

NOTE

AN IMPROVED SYNTHESIS OF CATECHOL-U-¹⁴C

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SUMMARY

The high yield, four-step synthesis of catechol-U-¹⁴C from benzene-U-¹⁴C is described. Intermediates in the preparation include phenol-U-¹⁴C and *o*-methoxyphenol-U-¹⁴C [guaiacol-(phenyl-U-¹⁴C)].

Key Words: Guaiacol-(phenyl-U-¹⁴C), catechol-U-¹⁴C, ortho-lithiation

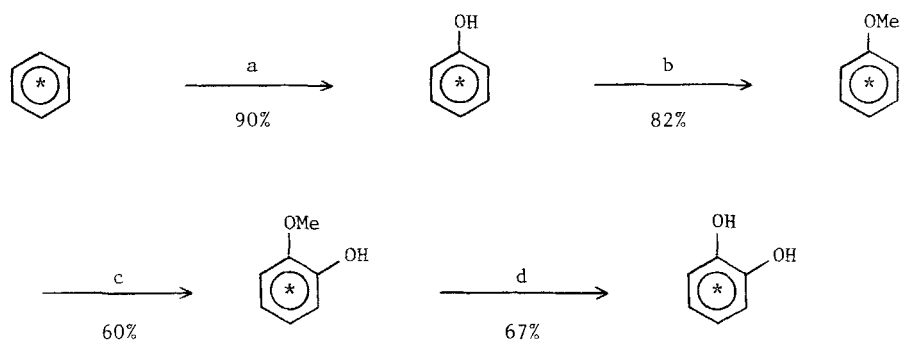
INTRODUCTION

Two of us (E. H. Chew and J. R. Heys) recently reported [1] the synthesis of catechol-U-¹⁴C and hydroquinone-U-¹⁴C and also their ¹³C-enriched analogs by a divergent procedure. The central step was nitration of the labeled phenol to produce a mixture of *o*- and *p*-nitro derivatives which were separated chromatographically and converted to labeled catechol and hydroquinone, respectively. This approach was acceptable for the occasion because we desired both labeled products.

Recently, however, we required only catechol-U-¹⁴C and we sought an approach which would provide the lone product efficiently. The following describes the result.

Benzene-U-¹⁴C was oxidized by the potent one-electron oxidant cobalt(III) trifluoroacetate in trifluoroacetic acid, using the procedure of Kochi et al. [2]. The resultant phenyl-U-¹⁴C trifluoroacetate was hydrolyzed *in situ* by addition of water and warming, to provide phenol-U-¹⁴C (see Scheme) in a yield of 90% and radio-GLC purity of $\geq 99\%$, following isolation by liquid-liquid extraction with benzene. Methylation using methyl iodide and potassium carbonate in acetone gave anisole-(phenyl-U-¹⁴C) in 75-85% yield and $\geq 98\%$ purity (radio-GLC).

Then, using a procedure similar to that of Byck and Dawson [3], based on that of Gilman [4], the labeled anisole was lithiated by *n*-butyllithium in refluxing ether. The resultant *o*-lithioanisole-(phenyl-U-¹⁴C) was transmetalated by



- a. $\text{Co}(\text{tfa})_3$, TFA; H_2O , 60°C
- b. MeI, K_2CO_3 , acetone
- c. nBuLi, Et_2O ; nBuMgCl; O_2
- d. TMSI, CHCl_3

Scheme

addition of *n*-butylmagnesium chloride, and the product mixture was exposed to oxygen while stirring. The ensuing exothermic reaction generated guaiacol-(phenyl- $\text{U-}^{14}\text{C}$), which was isolated by aqueous/organic partition and vacuum distillation to give a 60% yield of material $\geq 96\%$ pure by TLC analysis. This compound is a useful intermediate in the synthesis of various labeled natural products.

Finally, demethylation using trimethylsilyl iodide in chloroform [5] resulted in catechol- $\text{U-}^{14}\text{C}$, obtained in 67% yield after vacuum distillation and recrystallization with addition of cold diluent. A total of 206 mCi, specific activity 15.0 mCi/mmole, and radio-GLC purity of $\geq 99\%$, was obtained.

EXPERIMENTAL

Radioactivity measurements were carried out using a Packard Tricarb 2425 Liquid Scintillation Spectrometer using Liquifluor[™] (New England Nuclear); thin layer chromatographic radiochemical purity was determined using a Packard Model 7230 radiochromatogram scanner and by autoradiographic methods. Radio-GLC was performed with a Hewlett-Packard Model 5730A gas chromatograph coupled with a Packard Model 894 Gas Proportional Counter. The column used was 1.8 m x 2 mm ID

silylated glass packed with 3% SP-2250 on 100/120 Supelcoport. Ozonization was accomplished using a Welsbach Model T816 Ozonator.

Benzene-U-¹⁴C (43.4 mCi/mmol) was synthesized in these laboratories by the trimerization of acetylene-U-¹⁴C on Harshaw Vanadia catalyst V0701T 1/8. Acetylene-U-¹⁴C was obtained from Ba¹⁴CO₃ (Atomic Energy of Canada, Ltd.) by the method of Cox and Warner [6].

Phenol-U-¹⁴C

In a typical run, benzene-U-¹⁴C (595 mCi, 13.7 mmoles) was transferred (in vacuo) into a solution of cobalt(III) trifluoroacetate (12.2 g, 30.5 mmoles, prepared by the method of Tang and Kochi [7]) in trifluoroacetic acid (72 ml) and trifluoroacetic anhydride (7 ml) which had been stirred for more than 1 hr under argon. The reaction mixture was stirred overnight at room temperature and then treated with water (150 ml) and heated to 60°C for 6 hr. The crude phenol-U-¹⁴C solution was liquid-liquid extracted overnight with benzene (50-60 ml). Most of the benzene was removed by fractional distillation at atmospheric pressure. Radio-GLC (column temperature 120°C) indicated a radiochemical purity of > 99%. The yield was 532 mCi, 12.3 mmoles, 89.5%.

Anisole-(phenyl-U-¹⁴C)

In a typical reaction, phenol-U-¹⁴C (78.9 mCi, 1.8 mmoles) in a small volume of benzene was treated with acetone (20 ml), anhydrous potassium carbonate (570 mg, 4.13 mmoles), and methyl iodide (11.4 g, 81 mmoles) and refluxed under argon with stirring for 24 hr. Additional methyl iodide (8.66 g, 61 mmoles) and potassium carbonate (520 mg, 3.77 mmoles) were added and the mixture refluxed 24 hr, at which time TLC showed the reaction to be complete. The reaction was filtered and the inorganics washed twice with 6 ml of acetone. After reducing the volume of acetone by atmospheric pressure distillation, the crude product was partitioned between hexanes and water, and the combined organic phases dried (Na₂SO₄). Reduction of volume by atmospheric distillation of solvents yielded anisole-(phenyl-U-¹⁴C) (65 mCi, 1.5 mmoles, 82.4%). Purity by radio-GLC (column temperature 120°C) was determined to be ≥ 98%.

Guaiacol-(phenyl-U-¹⁴C)

To a refluxing solution of anisole (538 mCi, 18.5 mmoles) in dry ether (25 ml) under argon gas was added *n*-butyllithium in hexane (15.6 ml, 1.6 M). The reaction mixture was refluxed for 24 hr. The flask was then cooled in an ice bath, and a solution of *n*-butylmagnesium chloride in tetrahydrofuran (9.6 ml, 2.6 M) was added. The reaction mixture was stirred for 1 hr in an ice bath under argon, and afterwards a rapid stream of dry oxygen was passed through the reaction vessel. An exothermic reaction took place which caused rapid refluxing. After 1 hr the oxygen flow was discontinued, and hydrolysis of the viscous gray mixture was carried out by the addition of 10 g of ice, followed by 10 ml of concentrated HCl. The aqueous layer was extracted with ether (4 x 50 ml) and dried (MgSO₄). The ether was distilled off at atmospheric pressure to ~ 4-ml volume. Vacuum distillation yielded 323 mCi (60% yield) of guaiacol-(phenyl-U-¹⁴C). The radiochemical purity was $\geq 96\%$ as determined by TLC (SiO₂; hexanes:Et₂O 1:3).

Catechol-U-¹⁴C

In a typical run, to guaiacol-(phenyl-U-¹⁴C) (219 mCi, 7.3 mmoles) in chloroform (4 ml) under argon gas was added trimethyliodosilane (10.5 mmoles, 1.5 ml). After stirring for 24 hr at ambient temperature, the reaction was quenched with methanol (10 ml) and saturated sodium chloride solution (25 ml). The aqueous layer was extracted with ether (4 x 10 ml), and the extracts washed with sodium bisulfite solution and dried (MgSO₄). The solvent was distilled off at atmospheric pressure under argon. The crude radiochemical yield was 219 mCi. Another run from 89 mCi anisole yielded a crude product of 84 mCi. Recrystallization from benzene/hexane and dilution with cold standard yielded 206 mCi (1.513 g, 67%) catechol-U-¹⁴C with a specific activity of 15.0 mCi/mmole. Radio-GLC (program, 90-230°C at 4°C/min) revealed a purity of $\geq 99\%$. TLC-radiochromatogram scans and autoradiography indicated a purity in each case of $\geq 98\%$ (System I: SiO₂, hexanes:acetone 2:3, R_f = 0.59; System II: SiO₂, benzene:dioxane:acetic acid 90:25:6, R_f = 0.32; System III: SiO₂, ethyl acetate:methanol:acetic acid 75:20:5, R_f = 0.70). The ultraviolet-visible spectrum was identical to an authentic unlabeled standard, and the mass spectrum (70 ev) differed from

an authentic unlabeled standard only in the enhancement of the expected peaks due to the presence of isotopic carbon.

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