CONVENIENT ONE-POT SYNTHESIS OF BENZOQUINONE-[U-^{14}C] AND HYDROQUINONE-[U-^{14}C]*

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SUMMARY

Benzoquinone-[U-^{14}C] was synthesized in 90% yield from benzene-[U-^{14}C] via a three step sequence. Conditions were developed which allowed this conversion to be accomplished in a one pot closed system. The benzoquinone-[U-^{14}C] thus obtained could be reduced to hydroquinone-[U-^{14}C] in quantitative yield. Preparation of benzene-[U-^{14}C] is also described.

Key Words: Benzoquinone-[U-^{14}C], Hydroquinone-[U-^{14}C], Benzene-[U-^{14}C], Nitrobenzene-[U-^{14}C], Aniline-[U-^{14}C]

INTRODUCTION

We required a large quantity of high specific activity benzoquinone-[U-^{14}C], 1, for use as a dienophile in the synthesis of a naphthoquinone derivative. Despite the synthetic importance of 1 as a Diels-Alder dienophile[1], and as an intermediate in the synthesis of dyes and biological materials[1,2], we could find no reference to its preparation.

The synthesis of hydroquinone-[U-^{14}C], 2, in 17% yield from benzene-[U-^{14}C], has recently been reported.[3] Several steps in this synthesis involved extractive work ups of volatile intermediates. The low yield, coupled with potential safety problems led us to investigate a new approach.

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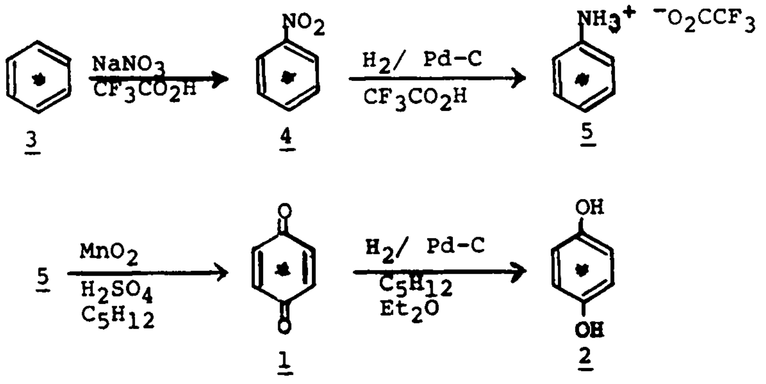
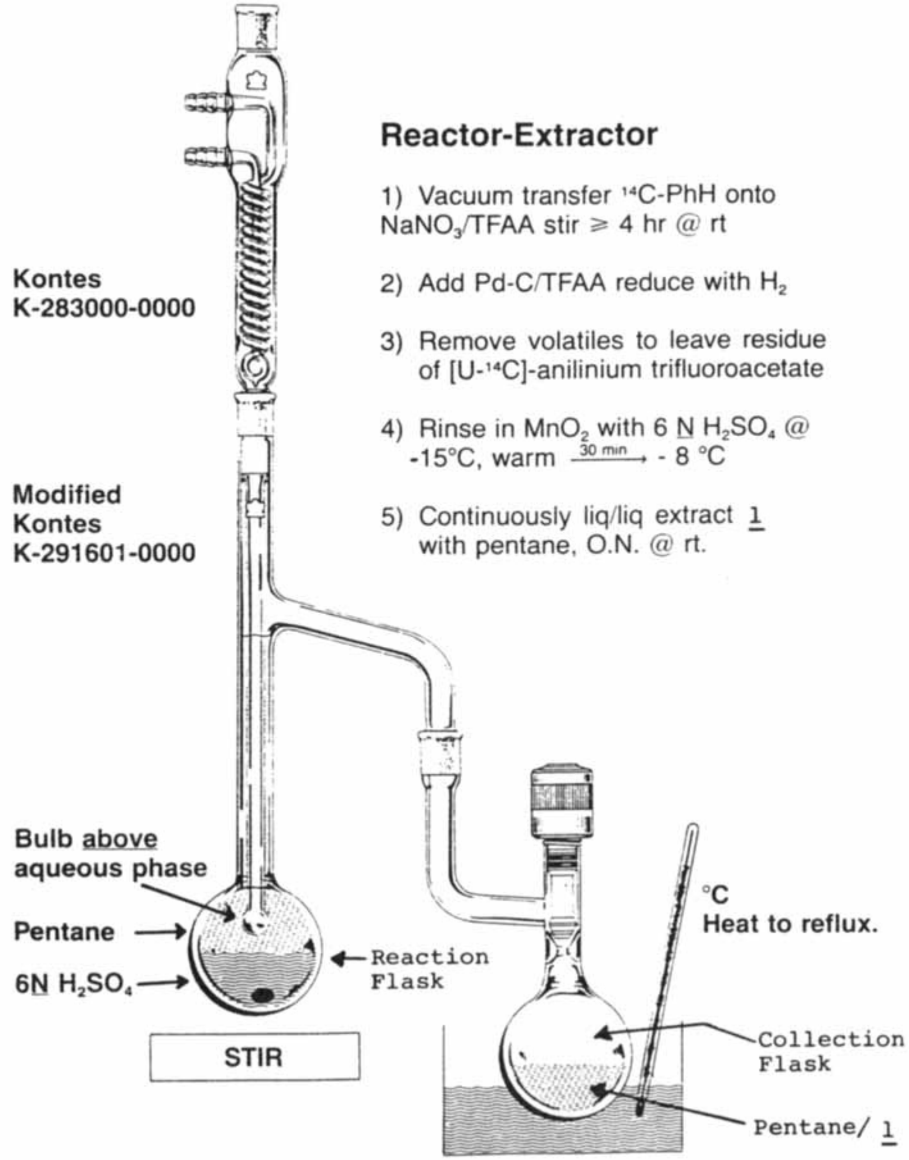


Scheme 1: One pot sequence for the conversion of benzene-(U-^{14}C) to benzoquinone-(U-^{14}C) and hydroquinone-(U-^{14}C)

RESULTS AND DISCUSSION

The commercial synthesis of benzoquinone involves oxidation of aniline with MnO_2 in sulfuric acid.[2] This general process was adapted to the hot synthesis in such a way as to avoid any work up of volatile materials. In fact, the entire sequence from benzene-[U-^{14}C], 3, to 1 was designed as a one pot process. The product was, thus, obtained in pure form and in 90% yield without isolation of any intermediates. Additionally, 1 was isolated in a closed system and could be reduced directly to 2. This synthesis is depicted in Scheme 1.

Benzene-[U-^{14}C], 3, (234 mCi) was prepared in 90% yield from $Ba^{14}CO_3$ via cyclotrimerization of acetylene-[U-^{14}C].[4] It was found that the yields of benzene increased with repeated use of fresh cyclotrimerization catalyst. In order to achieve 90% yield of 3, three cyclotrimerizations were done with cold acetylene thereby bringing the yield of benzene up to >90%. At this point the catalyst was used for the labelled reaction. The one pot conversion of 3 to 1 was accomplished in the custom made "reactor/extractor" shown in Figure 1.



Reactor-Extractor

1) Vacuum transfer ^{14}C-PhH onto $NaNO_3$/TFAA stir ≥ 4 hr @ rt

2) Add Pd-C/TFAA reduce with H_2

3) Remove volatiles to leave residue of [U-^{14}C]-anilinium trifluoroacetate

4) Rinse in MnO_2 with 6 N H_2SO_4 @ -15°C, warm $\xrightarrow{30\ min}$ - 8 °C

5) Continuously liq/liq extract 1 with pentane, O.N. @ rt.

Figure 1: Custom designed reaction/extraction system for the synthesis of benzoquinone-(U-^{14}C), 1, and hydroquinone-(U-^{14}C), 2.

The reaction flask was charged with $NaNO_3$ and trifluoroacetic acid (TFA).[5] After cooling in a liquid nitrogen bath, 3 was vacuum transferred into the flask. Stirring at ambient temperature overnight ensured complete conversion to nitrobenzene-[U-^{14}C] (4). The absence of the usual HNO_3/H_2SO_4 nitrating mixture made aqueous work up and isolation of the volatile 4 unnecessary. Thus, 5% Pd-C was rinsed into the reaction flask with TFA and hydrogen was introduced. The aniline-[U-^{14}C] initially formed was converted _in situ_ to the nonvolatile anilinium [U-^{14}C] TFA salt (5) by the solvent. As a result, TFA could be removed by vacuum transfer leaving 5 as a non-volatile residue ready for oxidation to 1.

MnO_2 was rinsed into the cooled (-15°) reaction flask with 6N H_2SO_4 and the aqueous phase was covered with pentane. The pentane was allowed to overflow into the collection flask as shown in _Figure 1_. The two phase oxidation system was stirred at ambient temperature overnight with concomitant continuous extraction of the product, 1. This process afforded 1 in 90% yield and greater than 98% radiochemical purity. Significantly lower yields of 1 were obtained if the product was not continuously removed from the reaction mixture.

A low specific activity trace run afforded 1 in similar yield and purity. In that case, 10% Pd-C was rinsed into the collection flask and 1 was hydrogenated to give 2 in quantitative yield and >99% purity.

The process described for the preparation of 1 and 2 is high yielding, affords the products at a high degree of purity directly, and is particularly convenient to implement because of the one pot nature of the synthesis.

EXPERIMENTAL

Ba^{14}CO$_3$ was purchased from General Electric Corp. The cyclotrimerization catalyst KC-Perlkator D-1 was obtained from Kali-Chemie, Hannover, Germany. All solvents were Reagent Grade and used without purification. Radiochromatography was performed on a Berthold Model 2760 Radiochromatography Scanner. Radioassays were obtained using a Packard Model Minaxi 4000 Liquid Scintillation counter. Products were identified by radiochromatographic mobility compared to authentic standards. TLC was performed on silica gel plates obtained from Analtech, Newark, DE.

Benzene-[U-^{14}C] (3)

Acetylene-[U-^{14}C] was prepared in 100.3% weight yield from Ba^{14}CO$_3$ (260 mCi, 39.7 mCi/mmol, 916 mg, 4.6 mmol) by the method of Cox[6]. To assure complete removal of water the acetylene-[U-^{14}C] was transferred two times from spiral traps at -40° to similar traps cooled in $N_{2(l)}$. The labelled acetylene was diluted with cold acetylene to an approximate specific activity of 25 mCi/mmol.

A flask containing 25 g of cyclotrimerization catalyst (KC-Perlkator D-1) was connected to the vacuum line, evacuated, and cooled in $N_{2(l)}$. Cold acetylene was admitted and the cooling bath was removed. Excess acetylene was removed by vacuum transfer after 30 min. The catalyst was heated to 200° and the cold benzene was collected in an liquid N_2 cooled receiver on the vacuum line. This process was repeated two more times until the yield of cold benzene exceeded 90%.

The acetylene-[U-^{14}C] was admitted into the $N_{2(l)}$ cooled catalyst flask and the cooling bath was removed. After 30 min. unabsorbed volatiles were removed by vacuum transfer. The catalyst was heated to 200° and the liberated benzene-[U-^{14}C] was collected in a $N_{2(l)}$ cooled, tared stopcock flask.

Benzene-[U-^{14}C] was thus obtained as a clear colorless liquid in 90% (246 mg) weight yield.

Nitrobenzene-[U-^{14}C] (4)

A custom made "reactor/extractor" apparatus (see Figure 1) was charged with $NaNO_3$ (267 mg, 3.14 mmol) and 5 ml of trifluoroacetic acid (TFA) was added. The apparatus, (with condenser removed) was connected to a vacuum line via a Claisen adaptor. One arm of the adaptor contained a rubber septum to allow for addition of reagents at a later time.

The system was cooled in $N_{2(l)}$ and evacuated. Benzene-[U-^{14}C] (204 mCi, 68 mCi/mmol, 3.0 mmol) was transferred into the reaction flask and the system was stirred at room temperature overnight. The crude nitrobenzene-[U-^{14}C] obtained in this manner was used directly in the next step.

Anilinium-[U-^{14}C] Trifluoroacetate (5)

The above reaction mixture was degassed and a suspension of 5% Pd-C (35 mg) in 1.0 ml of TFA was injected through the rubber septum in the Claisen adaptor arm. Hydrogen was admitted to atmospheric pressure on the vacuum line and the reaction was stirred at ambient temperature. When hydrogen uptake reached 104% theory (9.36 mmol, (@230 cc) radio-TLC (SiO_2, 20% EtOAc-hexane-2% NH_4OH) indicated complete reduction to the title compound. The product was >98% radiochemically pure.

All volatile materials were removed by vacuum transfer into a $N_{2(l)}$ cooled receiver leaving a residue of anilinium-[U-^{14}C] TFA salt, Pd-C, and NaO_2CCF_3. The recovered volatiles contained no radioactivity.

Benzoquinone-[U-^{14}C] (1)

The above residue of 5 was cooled to -15°. A suspension of MnO_2 in 2 ml of 6N H_2SO_4 was added via the Claisen adaptor arm and rinsed in with 2 ml of 6N H_2SO_4. Pentane was added and allowed to overflow into the collection flask as shown in Figure 1. The Claisen adaptor was removed and replaced with a condenser. The reaction temperature was raised to -8° and continuous extraction was initiated. After 30 min. the cooling bath was removed and the reaction was stirred at ambient temperature and extracted overnight.

A total of 185 mCi of 1 (90% yield from 3) having a specific activity of 67 mCi/mmol and a radiochemical purity in excess of 98% was isolated in this manner. Radio-TLC: SiO_2, 25% EtOAc-hexane; CH_2Cl_2; 90% toluene-hexane.

Hydroquinone-[U-^{14}C] (2)

In a trace run, 35 µCi of 1 was prepared as described above. The stopcock collection flask was removed from the apparatus shown in Figure 1. A suspension of 5% Pd-C in ether was rinsed in and the flask was connected to a vacuum line. The solution of 1 containing the catalyst was frozen in $N_{2(l)}$ and the system was evacuated. Hydrogen was admitted at ambient temperature and the reaction was stirred for 2 hours. The catalyst was removed by filtration affording the title compound 2 in quantitative yield. The radiochemical purity was >98%. Radio-TLC: SiO_2, 20% EtOAc-hexane.

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