

# Synthesis of Ethyl Benzoate with $^{18}\text{O}$ -Labeled Ether Bridge

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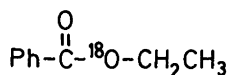
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Ethyl benzoate specifically labeled with  $^{18}\text{O}$  in the ether bridge has been prepared. Hydrolysis of benzaldehyde dimethyl acetal with [ $^{18}\text{O}$ ]water gave labeled benzaldehyde which, after reduction and subsequent ether formation with ethyl bromide, gave [ $^{18}\text{O}$ ]benzyl ethyl ether. Ruthenium-catalyzed oxidation of the ether resulted in the formation of  $^{18}\text{O}$ -ethyl [ $^{18}\text{O}_1$ ]benzoate as the exclusive product. Important isotope-induced shifts were observed in the IR spectrum of the 1277, 1109, 874 and 851  $\text{cm}^{-1}$  bands.

In a comprehensive analysis of the vibrational spectra of ethyl benzoate and the related titanium tetrachloride complexes, including several of their isotopic congeners,<sup>1</sup> the correlation between some of the IR absorption bands and the corresponding fundamental vibrations was unclear. In the further elucidation of this relationship, ethyl benzoate specifically labeled with  $^{18}\text{O}$  in the ether bridge may provide informative spectroscopic data. By force field calculations, the isotopic shift related to this labeling was predicted to be up to 20  $\text{cm}^{-1}$  for a restricted number of fundamentals hence improving and simplifying the interpretation of the ethyl benzoate spectrum. The spectroscopic information obtained from the title compound would be of particular interest, as vibrational spectra of  $^{18}\text{O}$ -labeled esters have not previously been reported. We were therefore interested in obtaining ethyl benzoate with  $^{18}\text{O}$  labeling exclusively in the ether bridge position, *1*.

The preparation of isotope-labeled molecules has been extensively reviewed by Ott.<sup>2</sup> No fully satisfactory synthesis has as yet been published



*1*

for *1*, nor for [ $^{18}\text{O}$ ]ethanol which may easily be transformed into the desired ester by means of standard methods. In most cases, spectroscopic studies of  $^{18}\text{O}$ -labeled compounds have been performed on substrates obtained by simple exchange reactions with [ $^{18}\text{O}$ ]water.<sup>3-6</sup> However, the desired selectivity may not easily be obtained by this method which is also uneconomical due to the required large excess of labeled water. On the other hand, Wasserman *et al.*<sup>7</sup> reported the synthesis of a number of labeled alcohols in moderate yields obtained by hydrolysis of trialkyl phosphates with [ $^{17}\text{O}$ ] and [ $^{18}\text{O}$ ]water. Another method has been published by Sawyer<sup>8</sup> where acetals are hydrolyzed with [ $^{18}\text{O}$ ]water and the resulting  $^{18}\text{O}$  aldehydes reduced with lithium aluminum hydride. In this way, labeled methanol and ethanol were obtained.

In the present paper, we report a new approach to *1* wherein [ $^{18}\text{O}$ ]benzaldehyde, *2*, was obtained in good yield by hydrolysis of the corresponding dimethyl acetal, *3*, with 90.4 atom % excess [ $^{18}\text{O}$ ]water. Reduction of *2* with sodium borohydride and subsequent treatment of the formed [ $^{18}\text{O}$ ]benzyl alcohol, *4*, with sodium hydride and ethyl bromide in *N,N*-dimethylformamide, yielded [ $^{18}\text{O}$ ]benzyl ethyl ether, *5*. This compound was further oxidized specifically in the benzylic position, applying the previously published improved ruthenium-catalyzed oxidation method using sodium metaperiodate as the stoichiometric oxidizing agent in a water/carbon te-

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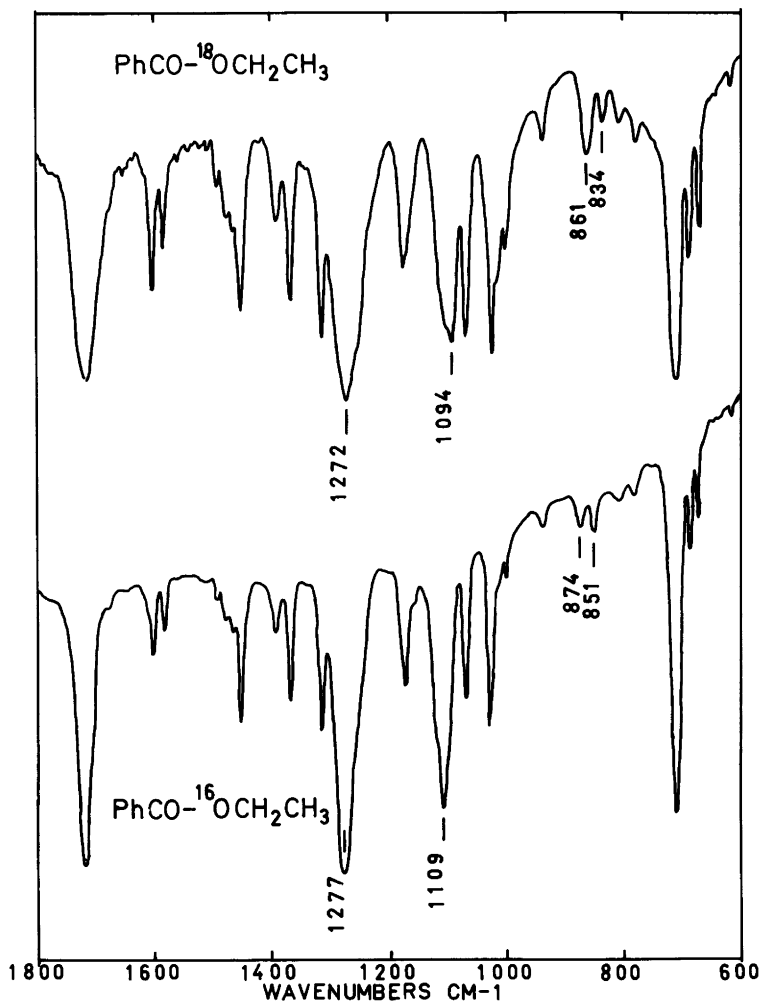


Fig. 1.

trichloride/acetonitrile solvent system.<sup>9</sup> The desired product, *I*, was isolated in good yield as the exclusive product. MS analysis of the product revealed an 89% <sup>18</sup>O isotope incorporation, corresponding to essentially no loss of excess <sup>18</sup>O isotope. The absence of a mass peak at *m/e* 107 also indicates that no oxygen scrambling had occurred.

The 1800–600  $\text{cm}^{-1}$  portions of the Fourier transform IR spectra of unlabeled ethyl benzoate and *I*, are shown in Fig. 1, and the bands sensitive to the isotope substitution are indicated. Important shifts are observed for the 1277, 1109, 874 and 851  $\text{cm}^{-1}$  bands of unlabeled ethyl benzoate. A series of bands in the 1100  $\text{cm}^{-1}$  region

was not satisfactorily resolved by the technique applied in these experiments; however, the important point is that the expected shifts due to isotope substitution were clearly demonstrated. A detailed study of the vibrational spectra will be published elsewhere.<sup>10</sup>

### Experimental

Analytical GLC was carried out on a Varian 3700 gas chromatograph equipped with a fused silica capillary column, 25 m  $\times$  0.33 mm, BP1. NMR spectra were obtained on a Varian EM 390 NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 257 grating infrared spectrometer

or on a Bruker IFS 113v Fourier transform infrared spectrophotometer using a thin film of the liquid samples between CsI windows. MS measurements were performed on an AEI-MS 902 MS spectrometer. [<sup>18</sup>O]water, 90.97 atom % excess <sup>18</sup>O and 3.49 atom % excess <sup>17</sup>O, was purchased from Ventron GmbH. Reagents were of analytical grade. All reactions were performed under nitrogen.

*Synthesis of [<sup>18</sup>O]benzaldehyde, 2.* A mixture containing 6.1 g (250 mmol) of benzaldehyde dimethyl acetal, (3), 1000 mg of [<sup>18</sup>]water and 50 mg of *p*-toluenesulfonic acid was stirred at room temperature for 12 h then heated to 70 °C for one h; methanol was distilled off at this point, GLC analysis indicated 95 % conversion to benzaldehyde. Distillation under reduced pressure gave 3.66 g, 83 %, of 2; b.p. 72 °C at 9 mmHg. All spectroscopic properties were in agreement with this structure. MS analysis revealed an 89 % <sup>18</sup>O isotope incorporation.

*[<sup>18</sup>O]Benzyl alcohol, 4.* In 20 ml of dry methanol and 20 ml of dry tetrahydrofuran, were dissolved 3.5 g of 2 and 0.5 g sodium borohydride added in small portions at 0 °C. After stirring at room temperature for 4 h, the product was isolated by extraction with ether and distilled under reduced pressure; b.p. 94–95 °C at 10 mmHg. The yield of pure 4 was 3.19 g, 89 %, with all spectroscopic properties in agreement with this structure. The <sup>18</sup>O isotope content was 86 % by mass spectral analysis.

*[<sup>18</sup>O]Benzyl ethyl ether, 5.* A reaction mixture containing 3.0 g of 4, 0.8 g sodium hydride and 3.9 g ethyl bromide in 20 ml of dry *N,N*-dimethylformamide was stirred at room temperature for 12 h. Addition of 50 ml of water, extraction with hexane and distillation under reduced pressure yielded 2.9 g, 77 %, of pure 5; b.p. 86–89 °C at 9 mmHg. All spectroscopic properties were in agreement with this structure. Mass spectral analysis revealed an 87 % content of <sup>18</sup>O.

*<sup>18</sup>O-Ethyl [<sup>18</sup>O<sub>1</sub>]benzoate, 1.* A mixture containing 2.0 g of 5, 50 mg RuCl<sub>3</sub> · 3H<sub>2</sub>O and 5 g sodium metaperiodate in a solvent system consisting of 20 ml acetonitrile, 20 ml carbon tetrachloride and 40 ml of water was stirred at room temperature for 18 h. Extraction and distillation gave 1.83 g, 77 %, of 1. All spectroscopic properties were in total agreement with this structure. Mass spectral analysis revealed an 89 % <sup>18</sup>O incorporation in compound 1.

MS [IP 70eV; *m/e* (% rel. int.)]: 153 (3), 152 (20), 151 (2.8), 150 (3.4), 137 (1.1), 125 (2), 124 (28), 123 (1.2), 122 (3.2), 106 (9.5), 105 (100), 77 (34), 51 (12). This mass spectrum is compared with that of *unlabeled* ethyl benzoate: 151 (2.8), 150 (29), 135 (1.4), 123 (2.4), 122 (28), 106 (9), 105 (100), 77 (36), 51 (14).

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