

AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF [ $^{18}\text{O}$ ]SULFOXIDES

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## SUMMARY

[ $^{18}\text{O}$ ]Sulfoxides are prepared in high yield with no loss of isotope enrichment by one-step sulfide oxidation with  $\text{CH}_2\text{Cl}_2/\text{Br}_2/\text{H}_2^{18}\text{O}/\text{py}$ -ridine.

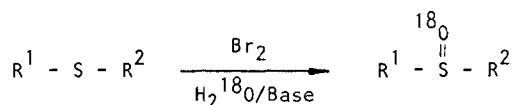
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## INTRODUCTION

It has been recently reported from our laboratory that [ $^{18}\text{O}$ ]dimethylsulfoxide (DMSO) can be successfully applied for stereospecific conversion of P-chiral dialkyl hydrogen phosphorothioates into corresponding dialkyl [ $^{18}\text{O}$ ]phosphates (1). These may be further applied for stereochemical studies on the mode of action of hydrolytic enzymes, which in the [ $^{17}\text{O}$ ]water medium convert dialkyl [ $^{18}\text{O}$ ]phosphates into P-chiral monoalkyl [ $^{17}\text{O}$ ,  $^{18}\text{O}$ ]phosphates (2). Since the latter compounds are ideal models for the studies of enzymatic processes involving phosphoryl transfer (3) and therefore require high isotope enrichment it was of interest to find the method of synthesis of highly enriched [ $^{18}\text{O}$ ]DMSO.

## DISCUSSION

The general method described in the literature for the synthesis of [ $^{18}\text{O}$ ]sulfoxides involves bromination of sulfide followed by hydrolysis of intermediate bromosulfonium salt with oxygen-labelled water in the presence of appropriate base acting as hydrogen bromide acceptor.



$\text{R}^1, \text{R}^2 = \text{alkyl, aryl}$

Oae et al. <sup>(4)</sup> used complexes of bromine with tertiary amines such as pyridine, quinoline or 1,4-diazabicyclo[2.2.2]octane for sulfide activation. The reaction was performed in acetic acid solution containing labelled water. Although the yields of sulfoxides were high, 12% loss of  $[^{18}\text{O}]$  enrichment was observed. The procedure works well in the case of aromatic sulfoxides but does not seem to be appropriate for the preparation of relatively volatile and hydrophylic DMSO and its alkyl congeners. In another approach Drabowicz et al. <sup>(5)</sup> applied for sulfide oxidation a two-phase procedure in  $\text{CH}_2\text{Cl}_2/10\% \text{H}_2^{18}\text{O}/\text{KHCO}_3$  system with elemental bromine as brominating agent. Despite the fact that chemical yields were high and the procedure of product isolation was relatively simple, a considerable (22-48%) loss of  $[^{18}\text{O}]$  enrichment was observed. The procedure requires also a big (23 fold) molar excess of labelled water with respect to the starting sulfide.

In this communication the procedure of sulfide oxidation is described which combines the simplicity of two-phase method with the effective binding of hydrogen bromide by tertiary amine\*.

#### PREPARATION OF $[^{18}\text{O}]$ SULFOXIDES

*To a magnetically stirred solution of corresponding sulfide (1 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added at room temperature a solution of labelled water (0.1 ml) in pyridine (0.5 ml) followed by dropwise addition of a solution of bromine (1.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 ml). Vigorous stirring was continued for 15 min\*\* and the excess of bromine was destroyed by addition of anhydrous  $\text{NaHSO}_3$  (0.3 g). Methylene chloride was evaporated and the residue was shaken with two 10 ml portions of benzene. The combined benzene solution was dried with anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. Crude sulfoxide was purified by distillation or crystallization. Yields, physical constants and  $[^{18}\text{O}]$  enrichment data for 4 different sulfoxides obtained by this procedure using  $[^{18}\text{O}]$  water (enrichment 69.6%) are collected in the Table.*

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\* The use of  $\text{KHCO}_3$  for neutralization of hydrogen bromide produces equimolar amounts of non-labelled water. This process may be in part responsible for the loss of isotope enrichment observed in the procedure of Drabowicz et al. <sup>(5)</sup>

\*\* In the case of less reactive diphenyl sulfide higher excess of bromine (1.5 mmol) and longer reaction time (6 hr.) was required.

TABLE

Sulfoxide	Yield <sup>a/</sup>	mp. (bp.)	Lit. mp. (bp.)	[ <sup>18</sup> O]enrichment <sup>d/</sup>	Ref.
(CH <sub>3</sub> ) <sub>2</sub> S <sup>18</sup> O	78%	32-4°/0.5mmHg	85-7°/25mmHg	69.0%	6
(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> S <sup>18</sup> O	87%	132-133° <sup>b/</sup>	132-134°	68.8%	5
4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> S <sup>18</sup> OCH <sub>3</sub>	81%	41-42° <sup>c/</sup>	41-43°	69.0%	5
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>18</sup> O	82%	69-71° <sup>c/</sup>	70-71°	69.1%	5

<sup>a/</sup> Calculated on purified product

<sup>b/</sup> After crystallization from ethanol-hexane

<sup>c/</sup> After crystallization from ether-hexane

<sup>d/</sup> Measured from the intensity of molecular ion peaks in Mass Spectra recorded with a LKB-2091 spectrometer at 70 eV ionizing energy

An inspection of the Table reveals that in addition to high chemical yields the presented method affords labelled sulfoxides with, practically, no loss of [<sup>18</sup>O]enrichment. The procedure seems to be specially appropriate for the synthesis of highly enriched [<sup>18</sup>O]DMSO and its alkyl analogs.

#### ACKNOWLEDGEMENTS

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