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# Convenient Syntheses of [$^{18}$O]Benzyl Alcohol and [$^{13}$C-*carboxy*,$^{18}O_1$]Benzoic Acid of High Isotopic Purity

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*Abstract*: The title compounds may be prepared with high isotopic incorporation and in good yield.

*Key words*: [$^{13}$C-*carboxy*, $^{18}O_1$]Benzoic acid, [$^{18}$O]benzyl alcohol, benzyl [$^{13}$C-*carboxy*, $^{18}$O-*ether*]benzoate.

Previous syntheses of [$^{18}$O]carboxylic acids[1] and of [$^{13}$C-*carboxy*, $^{18}$O]carboxylic acids[2,3] have resulted in mixtures containing the $^{18}O_2$, $^{18}O^{16}O$, and $^{16}O_2$ isotopomers. We required [$^{13}$C-*carboxy*, $^{18}O_1$]benzoic acid with high isotopic purity for the measurement of kinetic and equilibrium isotope effects by an NMR method. We have found it possible to prepare this isotopomer of benzoic acid *via* [$^{18}$O]benzyl alcohol and [$^{13}$C-*carboxy*]benzoic acid. This was achieved conveniently and with high incorporation (>98 at%) of $^{18}$O and with no detectable amount of the $^{18}O_2$ isotopomer (Figure 1b), using a simple synthesis (Scheme) with essential precautions to avoid isotopic contamination. It has been shown that oxygen isotopomers of benzoic acid can be separated on an analytical scale by reverse phase liquid chromatography[4] using the oxygen isotope effect on the acid dissociation constants of carboxylic acids,[5] but it seems unlikely that the very high efficiencies required (>$10^5$ theoretical plates) can be realised on a preparatively useful scale.

Efficient incorporation of $^{18}$O into benzyl alcohol was achieved by acid catalysed hydrolysis of methyl orthobenzoate with [$^{18}$O]water followed by $LiAlH_4$ reduction. In contrast to the hydrolysis of methyl orthocarbonate[6] there was no appreciable loss of $^{18}$O as [$^{18}$O]methanol or [$^{18}$O]methyl ether by methylation of the [$^{18}$O]water or of the resulting [$^{18}$O]methanol. [$^{18}$O]Benzyl alcohol is

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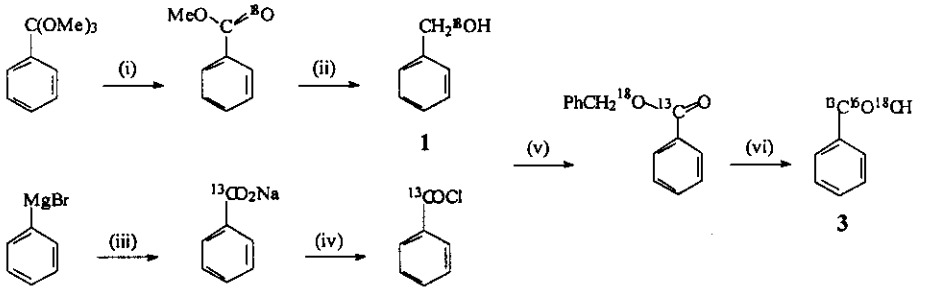
potentially a very useful reagent for selective isotopic substitution with $^{18}O$ but previous syntheses have been both less convenient and less economical.[2,7-10]




(i) $H_2{}^{18}O$ ($H^+$), (ii) $LiAlH_4$, (iii) $^{13}CO_2$; $H_2O$ ($H^+$); NaOH, (iv) $(COCl)_2$; $H_2O$ ($Et_3N$), (v) Pyridine, (vi) $H_2$ + Pd/C

**Scheme**

Following the preparation of [$^{13}$C-*carboxy*]benzoic acid we observed by $^{13}$C NMR that $^{13}CO_2$, *derived from commercial* $Ba^{13}CO_3$, *contains about 5% of* $^{13}C^{16}O^{18}O$ *(Figure 1a).* This isotopic contamination would often be unimportant but in the present synthesis would give rise to a significant amount of [$^{13}$C-carboxy, $^{18}O_2$]benzoic acid in the final product. The unwanted $^{18}$O in the [$^{13}$C-*carboxy*]benzoic acid was conveniently removed by exchange in hot dilute HCl before the reactions leading to selective isotopic substitution with $^{18}$O. The recovered [$^{13}$C-*carboxy*]benzoic acid was converted into the sodium salt which is much more readily dried than the free acid.

The efficient incorporation of $^{18}$O into [$^{13}$C-*carboxy*]benzoic acid using [$^{18}$O]benzyl alcohol requires the formation of benzyl benzoate in high yield with respect to both components. For this purpose the reaction between benzyl alcohol and benzoyl chloride in pyridine appeared the most promising method. Accordingly sodium [$^{13}$C-*carboxy*]benzoate was converted into [$^{13}$C-*carbonyl*]-benzoyl chloride by the action of oxalyl chloride followed by pyridine,[11] a reaction that gives a high yield of the acid chloride without leaving any problem of eliminating an excess of the chlorinating agent. This reaction, however, does form a small amount of benzoic anhydride. Although the anhydride would have been converted into the acid chloride by heating with an excess of oxalyl chloride[11] the latter was undesirable in the next step. In the present synthesis failure to eliminate [$^{13}C_2$-*carbonyl*]benzoic anhydride before the hydrogenolysis step (step vi in the Scheme) would diminish the extent of $^{18}$O isotopic substitution in the final benzoic acid. Benzoic anhydride reacts rather slowly with alcohols in pyridine and cannot be efficiently separated from benzyl benzoate by

distillation. It is, however, completely removed from benzyl benzoate by hydrolysis with water and triethylamine at room temperature. Finally, hydrogenolysis of benzyl benzoate over palladium on charcoal in ethanol gave a nearly quantitative yield of [$^{13}$C-*carboxy*, $^{18}O_1$]benzoic acid after sublimation. The acid contains >98 at% $^{18}O_1$ and <0.5 at% $^{18}O_2$ by $^{13}$C NMR (Figure 1b), the sensitivity of the analysis being limited by the intensities of the satellite peaks (1.1% of the main peak) caused by coupling with C-3(5) at natural abundance (the coupling $^2J_{CC}$=2.81Hz[12] is close to twice the $^{13}$C isotope shift for one $^{18}$O, 1.46Hz).

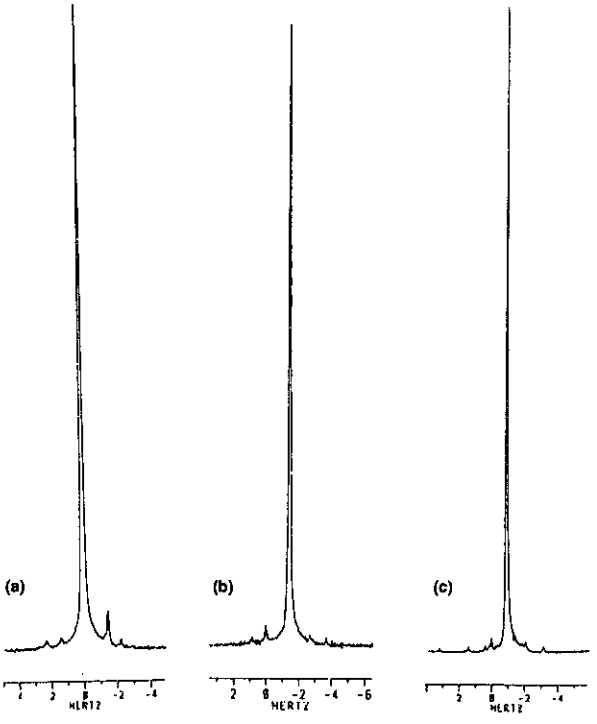



Figure 1. Narrow sweep $^{13}$C spectra ($^{16}O_2$-isotopomers as references) of [$^{13}$C-*carboxy*]benzoic acid and benzyl benzoate in $CS_2$ showing $^{18}$O incorporation (all resolvable satellites expected for coupling of the $^{13}$C in the main isotopomer to other $^{13}$C at natural abundance were observed, see Experimental):

(a) Benzoic acid prepared from commercial $Ba^{13}CO_3$ (about 5 at% $^{18}$O).

(b) [$^{13}C^{18}O^{16}O$-*carboxy*]benzoic acid, >98 at% $^{18}O_1$, <0.5 at% $^{18}O_2$.

(c) Benzyl [$^{13}$C-*carboxy*, $^{18}$O-*ether*]benzoate.

With the precautions given above, selectively isotopically substituted carboxylic acids can be prepared with the isotopic purity limited almost entirely by the level of enrichment in the starting materials. We have used **3** in a study of the degenerate 1,3-oxygen to oxygen rearrangements of groups IV esters[13] and of benzoic anhydride.[14]

## EXPERIMENTAL

Barium [$^{13}CO_3$]carbonate (90 at% $^{13}C$) and [$^{18}O$]water (99 at%), both from Amersham International, were used as received. Methyl orthobenzoate (Aldrich) showed no detectable amount of methyl benzoate by $^1H$ NMR and by IR spectroscopy.

All preparations with isotopically substituted compounds were first carried out with isotopically normal compounds and the products thoroughly characterised spectroscopically and by appropriate physical properties. Isotopically substituted products were characterised by $^1H$ NMR, to confirm chemical identity and purity, and by very high resolution, narrow sweep, $^{13}C$ NMR using a Brüker AM250 spectrometer operating at 62.8959MHz in order to confirm the isotopic subsititution. Samples were made up in $CS_2$ containing 5% by volume of cyclohexane-$d_{12}$: sodium benzoate was converted into free benzoic acid for $^{13}C$ NMR. The observed carbon-carbon couplings for benzoic acid ($^1J_{CC}$=72.47Hz, $^2J_{CC}$=2.81Hz, $^3J_{CC}$=4.54Hz) agree well with those previously observed for solutions in an unspecified solvent.[12]

[$^{18}O$]*Benzyl alcohol* (**1**).

A small crystal of toluene 4-sulfonic acid was added to dry methyl orthobenzoate (8.68 g, 47.6 mmol) and [$^{18}O$]water (0.982 g, 49.1 mmol) in a dry flask protected from moisture. The reaction mixture became homogeneous after an exothermic reaction and methanol was carefully removed under vacuum from the cooled product. The methyl [$^{18}O$-*carbonyl*]benzoate in ether was added to 1M lithium aluminium hydride in ether (50 ml) under nitrogen and after 1 hr the reaction mixture was quenched by the cautious addition of saturated aqueous sodium potassium tartrate and additional ether. The ethereal layer was dried ($MgSO_4$), the ether was evaporated, and the residue was flash distilled to give **1**, 4.85 g (93%), characterised by $^1H$ NMR.

[$^{13}C$-*carboxy*, $^{18}O$-*ether*]*Benzyl benzoate* (**2**)

Sodium [$^{13}C$-*carboxy*]benzoate (containing about 5% of $^{18}O$, see Figure 1a, 4.0 g), isolated from the reaction of phenyl magnesium bromide with $^{13}CO_2$ prepared from $Ba^{13}CO_3$ and dry $PbCl_2$, was heated with 1M HCl (100 ml) at 90°/20 hr. The resulting [$^{13}C$-*carboxy*]benzoic acid (no detectable $^{18}O$ by $^{13}C$ NMR: the $^{13}C$ satellite limited the sensitivity to about 0.5 at%) was recovered from the cooled solution by extraction into ether and converted back into the sodium salt by titration

with 1M NaOH followed by evaporation of water from the aqueous layer. Sodium [$^{13}C$-*carboxy*]benzoate (dried at 200°C/ 0.001 mm Hg for 4 hr, 2.9 g, 20.0 mmol) stirred in dry benzene (6 ml) under nitrogen was treated with oxalyl chloride (2.8 g, 22.0 mmol), added dropwise over 30 min, followed by dry pyridine (0.3 ml). The resulting mixture was stirred (1 hr) and treated with more dry pyridine (3.2 g) followed by [$^{18}O$]benzyl alcohol (2.2 g, 20.0 mmol) in benzene (5 ml). After 20 hr at room temperature the reaction mixture was poured onto ice cold 1M HCl (100 ml) and extracted into ether (100 ml), which was then washed with 1M HCl followed by saturated aqueous $NaHCO_3$. At this point $^{13}C$ NMR showed that the product contained about 4% of [$^{13}C_2$-*carbonyl*]benzoic anhydride, which could not be removed by distillation but which was quantitatively hydrolysed to benzoic acid by stirring the ethereal solution with triethylamine (2 ml) and water (7.0 ml)/60 hr. The ethereal solution was again washed with 1M HCl followed by sat. aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled (kugelrohr, oven temperature 170°C/0.7 mm Hg) to give **2**, (3.72 g, 86%), characterised by $^1H$ and $^{13}C$ NMR (Figure 1c). If **2** was not distilled the yield was somewhat higher (>90%) and the impurities (mainly solvents) did not interfere with the following reaction.

[$^{13}C$-*Carboxy*, $^{18}O$]benzoic acid (**3**)

The ester **2** (3.0 g, 14.0 mmol) in ethanol (30 ml) was reduced with hydrogen (1 atm) over Pd on charcoal (5%, 0.3 g) for 4 hr. The solution was filtered and the ethanol was distilled under reduced pressure. Sublimation of the residue (bath temperature 80-100°C/15 mm Hg) gave **3** (1.68 g, 97%), characterised by $^{13}C$ NMR (Figure 1b). Alternatively **3** could be converted into the sodium salt by titration with 1M NaOH followed by evaporation of the solvents.

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