Synthesis of 4-Fluoro-4' -Trifluoromethylbenzophenone Guanylhydrazone Hydrochloride Labeled With ^{14}C

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SUMMARY

Four steps were required to synthesize the title compound. This involved carboxylation, acid chloride formation, condensation, and hydrazone formation. The overall radiochemical yield was 12.5% amd the specific activity was 2.04 mCi/mmole. Because of the difficulty encountered in preparing the p-fluorobenzaldehyde-aldehyde-^{14}C, p-fluorobenzoyl chloride-carbonyl^{14}C was used for the condensation reaction.

Key Words: Carbon-14, antimalarial agent, carboxylation, acid chloride formation, condation, hydrazone formation.

INTRODUCTION

4-Fluoro-4' -trifluoromethylbenzophenone guanylhydrazone hydrochloride has been reported to possess an antimalarial (plasmodium berghei) activity in experimental animals.(1)

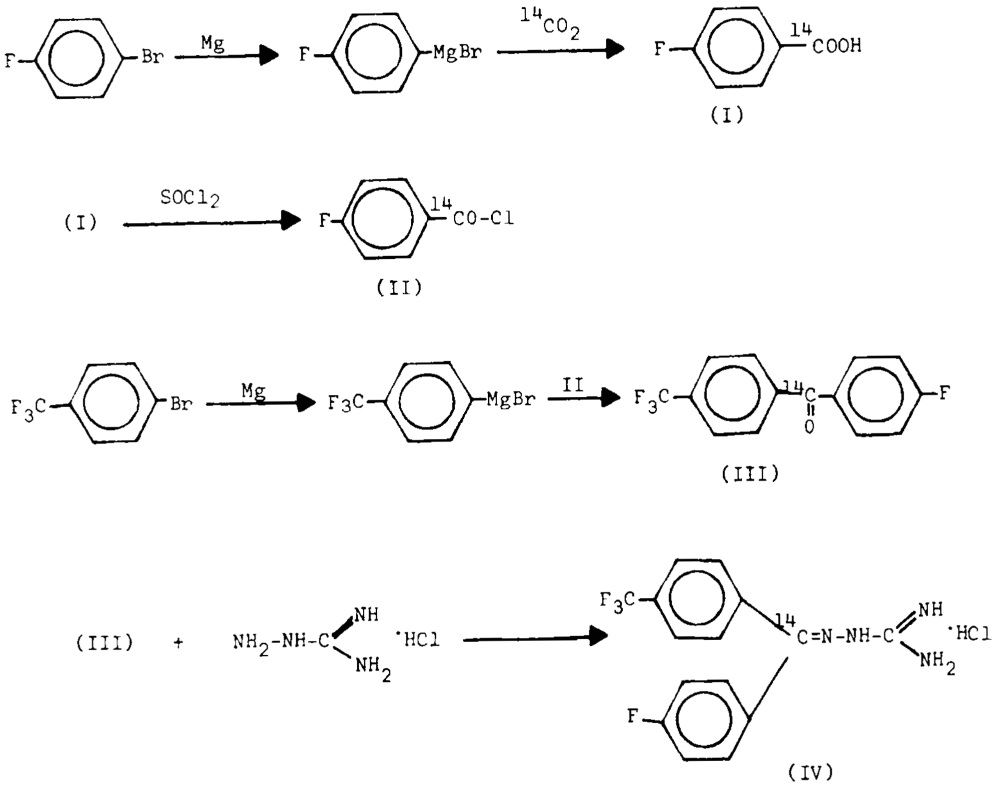
In order to determine the metabolic pathways involved and the mode of biodistribution, the carbon C-14 labeled compound was prepared.

The synthesis of 4-Fluoro-4' -trifluoromethylbenzophenone-^{14}C-guanylhydrazone hydrochloride (IV) consists first of carboxylation of the Grignard reagent, p-fluorobenzoyl magnesium bromide, by carbon dioxide-^{14}C to form p-fluorobenzoic acid-carboxyl-^{14}C (II), which in turn is reacted with thionyl chloride to yield p-fluorobenzoyl chloride-carbonyl-^{14}C (II). Compound II is condensed with trifluoromethylbenzoyl magnesium bromide, which is prepared by reacting the p-bromobenzotrifluoride with Mg in ether, to form 4-fluoro-4' -trifluoromethylbenzophenone-ketone-^{14}C (III). Compound III is finally converted

0362-4803/85/040405-05$01.00

Received September 21, 1984
Revised October 15, 1984

Chart 1



into guanylhydrazone salt (IV) by reacting with aminoguanidine hydrochloride. The synthetic scheme is outlined in Chart 1.

EXPERIMENTAL (5)

p-Fluorobenzoic Acid-carboxyl-^{14}C(2) (1)

In a three necked flask provided with a condenser and a calcium chloride tube, stirrer, dropping funnel and nitrogen inlet and outlet, was placed 1.26 g (50 mmol) of Mg turnings, 50 ml. of anhydrous ether and 100 mg. of iodine. When all of the iodine had reacted, a solution of 8.75 g (50 mmol) of 4-bromofluorobenzene in 50 ml. of anhydrous ether was added dropwise at room temperature. The mixture was then gently refluxed for one hour until a clear brown solution was formed. Titration of a 5 ml. aliquot was found to contain 0.38 mmole of p-fluorophenylmagnesium bromide per ml.

To an etheral solution of 3.0 mmole of p-fluorophenylmagnesium bromide (8 ml. of solution) was distilled 3.0 ml (20 mCi) of carbon dioxide-C^{14} at about - 190°C. The mixture was stirred at 0°C for 30 minutes. The Grignard complex was destroyed with 7 ml of 10% HCl and extracted twice with 30 ml of ether. The combined ether solutions were extracted with 10% NaOH. The alkaline solution was acidified with 5% HCl and extracted with ether. The extracts were neutralized with 5% NaHCO$_3$, and dried over anhydrous sodium sulfate. The solvent was evaporated. The product was crystallized twice from heptane. M.P. 180-181°C. (Lit. 182-184°C). The yield was 61% (284 mg; 12.2 mCi).

p-Fluorobenzoyl Chloride Carbonyl-^{14}C$^{(2)}$ (II)

A mixture of 284 mg (2.0 mmol, 12.2 mCi) of (I) and 4 ml of thionyl chloride was kept at 60-65°C for 5 hours until a clear solution was formed. The excess thionyl chloride was distilled off. The product was collected at 34°C/1 mm (Lit. 82°C/20 mm). The yield was 67% (215 mg; 8.17 mCi). The product was diluted with non-labeled p-fluorobenzoyl chloride to yield 1.285 g (8.0 mmol).

4-Fluoro-4'-trifluoromethylbenzophenone-ketone-^{14}C$^{(3)}$ (III)

In a three-necked flask equipped with a condenser and calcium chloride stirrer, dropping funnel and inlet-outlet of nitrogen gas, was placed 290 mg (12 mmol) of Mg turnings, 25 mg of iodine and 12 ml of anhydrous ether. As soon as the color of the iodine disappeared, a solution of 2.7 g (12 mmol) of p-bromobenzotrifluoride in 12 ml of anhydrous ether was added dropwise at room temperature. A clear red-brown solution was formed in about 30 minutes. Titration of a 5 ml aliquot was found to contain 0.45 mmole of 4-trifluoromethylphenyl magnesium bromide per ml of solution.

In another three-necked flask equipped with a condenser, stirrer, and dropping funnel was placed 8.0 mmole of 4-trifluoromethylphenyl magnesium bromide (18 ml of solution). To this stirred solution was added dropwise 1.285 g (8.0 mmol) of (II) in 15 ml of anhydrous ether at -78°C (by means of acetone-dry ice bath). The cooling bath was removed and the mixture was allowed to warm to room temperature, then was refluxed for 2 hours, and allowed to stand at room temperature for 3 days. The mixture was poured into 20 ml of 5% HCl. The ether was separated. The aqueous layer was extracted twice with 20 ml of ether. The combined etheral solutions were washed with 5% $NaHCO_3$ and were dried over anhydrous sodium sulfate. The extracts were evaporated. The product was crystallized from ether-heptane (10:90) solution and recrystallized from heptane. M.P. 99°C. (Lit. 98-100°C).$^{(1)}$

The yield was 44% (944 mg; 3.60 mCi). I.R. absorption λ nujal max. 5.8 µ (C=O).

4-Fluoro-4'-trifluoromethylbenzophenone-ketone-^{14}C guanylhydrazone Hydrochloride $^{(4)}$ IV

A mixture of 670 mg (2.5 mmol, 2.56 mCi), 660 mg (6.0 mmol) of aminoguanidine hydrochloride, and 5 ml of 2-ethoxyethanol was kept at 100-105°C for 5 hours. Three drops of glacial acetic acid was added to catalyze the reaction. The mixture was cooled to room temperature and the solvent was removed in vacuo until a thick slurry remained. To this residue was added 5 ml of water and 5 drops of 10% HCl, then filtered. The crystal was formed in 1-2 days from the filtrate, and was recrystallized from ethanol:water (1:6) solution with 5 drops of 10% HCl. The product was collected, washed with a small amount of cold water, then benzene. M.P. 261-263°C (Lit. 261-263°C).$^{(1)}$ The yield was 62% (562 mg; 1.59 mCi), at 1.02 mCi/mmol. The radiochemical purity was 99% as demonstrated by thin layer chromatography on Silica gel G employing 10% NH_4OH-Methanol as the solvent.

The compound was identified by comparing the mp, ir, uv spectra and the data with those of an authentic sample.$^{(1)}$

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5. Melting points are obtained on a Fisher-Johns hot stage and are corrected. Ir spectra are recorded on a Perkin-Elmer 337 grating ir spectrophotometer. Type QIF silica gel plates from Quantum Industries are used for tlc development. UV spectra are recorded on a Bausch & Lomb Spectronic 505 spectrophotometer. Ir, Uv, spectra and tlc are all appropriate. Radiochromatograms are recorded on a 4TT Tracer-Lab Scanner using tlc plates. Radioassays are performed using a Packard Tri-Carb Liquid Scintillation Spectrometer, Model 3320.