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A NEW FACILE SYNTHETIC METHOD FOR ^{18}O-LABELLED SULFOXIDES AND CARBONYL COMPOUNDS[1].

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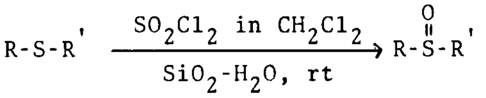
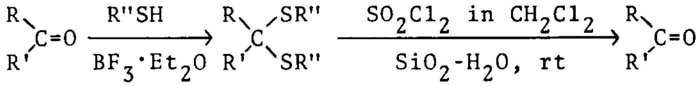
In our recent communication[2] it was reported that sulfides were conveniently and selectively oxidized to sulfoxides by sulfuryl chloride in the presence of a small amount of wet silica gel. This method of oxidation was further extended[3] to a facile and selective dethioacetalization to produce various



$$R\text{-}S\text{-}R' \xrightarrow[SiO_2\text{-}H_2O,\ rt]{SO_2Cl_2 \text{ in } CH_2Cl_2} R\text{-}\overset{O}{\overset{\|}{S}}\text{-}R' \qquad (1)$$

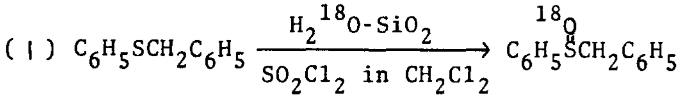


(2)

kinds of carbonyl compounds. These two methods prompted us to develop a new facile and convenient synthetic method for ^{18}O-labelled sulfoxides and carbonyl compounds, using ^{18}O-enriched water in reactions (1) and (2). We now wish to report the results.

As representative examples of labeling oxygens of sulfoxides and carbonyl compounds data are shown in the Table, with phenyl benzyl sulfoxide and p-chlorobenzaldehyde, respectively. As is seen in the Table, about two thirds of ^{18}O-enrichment, based on that of the original water, was found with the labelled sulfoxide. In the case of the aldehyde, the corresponding ^{18}O-enrichment was about a half as much as that of the added water. These somewhat incomplete incorporations are probably due to partial scrambling of ^{18}O between the added water and water loosely bound on the surface of the silica gel[4]. If more enriched products are necessary, use of increased amounts of

Table ^{18}O-Labeling with $H_2{}^{18}O$-Silica Gel and Sulfuryl Chloride

(i) 

$$C_6H_5SCH_2C_6H_5 \xrightarrow[SO_2Cl_2\ in\ CH_2Cl_2]{H_2{}^{18}O\text{-}SiO_2} C_6H_5\overset{^{18}O}{S}CH_2C_6H_5$$

	^{18}O Content (atom %)[a]
H_2O used	1.58
Sulfoxide (yield:97 %)	1.08

(ii) $$p\text{-}ClC_6H_4CHO \xrightarrow[BF_3\cdot Et_2O]{MeSH} p\text{-}ClC_6H_4CH(SMe)_2 \xrightarrow[SO_2Cl_2\ in\ CH_2Cl_2]{H_2{}^{18}O\text{-}SiO_2} p\text{-}ClC_6H_4CH^{18}O$$

	^{18}O Content (atom %)[a]
H_2O used	1.58
Aldehyde (yield:99 %)	0.65

[a] Determined as $^{12}C^{16}O^{18}O$.

enriched water and / or use of more enriched water would suffice the purpose.

As for labeling sulfoxide oxygen, oxygen-exchange in concentrated sulfuric acid[5], oxidations of sulfides with $H_2{}^{18}O$-N-bromosuccinimide[6], with $H_2{}^{18}O$-Br_2-1,4-diazabicyclo(2,2,2)octane[7] and with $H_2{}^{18}O$-iodobenzene dichloride-pyridine[8] and some other methods[9] have been reported. As mentioned earlier[2] the present method of oxidation is much simpler, less costly and has wider applicability (in both selectivity and yields) than any others. ^{18}O-Labelled carbonyl compounds have generally been prepared by oxygen-exchange between $H_2{}^{18}O$ and $>C=O$ groups in the presence of bases[10]. However, this kind of exchange is not efficient in general and usually requires prolonged heating and use of much $H_2{}^{18}O$ (or repeated treatment with $H_2{}^{18}O$). Base catalyzed reactions of carbonyl compounds during the exchange also limit its applicability. In contrast, the silica gel-catalyzed dethioacetalization proceeds quite cleanly and can be applicable to a wide variety of carbonyl compounds[3]. Therefore the present thioacetalization-dethioacetalization method may be utilized as a facile and general synthetic method for various ^{18}O-labelled carbonyl compounds.

Preparation of ^{18}O-Labelled Benzyl Phenyl Sulfoxide. A solution of sulfuryl chloride (1.55 mmol) in dichloromethane (5 ml) was added dropwise at 0° to a stirred mixture of silica gel (100 mg of silicic acid, Mallinckrodt, 100 mesh), $H_2{}^{18}O$ (202 mg, 1.58 atom % ^{18}O) and benzyl phenyl sulfide (209 mg, 1.04 mmol) in dichloromethane (5 ml). After stirring for 2 h at 0°, finely powdered, anhydrous potassium carbonate (0.6 g) was added to the reaction mixture and stirring was continued for another 10 min. Filtration and evaporation of the solvent in vacuo gave $PhS^{18}(O)CH_2Ph$: yield:221 mg (97.2 %); m.p. 123.5-124.5°. This material was repeatedly recrystallized from n-hexane-benzene for ^{18}O-analysis. The content of ^{18}O was determined[11] by combustion method (by measuring the relative heights of mass peaks for $^{12}C^{16}O^{18}O$ and $^{12}C^{16}O^{16}O$) and found to be 1.08 atom %.

Preparation of ^{18}O-Labelled p-Chlorobenzaldehyde. A mixture of p-chlorobenzaldehyde (5.95 g), methanethiol (25 g of 30 % methanolic solution) and boron trifluoride etherate (5 ml of 47 % ethereal solution) in benzene (20 ml) was stirred at room temperature for 24 h, which after usual work-up gave quantitatively dimethyl dithioacetal[12] of p-chlorobenzaldehyde, m.p. 35°.

A solution of sulfuryl chloride (263 mg, 1.95 mmol) in dichloromethane (5 ml) was added dropwise to a stirred mixture of the dimethyl dithioacetal (306 mg, 1.40 mmol), $H_2{}^{18}O$ (297 mg, 1.58 atom % of ^{18}O) and silica gel (149.5 mg) in dichloromethane (5 ml) and stirring was continued for 2 h at room temperature. A small amount of finely powdered potassium carbonate was added and the mixture was filtered. The filtrate and the washing was combined and allowed to evaporate in vacuo, which gave 198 mg (99 % yield) of p-chlorobenzaldehyde-^{18}O, m.p. 47-48°. This material was repeatedly recrystallized from n-hexane (m.p. 48°) and submitted to analysis for ^{18}O as described above. The ^{18}O content was 0.65 atom %.

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REFERENCES AND NOTES

1. Supported in part by a Grant-in-Aid (No. 911513), Ministry of Education, Japan.
2. M. Hojo and R. Masuda, *Tetrahedron Lett.*, **1976**, 613.
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4. The lower value for the aldehyde compared to the sulfoxide may be ascribed to that the dethioacetalization probably proceeds via monosulfoxide[3] and then it is hydrolyzed by external water (not an intramolecular oxygen migration). Thus, there are two chances of ^{18}O-scrambling in the case of the dethioacetalization.
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9. See references cited in ref. 8.
10. For example, I. Roberts and H. C. Urey, *J. Am. Chem. Soc.*, **60**, 880 (1938).
11. Determinations of ^{18}O-content were carried out by Profs. S. Oae, N.Furukawa, and K. Fujimori, Tsukuba University.
12. Dimethyl dithioacetals are most suited to the present purpose because dimethyl disulfide produced by the dethioacetalizations is easily removed during evaporation of solvents in vacuo and the residues are practically pure carbonyl compounds[3].