

SYNTHESIS OF ^{14}C -LABELED FLAME RETARDANTS. ^{14}C -LABELED-TETRABROMOPHTHALIC ANHYDRIDE AND TETRABROMOBISPHENOL-A

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SUMMARY

The multistep syntheses of tetrabromophthalic-1,2,3,4,5,6- ^{14}C anhydride 6, and 3,5,3',5'-tetrabromo-4,4'-isopropylidenedi-(phenol- ^{14}C) 11, are described. The synthesis pathway to 6 includes a novel preparation of phthalic acid-1,2,3,4,5,6- ^{14}C acid from benzene- ^{14}C . Both 6 and 11 were obtained in 9% overall radiochemical yield (based on benzene- ^{14}C).

Key words: Tetrabromophthalic-1,2,3,4,5,6- ^{14}C anhydride, Tetrabromobisphenol-A-(^{14}C -labeled), Flame retardants, Phthalic-1,2,3,4,5,6- ^{14}C acid

INTRODUCTION

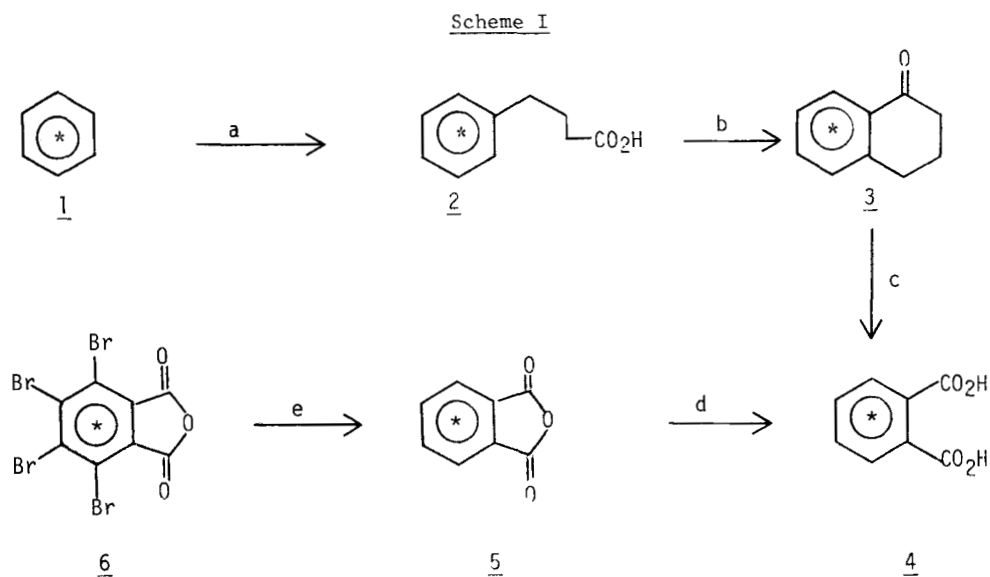
Tetrabromophthalic anhydride and tetrabromobisphenol-A are well-known flame-retarding agents primarily used in the production of flame retardant polyester, epoxy and polycarbonate resins [1]. Tetrabromophthalic anhydride has also been used as a flame retardant in wool and wood blends [2].

The finding that the widely used flame-retarding agents, tris-(2,3,-dibromopropyl)phosphate and tris-(1,3-dichloro-2-propyl)phosphate, are mutagenic [3,4] has caused increasing concern about the safety of other flame retardant materials [5]. However, tetrabromophthalic anhydride was recently found to be non-mutagenic in the Ames Salmonella/microsome mutagenicity test [6]. To facilitate toxicological, metabolic, and related studies of tetrabromophthalic anhydride and tetrabromobisphenol-A the synthesis of these compounds labeled uniformly in the phenyl moiety was required. The details of the syntheses of these compounds are reported herein.

DISCUSSION

Synthesis of tetrabromophthalic-1,2,3,4,5,6-U-¹⁴C anhydride

The pathway used for the preparation of tetrabromophthalic-1,2,3,4,5,6-U-¹⁴C anhydride is depicted in Scheme I. The sequence incorporates a rather novel synthesis of phthalic 1,2,3,4,5,6-U-¹⁴C acid in that all previously reported procedures for the synthesis of phthalic acid labeled in the ortho-phenylene ring have necessitated the use of less conveniently prepared



^a Succinic anhydride, AlCl₃, tetrachloroethane; Zn/Hg, conc. HCl, HOAc, toluene, reflux. ^b Trifluoroacetic anhydride, reflux. ^c KMnO₄, NaOH aq., reflux.

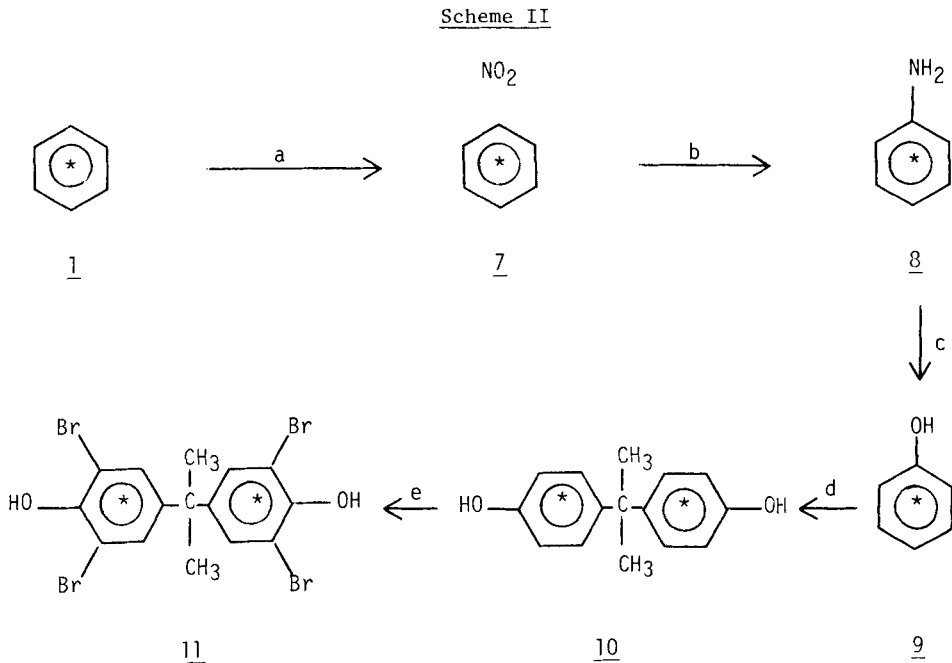
^d SOCl₂, Δ. ^e Br₂, S, ClSO₃H, reflux.

intermediates such as butadiene-¹⁴C and succinic anhydride-¹⁴C [7,8] or naphthalene-¹⁴C [9]. Thus, benzene-U-¹⁴C was converted to 2 by succinylation [10,11] followed by Clemmensen reduction [11].

Cyclization of 2 was accomplished using trifluoroacetic anhydride [12] and the resulting ketone, 3, was oxidized to 4 using potassium permanganate under basic conditions [13]. Dehydration of 4 was achieved via a standard technique using thionyl chloride [14] and the resulting anhydride, 5, was converted to 6 in 56% yield by bromination using bromine in chlorosulfonic acid [15].

Synthesis of 3,5,3',5'-Tetrabromo-4,4'-isopropylidenedi(phenol-U-¹⁴C)

The synthesis route for the preparation of 3,5,3',5'-tetrabromo-4,4'-isopropylidenedi(phenol-U-¹⁴C) is shown in Scheme II. This reaction sequence is a combination of reported methods for the preparation of bisphenol-A and



a NaNO_3 , trifluoroacetic acid. b H_2 , 10% Pd/C. c $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, Cu_2O .

d $\text{CH}_3\text{C}(\text{O})\text{CH}_3$, HCl conc., Na_2S . e Br_2 , $\text{MeOH}/\text{H}_2\text{O}$ (3:1).

tetrabromobisphenol-A. Benzene-U-¹⁴C was converted to nitrobenzene-U-¹⁴C in 89% yield [16] and 7 was subsequently hydrogenated to 8 in essentially quantitative yield. Diazotization of 8 and conversion of the diazonium salt to 9

was accomplished according to the recent method of Cohen, Dietz and Miser [17]. The reaction of 9 with acetone in concentrated hydrochloric acid using sodium sulfide as catalyst [18] afforded 10 in 40% yield. Bromination of 10 using bromine in methanol:water (3:1) [19] gave 11 in 50% yield after purification by column chromatography.

EXPERIMENTAL

Benzene-U-¹⁴C was obtained from Pathfinder Laboratories, St. Louis, Missouri. Radioactivity was determined with a Packard Model 3003 liquid scintillation counter using solutions of Liquifluor (New England Nuclear) and PCS (Amersham Corporation, Chicago, Illinois). Radiochemical purity was determined by autoradiography and radiochromatogram scanning of TLC plates. Radiochromatogram scans were obtained using a Packard Model 7201 radiochromatogram scanner. Known standards were used for comparison on TLC with the ¹⁴C-labeled compounds prepared as additional proof of their identity. Silica gel plates (Brinkmann 60F - 254) were used for TLC utilizing one of the following solvent systems as the developing solvent: (A) benzene:ethanol (9:1); (B) benzene:ethanol:acetic acid (18:2:1); (C) hexanes:acetone (4:1); (D) chloroform:methanol:acetic acid (8:2:1); (E) benzene:acetone:acetic acid (75:20:5); or (F) chloroform:methanol (97:3). The IR spectra were determined with a Beckman Acculab I, the UV spectra were recorded with a Varian Superscan III spectrophotometer, and the GC analyses were performed using a Varian Aerograph Model 1400 gas chromatograph.

4-Phenyl-U-¹⁴C-butyrlic acid (2)

A mixture of benzene-U-¹⁴C (388 mg, 5.0 mmol, 50 mCi), succinic anhydride (550 mg, 5.5 mmol), aluminum chloride (1.67 g, 12.5 mmol), and 3 ml of sym-tetrachloroethane was stirred overnight at room temperature and subsequently heated

at 50° for 5 hr. After cooling to ~ 0° (ice bath), the reaction mixture was carefully treated with ice and concentrated hydrochloric acid. The resulting aqueous solution was extracted with 2 x 50 ml of ether and the combined ether extracts treated with charcoal, filtered, and the solvent evaporated (in vacuo). The pure 3-oxo-4-phenyl-U-¹⁴C-butyric acid was precipitated with hexane and filtered, yielding 680 mg of white crystals (3.8 mmol, 38.5 mCi). Radiochemical purity (98%) was determined by TLC: solvent system A, R_f = 0.27.

To 1 g of mossy zinc amalgam, prepared in the usual manner [19], was added 6 ml of concentrated hydrochloric acid and 0.6 ml of acetic acid. The 3-oxo-4-phenyl-U-¹⁴C-butyric acid, 673 mg (3.8 mmol, 38.5 mCi), in 5 ml of toluene was added and the two-phase system was refluxed for a total of 48 hr. An additional 4 ml of concentrated hydrochloric acid was added periodically in 0.5 ml portions. Upon completion of the reaction, cold water was added to the reaction mixture and the product was extracted with 2 x 50 ml of ether. The combined ether extracts were backwashed with water and dried (Na₂SO₄). The solvent was removed (in vacuo) yielding 650 mg (33.4 mCi, 3.27 mmol) of pure 2. The radiochemical purity (> 98%) was determined by TLC: solvent system B, R_f 0.55.

1-Tetralone-1a,4a,5,6,7,8-U-¹⁴C (3)

A mixture of 2 (650 mg, 33.4 mCi) and 2 ml trifluoroacetic anhydride was refluxed under anhydrous conditions for 7 hr. The volatiles were removed (in vacuo) and the resulting oil was purified by preparative TLC on ten 2,000 μ silica gel plates/hexanes:acetone (4:1) followed by elution of the product with ether. Thus, 470 mg (28 mCi, 2.74 mmol) of pure 3 was collected, with a radiochemical purity of ≥ 95% as determined by TLC: solvent system C, R_f 0.45.

Phthalic-1,2,3,4,5,6-U-¹⁴C acid (4)

A mixture of 3 (230 mg, 1.37 mmol, 14 mCi), sodium hydroxide (230 mg, 5.75 mmol), potassium permanganate (970 mg, 6.1 mmol), and 5 ml of water was heated at 95° for 18 hr and, after cooling, the precipitated manganese dioxide was removed by filtration. The filter cake was washed with 2 N sodium hydroxide and water, and the combined filtrates were concentrated (in vacuo) to ~ 5 ml. The product was precipitated by addition of concentrated hydrochloric acid and isolated by extraction with 2 x 50 ml of ether. After removal of the ether (in vacuo), the light brown solid residue was washed twice with chloroform, yielding 155 mg (10.93 mmol, 8.2 mCi). The radiochemical purity (> 98%) was determined by TLC: solvent system D, R_f 0.40.

Phthalic-1,2,3,4,5,6-U-¹⁴C anhydride (5)

Phthalic-1,2,3,4,5,6-U-¹⁴C acid, 155 mg (8.2 mCi, 0.93 mmol), was dissolved in 2 ml of thionyl chloride and the solution was refluxed for 3 hr under anhydrous conditions. The excess thionyl chloride was removed (in vacuo) and the resulting 5, 140 mg, was taken to the next step without further purification.

Tetrabromophthalic-1,2,3,4,5,6-U-¹⁴C anhydride (6)

A mixture of 5 (140 mg, 0.93 mmol, 8.2 mCi), chlorosulfonic acid (1 ml), and powdered sulfur (50 mg) was brought to 95° and 0.1 ml of bromine was added. After stirring for 8 hr at this temperature, an additional 0.1 ml portion of bromine was added. At the end of 18 hr, the reaction temperature was raised to 195°, two more 0.1 ml portions of bromine were added, and the reaction mixture was stirred for an additional 24 hr. After cooling to room temperature, the excess bromine was removed (in vacuo) yielding a light brown solid which was first recrystallized from ethyl acetate and subsequently sublimed at 160°/0.2 mm Hg,

affording 205 mg (0.44 mmol, 4.5 mCi) of 3,4,5,6-tetrabromophthalic-1,2,3,4,5,6-U- ^{14}C anhydride at a specific activity of 10.1 mCi/mmol. The radiochemical purity ($\geq 98\%$) was determined by radiochromatogram scanning and autoradiography of the TLC plate: solvent system E, $R_f = 0.72$. The overall radiochemical yield was 9% (based on benzene-U- ^{14}C).

Nitrobenzene-U- ^{14}C (7)

Benzene-U- ^{14}C (312 mg, 4 mmol, 100 mCi) was distilled into a solution of sodium nitrate (340 mg, 4 mmol) and trifluoroacetic acid (10 ml) using standard vacuum transfer techniques. The reaction mixture was stirred at room temperature and atmospheric pressure for 20 hr. After this time the resulting reaction mixture was dissolved in 40 ml of ether and washed with 3 N sodium hydroxide until the pH of the aqueous layer remained alkaline (pH > 10). The resulting organic extract was dried (anhydrous Na_2SO_4) and evaporated at 0° (in vacuo). The oily residue was dissolved in 150 ml of ethanol, analyzed by GC, and assayed. A total of 89 mCi (89%) of $\geq 98\%$ pure 7 was isolated as an ethanol solution.

Aniline-U- ^{14}C (8)

A suspension of 100 mg of 10% Pd/C catalyst and the 150 ml of ethanol containing 7 (3.56 mmol, 85 mCi) was shaken in a Parr hydrogenation apparatus at room temperature and an initial hydrogen pressure of 57 psi. The reduction was completed in a few minutes as indicated by the uptake of hydrogen. Approximately 5 ml of 1 N hydrochloric acid was added to the reaction mixture, the catalyst was removed by filtration, and the filtrate was evaporated (in vacuo). The slightly colored residue was washed a few times with 5 ml of dry ether, yielding 425 mg (3.36 mmol, 84 mCi) of radiochemically pure ($\geq 98\%$) aniline-U- ^{14}C hydrochloride.

Phenol-U-¹⁴C (9)

Aniline-U-¹⁴C hydrochloride (435 mg, 3.36 mmol, 84 mCi) was first converted to the corresponding bisulfate via the reaction of the free base with 1 ml of 35% sulfuric acid. This salt was subsequently suspended in a total of 3.6 ml 35% sulfuric acid and 3.6 g of ice and diazotized at ~ 0° with a solution of 320 mg of sodium nitrite in 7 ml of ice water. After diazotization was completed, the excess nitrous acid was destroyed by addition of urea.

The clear solution containing the diazonium salt was quickly transferred into a flask containing a solution of 13.93 g (55.8 mmol) cupric sulfate pentahydrate in 125 ml water. Cuprous oxide (477 mg, 3.27 mmol) was added at once to the above solution with vigorous stirring at room temperature. After 5 min the evolution of nitrogen had ceased and the color of the solution changed to green.

The aqueous reaction mixture was extracted with 3 x 50 ml of ether and the combined ether extracts stirred with 3 N sodium hydroxide. The alkaline solution containing the sodium phenolate-U-¹⁴C was washed with 3 x 10 ml of ether and acidified with 1 N hydrochloric acid to pH 3. Ether extraction with 3 x 50 ml of the acidified solution afforded 60 mCi of \geq 98% pure phenol-U-¹⁴C.

4,4'-Isopropylidenedi(phenol-U-¹⁴C) (10)

A mixture of 9 (4 mmol, 60 mCi), acetone (2 mmol, 0.2 ml), concentrated HCl, and a few crystals of Na₂S (catalyst) was stirred at 50° in a 5 ml stoppered flask for 6 days. The progress of the reaction was followed by TLC of small samples of the reaction mixture using silica gel plates and a mixture of chloroform:methanol (97:3) as developing solvent. The reaction mixture was subsequently dissolved in ether and washed with saturated NaHCO₃ until neutralized. The resulting ether solution was evaporated to dryness (in vacuo) and the oily residue was dissolved

in 1 ml of CHCl₃ and purified by column chromatography [silica gel - 30 g, 2 x 20 cm, first eluent - chloroform:methanol (97:3), second eluent - chloroform]. After collecting 20 x 10 ml fractions with the first eluent (consisting of 9 and a few minor impurities) a total of 15 x 10 ml fractions of the second eluent were collected. Appropriate fractions were combined, as indicated by TLC analysis of each fraction, and the solvent removed (in vacuo) yielding 25 mCi of ≥ 98% radiochemically pure 10 as shown by TLC: solvent system F, R_F 0.35.

3,5,3',5'-Tetrabromo-4,4'-isopropylidenedi(phenol-U-¹⁴C)

Bromine (1.029 g, 6.44 mmol) was added, with stirring at room temperature, to a solution of 367.5 mg (1.61 mmol, 18.3 mCi) of 10 in 1.6 ml of methanol:water (3:1) over a period of 15 min. The temperature was kept below 35° by external cooling with a water bath. A white precipitate formed during the latter stages of the addition. The resulting orange-colored slurry was refluxed (~ 65°) for 2 hr and cooled to room temperature. The white solid was collected by suction filtration and washed with 4 x 1 ml of water. The crude product was dissolved in 1 ml of ether and purified by column chromatography, silica gel (30 g), 2 x 20 cm, using hexanes:acetone (4:1) as the eluent. A total of 25 x 5 ml fractions were collected and analyzed individually by TLC, silica gel, hexanes:acetone (4:1). Appropriate fractions were combined and the solvent removed (in vacuo) yielding a white crystalline solid. After recrystallization from hexanes:acetone (1:1), the resulting white solid was collected by filtration, yielding 500 mg, 9.00 mCi, of ≥ 98% pure 11 at a specific activity of 9.32 mCi/mmol.

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