

Synthesis of [$^{14}\text{C}_2$] SDZ FOX 988, A Hypoglycemic Agent¹

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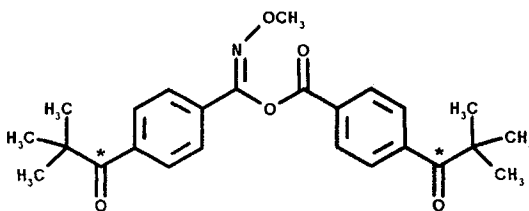
Summary

4-[2,2-Dimethyl-1-oxopropyl-1- ^{14}C]-4-[2,2-dimethyl-1-oxopropyl-1- ^{14}C]-phenyl(methoxyimino)-benzoic acid, methyl ester, [$^{14}\text{C}_2$] SDZ FOX 988, doubly labelled in the two keto carbons, was prepared from 4-bromotoluene in four steps. The final condensation featured a novel method for preparation of N-oxyimide acid derivatives.

Key Words : Carbon-14, non-insulin dependent diabetes mellitus, N-oxyimide acid derivatives.

INTRODUCTION

SDZ FOX 988, **1**, has been shown to lower blood glucose levels to within normal range in laboratory animals used as models for non-insulin dependent diabetes mellitus (NIDDM)¹. This compound also effected significant decreases in serum triglyceride and

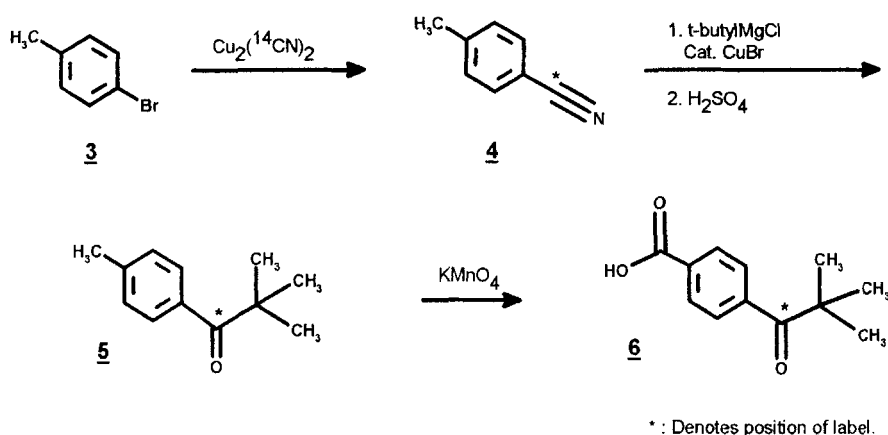


1 *: C-12, SDZ FOX 988
2 *: C-14, [$^{14}\text{C}_2$] SDZ FOX 988

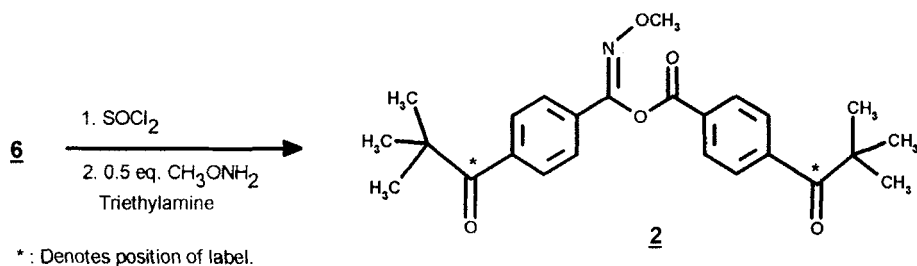
cholesterol levels following multiple dose administration in rats. In order to study the absorption, distribution, metabolism and excretion mechanisms of this drug in animals and man, a synthesis

of a carbon-14 isotopomer was undertaken. It is of importance to highlight that for these studies a labelling pattern that distributed carbon-14 equally in both "hemispheres" of the drug substance was a major goal. Therefore, a methodology that ensured only doubly labelled material had to be developed.

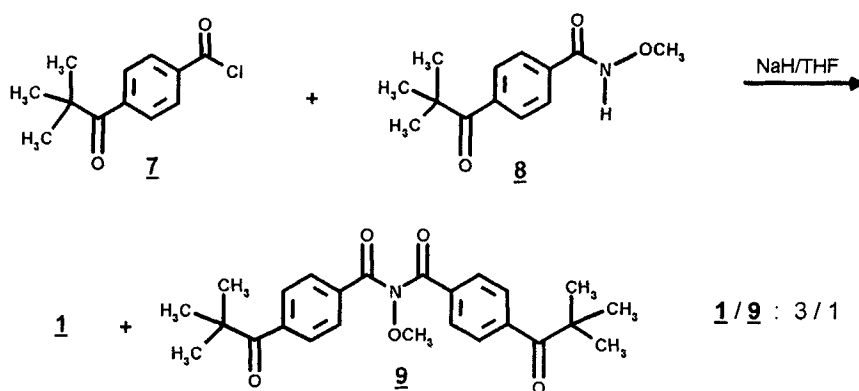
The synthesis of the title compound closely resembled the methodology developed for the unlabelled counterpart⁵. The point of convergence of the two approaches was 4-methylbenzo[¹⁴C]-nitrile, **4**, which was prepared in 49% radiochemical yield from 4-bromotoluene, **3**, by the action



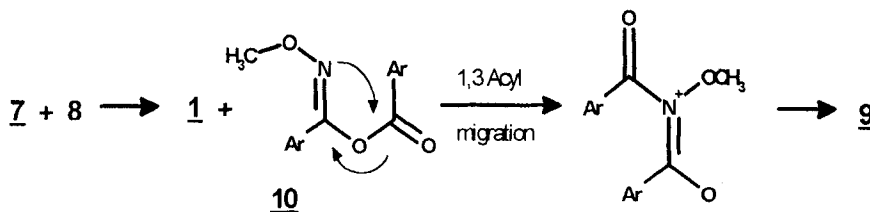
of cuprous[¹⁴C]cyanide⁶. The resultant nitrile was reacted with an excess of *tert*-butylmagnesium chloride in the presence of a catalytic amount of copper bromide⁷, and the intermediate imine was hydrolyzed without isolation with aqueous sulfuric acid to give the ketone **5**. Benzylic oxidation was accomplished with KMnO_4 ⁸ to give keto-acid **6** in 47% overall radiochemical yield from **4**. This material was converted to the acid chloride with SOCl_2 , and without isolation, treated with



triethylamine and methoxyamine (0.5 equivalents, prepared *in situ* from methoxyamine hydrochloride and aqueous sodium hydroxide) in toluene/water to give the title compound in 80% radiochemical yield after purification. In order to ensure as high an amount of doubly labelled material as possible, no intermediates were diluted with "cold" analogs until the final product was in hand. It is interesting to note that when the final step described above was conducted in a step-wise manner (i.e. coupling of acid chloride 7 with hydroxamic acid ester 8) and under aprotic



conditions, a substantial amount of the N-acylated product 9 was isolated as a side product. While this product ratio may be first assumed to be arising from competition between N vs. O acylation, it is more likely that the origin of 9 is also initial O-acylation. Thus reaction of 7 and 8 generates a mixture of *E*, *Z* isomers 1 and 10; however, the *E*-isomer 10 is susceptible to facile 1,3-acyl migration⁹, giving rise to 9



It is therefore the initial *E*,*Z* ratio that controls the distribution of 1 and 9. It is clear then that the reaction conditions employed in the one-pot operation heavily favor the formation of *Z*-isomer, since in this protocol the ratio of 1 to 9 is greater than 98:2.

Experimental

Sodium ^{14}C -cyanide was purchased from American Radiolabeled Chemicals, Inc. Chemical ionization mass spectroscopy was performed on a Finnigan 4600 mass spectrometer utilizing ammonia as the reagent gas. Radio-TLC chromatograms were conducted on 5 x 20 cm E. Merck silica gel F-254 plates (250 micron thickness). Radiochemical purities were determined by scanning the chromatograms for radioactivity with a Vanguard gas proportional scanner with a 1 mm x 10 mm collimator, as well as radio-HPLC. Identities of intermediates were determined by comparative TLC versus non-labelled standards that were identified by mass spectroscopy, ^1H - and ^{13}C -NMR spectroscopy. Specific activities were determined by the "weight-in-volume assay" method.

4-Methylbenzo- ^{14}C -nitrile, **4**

A solution of Na^{14}CN (262.5 mg, 5.14 mmol, 300 mCi) in 5 mL of water was added to a solution of copper(II) sulfate pentahydrate (3.346 g, 13.4 mmol) and sodium sulfite (372 mg, 2.95 mmol) in 15 mL of water. The suspension was allowed to stir at room temperature for 16 hours and then filtered. The filter cake, consisting of ^{14}C cuprous cyanide was dried *in vacuo*, combined with 4-bromotoluene, **3**, (1.832 g, 10.7 mmol) in 15 mL of DMSO (dried over 4A molecular sieves) and heated at 180 °C for 1.5 hours. At the end of this period, the mixture was cooled to room temperature, diluted with 45 mL of water and extracted with three 45-mL portions of methylene chloride. The combined organic phases were consecutively washed with ferric chloride solution (0.8 g in 50 mL of 2 N HCl), 50 mL of 2 N sulfuric acid, 50 mL of 5% sodium sulfite solution, two 50-mL portions of water and finally with 50 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness under slightly reduced pressure. The residue was subjected to flash column chromatography¹⁰ on 60 g of silica gel. After elution with 100 mL of hexane, 100 mL of 1% ethyl acetate in hexane and 225 mL of 2.5% ethyl acetate in hexane, the product eluted in the following 600 mL of 2.5% ethyl acetate in hexane fraction. This portion was concentrated under slightly reduced pressure to give 147.8 mCi, 308.9 mg (49.3% radiochemical yield) of the title compound. This material had an identical R_f value with unlabelled standard in the TLC system used (10% ethyl acetate in hexane).

2,2-Dimethyl-1-(4-methylphenyl)-1- ^{14}C -1-propanone, 5

Under a nitrogen atmosphere, *tert*-butylmagnesiumchloride (1.75 mL of a 2 M solution in THF, 3.5 mmol) was added over a thirty-minute period *via* syringe to a solution of 308.9 mg (147.8 mCi, 2.639 mmol) of 4 in 5 mL of dry THF at 0 °C. After the addition was completed, the solution was allowed to warm to *ca.* 15 °C and 8.7 mg of copper(I) bromide was added to the mixture. The reaction contents were heated at reflux for four hours and then cooled in an ice-water bath. To it was slowly added 2.1 mL of 15% sulfuric acid and stirring was continued for an additional 30 minutes. At this point, the solution was diluted with 25 mL of water and 25 mL of ethyl acetate. The layers were separated and the aqueous layer was extracted with 25 mL of ethyl acetate. The combined organic phases were washed with three 25-mL portions of water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography¹⁰ on 30 g of silica gel yielded 321 mg (102 mCi, 69% radiochemical yield) of the title compound in 200 mL of 1% of ethyl acetate in hexane after foreruns of 200 mL of hexane and 200 mL of 1% ethyl acetate-hexane. TLC indicated an identical R_f value for the radioactive material and standard (10% ethyl acetate-hexane).

4-(2,2-Dimethyl-1-oxopropyl-1- ^{14}C)benzoic acid, 6

To a solution of potassium permanganate (800 mg, 5.06 mmol) in 2.4 mL of water at 80 °C was added *via* syringe a solution of 5 (321 mg, 1.821 mmol, 102 mCi) in 4 mL of *tert*-butanol. After the addition was completed, heating was continued for four hours, followed by 16 hours of stirring at room temperature. At this stage, an additional portion of potassium permanganate (62 mg, 0.39 mmol) was added to the mixture, and heating at 80 °C was resumed for an additional two hours. The mixture was allowed to cool to 50 °C and filtered. The filter cake was washed with warm water and the combined filtrate and washings were treated with 90 mg (0.47 mmol) of sodium bisulfite and stirred at room temperature for 20 minutes. The reaction mixture was acidified with 1 mL of 37% HCl, and the resultant suspension was extracted with two 25-mL portions of ethyl ether. The combined organic phases were extracted with two 25-mL portions of 10% sodium bicarbonate. The combined basic layers were carefully titrated to pH 3 with 2 N

HCl and then extracted with two 25-mL portions of ethyl ether. The organic extracts were washed with 25 mL of water, dried over sodium sulfate and concentrated under reduced pressure to give 243.7 mg (60.93 mCi, 67.9% radiochemical yield) of the title compound that was used in the next step without further manipulation. Comparative-TLC indicated identical R_f values for this material and unlabelled standard (10% ethyl acetate-hexane).

4-(2,2-Dimethyl-1-oxopropyl-1- ^{14}C)-[4-((2,2-dimethyl-1-oxopropyl-1- ^{14}C))phenyl](methoxyimino)benzoic acid, methyl ester, 2

Under a nitrogen atmosphere, a mixture of 6 (243.7 mg, 1.088 mmol, 60.93 mCi), 0.53 mL of thionyl chloride and 0.05 mL of DMF was heated at 95 °C for 1.5 hours. Excess thionyl chloride was distilled off at 65 °C under reduced pressure. Residual SOCl_2 and HCl was chased off by addition of 5 mL of toluene and distillation. The residue was taken up in 2 mL of toluene and cooled to 0 °C. To it was added dropwise over a two minute period 0.39 mL (2.785 mmol) of triethylamine. After the addition was completed, the solution was stirred at *ca.* 15 °C for 15 minutes and then cooled to -10 °C. To this was added a premixed solution of 41.3 mg (0.49 mmol) of methoxyamine hydrochloride and 19.4 mg (0.485 mmol) of NaOH in 1 mL of water. The reaction contents were heated to 50 °C for 15 minutes, cooled to room temperature and diluted with 15 mL of toluene. The layers were separated and the aqueous phase was extracted with 15 mL of toluene. The combined organic extracts were washed with two 10-mL portions of saturated sodium bicarbonate solution followed by 10 mL of water and dried over sodium sulfate. To this material was added unlabelled SDZ FOX 988, 1, (977 mg) and the solvent was removed under reduced pressure. The residue was crystallized from 15 mL of ethanol yielding a crop of crystals with a radiochemical purity of 94%. This material was subjected to flash column chromatography¹⁰ on 60 g of silica gel using a 9:1 mixture of hexane and ethyl acetate as eluent. The fractions of interest were combined and concentrated, and the residue was recrystallized once again from ethanol giving 48.74 mCi (80% radiochemical yield) of the title compound.

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