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# PREPARATION OF $[^{14}C]$MUSK XYLOL

Anita H. Lewin* and Usha Ramesh‡

Research Triangle Institute, P. O. Box 12194
Research Triangle Park, North Carolina 27709-2194 USA

*Author to whom correspondence should be addressed.

‡ Current Address: Medicinal Chemistry Group, Nippon Glaxo Ltd.
43-Wadai, Tsukuba-shi, Ibaraki 300-42, Japan

## SUMMARY

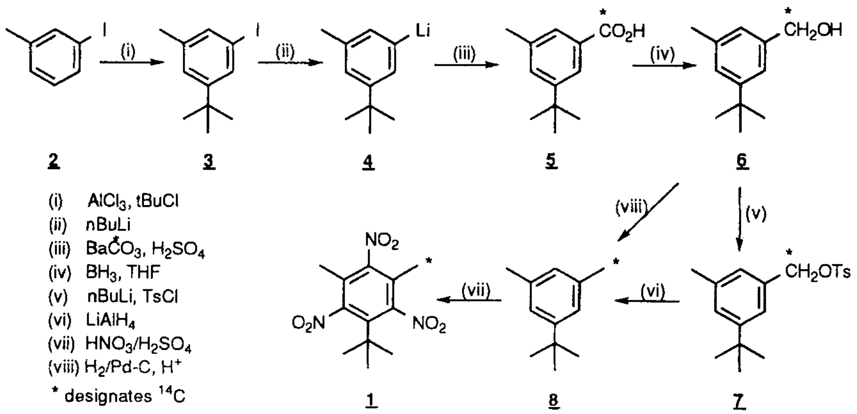
Carbonation of the aryl lithium obtained from 5-t-butyl-3-iodotoluene with carbon-14 labeled carbon dioxide, followed by reduction gave $[ArCH_3\text{-}^{14}C]$-5-t-butyl-m-xylene. Nitration of this material gave $[ArCH_3\text{-}^{14}C]$-5-t-butyl-2,4,6-trinitro-m-xylene, known as Musk Xylol. The overall yield was 32% and the product had specific activity 19.8 mCi/mmol (66 mCi/mg) and was >99% pure.

**Key Words:** musk xylol, carbon-14, 5-t-butyl-3-methylbenzyl alcohol, 5-t-butyl-3-toluic acid, 5-t-butyl-m-xylene

## 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



(i) $AlCl_3$, tBuCl
(ii) nBuLi
(iii) $Ba^{*}CO_3$, $H_2SO_4$
(iv) $BH_3$, THF
(v) nBuLi, TsCl
(vi) $LiAlH_4$
(vii) $HNO_3/H_2SO_4$
(viii) $H_2$/Pd-C, $H^+$
* designates $^{14}C$

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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 ([$^{14}$C]-**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 ([$^{14}$C]-**5**) in 41.6% radiochemical yield. Reduction to the alcohol **6** followed by hydrogenolysis gave carbon-14 labeled 5-t-butyl-m-xylene ([$^{14}$C]-**8**) in 89% yield. Nitration proceeded in 68% yield to give the final product, carbon-14 labeled musk xylol ([$^{14}$C]-**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 (3).** To a mixture of 3-iodotoluene (2) (26.2 g, 0.124 mol) and t-butyl chloride (17 g, 0.167 mol) under $N_2$ at 0°C was added very slowly $AlCl_3$ (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 $H_2O$ and extracted with $CHCl_3$. The combined extract was washed with aq. $NaHCO_3$, 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. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.27 (S, 9, $C(CH_3)_3$), 2.28 (S, 3, $PhCH_3$), 7.13 (S, 1, ArH), 7.35 (S, 1, ArH), 7.5 (S, 1, ArH).

**[$CO_2H$-$^{14}$C]-5-t-Butyl-3-toluic Acid ([$^{14}$C]-5).** A solution of 5-t-butyl-3-iodotoluene (3) (485 mg, 1.81 mmol) in dry $Et_2O$ (7 mL) was placed in a $N_2$ 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 $N_2$ for 2 h. The flask was then attached to a high vacuum manifold and cooled in liquid $N_2$. In a separate flask, a mixture of [$^{14}$C]$BaCO_3$ (45.73 mCi, 155 mg, 0.755 mmol) and unlabeled $BaCO_3$ (240 mg, 1.17 mmol) was treated with $H_2SO_4$ (10 mL) and the $CO_2$ produced was transferred to the original reaction flask. The reaction mixture was allowed to come to room temperature and $H_2O$ (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 $CO_2$ liberated was absorbed into a solution of $Ba(OH)_2$. The reaction flask was then removed from the manifold and the precipitated product [$^{14}$C]-5 was extracted into $Et_2O$. Evaporation of the solvent gave a residue (19.1 mCi, 41.8% radiochemical yield) which was purified by flash chromatography ($SiO_2$, 5:20:80, MeOH:AcOEt:hexane), to afford 19 mCi of [$^{14}$C]-5, m.p. 162-163°C.

**[$CH_2OH$-$^{14}$C]-5-t-Butyl-3-methylbenzyl Alcohol ([$^{14}$C]-6).** To a cooled (0°C) solution of [$CO_2H$-$^{14}$C]-5-t-butyl-3-toluic acid ([$^{14}$C]-5, 19 mCi, 1.04 mmol) in anhydrous THF (10 mL) was added 1 M $BH_3 \cdot THF$ (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 $BH_3 \cdot THF$ (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:$H_2O$ (1:1). The aqueous layer was saturated with $K_2CO_3$ and the organic layer was separated. Evaporation afforded the alcohol [$^{14}$C]-6 as a clear oil which was purified by column chromatography ($SiO_2$, 60:40, AcOEt:hexane) to afford 17 mCi (89.5% yield).

**[$CH_3$-$^{14}$C]-5-t-Butyl-m-xylene ([$^{14}$C]-8).** To a solution of [$CH_2OH$-$^{14}$C]-5-t-butyl-3-methylbenzyl alcohol ([$^{14}$C]-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 $N_2$ and conc. HCl (1 drop). The vial was placed in a stainless steel bomb and sealed under $H_2$ 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 [$^{14}$C]-<u>8</u>.

**[$CH_3$-$^{14}$C]-5-t-Butyl-2,4,6-trinitro-m-xylene ([$^{14}$C]-<u>1</u>).** To a cooled (0°C) mixture of fuming $HNO_3$ (2 mL) and conc. $H_2SO_4$ (4 mL) was added [$CH_3$-$^{14}$C]-5-t-butyl-m-xylene ([$^{14}$C]-<u>8</u>, 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 $H_2O$ and the solvent was evaporated. The residue was purified by flash column chromatography ($SiO_2$, 20:80, AcOEt:hexane) to afford 11.5 mCi (67.8% yield) of pure [$^{14}$C]-<u>1</u>, 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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**Correspondence may be addressed to:**

Dr. Anita H. Lewin
Chemistry and Life Sciences
Medicinal Chemistry Building
Research Triangle Institute
P.O. Box 12194
Research Triangle Park, North Carolina 27709-2194
Phone (919) 541-6691
Fax (919) 541-6499