SYNTHESIS OF 4-CHLORO-N-FURFURYL-5-BUTOXYMETHYLENE-SULFAMOYLANTHRANILIC ACID-[$^{14}CO_2H$] (FFBu-^{14}C)*

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SUMMARY

FFBu, a pro-drug of the diuretic furosemide, has been prepared by reaction of the latter with n-butanol and formaldehyde. A much improved synthesis of furosemide-[$^{14}CO_2H$] is described based on a new, high yielding route to the key intermediate, 2-fluoro-4-chlorobenzoic acid-[$^{14}CO_2H$]. This intermediate is prepared by selective lithiation, followed by carbonation, of 2-fluoro-4-chlorobromobenzene. Modified reaction conditions and workup procedures resulted in much improved yields in the reaction sequence.

Key Words: Selective lithiation, carbonation

INTRODUCTION

FFBu-^{14}C (9) can be prepared from furosemide-[$^{14}CO_2H$] (8) in about 20% yield by reaction of the latter with n-butanol and aq. formaldehyde. FFBu-^{14}C is a labile pro-drug of (8) which decomposes rapidly in solution to regenerate (8). Purified samples of (9) are always contaminated with traces of (8) which must be generated during the workup procedure. In light of the low yield conversion of (8) to (9), and the difficulty in working with (9), it was essential to develop a synthetic route which afforded (8) in high radiochemical yield and utilized inexpensive labeled starting materials.

A recent report[1] describes the preparation of (8) in 4.5% overall

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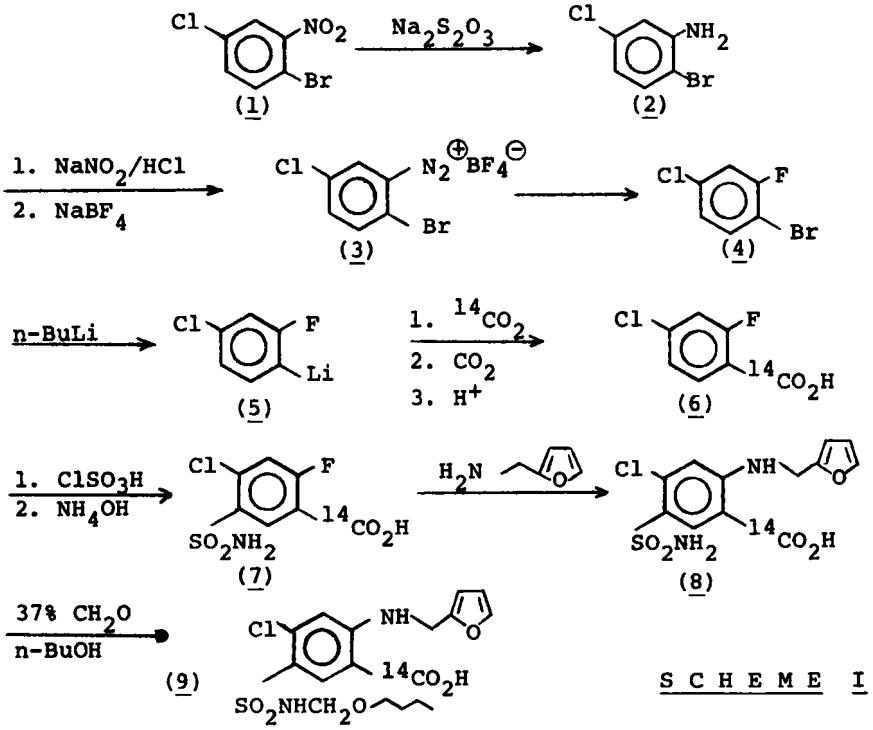
radiochemical yield in which $K^{14}CN$ is used in a modified Sandmeyer reaction to prepare the key intermediate 2-fluoro-4-chlorobenzoic acid-[$^{14}CO_2H$] (6) in 24% radiochemical yield. The procedure described here affords (6) and (8) in 87.5% and 44% yield respectively.

DISCUSSION

The most efficient and economical method of incorporating ^{14}C is by carbonation of a suitable precursor. It occurred to us that, at low temperature, it might be possible to lithiate[2] 2-fluoro-4-chlorobromobenzene (4) selectively at C-1 and carbonate the resulting aryl lithium compound (5) to produce 2-fluoro-4-chlorobenzoic acid-[$^{14}CO_2H$] (6) directly. Conversion of (6) to (8) and (9) could then be effected by previously described methods[4,5].

The required precursor (4) was prepared by dithionite reduction of 2-bromo-5-chloronitrobenzene (1) to the amine (2) followed by diazotization and Schiemann reaction as outlined in Scheme 1.



SCHEME I

Experiments with unlabeled CO_2 showed that the desired acid (6) was, indeed, the exclusive product when (4) was lithiated at -90° to -100° and carbonated at -78°. The yield of (6) was only 35%, however. In the hot reaction, (6) was obtained in 87.5% yield and >98% purity by the simple expedient of reacting $^{14}CO_2$ with a large excess of (5)**, then quenching the reaction with unlabeled CO_2.

Treatment of (6) with chlorosulfonic acid at reflux followed by addition of conc. NH_4OH to the crude chlorosulfonate gave (7) in 60% yield and >90% purity. Crude (7) was then heated at 80° with a large excess of furfurylamine for two hours and poured into water. The resulting product (8) was water soluble, while the excess furfurylamine could be completely removed by ether extraction. Acidification of the aqueous phase with acetic acid followed by ether extraction afforded (8) in 90% yield and >95% purity.

In our experience, when working on micro or semi-micro scale, it is always preferable (if not essential) to remove impurities and isolate products from reaction mixtures by extraction procedures. Precipitation and filtration of products is always less efficient on this scale. The workup procedure described above increased the yield of (8) from 57%[1] to 90%.

Purified (8) was dissolved in n-butanol and treated with 37% aqueous formaldehyde. Heating at 80° for 2 hours, followed by column chromatography of the reaction mixture, afforded pure FFBU-^{14}C (9).

The appropriate fractions were diluted with toluene (to azeotrope out the acetic acid used in the eluting solvent mixture) and evaporated to dryness at reduced pressure. Examination (tlc) of the solid residue showed that decomposition had already taken place to regenerate about 10% of (8). Two crystallizations from acetone-hexane afforded (9) of >95% purity, the only contaminant being a trace of (8).

** The experiment was designed to yield a product having a specific activity of 5-10 mCi/mmol. Radiochemical yields with smaller excesses of (5) were therefore not investigated. However, we believe that an excess of 2:1 or even less would be adequate to consume all the $^{14}CO_2$, thus affording a product of higher specific activity.

Subsequent chromatographic fractions contained a mixture of (8) and (9) and finally pure (8). These fractions could be combined and recycled to generate additional (9).

The reactions and workup conditions described resulted in greatly increased yields of (8) and modest yields of (9). In addition, the selective carbonation of the polyhalogenated (4) should be useful in preparing a variety of substituted ^{14}C labeled benzoic acids.

EXPERIMENTAL

Barium carbonate-^{14}C (58.2 mCi/mmol) was purchased from ICN Corp. All solvents were reagent grade and, except as noted, were used without purification. Radiochemical purity was determined by radio-tlc using a Packard Model 7201 Radiochromatogram Scanner. Radioactivity was determined using a Packard Tricarb Model 574 Liquid Scintillation Counter. C-13 nmr spectra were obtained using a Brucker WH90 spectrometer. Chemical shifts and coupling constants are reported in ppm.

2-Bromo-5-Chloroaniline (2)

A solution of 2-bromo-5-chloronitrobenzene (24 g; 101 mmol) in methanol (600 ml) was cooled to 0° and treated with sodium dithionite (20 g; 115 mmol) followed by 120 ml of water. The yellow reaction mixture was stirred for 15 minutes at 0°, 30 minutes at room temperature and 15 minutes on a steam bath. By this time the yellow color had dissipated resulting in a white, heterogeneous mixture. Most of the methanol was removed *in vacuo*, concentrated ammonium hydroxide (150 ml) was added, and the product was extracted with ethyl acetate-ether (1:1; 300 ml). The organic phase was washed with water (2x) then brine, dried over sodium sulfate and taken to dryness. The residue (10.5 g; 50% yield) was about 95% pure by tlc (5% ethyl acetate-hexane) and was used without purification; ms M^+ 205; 126 (-Br); 90 (-Br, -Cl).

2-Fluoro-4-Chlorobromobenzene (3)

To (2) (15 g; 72.8 mmol) was added 5N HCl (50 ml). The resulting gum was broken up by heating on a steam bath for several minutes, giving a suspension

which was cooled to 0° and treated with a solution of sodium nitrite (5.52 g; 80 mmol) in water (20 ml). The reaction was stirred until all the solid dissolved and then was filtered to remove an orange oil which had formed. To the clear yellow solution thus obtained was added sodium tetrafluoroborate (17.3 g; 157 mmol) in water (50 ml). After stirring for one hour the precipitated diazonium tetrafluoroborate was filtered and dried (14.8 g; 67% yield).

The diazonium salt was heated with a luminous flame until gas evolution ceased. The dark liquid residue was taken up in chloroform, washed with 10% NaOH, water and dried over sodium sulfate. The solution was filtered and the chloroform was evaporated at reduced pressure leaving a dark liquid residue. Distillation afforded the product as a colorless liquid (5.7 g; 37% yield); $bp_{.5mm/Hg}$ 26-29°; C-13 nmr ($CHCl_3$) C_1d, 107.46, J_{C_1-F}=0.94; C_2d, 159.19, J_{C_2-F}= 11.09; C_3d, 117.47, J_{C_3-F}=1.14; C_4d, 134.33, J_{C_4-F}=0.33; C_5d, 125.78, J_{C_5-F}=0.1; C_6s, 134.17; tlc: (5% acetone-hexane) one spot.

2-Fluoro-4-Chlorobenzoic acid-[$^{14}CO_2H$] (6)

A dry 250 ml side-arm flask containing (3) (2.25 g; 10.77 mmol) was connected to a vacuum line, cooled to -78° and evacuated. Ether (50 ml) was distilled from $LiAlH_4$ into the reaction vessel, the temperature was lowered to -90° to -100° (ether/$N_{2(l)}$), and n-BuLi (5 ml of a 1.6M hexane solution; 8 mmol) was injected through a rubber septum in the side arm. After stirring for 20 minutes, $Ba^{14}CO_3$ (50 mCi; 58.2 mCi/mmol; 0.86 mmol) (in a second side-arm flask connected to the vacuum line through a Drierite tower) was acidified with H_2SO_4 and the liberated $^{14}CO_2$ was distilled into the reaction vessel. The temperature was raised to -78° and after 5 minutes the reaction was quenched with a large excess of unlabeled CO_2. Labile radioactivity was removed by distillation into a trap cooled with $N_{2(l)}$. The still basic reaction mixture was poured into water and extracted with ether to remove neutrals.

Acidification of the aqueous phase with 10% HCl and ether extraction afforded the product (43.75 mCi; 6.52 mCi/mmol) in 87.5% radiochemical yield and >99% purity (radio-tlc: hexane-ether-acetic acid 70:30:2); C-13 nmr (of unlabeled product from analogous cold reaction) (acetone) C_2d, 162.92,

J_{C_2-F}=11.6; -CO_2H d, 164.57, J_{CO_2H-F}=0.16.

2-Fluoro-4-Chloro-5-Sulfamoylbenzoic Acid-[$^{14}CO_2H$] (7)

To neat (6) (42 mCi; 6.52 mCi/mmol) was added distilled chlorosulfonic acid (10 ml). After heating at reflux for 2.5 hours the reaction was pipetted carefully over ice and extracted with ether. The ether extract was dried over sodium sulfate, filtered and evaporated to dryness at reduced pressure. The residue was cooled to 0° and treated with conc. ammonium hydroxide (10 ml). The reaction was stirred for 3 hours, acidified with conc. HCl, and extracted with ether. The ether extract was dried over sodium sulfate and filtered to afford (7) (25 mCi; 6.52 mCi/mmol) in 60% yield and >90% purity (radio-tlc: hexane-ether-acetic acid 45:45:8).

4-Chloro-N-Furfuryl-5-Sulfamoylanthranilic Acid-[$^{14}CO_2H$] (8)

Crude (7) (25 mCi; 6.52 mCi/mmol) was stirred for two hours at 80-90° with freshly distilled furfurylamine (15 ml). After cooling to room temperature the reaction mixture was poured into water and the excess furfurylamine was removed by extraction into ether. Acidification of the aqueous phase with acetic acid (20 ml) followed by ether extraction afforded (8) (22.6 mCi) in 90% yield and >95% purity (radio-tlc: hexane-ether-acetic acid 45:45:8). A product of >99% purity was obtained by crystallization from acetone-hexane (19.55 mCi; 6.54 mCi/mmol). Column chromatography (SiO_2; hexane-ether-acetic acid 45:45:8) of the mother liquors afforded an additional 1.9 mCi of pure (8). Total radiochemical yield of (8) at >99% purity was 85.5%.

4-Chloro-N-Furfuryl-5-Butoxymethylene-Sulfamoylanthranilic Acid-[$^{14}CO_2H$] (FFBu-^{14}C) (9)

A solution of 37% aq. formaldehyde (1.25 ml) in n-butanol (7 ml) was added to (8) (19 mCi; 6.54 mCi/mmol) and the reaction was stirred at 80° for two hours. After cooling to room temperature, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in a small volume of acetone and applied to a silica gel chromatography column. Elution with hexane-ether-acetic acid (45:45:10) afforded pure FFBu-^{14}C followed by a mixture of (8)

and (9) and finally pure (8). The FFBu-^{14}C fractions were taken to dryness and the residue was crystallized from acetone-hexane to give (9) (3.86 mCi; 6.65 mCi/mmol; 195 mg; >95% pure) containing only a trace of (8).

REFERENCES

1. Liebman A. A., et al. - J. Labelled Compounds X, No. 7, 399 (1974).
2. Murray A., et al. - J. Am. Chem. Soc. 62: 1037 (1940).
3. Gilman H., et al. - ibid 62: 2327 (1940).
4. Sturm K., et al. - Chem. Ber. 99: 328 (1966).
5. Siedel W., et al. - ibid 99: 345 (1966).