

THE SYNTHESIS OF OXYGEN-18 ENRICHED
PHENOL AND NAPHTHOL FROM $^{18}\text{O}_2$

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Summary

Phenols enriched with oxygen-18 can be synthesized using an acid exchange reaction in H_2^{18}O at elevated temperature, however, to obtain highly enriched products very large quantities of water must be used and recycled. Grignard reagents will react readily with oxygen gas with almost no isotopic dilution to produce the ^{18}O enriched alcohol or phenol. Aromatic Grignards do not produce as high a yield as the aliphatic Grignards, however, both provide convenient routes to labeled products. The yield of naphthol from an aryl halide can be improved by the addition of an aliphatic halide (which produces the alcohol as a by product), however, the yield of naphthol from $^{18}\text{O}_2$ gas is not improved by this approach. Either 1-bromonaphthalene or bromobenzene was converted into the Grignard reagent and reacted with oxygen-18 enriched gas at 0° in a sealed reaction system. The reaction was worked up in the conventional manner and the yields from $^{18}\text{O}_2$ were 34% for [^{18}O]phenol and 23% for 1-[^{18}O]naphthol.

Key words: [^{18}O]Naphthol, [^{18}O]Phenol, Oxygen-18, Grignard, Alcohols

INTRODUCTION

Compounds labeled with ^{18}O and ^{17}O are very valuable as biological probes for a variety of studies which are often limited by the availability of labeled precursors for the preparation of the compounds of interest. The dual need for [^{18}O]phenol as a precursor for L-[4'- ^{18}O]tyrosine (1) and for 1-[^{18}O]naphthol as a precursor of [^{18}O]propranolol (2) prompted us to develop a synthesis for the incorporation of oxygen isotopes into aromatics.

A technique for exchanging ^{18}O into phenol has been reported by Oae, *et al* (3). Their procedure involves heating an unlabeled phenol at 180°C in 10 N HCl in H_2^{18}O for 24h. An exchange reaction is a convenient

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approach to oxygen labeling, providing it is easy to recover the excess ^{18}O water (e.g. distillation from the reaction mixture) and providing that very high enrichments are not needed which would require several exchange reactions or a very large excess of water. The strong acid and high temperature required for this exchange make it a poor choice as a synthetic approach, particularly given the tarry nature of the product and the effort involved in quantitatively recovering H_2^{18}O from 10 N HCl.

Classically, one can synthesize phenols by the alkali fusion of arylsulfonates acids or by the hydrolysis of aryl diazonium salts (4). For ^{18}O enriched products, the first approach would require the synthesis of K^{18}OH and the second would require either a large amount of H_2^{18}O or use of an organic solvent with labeled water as the limiting reactant. In special cases, a keto oxygen can be exchanged in H_2^{18}O followed by conversion to a phenol (eg. α -tetralone to 1-naphthol). Peroxide can also be used as the source of ^{18}O using for example aluminum chloride (5) or the aryl boronic acid made from methyl borate (6). Another approach is to use metal-oxygen complexes such as the transition metal peroxide $\text{MoO}_5\text{-Py-HMPA}$ described by Lewis (7) or the hydroxylation of naphthalene by molecular oxygen in the presence of molybdenum hexacarbonyl to give a mixture of 1- and 2-naphthol as described by Akhrem (8). Unfortunately, none of these techniques appear attractive for the synthesis of ^{18}O enriched products.

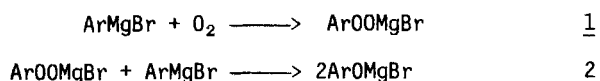
We have utilized the reaction of molecular oxygen with an aryl Grignard reagent as the route to ^{18}O enriched phenols because of its simplicity. Generally, this reaction is viewed as an undesired side reaction, however, Kharasch and Reynolds (9) have described the synthesis in detail and other workers have used it, including a synthesis for perdeutero-1-naphthol (10). The yields, unfortunately, are relatively low and although the yield from the aryl bromide could be improved by the addition of an alkyl halide, the yield from $^{18}\text{O}_2$ was not improved.

The synthesis of ^{18}O enriched alcohols from a Grignard has been described by Wiberg (11) for the preparation of ^{18}O methanol and the technique has been discussed by Borowitz *et al.* (12) who found the reaction difficult to use. With the conditions described here for the preparation of phenol and naphthol, the reaction is fast, the workup is easy and the isotopic dilution is negligible, although additional difficulties could be encountered with the recovery of volatile alcohols.

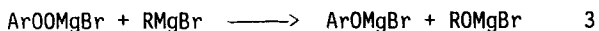
RESULTS AND DISCUSSION

The oxidation of a Grignard reagent with $^{18}\text{O}_2$ has proven to be an effective technique for the synthesis of 1- ^{18}O naphthol and ^{18}O phenol. The reaction will be equally useful for the preparation of oxygen-17 enriched products from $^{17}\text{O}_2$ and should provide even better yields of oxygen-17 or 18 enriched alkyl alcohols. To conserve the labeled oxygen, the reaction is carried out under an atmosphere that contained $^{18}\text{O}_2$ in a pressure controlled apparatus, rather than by bubbling oxygen gas through the reaction mixture as described by Kharasch and Reynolds (9). Although the yield of 1- ^{18}O naphthol (23%) and ^{18}O phenol (34%) are relatively low, the convenience and high enrichment make this synthetic approach attractive.

Kharasch and Reynolds (9) report that the yield of phenol from the Grignard can be improved from 28% to 64% by adding an alkyl Grignard to the reaction mixture. The explanation given is that oxygen reacts with a Grignard to form the peroxide as shown in 1, which is reduced by reaction with fresh Grignard (Step 2). The aryl Grignard, however, is a relatively poor



reducing agent compared to an alkyl Grignard (7) and therefore inclusion of an alkyl Grignard facilitates the reduction (step 3) and improves the yield



of the aryl hydroxyl compound. The results of a series of experiments utilizing aryl and alkyl Grignards are summarized in Table 1. The yield of 1-[¹⁸O]naphthol was 23% from ¹⁸O₂ in the absence of an alkyl Grignard and the overall yield from ¹⁸O₂ decreased with the addition of either 0.5 or 1.0 equivalent of 2-bromopropane. The overall amount of naphthol produced was increased with the addition of the alkyl Grignard (the yield from the halide was improved as reported), however, the fraction of ¹⁸O incorporated into the aryl product decreased. Since the addition of an alkyl Grignard results in an [¹⁸O] alkyl alcohol, the overall ¹⁸O recovery is, of course, much higher when an alkyl Grignard is included and the decision to include it or not depends entirely on whether the alkyl alcohol is a useful product. Unfortunately, the reaction conditions yield a small amount of unlabeled ethanol which is derived from the reaction of the Grignard reagent with the ether solvent (9). The ethanol must be removed to prepare a pure labeled alkyl alcohol. This problem could be eliminated by the judicious selection of a solvent, which could also facilitate the distillation of the alkyl alcohol.

The 70ev electron impact mass spectrum of the 1-[¹⁸O]naphthol is shown in figure 1. The features are similar to that reported by Klasinc and

TABLE 1

The Yield of 1-[¹⁸O]Naphthol from 1-Bromonaphthalene and ¹⁸O₂ Gas

Equivalents AR-Br	Equivalents R-Br	Yield from ¹⁸ O ₂		Yield from		¹⁸ O Incorporation
		Ar-OH	R-OH	Ar-Br	R-Br	
1	0	23%	--	15%	--	23%
1	0.5	20%	26%	23%	61%	46%
1	1.0	17%	37%	28%	61%	54%

Güsten (10) for unlabeled naphthol. The base peak at m/e 115 in the 1-[^{18}O] naphthol is unchanged from the unlabeled material, consistent with the elimination of HCO^+ . The molecular ion at m/e 146 is two mass units higher than the unlabeled material as expected. The relative intensities of the molecular ions at m/e 146, 145, and 144 were used to calculate the isotopic enrichment (Table 2).

Table 2
 ^{18}O Enrichments Determined by MS

Compound	^{16}O	^{17}O	^{18}O
$^{18}O_2$	2.42%	2.93%	94.64%
1-[^{18}O]Naphthol	2.8%	2.9%	94.3%

As is common with ^{18}O enriched materials, the ^{17}O enrichment is about 3% and represents an excellent source of low level ^{17}O enrichment for ^{17}O NMR experiments.

The ^{13}C NMR spectra of [^{18}O]naphthol and [^{18}O]phenol showed no significant impurities and were consistent with the literature (14).

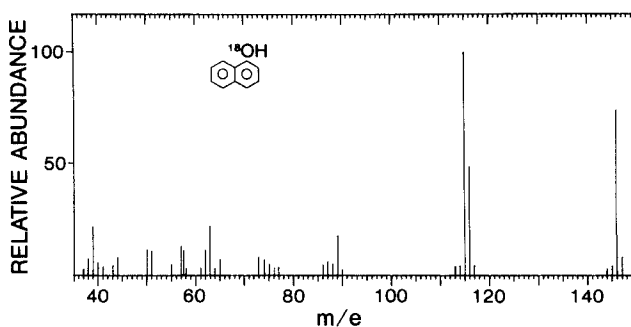


Figure 1. The 70 ev electron impact mass spectrum of 1-[^{18}O]naphthol. Experimental details are given in the text.

EXPERIMENTAL

Materials and Methods--1-Bromonaphthalene, bromobenzene and 2-bromopropane were purchased from J. T. Baker, Eastman and Aldrich respectively. The $^{18}\text{O}_2$ gas was prepared by electrolysis from H_2^{18}O supplied by Dr. Tom Mills of the Los Alamos Stable Isotopes Facility. ^{13}C NMR spectra were recorded using a Bruker WM-300 spectrometer. Mass spectra of the 1-naphthol were obtained using the direct insertion probe on an Extranuclear Spectrel quadrupole mass spectrometer. Gas chromatographic separations were performed on a column of Porapak QS using a Hewlett Packard 5710A gas chromatograph equipped with a thermal conductivity detector. Alternatively, samples were admitted into the mass spectrometer through a jet type separator from Scientific Glass Engineering. Melting Points were determined using a Thomas melting point apparatus.

Preparation of 1- ^{18}O Naphthol--A 300 ml 3-neck round-bottom flask was fitted with a mechanical stirrer, a condenser with a glass stopper and a 60 ml pressure equalizing addition funnel. The funnel was then connected to a vacuum manifold (total gas volume 238 ml) which was equipped with a vacuum gauge and a pressure gauge. A cylinder of nitrogen gas fitted with an oxygen trap (Oxy-trap from Alltech Associates) and a cylinder of $^{18}\text{O}_2$ were also connected to the manifold. The stirrer assembly was obtained from Kontes and utilized a metal stuffing box for reactions requiring vacuum. The box was filled with silicon high vacuum grease rather than the recommended stirrer packing, and the bearing surface was coated with a combination of vacuum grease and silicon oil to provide a leak tight seal.

The flask was evacuated to less than 10 microns pressure, filled with nitrogen and charged with magnesium (200 mmoles, 5.0 g). The flask was again evacuated and 100 ml of ether (which had been twice freeze-thawed) was distilled (bulb to bulb) into the flask. Nitrogen was again added, the ether was thawed and 1-bromonaphthalene (200 mmoles, 41.2 g) was added to the addition funnel and a crystal of iodine was added to the ether. The

mixture was heated with warm water to initiate the reaction and the 1-bromonaphthalene was added at a rate to maintain gentle refluxing. As the pressure rose to about 50 mm above atmospheric, the vapors were vented until the ether would reflux gently in a closed system composed primarily of ether vapor. After the addition of halide was complete, the mixture was stirred for an additional 30 min, at which time the condenser and addition funnel were removed while maintaining a positive pressure of nitrogen, and the flask was stoppered. The ether solution was then frozen with liquid nitrogen, the system was evacuated and the mixture was warmed to 0° C. Enriched $^{18}\text{O}_2$ gas was admitted to the manifold to a pressure slightly above atmospheric, and the pressure noted to allow calculation of the quantity of gas used. As the $^{18}\text{O}_2$ pressure decreased over a period of 5-10 min, the pressure was again noted and fresh $^{18}\text{O}_2$ was added. After 12 additions of $^{18}\text{O}_2$ over a period of 1.5-2 hours, the reaction mixture had consumed 66 mmoles of $^{18}\text{O}_2$ and no longer took up oxygen. The Grignard complex was decomposed by the slow addition of 35 ml of 6 N H_2SO_4 and the organic products extracted into ether. The ether was washed once with water and then 3 times with 0.5 N NaOH to remove the naphthol. The aqueous solution was washed twice with ether and acidified with 6 N H_2SO_4 and the naphthol was then extracted back into ether. The ether layer was washed once with water, dried over anhydrous sodium sulfate and the solvent evaporated in vacuo. The resultant oil was dissolved in hot hexane, decanted from a black tar, and the 1- ^{18}O naphthol allowed to crystallize (22.4 mmoles, 3.27 g). The mother liquor was evaporated and the residue was sublimed to provide an additional 7.5 mmoles, 1.09 g. Total yield: 4.36 g, 29.9 mmoles, (23% yield from $^{18}\text{O}_2$), mp. 94-95° uncorr., lit. 96° (15).

Preparation of 1- ^{18}O Naphthol in Presence of Alkyl Grignard--The technique for preparing 1-naphthol with an alkyl Grignard was identical to that described above except that 1-bromonaphthalene and 2-bromopropane were added to the magnesium. After decomposition of the Grignard complex, the

ether--water mixture was distilled through a small column (1.5 x 16 cm) of glass helicies. Ether was removed first followed by an azeotropic mixture of 2-[¹⁸O]propanol and water. The quantity of water present was determined by GC; the sample could be dried by distillation from type 3A molecular sieve. The mixture also contained a small amount of ethanol (ca. 15%) which was not enriched in ¹⁸O as determined by GC-MS analysis. The 1-naphthol present in the distillation pot was isolated as described above and the results are summarized in Table 1.

Preparation of [¹⁸O]Phenol--[¹⁸O]Phenol was synthesized by the same technique described for the synthesis of 1-[¹⁸O]naphthol except that bromobenzene (15.7 g, 100 mmoles) was used in place of 1-bromonaphthalene and 44.9 mmoles of ¹⁸O₂ were consumed. The reaction mixture was processed in the same manner to provide an ether extract of [¹⁸O]phenol which was evaporated to a solid 2.94 g, 30.6 mmoles, 34%) and not further purified. A sample of an aqueous solution was analyzed by liquid chromatography using a C-8 reverse phase column and 40:60 methanol:water eluant, and no significant impurities were found.

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