TWO SYNTHESES OF 7,8-DICHLORO-1,2,3,4-TETRAHYDROISOQUINOLINE-1-^{14}C

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SUMMARY

Two complementary radiosynthetic routes to the potent PNMT inhibitor 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline-1-^{14}C(1) from 2,3-dichlorobenzaldehyde-formyl-^{14}C(4) are described. In the Pomeranz-Fritsch sequence isoquinoline 6 was prepared from Schiff's base 5. Catalytic hydrogenation of 6 (H_2/PtO_2) furnished 1 in 28% radiochemical yield from 4. In the aluminum chloride fusion sequence, 4 was converted via amino alcohol 7 to chloro amine 8. Treatment of the latter with aluminum chloride/ammonium chloride (fusion, 190 °C) yielded labeled 1 in 31% radiochemical yield from 4.

Key Words: 7,8-Dichloro-1,2,3,4-Tetrahydroisoquinoline-1-^{14}C, 7,8-Dichloro-isoquinoline-1-^{14}C, Intramolecular Cyclization, Aluminum Chloride Fusion, Pomeranz-Fritsch

INTRODUCTION

A number of chloro-substituted 1,2,3,4-tetrahydroisoquinolines have been found to be biologically active as inhibitors of the enzyme phenylethanolamine

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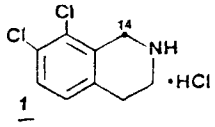
N-methyltransferase (PNMT).[1,2,3] One of the most potent of these agents, *in vivo*, is 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline hydrochloride (1, SK&F 64139-A).[4] In order to prepare carbon-14 tagged material for metabolite studies, we explored two complementary synthetic approaches both of which positioned the carbon label in the 1-position of the tetrahydroisoquinoline.[5] The common intermediate for the herein described methods was 2,3-dichlorobenzaldehyde-*formyl*-^{14}C, readily prepared from $K^{14}CN$.



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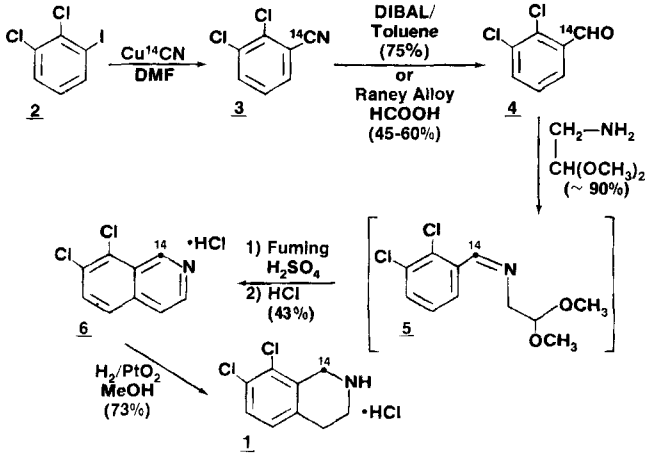
RESULTS

The classical approach is illustrated in SCHEME 1. This method, which utilized the Pomeranz-Fritsch reaction[6a] for cyclization, produced 1 in 26-28% radiochemical yield from aldehyde 4. Commercial 2,3-dichloroiodobenzene

SCHEME 1

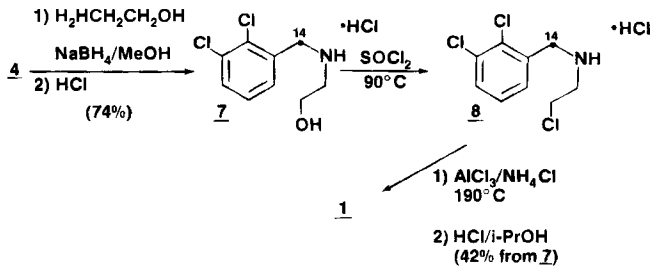


2 3 4 6 5 1

was reacted with cuprous cyanide-^{14}C (44 mCi) in DMF (3 h, reflux) to produce 3 in 95% yield. Prior study had shown that even reaction of 2 with a large excess of cuprous cyanide gave no displacement of aromatic chlorine, and produced 3 with a purity of 97% (GLC). The benzonitrile without purification was converted to 4 with Raney nickel alloy/formic acid by the method of van Es and Staskun,[9] in 50% yield. This conversion was improved in a separate experiment whereby reduction of benzonitrile 3 to aldehyde 4 was accomplished with diisobutylaluminum hydride/toluene in 75% yield. Aldehyde 4, purified by the sodium bisulfite adduct, was converted to the Schiff's base 5 by treatment with aminoacetaldehyde dimethylacetal in refluxing benzene with azeotropic water entrainment. The resulting product without purification was added to a solution of concentrated sulfuric acid containing 30% oleum by volume at 142 ± 2 °C. This acid mixture removed water and helped avoid the resinous side-products that often accompanied the formation of 6, and the cyclization yielded 7,8-dicnloro-isoquinoline-1-^{14}C (6) in 43% yield (radiopurity 96-97%). This yield was most satisfactory when compared to the poor yields reported for similar deactivated 1-unsubstituted tetrahydroisoquinolines prepared by the Pomeranz-Fritsch reaction.[6b] Catalytic hydrogenation of 6 with PtO_2 in methanol[2] produced 1 in 73% chemical yield (4.58 mCi; 28% radiochemical yield from aldehyde 4); specific activity 4.54 mCi/mmol. Radiochromatography showed a single component, purity ≥99.8%.

In the Friedel-Crafts approach to 1, SCHEME 2, aldehyde 4 was transformed into 2-(2,3-dichlorobenzyl-α-^{14}C-amino)ethanol hydrochloride by treatment

SCHEME 2



with ethanolamine in toluene followed by reduction of the crude Schiff's base by sodium borohydride in methanol. Treatment of the base with hydrogen chloride in isopropanol gave 7 (combined chemical yield from 4, 74%). The carbinol 7 was chlorinated with excess thionyl chloride at 90 °C (catalyst DMF) and the crude 8 was heated at 185-190 °C for 16 h with a mixture of aluminum chloride and ammonium chloride.[7,8] Bulb to bulb distillation of the crude product followed by hydrochloride salt formation gave 1 in 42% yield from the amino alcohol 7, (31.8 mCi; 31% radiochemical yield from aldehyde 4 (22% from $K^{14}CN$)) specific activity 12.6 mCi/mmol. Radiochromatography showed the desired component, purity 98.3% (see radioscan).

DISCUSSION

Of the two radiosyntheses evaluated to produce 1, it appears that the Pomeranz-Fritsch sequence produced material of slightly higher purity. In other respects the aluminum chloride fusion (Friedel-Crafts) is superior. The latter methodology lends itself to radiochemical manipulations, gives a higher yield, and avoids the catalytic reduction. Additionally, this Friedel-Crafts method can be applied to the preparation of other isotopically labeled tetrahydroisoquinolines. Straightforward procedures for the preparation of aminoethanol-1-^{14}C[11] and aminoethanol-2-^{14}C[12] have been developed. Utilization of these materials in the preparation of carbinol 7 would ultimately yield the tetrahydroisoquinoline, carbon labeled in the 4 and 3 positions, respectively. Similarly, use of aminoethanol-^{15}N[13a,b] in the preparation of 7 would yield tetrahydroisoquinoline-^{15}N in an efficient manner.

EXPERIMENTAL

Analytical TLC was carried out on 250 μm, 5 x 20 cm, silica gel GF plates (Analtech, Inc), using short wavelength ultraviolet light and Dragendorff

spray for visualization. Radiochromatography was performed on a Varian-Berthold scanner model 6000-10. Potassium cyanide-^{14}C was obtained from New England Nuclear. Cuprous cyanide-^{14}C was prepared from K^{14}CN by the method of Chaudhuri.[10] Raney nickel catalyst was obtained from W. R. Grace. Unless otherwise indicated, organic layers were dried over sodium sulfate.

Preparation of 2,3-Dichlorobenzonitrile-^{14}C (3).

A solution of 2,3-dichloroiodobenzene (0.783 g, 2.87 mmol, Fairfield Chemical Company) and cuprous cyanide-^{14}C (44 mCi, 0.259 g, 2.87 mmol) in DMF (20 ml) were stirred at 160 °C for 3 h. The reaction was allowed to cool to 60 °C and then quenched in water (60 ml) containing ferric chloride (0.5 g) and 6N HCl (5 ml). The mixture was filtered, and the insolubles washed with benzene, ether, and water (ca. 70 ml each). The layers were separated and the aqueous layer washed with 3 portions of ether, and the combined organic layers washed with dilute sodium bisulfite, water, and saturated sodium chloride. The organic layer was dried and evaporated to give an oil which on standing became a semi-solid (0.572 g), cohering to DMF. Thin layer chromatography (cyclohexane/ethyl acetate - 60:40 v/v) showed a single component (Dragendorff + H_2SO_4) identical to a unlabelled sample of 3. Radiopurity > 98% by TLC radiochromatography; R_f = .65.

Preparation of 2,3-Dichlorobenzaldehyde-Formyl-^{14}C (4).

I. Raney Nickel Alloy-Formic Acid Procedure.[9]

Nitrile 3 (0.55 g, unpurified) was added to formic acid (90%, 7.5 ml) and water (1.7 ml) followed by Raney nickel powder (0.57 g) and the mixture stirred at 85 °C bath temperature for 2.2 h. Although the cold runs were complete after 1.5 h, the hot run contained 62% of the starting nitrile 3 (R_f=.65) and 29% of 4 (R_f=.74) by radiochromatography (cyclohexane/ethyl acetate - 60:40 v/v)). Addition of Raney nickel alloy (0.50 g) and formic acid (90%, 7 ml) followed by reflux at 100 °C for 3 h, increased the relative amount of the aldehyde 4 to 55%.

The reaction was cooled to 50 °C and filtered through Super-Cel, and the filter pad washed with several 20 ml portions of warm methylene chloride and water. The layers were separated and the aqueous layer washed with 2 portions of methylene chloride. The combined organic layers were washed with water and evaporated to an oil. For purification, the crude aldehyde 4 was converted to the sodium bisulfite adduct by treatment with saturated sodium bisulfite solution. The thick solid which formed on stirring was collected on a sintered glass funnel and washed with ether. The bisulfite salt was placed in an Erlenmeyer flask, overlayed with ethyl ether, and treated with cold, dilute hydrochloric acid. After stirring for 10 min, the layers were separated and the organic layer dried and evaporated to yield 4 (0.25 g, 1.43 mmol, 50% from $Cu^{14}CN$). Radiopurity 98-99% by TLC radiochromatography (cyclohexane/ethyl acetate - 60:40 v/v).

II. Diisobutylaluminum Hydride Procedure.

To the nitrile 3 (1.62 g, 9.4 mmol) in toluene (20 ml) was added diisobutylaluminum hydride (8 ml, 25% in toluene) over a period of 1 min. The solution was stirred for 15 min at 25 °C and the thin layer chromatogram of the neat reaction (or an aliquot quenched with dilute HCl) showed no starting material (Petroleum ether/ether - 9:1 v/v, R_f 3 = 0.45; R_f 4 = 0.70). The reaction was cooled and cautiously treated with 1N HCl (40 ml) and ether (50 ml). After stirring for 20 min, the layers were separated and the organic layer washed with 25 ml portions of 3N HCl, water, dilute $NaHCO_3$, water and dried ($MgSO_4$). Evaporation at 30 °C gave an oil which gradually solidified, chemical yield 75%. This aldehyde was identical (IR, TLC) to the labeled material produced above. Radiopurity > 98% by TLC radiochromatography.

Preparation of 7,8-Dichloroisoquinoline-^{14}C (6) via 2,3-Dichloro-N-(2,2-dimethoxyethyl)benzyliden-α-^{14}C-amine (5). [Pomeranz-Fritsch Method][2]

The labeled aldehyde 4 produced by the Raney nickel catalyst procedure (0.250 g, 1.43 mmol) and carrier (0.250 g, 1.43 mmol) and aminoacetaldehyde dimethyl acetal (0.304 g, 2.9 mmol) in benzene (10 ml) were refluxed azeotropically until water separation was completed plus an additional 1 h (3 h total). The solvent was removed at reduced pressure, and the product was treated with benzene (20 ml) and the solution stripped to an oil. The crude product was adjusted with carrier to a specific activity of ca. 4 mCi/mmol, 0.840 g. This material was used directly in the next step. In the cold runs 5 had been purified by bulb to bulb distillation with only slight improvement in purity; bp 118-123 °C (0.2 mm Hg) pot 150-165 °C.

Benzylideneamine 5 (0.840 g, 3.21 mmol) was added portionwise to a mixture of concentrated sulfuric acid (6 ml) and fuming sulfuric acid (oleum, 2.8 ml) stirred at 140-144 °C. After stirring at 140-142 °C for 20 min, the reaction was cooled to 60 °C and poured into ice. After stirring at 0-5 °C for 10 min, the solution was filtered to remove a black tarry substance, which contained a large amount of radioactivity. The filtrate was cautiously treated with 50% sodium hydroxide solution to a pH of 10 (via pH paper). The solution was extracted with ether and benzene until radiomonitoring showed little activity remained in the aqueous layer. The organic layer was washed with sodium chloride and dried (Na_2SO_4). The resulting oil after evaporation weighed 0.41 g (2.07 mmol, 64% yield). Thin layer chromatography ($CHCl_3/CH_3OH$ - 9:1 v/v) showed a single component corresponding to 6, R_f=.77. Radiopurity 96.5%. No impurity in amount greater than 2% was detected. The free base was dissolved in acetone (10 ml), treated with Darco, warmed, and filtered. The

filtrate was treated with ethereal hydrogen chloride. The yield of white hydrochloride salt was 0.325 g (1.38 mmol, 43%).

Preparation of 7,8-Dichloro-1,2,3,4-Tetrahydroisoquinoline-1-^{14}C (1) (SCHEME 1)

Platinum oxide (0.030 g) in methanol (15 ml) was reduced with hydrogen (40 psi) in a Parr apparatus for 20 min at which time the isoquinoline hydrochloride 6 (0.324 g) in methanol (5 ml) was added.[2] The hydrogenation was carried out at room temperature at 60 psi for 1 hr. The hydrogen was replaced by nitrogen to prevent ignition, and the reaction was filtered through Super-Cel and the catalyst was washed with hot methanol. The filtrate was evaporated to 4 ml, and ether (5 ml) was added. On cooling crystals of 1 formed, and the product was collected and dried at 40 °C. Yield 0.240 g, 1.01 mmol (73%). The infrared spectrum was identical to an authentic sample of 1.[2] Specific activity 4.54 mCi/mmol (0.0191 mCi/mg). Total activity 4.58 mCi; 28% radiochemical yield from 4, 10% radiochemical yield from Cu^{14}CN. The low yield reflects losses in Raney nickel alloy reduction of 3. Radiopurity $\geq$ 99.8% by TLC radiochromatography ($CHCl_3/CH_3OH/NH_4OH$ - 80:20:0.5%), R_f=.65.

Preparation of 1 by Friedel Crafts Reaction (SCHEME 2)

Preparation of 2-(2,3-Dichlorobenzyl-α-^{14}C-amino) Ethanol Hydrochloride (7).

Aldehyde 4, prepared from 3 via diisobutylaluminum hydride reduction, (1.57 g, 9.0 mmol, radiopurity 98%; 108 mCi) in toluene (20 ml) was treated with ethanolamine (0.61 g, 10 mmol) and stirred overnight. The reaction was diluted with ether, dried over $MgSO_4$ for 2 h, and evaporated. The crude imine was dissolved in absolute methanol (20 ml) and sodium borohydride (0.379 g, 10 mmol) was added in a single portion. The reaction was stirred for 2 h at room temperature. The thin layer chromatogram (toluene/$CHCl_3/CH_3OH/NH_4OH$ - 60:40:10:0.2) and visualization (I_6Pt) showed a major component R_f = 0.3, iden-

tical to an authentic sample of 7. The reaction was cooled and treated with water (60 ml) and the product extracted with several portions of ether. The ether layers were washed with saturated sodium chloride and dried. The filtered ether layer was treated with hydrogen chloride in isopropanol until acid (congo red). The resulting white precipitate was stirred at 5 °C and collected and dried at 40 °C. Yield: 1.7 g, 6.64 mmol 74% (66% from $Cu^{14}CN$). The thin layer chromatogram of the salt was a single component on the above system. Radiopurity 99-100% by TLC radiochromtography.

Preparation of 2-(2,3-Dichlorobenzyl-α-^{14}C-amino)-1-Chloroethane Hydrochloride (8).

Amino alcohol hydrochloride 7 (12.6 mCi/mmol) (1.55 g, 76 mCi, 6.04 mmol) was treated with redistilled thionyl chloride (5 ml) at room temperature, and a vigorous reaction ensued. The reaction was stirred at room temperature for 30 min and at the end of that period DMF (0.05 g) was added. The reaction was slowly heated to 90 °C and then stirred for 30 min. The evolution of HCl had stopped by this time. The majority of the thionyl chloride was distilled (15 mm Hg) and the oily residue was reevaporated several times using anhydrous toluene to aid in the removal of residual thionyl chloride.

The residue was treated with ether (30 ml) and isopropanol (1 ml) and the cloudy solution formed a thick precipitate on stirring. After 2 h the solid was filtered, washed (ether) and dried in vacuo at 50 °C; yield 1.40 g (84%) The thin layer chromatogram (toluene/$CHCl_3$/CH_3OH/NH_4OH-60:40:10:0.2) showed the expected product 8, R_f = 0.7. Radiopurity 85% by TLC radiochromatography.

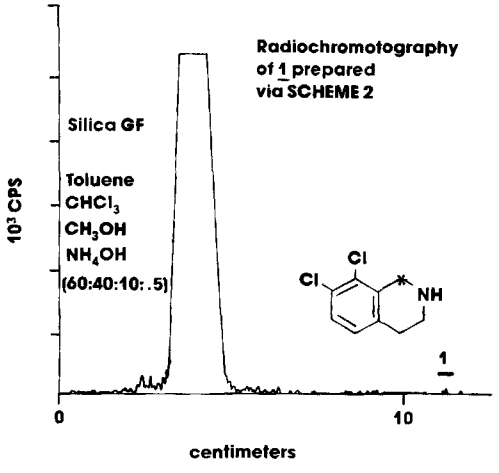
Preparation of 7,8-Dichloro-1,2,3,4-Tetrahydroisoquinoline-1-^{14}C (1). [Aluminum Chloride Fusion]

Chloroethylamine hydrochloride 8 (1.40 g, 5.1 mmol, radiopurity 80-85%) was mixed with ammonium chloride (0.30 g, 5.61 mmol) and aluminum chloride (5.0

g, 5.61 mmol) in a test tube reactor equipped with an efficient overhead glass paddle stirrer. The reactor was immersed in an oil bath preheated to 190 °C and stirred for 4 h. (Evolution of an acidic gas was noted in the first 5 min. of the reaction.)

Additional aluminum chloride (2.0 g, 14.99 mmol) was added after 4 h, and the dark mobile reaction was stirred and heated at 185-190 °C for 16 h. The reaction was cooled to 100 °C and chlorobenzene (4 ml) was added to prevent the reaction from solidifying. The reaction was allowed to cool to room temperature and pipetted into a vigorously stirred cold solution of 1 N HCl. The aqueous layer was extracted with two 50 ml portions of diethyl ether, which were discarded. The aqueous layer was cautiously treated with 19.3 M NaOH solution to pH 12, and the basic solution extracted with ether (3 X 50 ml). After drying the crude oil was distilled in a bulb to bulb still (0.1-0.2 mm of Hg; pot temperature 130-160 °C).

The distilled oil was dissolved in ether (30 ml) cooled, and treated with 4 ml of 1.5 N HCl in isopropanol. The resulting white precipitate was stirred at 10 °C for 1 h and filtered. Recrystallization from ethanol-ethyl acetate (1:1) yielded 1; 0.60 g, 2.52 mmol (42% from 7); specific activity 12.6 mCi/mmol (0.053 mCi/mg). Total activity 31.8 mCi (22% radiochemical yield from $Cu^{14}CN$). Radiopurity 98.3% by TLC radiochromatography (toluene/$CHCl_3$/CH_3OH/NH_4OH - 60:40:10:0.2), R_f=.45.



Radiolytic Decomposition of 1.

The sample of 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline-1-^{14}C was diluted with an equal weight of carrier in ethanol to a specific activity of 6.11 mCi/mmol (0.0256 mCi/mg).

The sample was stored under nitrogen at 5 °C. This sample was found to undergo radiolytic decomposition ca. 1.5%/year (via radiochromatography).

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