SYNTHESES OF 2-(DIACETOXYMETHYL-^{14}C)-5-NITROFURAN AND CARBON-14 LABELED NITROFURAZONE

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SUMMARY

A new method for the microscale syntheses of carbon-14 labeled 5-nitrofuran derivatives of high specific activities was developed. Ethyl 2-furancarboxylate-carboxy-^{14}C (**3**) was prepared in an improved yield from $Ba^{14}CO_3$. 2-Furancarboxaldehyde-formyl-^{14}C (**5**) was prepared by reduction of the ester **3** followed by γ-MnO_2 oxidation of 2-(hydroxymethyl-^{14}C)furan (**4**). 2-(Diacetoxymethyl-^{14}C)-5-nitrofuran (**7**), an immediate precursor of many radiolabeled 5-nitrofuran drugs, was prepared in a new two-reaction one-flask procedure from 2-furancarboxaldehyde-formyl-^{14}C (**5**) in 7.3% overall radiochemical yield from $Ba^{14}CO_3$. Carbon-14 labeled nitrofurazone (**8**) was then prepared from **7**.

Key Words: Carbon-^{14}C dioxide, γ-Manganese dioxide, 2-(Diacetoxymethyl-^{14}C)-5-nitrofuran, 5-Nitro-2-(semicarbazonomethyl-^{14}C)furan, Nitrofurazone.

INTRODUCTION

The human and/or veterinary uses of 5-nitrofuran derivatives have been reviewed.[1,2] For our research into the metabolism and disposition of 5-nitrofuran derivatives, the syntheses of carbon-14 labeled 5-nitrofuran

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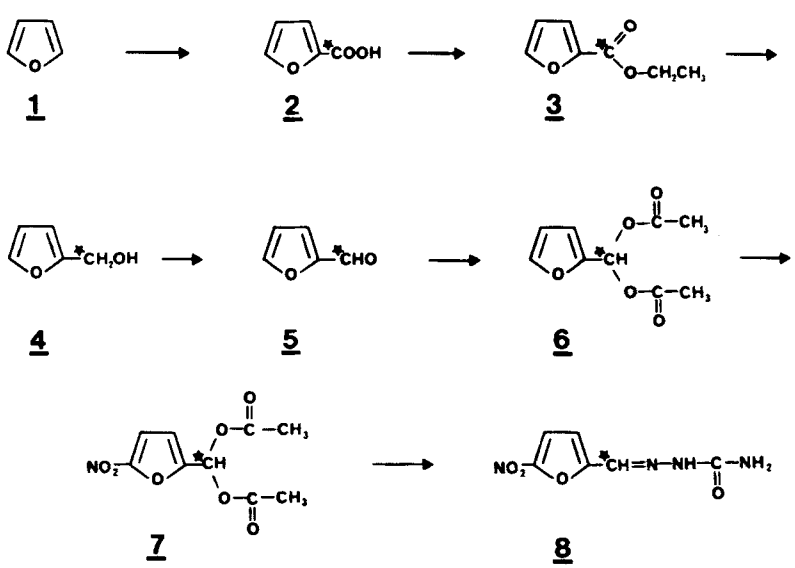
derivatives were required. For reasons previously detailed,[3] including the essential requirement of high specific activities and the goal of a general method for the syntheses of several carbon-14 labeled 5-nitrofuran derivatives via a common intermediate, the synthesis of carbon-14 labeled nitrofurazone (8) was performed by a new procedure using 2-(diacetoxymethyl-^{14}C)-5-nitrofuran (7).

RESULTS AND DISCUSSION

The synthesis of 2-(diacetoxymethyl-^{14}C)-5-nitrofuran (7) was performed via a new synthetic approach (Scheme I). The formylation of furan (Vilsmeier reaction) to prepare 2-furancarboxaldehyde-formyl-^{14}C (5) directly has been demonstrated,[4] but would be applicable to the syntheses of labeled 5-nitrofurans of high specific activities only if carbon-14 labeled dimethylformamide were available at such a specific activity. Synthetic approaches involving reduction of carbon-14 labeled 5-nitro-2-furancarboxylic acid or a corresponding ester derivative were not considered due to the instability of 5-nitrofurans to alkali.



SCHEME I

Preparation of ethyl 2-furancarboxylate-carboxy-^{14}C (**3**) (75% yield) by the treatment of crude 2-furancarboxylic-carboxy-^{14}C acid (**2**) with diazoethane[3] rather than preparation of the corresponding methyl ester (15% yield) was clearly demonstrated. Consistently higher yields of ethylations (75-90% yields) relative to methylations (15-40% yields) were observed with crude non-radiolabeled 2-furancarboxylic acid extracted from aqueous solution (acidified with either HCl or H_3PO_4) following the carboxylation of furan. Control experiments demonstrated that the same diethyl ether solutions of diazoethane and diazomethane esterified pure 2-furancarboxylic acid (Pfaltz and Bauer) in diethyl ether in yields of 85% and 90%, respectively. Thus, decomposition of crude methyl 2-furancarboxylate-carboxy-^{14}C and methyl 2-furancarboxylate were demonstrated under the reaction conditions, while crude ethyl 2-furancarboxylate-carboxy-^{14}C (**3**) and ethyl 2-furancarboxylate and were relatively stable.

Ethyl 2-furancarboxylate-carboxy-^{14}C (**3**) was reduced to 2-(hydroxymethyl-^{14}C)furan (**4**) with excess lithium aluminum hydride. The excess hydride was necessary to consume the moisture present with the ester **3**. Oxidation of 2-(hydroxymethyl-^{14}C)furan (**4**) to 2-furancarboxaldehyde-formyl-^{14}C (**5**) was performed according to the general method for the oxidation of benzylic or allylic alcohols.[6] The γ-MnO_2 oxidation of a furfuryldiol has been previously demonstrated.[7]

The nitration of 2-furancarboxaldehyde-formyl-^{14}C (**5**) was performed by a new variation in which **5** was converted to 2-(diacetoxymethyl-^{14}C)furan (**6**) *in situ* and nitrated directly. The reported yields for the nitration of 2-(diacetoxymethyl)furan (250 mmol[8] and 11 mmol[5]) to yield 2-(diacetoxymethyl)-5-nitrofuran (40% and 38% yields, respectively) were improved to 49% yield with the new two-reaction one-flask procedure with 12 mmol of 2-furancarboxaldehyde. However, reaction yields were consistently 20-25% on scales of under 0.5 mmol of 2-furancarboxaldehyde where inverse addition and inverse quenching were performed because of the small reaction volumes. The synthesis

of 2-(diacetoxymethyl-^{14}C)-5-nitrofuran (**7**), therefore, was performed in 21% yield from **5** and in 7.3% overall radiochemical yield from $Ba^{14}CO_3$.

The conversion of 2-(diacetoxymethyl-^{14}C)-5-nitrofuran (**7**) to 5-nitro-2-(semicarbazonomethyl-^{14}C)furan (**8**) was performed and monitored by HPLC. This new synthetic approach was particularly useful for the microscale synthesis of carbon-14 labeled nitrofurazone (**8**) of high specific activity. The conversion of **7** to other carbon-14 labeled 5-nitrofuran derivatives of high specific activities can be envisioned.

EXPERIMENTAL

General. All reagents and chemicals were obtained from commercial suppliers. The $Ba^{14}CO_3$ was obtained from New England Nuclear (59.0 mCi/mmol, lot # 1012-202). The diethyl ether was freshly distilled from benzophenone/sodium. All reactions were protected from light and stirred magnetically under a nitrogen atmosphere. High pressure liquid chromatography (HPLC) was performed with an Alltech C-18 column (0.46 x 25 cm, 10 μm) using UV detection. ^{1}H NMR spectra were recorded in $CDCl_3$ with a Varian FT-80 instrument, and the chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Radioactivity measurements were made using a Beckman 7800 liquid scintillation counter with Fisher Scinti Verse E scintillation cocktail. Specific activities and radiochemical purities were determined by HPLC using a Beckman-Altex analytical system consisting of two 110A pumps, a UV detector, and a Qume model 421 microprocessor controller/programmer in combination with a Radiomatic Instruments Flo-One/βeta radioactive flow detector using Radiomatic Flo-Scint II.

Ethyl 2-furancarboxylate-carboxy-^{14}C (**3**). Ethyl 2-furancarboxylate-carboxy-^{14}C (**3**)[3,5] was prepared in 75% yield from $Ba^{14}CO_3$ (59.0 mCi/mmol, 164 mg, 0.824 mmol). The homogeneous product **3** co-chromatrographed on HPLC (45/55 CH_3OH/H_2O, λ = 254 nm, retention time = 7 min) with fully-characterized non-radiolabeled ethyl 2-furancarboxylate.

2-Furancarboxaldehyde-formyl-^{14}C (**5**). Ethyl 2-furancarboxylate-carboxy-^{14}C (**3**) (100 mg, 0.62 mmol, 37 mCi) was reduced with $LiAlH_4$ (160 mg, 4.0 mmol) in diethyl ether (10 mL) at reflux for 3 h. The excess hydride was decomposed with H_2O (5 mL). After centrifugation, the ether phase was separated and the solvent removed under reduced pressure. The heterogenous alkaline aqueous mixture was neutralized with 4 M HCl and extracted with CH_2Cl_2 (3 x 5 mL) using vortex mixing followed by centrifugation. The CH_2Cl_2 extracts were combined with the residue of the ether extraction, dried over $MgSO_4$ and the desiccant removed by gravity filtration through cotton to afford a quantitative recovery of crude 2-(hydroxymethyl-^{14}C)furan (**4**) which was demonstrated to be free of **3** by HPLC. Portions of active γ-MnO_2 (900 mg, 450 mg, and 270 mg) were added at 12 h intervals, and after 36 h the γ-MnO_2 was removed by filtration through cotton. The filtrate was then eluted through 1 g of Bio-Sil A (100-200 mesh) with CH_2Cl_2 and the solvent removed under reduced pressure to afford pure 2-furancarboxaldehyde-formyl-^{14}C (**5**) (35 mg, 0.36 mmol, 21 mCi, 58% yield): ^{1}H NMR δ 9.65 (1H, s), 7.69 (1H, dd, J = 1.7, 0.7 Hz), 7.24 (1H, dd, J = 3.6, 0.7 Hz), 6.60 (1H, dd, J = 3.6, 1.7 Hz).

2-(Diacetoxymethyl-^{14}C)-5-nitrofuran (**7**). A solution was prepared by adding 1.0 µL of 18 M H_2SO_4 to 620 µL of acetic anhydride at 0°C. Then 150 µL of this solution was added to 2-furancarboxaldehyde-formyl-^{14}C (**5**) (35 mg, 0.36 mmol, 21 mCi) at 0°C. The mixture was warmed to ambient temperature for 30 min, then cooled to -20°C (CCl_4/CO_2 bath). A mixture of fuming HNO_3 (44 µL, 90% HNO_3) and acetic anhydride (190 µL) was added dropwise, and after 45 min the reaction mixture was warmed to 0°C. After 3 h, 2 mL of ice and water were added. The mixture was stirred continuously in a 0°C bath while 10% aqueous NaOH was added slowly dropwise to neutralize the pH. The mixture was extracted with CH_2Cl_2 (4 x 2 mL), and the organic extracts combined and backwashed with H_2O (5 mL). The solvent was removed under reduced pressure. The residue was cooled in a 0°C bath and triethylamine (0.2 mL) was added. A vigorous reaction was observed. The excess amine was removed under reduced pressure, CH_3OH was added, and the 2-

(diacetoxymethyl-^{14}C)-5-nitrofuran (**7**) (15 mg, 0.061 mmol, 3.6 mCi, 21% yield) isolated by preparative HPLC (45/55 CH_3OH/H_2O, 2.0 mL/min, λ = 280 nm and 365 nm, retention time = 8 min, 14 injections) followed by removal of solvents by lyophylization.

5-Nitro-2-(semicarbazonomethyl-^{14}C)furan (**8**). 2-(Diacetoxymethyl-^{14}C)-5-nitrofuran (**7**) was converted to 5-nitro-2-(semicarbazonomethyl-^{14}C)furan (**8**) by the microscale version of the reported procedure for the corresponding non-radiolabeled compound.[9,10] A homogeneous solution of **7** and excess semicarbazide hydrochloride (400 mol%) in 0.15 M H_2SO_4 in 10/30 H_2O/CH_3CH_2OH was refluxed at 80°C (bath) and the course of the reaction followed by HPLC (30/70 CH_3OH/H_2O, 2.0 mL/min, λ = 280 nm and 365 nm). 2-(Diacetoxymethyl-^{14}C)-5-nitrofuran (**7**) (retention time = 21 min) was completely consumed to afford 5-nitro-2-(semicarbazonomethyl-^{14}C)furan (**8**) (59 mCi/mmol, retention time = 4 min) which could be isolated by crystallization and/or the addition of $(CH_3)_2SO$ to solubilize **8** followed by preparative HPLC separation with solvent removal via lyophylization. Carbon-14 labeled nitrofurazone (**8**) prepared from **7** in 85% yield was homogeneous and identical to non-radiolabeled nitrofurazone which had also been characterized by mp and ^{1}H NMR ($(CH_3)_2SO$-d_6). The radiochemical purity of **8** was 98%.

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