (16) The reaction of dimethylsulfoxide with KO_2 without the substrate (**1**) did not yield any dimethylsulfone in a control experimental.