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## THE REDUCTION OF SULFOXIDE BY IODIDE/ORGANIC ACID SYSTEM IN THE SOLID STATE

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**ABSTRACT:** A novel solid state reduction of sulfoxides including methionine sulfoxide to the corresponding sulfides by iodide/organic acid system is described.

With recognition that in some cases organic reactions may proceed more efficiently and even more selectively in the absence of solvent<sup>1</sup>, recently it has become common to study reactions in the solid state<sup>2</sup>. Many biological reactions also

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seem to occur in an almost solid state. Enzymes retaining small amounts of water at their active site appear therefore to operate under near unhydrous conditions<sup>3</sup>. Thus hydrophobic lipases work well in partially aqueous solvent mixtures.

The natural occurrence of sulfoxides and their metabolic reactions have been recognized as illustrated by the deoxygenation of methionine sulfoxide to methionine with NADPH, known to be catalysed by an enzyme isolated from yeast<sup>4</sup>. The reduction of methionine sulfoxide, as a protector of S-alkylation, to methionine at the final stage of the peptide synthesis and the removal of residual sulfoxide moiety in synthetic applications of optically active sulfoxides have required easy and simple operations, so that numerous researches on the reduction of sulfoxides<sup>5</sup> especially with iodide ion in solution have been studied<sup>6</sup> because of its simplicity and effectiveness.

Generally the reaction has been described by the equation.

$$\mathbf{R}^{1}-\mathbf{S}(\mathbf{O})-\mathbf{R}^{2}+2\mathbf{H}\mathbf{I}\longrightarrow\mathbf{R}^{1}-\mathbf{S}-\mathbf{R}^{2}+\mathbf{I}_{2}+\mathbf{H}_{2}\mathbf{O}$$

Here we wish to report the facile deoxygenation of wide classes of solid sulfoxides 1 to sulfides 3 in the solid state in which organic solid acids 2 such as p-toluenesulfonic acid monohydrate (TsOH) or trichloroacetic acid serve as an effective activator with potassium or sodium iodide as reducing agent. The reaction is shown in the following equation.

$$\begin{array}{ccc} R^{1}-S(O)-R^{2}+2TsOH+2KI(2NaI) & \longrightarrow & R^{1}SR^{2}+I_{2}+2TsOK+H_{2}O\\ 1 & 2 & 3\\ & 2T:TsOH & ; & 2C:Cl_{3}CCOOH \end{array}$$

After the addition of the acid to the finely powdered mixture of sulfoxide and iodide, the whole mixture was allowed to stand at 30°C, and was sometimes irradiated with ultrasonic waves for several seconds if longer reaction time would be required.

Yield of sulfides 3 was generally high (77-100%) from dialkyl, alkyl aryl, dibenzyl, cyclic and diaryl sulfoxides (Table 1), and methionine sulfoxide (Table 2). Since the reaction probably assisted under the strongly acidic conditions, especially in methionine sulfoxide, a reactant ratio of 1:2: iodide=1:3:3 or 1:3:2 in MetO was more effective for rapid reduction and good yields. The usefulness of the method is shown to advantage with the yield of sulfide obtained from reduction of dibenzyl sulfoxide which with some other methods has been shown difficult to reduce without decomposition due to C-S bond fission. It is noted that the effective combination of KI and TsOH was apparently demonstrated by good yield of the sulfides in comparison with NaI/2T, KI/2C and NaI/2C system, dibenzyl sulfide excepted. The reaction was the fastest with dialkyl sulfoxides, was slower with mixed alkyl aryl derivatives and the slowest with diaryl sulfoxides which give the yield depending on their basicity<sup>7</sup> (p-tolyl > phenyl > p-

### Table 1

Reduction of Sulfoxides 1 to Sulfide 3 with Iodide/Solid Organic Acid 2 System<sup>\*</sup>  $R^{1}S(O)R^{2} \longrightarrow R^{1}SR^{2}$ 

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1

			Acid $2^{\flat}$ ,	React.	Isolated	Bp°C/Torr
<u>E x</u>	$\mathbf{R}^{1}$	$\mathbf{R}^2$	Iodide	Time(hr)	Yield(%)	(Mp/Lit.)
1	<i>n</i> −C₄H <sub>9</sub>	n−C₄H9	T,KI	0.25	73	liq./186
2	$n-C_4H_9$	$n-C_4H_9$	T,NaI	0.5	81	liq.80/20°
3	$C_6H_5CH_2$	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Cl,KI	5.0	77	(48/49.5)
4	$C_6H_5CH_2$	$C_6H_5CH_2$	Cl,NaI	5.0	67	(48/49.5)
5	Dibenzot	hiophene	T,KI	4.0	100	(99/99)
	5-oxi	de				
6	Dibenzot	hiophene	Cl,KI	96.0	100	(99/99)
	5-oxi	de				
7	CH₃	$C_6H_5$	T,KI	4.0	97	liq./193
8	CH₃	$C_6H_5$	T,NaI	6.0	86	liq./85/13
9	$C_6H_5$	$C_6H_5$	T,KI	4.0	76	liq./296
10	$C_6H_5$	C <sub>6</sub> H <sub>5</sub>	T,KI	8.0	97 1	iq./152/15 <sup>5</sup> *
11	C <sub>6</sub> H <sub>5</sub>	$C_6H_5$	Cl,KI	52.0	85	liq./296
12 p	-CH <sub>3</sub> C <sub>6</sub> H	₄ <i>p</i> −CH₃C₅	H₄ T,KI	4.0	89	(57/57)
13 p	-CH <sub>3</sub> C <sub>6</sub> H	₄ <i>p</i> −CH₃C₅	H₄ T,KI	30.0	100	(56/57)
14 p	-ClC <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H	₄ T,KI	4.0	49	(94/94)
<u>15 p</u>	-ClC <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H	<u>₄ T,KI</u>	8.5	91	(94/94)

a: 1 mmol of sulfoxide was used. The reaction temperature:  $30^{\circ}$ C. b: Acid 2, Cl:Trichloroacetic acid. T: *p*-Toluenesulfonic acid monohydrate. The molar ratio of **1:2:iodide** = 1:3:3

#### Table 2

## Reduction of DL-Methionine Sulfoxide to Methionine with

Potassium or Sodiun Iodide / p-Toluene Sulfonic Acid

## CH<sub>3</sub>S(O)CH<sub>2</sub>CH<sub>2</sub>CH(NH<sub>2</sub>)COOH + 2T<sub>5</sub>OH + 2KI $\longrightarrow$ 1 3 CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>CH(NH<sub>2</sub>)COOH + I<sub>2</sub> + 2T<sub>5</sub>OK + H<sub>2</sub>O 2

Ex	Molar Ratio 1:3:KI(NaI)	Reaction time(hr)	Reaction temp ( $^{\circ}C$ )	0.1 M Na2S2O3(ml)	Yield* (%)
1	1:3:2	18	30	17.08	85.4
2	1:3:2	18	50	18.70	93.5
3	1:3:(2)	18	50	18.33	91.7
4	1:3:2	3	50	14.02	70.1
5	1:2:2	3	50	9.90	49.5

\* Calculated yield for conversion to sulfide.

chlorophenyl) at the same reaction time, 4hours, (Exs 12, 9 and 14 in the Table 1). Reduction of dibenzyl sulfoxide was also slower. The reduction seems to be affected by steric interferenc around the sulfur atom. Higher reaction temperature induced shorter reaction time in methionine sulfoxide. Inspection of the data in the Table 1 shows that TsOH was more active as an activator than Cl<sub>3</sub>CCOOH, remarkably in dibenzothiophene 5-oxide (Exs 5 and 6) and diphenyl sulfoxides (Exs 10 and 11). This indicates that hydrogen iodide, which can be formed *in situ* from iodide anion and an acid ( $\mathbf{T}$  and  $\mathbf{C}$ ), is unable to become a reducing agent, therefore the reaction begins undoubtedly by the protonation<sup>8</sup> of the sulfinyl oxygen followed by the formation of a sulfurane

$$R^{1}S(O)R^{2} + TsOH \xrightarrow{H^{+}} R^{1}S^{+}(OH)R^{2} + TsO^{-}$$

$$R^{1}S^{+}(OH)R^{2} \xrightarrow{I^{-}} R^{1} - S - (OH)R^{2} \xrightarrow{H^{+}} R^{1} - S - (OH_{2}^{+})R^{2}$$

$$\stackrel{I}{\longrightarrow} R^{1} - S - R^{2} + I_{2} + H_{2}O$$

$$Scheme$$

intermediate 4 by nucleophilic addition of iodide anion. Subsequently 4 is converted by further protonation into the corresponding sulfurane 5, which is decomposed by iodide anion to give final product, sulfide. The reduction pathway in the solid state would be similar to that occurring in solution<sup>6h</sup>(Scheme).

### General experimental procedure

To a mixture of finely powdered sulfoxide (1 mmol) and iodide (3 mmol) was added with mixing the appropriate acid (3 mmol). The reaction mixture was maintained at 30°C and monitored by thin layer chromatography on silica gel using benzene, benzene/ethylacetate (10:1) or cyclohexane as developing solvent until sulfoxide was consumed or for the appropriate reaction time. Then liberated iodine was treated with 0.1 M sodium thiosulfate to a starch end point. The residue was extracted with n-hexane and the extract was dried and freed of solvent *in vacuo*. The crude sulfide, purified by recrystallization or by preparative thin layer or liquid chromatography, if necessary, was identified by comparison of its IR spectrum and Rf with that of the authentic sample and by mixed melting point determination with the authentic sulfide. Methionine was confirmed as N-acetyl methionine (Mp 114–115<sup>°</sup>C)<sup>10</sup>.

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