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Research Article

An improved synthesis of [phenyl-^{14}C(U)] Lawsone

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Summary

Synthesis of ^{14}C-labelled Lawsone or 2-hydroxy-1,4-naphthoquinone was achieved by auto-oxidation of [phenyl-^{14}C(U)]α-tetralone; the latter was prepared from [^{14}C(U)] benzene in a reaction sequence more convenient than reported earlier. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: Lawsone; [phenyl-^{14}C(U)]2-hydroxy-1,4-naphthoquinone; [phenyl-^{14}C(U)]α-tetralone; [phenyl-^{14}C(U)]4-phenylbutyric acid

Introduction

The leaves of *Lawsonia inermis* L. have been used in the Indian subcontinent for decorating and dying skin and hair. Lawsone or 2-hydroxy-1,4-naphthoquinone was first isolated from the leaves of *Lawsonia inermis* L. in 1959.[1] 2-Hydroxy-1,4-naphthoquinone and related compounds have been reported to possess interesting biological activities such as antitumor, antibacterial and antifungal properties.[2–4] It is also used as a hair dye[5] and as an ultra-violet (UV) filter in sunscreen formulation.[6] 2-Hydroxy-1,4-naphthoquinone is mainly obtained from plants[7] and the synthetic preparation is generally complex.[8] Herein we present an improved synthesis of [phenyl-^{14}C(U)] 2-hydroxy-1,4-naphthoquinone from [^{14}C(U)]benzene.

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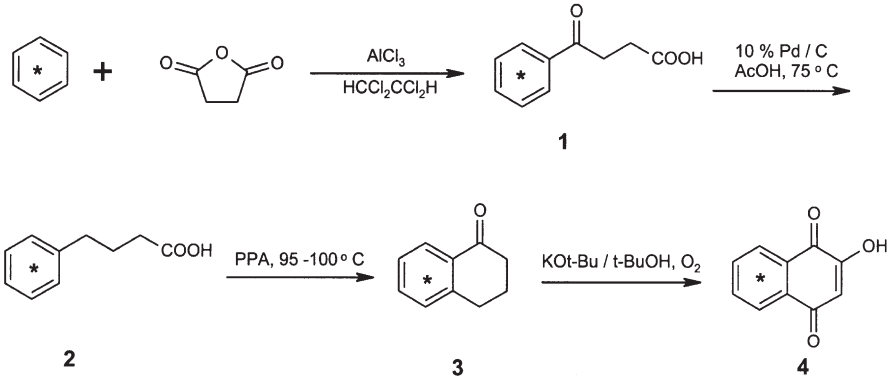
Results and discussion

The synthetic methodology adapted for [phenyl-^{14}C(U)]2-hydroxy-1,4-naphthoquinone is depicted in Scheme 1. Reaction of succinic anhydride with [^{14}C(U)]benzene in the presence of $AlCl_3$ according to the procedure reported earlier[9] yielded [phenyl-^{14}C(U)]3-benzoylpropionic acid (**1**). Compound **1** had been earlier converted to [phenyl-^{14}C(U)]4-phenylbutyric acid (**2**) by a time-consuming reduction process involving mossy zinc amalgam.[9] We have been successful in carrying out this conversion in a shorter time of 3 h by catalytic hydrogenation[10] using 10% Pd/C in glacial acetic acid at 75°C. The reduction of **1** proceeded smoothly giving a comparable yield of **2** after a simple work up. Polyphoshoric acid catalyzed cyclization[11] of [phenyl-^{14}C(U)]4-phenylbutyric acid (**2**) gave [phenyl-^{14}C(U)]α-tetralone (**3**) in good yield. α- and β-Tetralones have been reported to give 2-hydroxy-1,4-naphthoquinones by auto-oxidation[12,13] in the presence of potassium *t*-butoxide. Auto-oxidation of [phenyl-^{14}C(U)]α-tetralone (**3**) under identical conditions resulted in the formation of [phenyl-^{14}C(U)]2-hydroxy-1,4-naphthoquinone (**4**). The reaction was carried out by simply stirring a solution of **3** in *t*-butanol with potassium *t*-butoxide under an oxygen balloon and the product was isolated by acid–base work up and purified by crystallization.

Experimental

General

All reagents and solvents were purchased from Aldrich Chemical Company. ^{1}H NMR spectra were recorded on a Bruker Aspect 3000



Scheme 1. Synthesis of [phenyl-^{14}C(U)]-2-hydroxy-1,4-naphthoquinone

spectrometer and are referenced to the residual solvent peak. Mass spectral analysis was done on a Finnigan LCQ Deca spectrometer or Kratos MS25RFA spectrometer. Thin layer chromatography was performed on silica gel GF plates (Analtech) using the solvent system hexane: ether: acetic acid (7: 3: 0.1). Flash column chromatography was performed on Fluka Silica Gel 60 (220–240 mesh). The final product was identified by HPLC comparison with commercially available material on a Zorbax SB C-18 column using 0.1% trifluoroacetic acid: acetonitrile (65:35), 1 ml/min, UV 254 nm.

*[Phenyl-^{14}C(U)]4-phenylbutyric acid (**2**)*

A mixture of [phenyl-^{14}C(U)]3-benzoylpropionic acid (**1**) (250 mCi, 4.95 mmol), 10% Pd/C (0.256 g) in glacial acetic acid (6.6 ml) was hydrogenated at 75°C for 3 h. TLC indicated a complete conversion to **2**. The reaction mixture was filtered through a Celite pad which was washed with acetic acid. The filtrate and washings were combined and evaporated under reduced pressure to give a pale yellow solid (218 mCi, 87%) of **2** with a radiochemical purity of 98% as determined by TLC.

*[Phenyl-^{14}C(U)]α-tetralone (**3**)*

A mixture of **2** (218 mCi, 4.31 mmol) and polyphosphoric acid (5.8 g) was heated at 95–100°C for 25 min.The reaction mixture was cooled to room temperature, quenched with crushed ice and extracted with ether (3×30 ml). The combined ethereal extract was washed with a saturated solution of $NaHCO_3$ (1×20 ml) and dried ($MgSO_4$). Evaporation of the solvent yielded an orange–brown oily residue. Purification by silica gel flash chromatography using hexane: ethyl acetate (19:1) gave **3** (185 mCi, 84.8%) as a pale brown oil, ^{1}H NMR ($CDCl_3$): δ2.0–2.15 (m, 2 H). 2.65 (t, 2 H), 2.95 (t, 2 H), 7.26 (dd, 2 H), 7.45 (t, 1 H) and 8.0 (d, 1 H). ESI-MS ($M + H^+$): 147.

*[Phenyl-^{14}C(U)]2-hydroxy-1,4-naphthoquinone (**4**)*

To a solution of **3** (185 mCi, 3.6 mmol) in t-butanol (5 ml) was added a solution of potassium t-butoxide in t-butanol (1 M, 20 ml). The reaction flask was evacuated and the mixture was stirred under an oxygen atmosphere for 2 h. TLC of an aliquot quenched with 2 N HCl showed complete absence of **3**. The reaction mixture was acidified with 2 N HCl

(6 ml) and extracted with $CHCl_3$ (3×20 ml). The combined organic solution was extracted with a saturated solution of $NaHCO_3$ (3×10 ml). Acidification of the $NaHCO_3$ extract (128 mCi) with 6 N HCl yielded a yellow solid, which was filtered and dried. Recrystallization from ethanol–water (19:1) gave 0.26 g (75.45 mCi, 40.7%) of bright yellow needles of **4** with a radiochemical purity of 99% (HPLC), ^{1}H NMR ($^2H_6$-DMSO): δ 11.7 (s, 1 H, OH,) 7.92–8.04 (m, 2 H, H-5 and H-8), 7.77–7.88 (m, 2 H, H-6 and H-7), 6.17 (s, 1 H,H-3), DCI-MS ($M + H^+$): 175, specific activity: 50.5 mCi/mmol by mass spectral analysis.

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