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Selective Lithiation/Carbonation of Polyhalobenzenes: An Improved Synthesis of Furosemide-7-^{14}C

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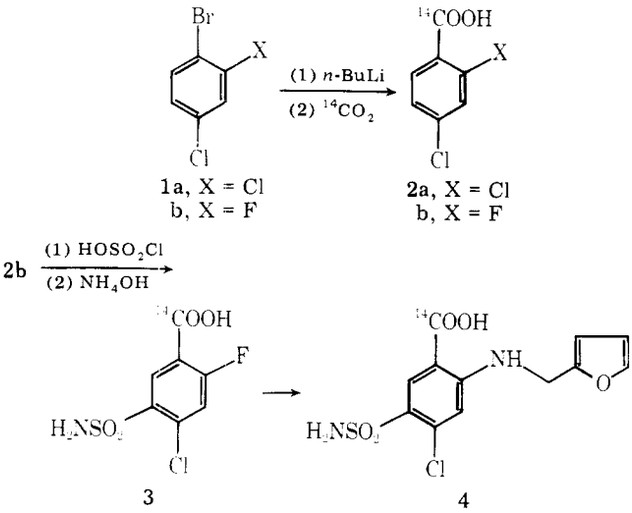
Received June 19, 1978

Furosemide (4) usually has been prepared from 4-chloro-2-fluorobenzoic acid (**2b**) by chlorosulfonation and ammonolysis to the sulfonamide (**3**) followed by reaction with furfurylamine.[1-3] In an earlier synthesis of furosemide-7-^{14}C,[4] the required labeled intermediate **2b** was prepared from 4-chloro-2-fluoroaniline and dipotassium diamminocupricyanide-^{14}C by a modified Sandmeyer reaction followed by hydrolysis of the resulting 4-chloro-2-fluorobenzo-^{14}C-nitrile.



The more direct preparation of **2b** from 4-chloro-2-fluorobromobenzene (**1b**) by butyllithium exchange and carbonation was not attempted because the closely related 2,4-dichlorobromobenzene (**1a**) reportedly did not afford 2,4-dichlorobenzoic acid (**2a**) by that procedure.[5]

We now report that, in fact, both **1a** and **1b** do undergo selective lithiation/carbonation to afford the corresponding acids **2a** and **2b** in high yields. The conversion of carbon-14 labeled **2b** to furosemide-7-^{14}C (**4**) by a simplified version of the earlier process[4] is also described.

Reaction of **1a**[6] in ether with *n*-butyllithium at −80 °C for a short time followed by carbonation at −80 °C with carbon-14 dioxide afforded the acid **2a** in 98% yield based on carbon-14 dioxide. Similarly, lithiation/carbonation of **1b**[7] gave **2b** in quantitative radiochemical yield. Treatment of the labeled **2b** with chlorosulfonic acid followed by concentrated ammonium hydroxide afforded labeled **3** in 91.5% yield (crude). Reaction of the crude **3** with furfurylamine gave crude furosemide-7-^{14}C (**4**) in 32% yield.

Experimental Section

Melting and boiling points are uncorrected. Radioactivity was measured by the liquid scintillation technique using a Packard Tricarb Model 2010 spectrometer. Radiochemical purity was determined on thin-layer chromatograms with a Packard Model 7201 radiochromatogram scanner system. Spectra were recorded on standard instruments. All reactions were conducted under nitrogen unless otherwise indicated.

2,4-Dichlorobenzoic-7-^{14}C Acid (2a). A solution of 1-bromo-2,4-dichlorobenzene[8] (**1a**; 1.02 g, 4.5 mmol) in anhydrous diethyl ether (15 mL) contained in an ordinary round-bottom flask was frozen with liquid nitrogen, and a solution of *n*-butyllithium in hexane (3 mL, 2.8 mmol) was added and frozen. The flask was evacuated and then warmed to −80 °C with stirring. From 2 to 5 min after the reaction mixture became a homogeneous solution, it was refrozen with liquid nitrogen and carbon-14 dioxide (1.51 mmol) was transferred into the flask. The mixture was warmed to −80 °C, stirred for 20 min, made alkaline with 0.9 N sodium hydroxide solution (10 mL, 9 mmol), and thoroughly extracted with ether, which was discarded. Acidification of the aqueous phase with dilute sulfuric acid and extraction with ether afforded **2a** (282 mg, 1.48 mmol), 98% yield based on carbon-14 dioxide. Nonradioactive material prepared by the same procedure from ordinary carbon dioxide was found to be identical with authentic 2,4-dichlorobenzoic acid by melting point, IR, and TLC (silica gel; dichloromethane-ethyl acetate–acetic acid, 8:1:1 v/v/v).

4-Chloro-2-fluorobenzoic-7-^{14}C Acid (2b). In the same manner, 4-chloro-2-fluorobromobenzene[7] (**1b**; 440.3 mg, 2.1 mmol) was metalated with *n*-butyllithium (1.17 mmol) and carbonated with carbon-14 dioxide (1.08 mmol; specific activity 59.1 mCi/mmol) to afford **2b** in quantitative yield (209 mg). The product was radiochemically pure (TLC on silica gel; benzene-ethyl acetate–formic acid, 8:1:1 v/v/v). Material prepared with ordinary carbon dioxide in the same way was identical with authentic 4-chloro-2-fluorobenzoic acid.[1]

4-Chloro-2-fluoro-5-sulfamoylbenzoic-7-^{14}C Acid (3). The dry 4-chloro-2-fluorobenzoic-7-^{14}C acid was heated with freshly distilled chlorosulfonic acid (0.635 mL, 9.7 mmol) at 155 °C for 2 h. When cool, the entire reaction mixture was diluted with dichloromethane (4 mL) and transferred to a 10 mL addition funnel using additional dichloromethane (4 mL). The addition funnel was attached to a 100-mL flask containing concentrated ammonium hydroxide (4 mL) cooled to −30 °C, the dichloromethane solution was added dropwise very slowly with stirring, and the mixture was allowed to warm to room temperature. Evaporation of the dichloromethane under reduced pressure left an aqueous phase which was transferred to a liquid–liquid extractor, acidified with 6 N hydrochloric acid (1 mL), and extracted with diethyl ether for 20 h to afford the crude product (**3**; 248 mg, 0.98 mmol). Thin-layer chromatography (silica gel; ethylene dichloride–ethyl acetate, 2:3) showed the product to be approximately 60% of **3**, which was used in the next step without purification.

4-Chloro-*N*-furfuryl-5-sulfamoylanthranilic-7-^{14}C Acid (Furosemide-7-^{14}C; 4). The crude **3** (248 mg) was stirred with dioxane (1 mL) and freshly distilled furfurylamine (0.32 mL) at 110 °C for 2.5 h. Concentration of the reaction mixture under reduced pressure left a dark brown residual oil which was stirred vigorously with ethyl acetate (3 mL) and extracted six times with water (3 mL). Concentration of the aqueous extracts left a residue which was crystallized from methanol–water, 1:1 (4 mL), to give crude **4** (114.5 mg; radiochemical purity 95% by TLC using silica gel plates developed with acetonitrile–acetic acid, 99:1; R_f 0.68). Recrystallization of 15.1 mg of crude **4** with 20.2 mg of unlabeled furosemide (**4**) from methanol–water, 1:1 (2 mL), afforded 23 mg of radiochemically pure **4** of specific activity 57.2 μCi/mg.

Registry No.—**1a**, 1193-72-2; **1b**, 1996-29-8; **2a**, 67700-16-7; **2b**, 54416-83-0; **3**, 54416-84-1; **4**, 54416-85-2; $^{14}CO_2$, 51-90-1; furfurylamine, 617-89-0.

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