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A SHORT SYNTHESIS OF 5-AMINO[4-^{14}C]LAEVULINIC ACID HYDROCHLORIDE

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SUMMARY

5-Amino[4-^{14}C]laevulinic acid hydrochloride has been prepared from potassium [^{14}C]cyanide in 56% overall yield. The key step is the palladium[0] catalysed coupling of 2-phthalimido[1-^{14}C]acetyl chloride with 2-carboethoxyethylzinc iodide to give 5-phthalimido[4-^{14}C]laevulinic acid ethyl ester in 86% yield. The synthesis was carried out at high specific activity from 720mCi of starting material.

Keywords: Carbon-14, preparation, 5-aminolaevulinic acid, 2-carboethoxyethylzinc iodide

INTRODUCTION

5-Amino[4-^{14}C]laevulinic acid hydrochloride (1) was prepared previously from [1-^{14}C]glycine in six steps by Pichat et al.[1], in an average yield of only 30%[2]. A yield of 56% has been claimed[3] by a modification of this route from potassium[^{14}C]cyanide. However in our hands yields from [1-^{14}C]glycine were very variable and only up to 28%. Pichat et al.[2] have introduced an alternative route in which 2-phthalimido[1-^{14}C]acetyl chloride was reacted with the anion of tris-(trimethylsilyl)-1,1,2-ethanetricarboxylate. The adduct on acid hydrolysis underwent spontaneous bis-decarboxylation to give 5-amino [4-^{14}C]laevulinic acid hydrochloride (1) in 60% yield after chromatography. Another synthesis of 5-amino[^{13}C] laevulinic acids has been published

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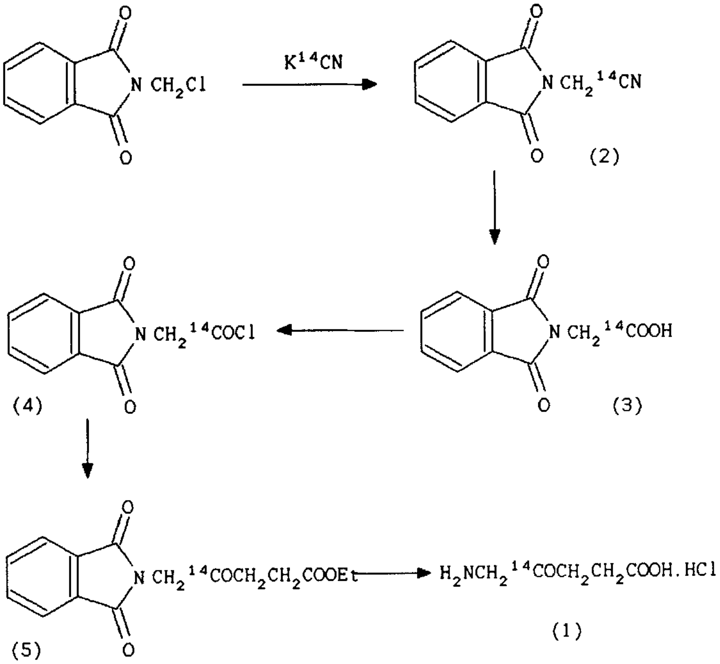
recently[6] but the yield of 5-amino [4^{13}C]laevulinic acid hydrochloride from [1-^{13}C]glycine was only 17%.

The synthesis of gamma-keto esters by coupling of 2-carboethoxyethylzinc iodide and various acid chlorides also has recently been described[4]. A synthesis of 5-amino[4-^{14}C]laevulinic acid (1) via the coupling of 2-phthalimido[1-^{14}C]acetyl chloride (4) and 2-carboethoxyethylzinc iodide was selected as a promising short and convenient alternative route (scheme 1).



Scheme 1

RESULTS AND DISCUSSION

2-Phthalimido[1-^{14}C]acetic acid (3) was prepared in 70% yield after chromatography from potassium[^{14}C]cyanide (720mCi, 56mCi/mmol) essentially by a reported method[3], and was converted into the acid chloride (4) with oxalyl chloride. Ethyl 3-iodopropionate was reacted for 1 hour at room temperature and 4.5 hours at 60°C with zinc-copper couple[5] in toluene:dimethylacetamide (15:1). A suspension of tetrakis(triphenylphosphine)palladium[0] was added followed by 2-phthalimido[1-^{14}C]acetyl chloride (4). The reaction was essentially complete after 15 minutes. 10 minutes later the product was isolated by work up and flash chromatography in 86% yield and a radiochemical purity of ≥98%. TLC analysis showed that a shorter reaction time, about 10 minutes, gave purer product which would not require chromatography. Acidic hydrolysis gave 5-amino[4-^{14}C]laevulinic acid as its hydrochloride salt (1) which was purified by simple ion-exchange chromatography to give 406mCi of material at ≥98% radiochemical purity (by cellulose TLC and by HPLC ion-exchange chromatography) in 93% yield. The overall yield from potassium [^{14}C]cyanide is 56% and from 2-phthalimido[1-^{14}C]acetic acid is 80% which is a substantial improvement upon earlier methods. The same method could be used to prepare 1-, 2- or 3-[^{14}C]labelled ethyl 3-iodopropionate. 5-amino[4-^{14}C]laevulinic acid by using appropriately labelled ethyl 3-iodopropionate.

EXPERIMENTAL

Potassium[^{14}C]cyanide was obtained from Amersham International plc. All other chemicals were purchased from Aldrich or BDH with the exception of ethyl 3-bromopropionate which was purchased from Koch-Light. All solvents were used as received unless otherwise stated. Flash chromatography was carried out using Merck silica gel 60, 0.040-0.063mm.

Nuclear magnetic resonance spectra were determined on a Hitachi Perkin Elmer R-24B spectrometer at 60MHz. Mass spectra were determined on a Jeol JMS-DX300 mass spectrometer. Radioactivity was measured on a LKB Wallac 1209 rackbeta liquid scintillation counter using Amersham ACS II scintillant. Radiochemical purity (RCP) was determined by thin layer chromatography on Merck silica gel 60 F_{254} or Merck cellulose F_{254} plates or by high performance liquid chromatography on a Spectrophysics SP8100 liquid chromatograph with Nuclear Enterprises Isoflow radioactivity detector.

Ethyl 3-iodopropionate Ethyl 3-bromopropionate (7.24g, 40mmol) and sodium iodide (9.74g, 65mmol) in butan-2-one (50ml) were stirred at 90°C for 17 hours. The reaction mixture was cooled, filtered and evaporated. The residue was purified by column chromatography eluting with hexane:ether (1:1) to yield ethyl 3-iodopropionate as an oil (8.78g, 91%). ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H, CH_3); 3.1(m, 4H, CH_2CH_2); 4.2 (q, 2H, CH_2O). GCMS (OV1, E.I., 70Ev): one peak, m/z 228 (M^+).

2-Phthalimido[1-^{14}C]acetonitrile (2) A solution of N-(chloromethyl)-phthalimide(2.88g, 14.72mmol) in warm, anhydrous dioxan (6.5ml) was added to a solution of potassium[^{14}C]cyanide (720mCi, 12.88mmol, 55.9mCi/mmol) in drymethanol (26ml). The reaction mixture was stirred at room temperature under nitrogen for 17 hours. The precipitate was filtered off and washed with warm dioxan (3 x 3ml). The filtrate was diluted with methanol to give a clear solution (683mCi). The solvent was evaporated under reduced pressure to give a solid which was dried in vacuo over P_2O_5 (2.91g). TLC (silica, diethyl ether): Rf 0.58; RCP = 80%.

2-Phthalimido[1-^{14}C]acetic acid (3) A solution of crude(2) (683mCi) in glacial acetic acid: conc. hydrochloric acid (3:1) (40ml) was heated under reflux for 1 hour. The reaction mixture was evaporated, water (2 x 10ml) was added and then evaporated.

The residue was dried in vacuo over P_2O_5. The solid (3.64g) was dissolved in THF (100ml) and evaporated onto silica gel (8g). Flash chromatography eluting with dichloromethane:methanol (19:1) going to dichloromethane:methanol:acetic acid (95:5:1) gave pure fractions which were pooled and evaporated. The residue was dissolved in THF (8ml), filtered (0.45μ) and counted (506mCi, 70%). Evaporation gave (3) as a white solid, which was dried in vacuo over P_2O_5 (2.16g). TLC (silica, dichloromethane:methanol:acetic acid (90:10:1)): Rf 0.34; RCP≥98%. Co-chromatographs with authentic material.

2-Phthalimido[1-^{14}C]acetyl chloride (4) To a stirred suspension of (3) (2.16g, 9.05mmol) in sodium-dried ether (90ml) was added oxalyl chloride (1.84ml, 21.1mmol) and DMF (2μl). After 45 minutes more oxalyl chloride

(1.5ml) and DMF (2μl) were added. After a further 45 minutes TLC (silica, diethyl ether, on the methyl ester) indicated approximately 2% acid remaining. The reaction was evaporated, dry ether (50ml) was added and evaporated to give (4) as a white solid (2.20g).

5-Phthalimido[4-^{14}C]laevulinic acid ethyl ester (5) Ethyl 3-iodopropionate (3.10g, 13.61mmol) was added to zinc-copper couple (1.35g) in sodium-dried toluene (27ml) and anhydrous dimethylacetamide (1.8ml). The mixture was stirred under argon for 1 hour at room temperature and for 4.5 hours at 60°C. A suspension of tetrakis(triphenylphosphine) palladium[0] (418mg, 0.36mmol) in dry toluene (9ml) was added and heating continued for 5 minutes. A solution of (4) (2.20g, 9.76mmol) in dry toluene (7.5ml) and washings (2 x 1.5ml) were added and heating then continued at 60°C for 25 minutes. The reaction mixture was cooled to room temperature and poured into ethyl acetate (200ml). The organic phase was washed with 1N hydrochloric acid (50ml), sat. sodium hydrogen carbonate (50ml) and brine (50ml), was dried (Mg_2SO_4) and filtered to give an orange solution which was evaporated.

TLC as above showed approximately 90% product. Flash chromatography eluting with a gradient of hexane:ether (3:1→1:3) gave pure fractions which were pooled, counted (434mCi, 86% from (3)) and evaporated to give (5) as a light yellow solid (2.34g). TLC (silica, diethyl ether): Rf 0.48, RCP≥98%. ^{1}H NMR ($CDCl_3$) (of tracer material similarly prepared) δ 1.2 (t, 3H, CH_3); 2.8 (m, 4H, CH_2CH_2); 4.1 (q, 2H, O-CH_2); 4.6 (s, 2H, N-CH_2; 7.7 (m, 4H, Ar).

5-Amino[4-^{14}C]laevulinic acid hydrochloride (1) A solution of (5) (434mCi) in glacial acetic acid: conc. hydrochloric acid (1:1) (70ml) was stirred at reflux for 20 hours. The mixture was evaporated, water (4 x 20ml) added and evaporated. The residue was suspended in water (20ml) and filtered. The filtrate was applied to a Dowex AG50W-X8 (H^+ form) column and eluted with water (500ml) followed by 2N hydrochloric acid (300ml). The clear acid fraction (405.6mCi, 93% from (5)) was evaporated and the residue dried in vacuo over P_2O_5 to give (1) as a solid (1.2253g, 7.23mmol, 55.9mCi/mmol). TLC (cellulose, n-butanol:water:acetic acid, 12:5:3); RCP=98%. HPLC (on microparticulate cation exchange resin using 0.2M sodium citrate at constant ionic strength with a pH gradient); 98.3±0.5%. The material co-chromatographed with authentic material in both of the above systems. MS (DCI with NH_3): MH^+ 143/4, MNH_4^+ 149/151.

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