

PREPARATION OF [¹⁴C]MUSK XYLOL

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SUMMARY

Carbonation of the aryl lithium obtained from 5-t-butyl-3-iodotoluene with carbon-14 labeled carbon dioxide, followed by reduction gave [ArCH₃-¹⁴C]-5-t-butyl-m-xylene. Nitration of this material gave [ArCH₃-¹⁴C]-5-t-butyl-2,4,6-trinitro-m-xylene, known as Musk Xylol. The overall yield was 32% and the product had specific activity 19.8 mCi/mmol (66 mCi/mg) and was >99% pure.

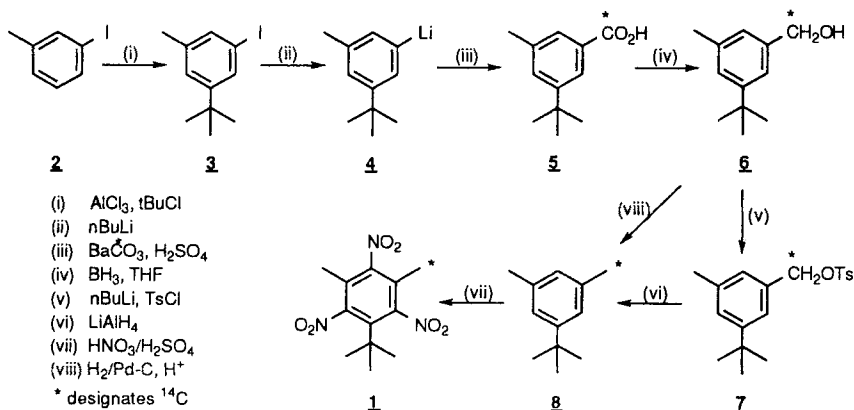
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INTRODUCTION

Musk xylol, 5-t-butyl-2,4,6-trinitro-m-xylene (**1**) is a common component in many fragrances.

To investigate the skin penetration of this substance it was prepared for the FDA labeled with carbon-14.

Chart 1



The reaction sequence selected for the preparation of carbon-14 labeled musk xylol (Chart 1) utilizes carbon-14 labeled barium carbonate as an inexpensive source of the label. The approach involves the preparation carbon-14 labeled 5-t-butyl-3-toluic acid ($[^{14}\text{C}]\text{-5}$) by carbonation of the aryl lithium compound **4**, which would be obtained from the known (1) 5-t-butyl-3-iodotoluene (**3**). Reduction of the acid **5** to 5-t-butyl-m-xylene (**8**), followed by nitration, would then afford musk xylol (**1**).

The starting material for the synthesis, **3**, was prepared in 72% yield by Friedl-Crafts alkylation of commercially available 3-iodotoluene (**2**) with t-butyl chloride, following the literature (1). Treatment of **3** with n-butyl lithium, followed by exposure to carbon dioxide (generated from barium carbonate), afforded 5-t-butyl-3-toluic acid (**5**) (2) in 46% yield, and reduction with diborane (3) produced the alcohol (**6**) in >92% yield. To obtain the 5-t-butyl-m-xylene (**8**) it was planned to reduce the tosylate **7**, however, although **7** was successfully prepared, the yield was low and the compound was found to be quite unstable. Therefore, direct hydrogenolysis of the alcohol **6** was investigated. It was found that hydrogenolysis proceeded readily in the presence of palladium on carbon in acidic medium. The product, isolated in 85% yield, was identical to an authentic sample. Trinitration of this sample with fuming nitric acid, on the scale of the radiosynthesis, afforded musk xylol (**1**) in 78% yield.

This procedure was followed (Chart 1) to prepare carbon-14 labeled musk xylol. Lithiation of 5-t-butyl-3-iodotoluene (**3**) to afford the aryl lithium **4**, followed by treatment with carbon-14 labeled carbon dioxide, obtained from carbon-14 labeled barium carbonate, gave carbon-14 labeled 5-t-butyl-3-toluic acid ($[^{14}\text{C}]\text{-5}$) in 41.6% radiochemical yield. Reduction to the alcohol **6** followed by hydrogenolysis gave carbon-14 labeled 5-t-butyl-m-xylene ($[^{14}\text{C}]\text{-8}$) in 89% yield. Nitration proceeded in 68% yield to give the final product, carbon-14 labeled musk xylol ($[^{14}\text{C}]\text{-1}$).

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary tube apparatus. NMR spectra were recorded on a Bruker WM-250 spectrometer using tetramethylsilane as internal standard. Thin layer chromatography (TLC) was carried out on Whatman silica gel 60 plates using 2% AcOEt in hexanes as the eluant. Visualization was accomplished using UV or in an iodine chamber. TLC-radioscan analyses were performed using E. Merck Silica gel 60F-254 plates on a Berthold model LB Linear Analyzer. Samples were counted using Ultima Gold as scintillant on a Packard Tri-carb 4000 liquid Scintillation spectrometer.

5-t-butyl-3-iodotoluene (2). To a mixture of 3-iodotoluene (**2**) (26.2 g, 0.124 mol) and t-butyl chloride (17 g, 0.167 mol) under N₂ at 0°C was added very slowly AlCl₃ (0.5 g, 0.004 mol). A vigorous reaction ensued. After the addition was complete the mixture was stirred at 0°C for 20 min. It was then poured into H₂O and extracted with CHCl₃. The combined extract was washed with aq. NaHCO₃, dried and evaporated. The dark red residue was distilled at 2 mm: the first fractions were unreacted **2** (13 g); the product **3** distilled at 86°C. The colorless oil (11.97 g, 72% yield) solidified upon standing. ¹H NMR (250 MHz, CDCl₃): δ 1.27 (s, 9, C(CH₃)₃), 2.28 (s, 3, PhCH₃), 7.13 (s, 1, ArH), 7.35 (s, 1, ArH), 7.5 (s, 1, ArH).

[CO₂H-¹⁴C]-5-t-Butyl-3-toluic Acid ([¹⁴C]-5). A solution of 5-t-butyl-3-iodotoluene (**3**) (485 mg, 1.81 mmol) in dry Et₂O (7 mL) was placed in a N₂ flushed 25 mL round bottomed, 2-necked flask, equipped with a rubber septum. After addition of n-BuLi (1.1 mL of 1.6 M solution, 1.76 mmol), the reaction mixture was stirred under N₂ for 2 h. The flask was then attached to a high vacuum manifold and cooled in liquid N₂. In a separate flask, a mixture of [¹⁴C]BaCO₃ (45.73 mCi, 155 mg, 0.755 mmol) and unlabeled BaCO₃ (240 mg, 1.17 mmol) was treated with H₂SO₄ (10 mL) and the CO₂ produced was transferred to the original reaction flask. The reaction mixture was allowed to come to room temperature and H₂O (15 mL) was added. The aqueous layer was separated and transferred to a 2-necked flask. The solution was treated with 5% HCl and any CO₂ liberated was absorbed into a solution of Ba(OH)₂. The reaction flask was then removed from the manifold and the precipitated product [¹⁴C]-**5** was extracted into Et₂O. Evaporation of the solvent gave a residue (19.1 mCi, 41.8% radiochemical yield) which was purified by flash chromatography (SiO₂, 5:20:80, MeOH:AcOEt:hexane), to afford 19 mCi of [¹⁴C]-**5**, m.p. 162-163°C.

[CH₂OH-¹⁴C]-5-t-Butyl-3-methylbenzyl Alcohol ([¹⁴C]-6). To a cooled (0°C) solution of [CO₂H-¹⁴C]-5-t-butyl-3-toluic acid ([¹⁴C]-**5**, 19 mCi, 1.04 mmol) in anhydrous THF (10 mL) was added 1 M BH₃ • THF (3 mL, 3 mmol). The addition caused considerable effervescence. After stirring at 0°C for 2 h and at room temperature for 2 h the reaction was found to be 80% complete (TLC). A further portion of BH₃ • THF (0.5 mL, 0.5 mmol) was added and stirring was continued for an additional hour. At this time the reaction appeared to be complete. The mixture was cooled to 0°C and quenched by the dropwise addition of THF:H₂O (1:1). The aqueous layer was saturated with K₂CO₃ and the organic layer was separated. Evaporation afforded the alcohol [¹⁴C]-**6** as a clear oil which was purified by column chromatography (SiO₂, 60:40, AcOEt:hexane) to afford 17 mCi (89.5% yield).

[CH₃-¹⁴C]-5-t-Butyl-m-xylene ([¹⁴C]-8). To a solution of [CH₂OH-¹⁴C]-5-t-butyl-3-methylbenzyl alcohol ([¹⁴C]-**6**, 17 mCi, 0.93 mmol) in abs EtOH (7 mL) in a vial equipped with a stir

bar was added Pd/C (100 mg) under N₂ and conc. HCl (1 drop). The vial was placed in a stainless steel bomb and sealed under H₂ for 2 h. Analysis by TLC indicated the reaction to be completed. The reaction mixture was filtered through a celite plug and the solvent was evaporated to give 16.9 mCi (99.4%) of the product [¹⁴C]-**8**.

[CH₃-¹⁴C]-5-t-Butyl-2,4,6-trinitro-m-xylene ([¹⁴C]-1**)**. To a cooled (0°C) mixture of fuming HNO₃ (2 mL) and conc. H₂SO₄ (4 mL) was added [CH₃-¹⁴C]-5-t-butyl-m-xylene ([¹⁴C]-**8**, 16.9 mCi, 0.92 mmol). After stirring for 3 h at room temperature there was a pale yellow solid floating in the reaction mixture. The mixture was poured carefully onto crushed ice (100 g) and extracted with AcOEt. The organic extract was washed twice with H₂O and the solvent was evaporated. The residue was purified by flash column chromatography (SiO₂, 20:80, AcOEt:hexane) to afford 11.5 mCi (67.8% yield) of pure [¹⁴C]-**1**, m.p. 111-113°C (lit. (4) 112-113°C). The specific activity, determined gravimetrically, is 19.8 mCi/mol (66 mCi/mg).

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