*Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXVIII, No. 7*

# SYNTHESIS OF $^{13}C$- AND $^{14}C$-LABELED 3-(DICHLOROACETYL)-5-(2-FURANYL)-2,2-DIMETHYLOXAZOLIDINE

Akbar Mehrsheikh

Environmental Science Department
Ceregen, A Unit of Monsanto Company
St. Louis, Missouri 63198

## SUMMARY

Synthesis of 3-(dichloroacetyl)-5-(2-furanyl)-2,2-dimethyloxazolidine ( common name: furilazole) labeled with carbon-14 and carbon-13 are described. Two routes for the synthesis of labeled trimethylsilyl cyanide, a precursor to furilazole, are described. One method can be carried out on milligram scale and is suitable for a high specific activity preparation while the second method is suitable for preparation on gram scale. Carbon-14 labeled furilazole was obtain from isotopically labeled potassium cyanide in 5 steps with an overall yield of 28-34%.

Key Words: trimethylsilyl cyanide, potassium cyanide, carbon-14, carbon-13, furilazole

## INTRODUCTION

3-(Dichloroacetyl)-5-(2-furanyl)-2,2-dimethyloxazolidine (5), furilazole, is Monsanto's new chemical safening agent registered by the US EPA in 1994. Furilazole, like other herbicide safeners, functions as an antidote to acetanilide and sulfonylurea herbicides by selectively protecting crops such as corn and sorghum from injury without adversely impacting herbicidal activity on annual weeds[1].

For the environmental chemistry, animal and plant metabolism studies, $^{14}C$-labeled and $^{13}C$-enriched samples of the safener were required. This report describes the synthetic and analytical procedures utilized in the preparation of these compounds and their precursors.

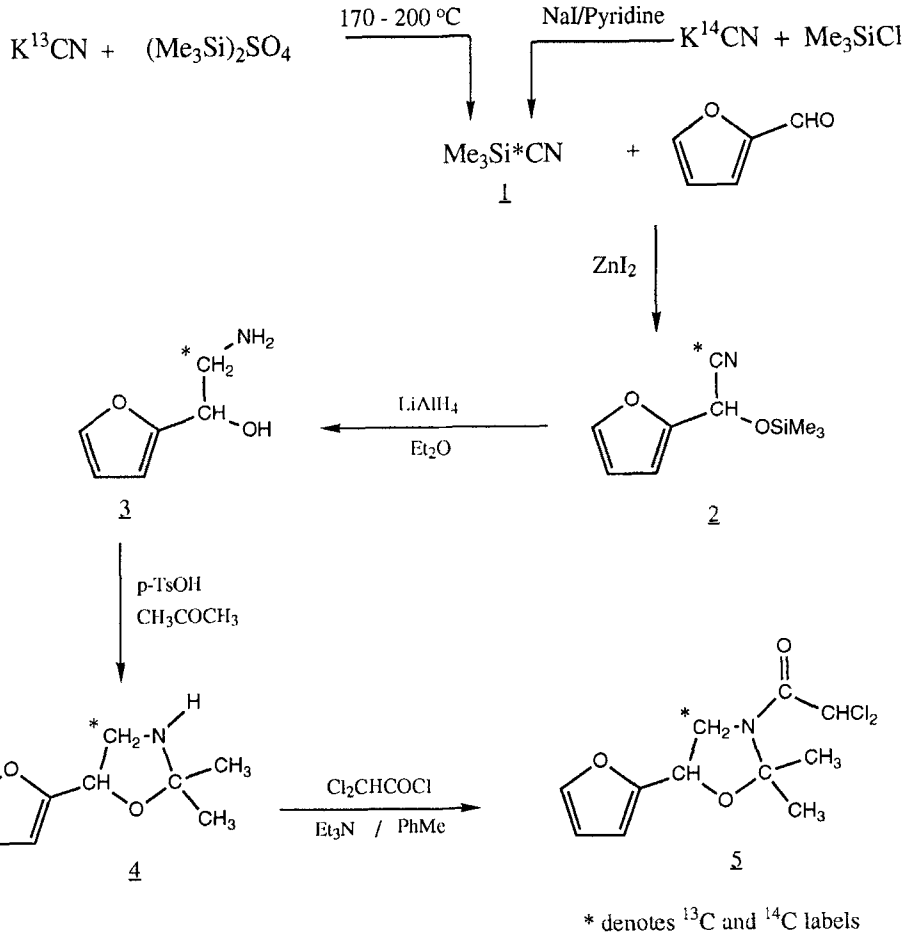
CCC 0362–4803/96/070631–06


Received 16 November 1995
Revised 26 January 1996

## RESULTS AND DISCUSSION

The synthetic pathway for preparation of $^{14}C$-labeled and $^{13}C$-enriched furilazole 5 is outlined in the Scheme shown below.

### SCHEME




* denotes $^{13}C$ and $^{14}C$ labels

The synthetic strategy for preparation of the $^{13}C$-enriched sample included the initial reaction of bis(trimethylsilyl) sulfate with $^{13}C$-enriched potassium cyanide to form $^{13}C$-enriched trimethylsilyl cyanide (1), which was isolated from the reaction mixture by distillation[2]. Cyanosilylation was accomplished by zinc iodide catalyzed addition of trimethylsilyl cyanide to 2-furaldehyde[3]. A modified synthetic approach was employed for the synthesis of $^{14}C$-labeled cyanohydrin 2, due to safety concerns associated with distillation of the relatively volatile

radiolabeled trimethylsilyl cyanide. The $^{14}C$-labeled trimethylsilyl cyanide was generated *in situ* by the reaction of stoichiometric quantities of $K^{14}CN$ and trimethylsilyl chloride[4]. Cyanosilylation was then accomplished by the zinc iodide catalyzed condensation of the *in situ* generated $^{14}C$-labeled trimethylsilyl cyanide to 2-furaldehyde. The method utilized in the *in situ* generated trimethylsilyl cyanide proved to be a more advantageous method due to the higher yield of the final product and the possibility of conducting the reaction in milligram quantities of reagents. Reduction of cyanohydrin 2 with lithium aluminum hydride gave the amino alcohol 3. Condensation of the amino alcohol 3 with acetone, and subsequent reaction of the oxazolidine 4 with dichloroacetyl chloride furnished the desired products 5. The $^{14}C$-labeled sample was prepared in an overall yield of 34% starting with one Curie of $K^{14}CN$. The reaction sequence afforded the desired product as a white crystalline solid. The radiochemical purity of the sample was determined to be 98% by HPLC analysis with monitoring of collected fractions by liquid scintillation counting (HPLC/LSC). The specific activity of the sample was determined to be 27.6 mCi/mmol, and the chemical purity was established as 99% by GLC and 98% by HPLC analyses by comparison with an unlabeled analytical standard of 5. The $^{13}C$-enriched sample was prepared in an overall yield of 28%. The chemical purity of this sample was determined to be 100% by GLC analysis, and the isotopic enrichment was determined as 97 atom % by GC/MS analysis.

## EXPERIMENTAL

All boiling points and melting points are uncorrected. To monitor the progress of selected reactions and to assay the purity of the products, a Varian model 3700 gas chromatograph equipped with a flame ionization detector and 3% DC-200 on Chromosorb W (80-100 mesh, 6 ft X 2 mm) column, a Waters HPLC system equipped with a Waters model U6K injector, Waters model 481 UV detector, Waters model 680 controller, Waters model 510 solvent pumps, and a Waters radial compression module with NOVA-PAK $C_{18}$, cartridge (5μ, 8 mm X 10 cm) , and a Varian VXR-300 NMR spectrometer were utilized. Liquid scintillation counting (LSC) was performed on Tracor Analytic Mark III Model 6881 counters which were interfaced with a Monsanto-developed data acquisition and processing software system. The mass spectra of the isotopically labeled samples were obtained on a Finnigan 4515 quadrupole mass spectrometer. The samples were introduced into the mass spectrometer using a Finnigan 9610 Scientific DB-5 Capillary column (30 m X 0.32 mm). Potassium cyanide-$^{14}C$ was purchased from New England Nuclear, Boston Massachusetts. Potassium cyanide-$^{13}C$ was purchased from Merck Sharp &

Dohme Isotopes, Quebec, Canada. All other solvents and reagents were reagent grade and obtained from readily available commercial sources.

**α-[(Trimethylsilyl)oxy]-2-furanacetonitrile-1-$^{14}$C (2)** In an oven dried 50 mL round bottom flask, filled with nitrogen and equipped with a magnetic stirring bar, were placed sodium iodide (0.5 g, 3.3 mmol) and potassium cyanide-$^{14}$C (1.29 g, 19.77 mmol, 1054.2 mCi, spec. act. = 53.3 mCi/mmol) in anhydrous acetonitrile (10 mL). After stirring for 10 minutes, trimethylsilyl chloride (2.36 g, 21.7 mmol), pyridine (0.4 g, 5 mmol), 2-furaldehyde (1.99 g, 20.76 mmol), and zinc iodide (20 mg) were added. The reaction mixture was heated at gentle reflux under nitrogen, and the progress of the reaction was followed by $^{1}$H NMR spectroscopy. After 44 hours of reflux, the reaction was complete by $^{1}$H NMR. The reaction mixture was cooled to room temperature, filtered through a pad of celite, and the filter cake was washed with pentane (100 mL). The solution was then concentrated to give a clear colorless liquid which was used without further purification in the next step.

**α-(Aminomethyl-$^{14}$C)-2-furanmethanol (3)** A solution of the O-silylfuran cyanohydrin-2-$^{14}$C in ethyl ether (50 mL) was added dropwise to a suspension of lithium aluminium hydride (1.13 g, 30 mmol) in ethyl ether (150 mL), which was cooled with an ice water bath. The reaction mixture was stirred at room temperature for 2 hours, then again cooled in an ice bath as water (2.5 mL) was slowly added, followed by a 10% sodium hydroxide solution (2.5 mL). After stirring for 2 hours at room temperature, the ethyl ether was removed by rotary evaporation and THF (300 mL) was added to the solid residue. The mixture was then filtered, the precipitate was washed with additional THF (300 mL) and again filtered. The combined filtrates were dried over magnesium sulfate, filtered and concentrated to give the desired product (1.90 g, 75.6%) as a yellow crystalline solid. This material was used in the next step without further purification.

**5-(2-Furanyl)-2,2-dimethyloxazolidine-4-$^{14}$C (4)** A solution of 3-$^{14}$C (1.90 g, 15 mmol) and p-toluenesulfonic acid (20 mg) in anhydrous toluene (50 mL) was stirred and heated to about 100°C as acetone (1.2 g, 20 mmol) was added in one portion. The reaction mixture was heated at reflux for three hours with azeotropic removal of water ,then cooled to room temperature and used in the next step without isolation or purification of the oxazolidine 4-$^{14}$C.

**3-(Dichloroacetyl)-5-(2-furanyl)-2,2-dimethyloxazolidine-4-$^{14}$C (5)** Triethylamine (2.39 g, 23.6 mmol) was added to the toluene solution of oxazolidine 4-$^{14}$C, which was cooled in an ice

bath. Then dichloroacetyl chloride (2.78 g, 18.9 mmol) was added dropwise, and the solution was stirred for 16 hours at room temperature. The reaction mixture was poured into water (300 mL) and the organic layer was separated, washed with saturated sodium chloride, and dried over magnesium sulfate. Concentration gave a brown residue, which was subjected to flash chromatography on silica gel (250 g), using 5% ethyl acetate in hexane as eluent. The appropriate fractions were combined and concentrated to give the desired product (1.85 g) as a yellow crystalline solid. The specific activity of this sample was determined to be 53.7 mCi/mmol with radiochemical purity of 97%. This material was unstable and slowly decomposed even when stored at -30°C, due to its high specific activity. After isotopic dilution with 1.75 g of an unlabeled sample of 5, the mixture was again subjected to flash chromatography as above. The appropriate fractions were combined and concentrated, and the residue was recrystallized from 50 ml of 2% ethyl acetate in hexane to give the desired product (3.43 g, 34% overall yield) as a white crystalline solid. The chemical purity of the sample was determined to be 99% by GLC and 98% by HPLC analyses by comparison with an unlabeled analytical standard of 5. The radiochemical purity was established as 98% by HPLC/LSC evaluation, and the specific activity was determined to be 27.6 mCi/mmol. A GLC/mass spectral evaluation (GC/MS) of the sample was also obtained and gave the expected parent peaks and isotopic cluster.

**Trimethylsilyl cyanide-$^{13}C$ (1)** A one-necked 50-mL round-bottomed flask equipped with a 14 cm Vigreaux column and a short-path condenser, was charged with bis(trimethylsilyl) sulfate (25.10 g, 103 mmol) and potassium cyanide-$^{13}C$ (13.47 g, 204 mmol) (potassium cyanide was finely divided and was dried in a vacuum oven for 36 hours at 120°C and 0.5 Torr before use). The reaction flask was gradually heated to 200°C, and the trimethylsilyl cyanide distilled over as it was formed. The $^{13}C$-enriched trimethylsilyl cyanide (18.01 g, 88%, b.p. 115 - 118°C), was obtained as a colorless liquid, which was used without further purification in the next step. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.05 (d, J=3 Hz).

**α-[Trimethylsilyl)oxyl-2-furanacetonitrile-1-$^{13}C$ (2)** A mixture of trimethylsilyl cyanide-$^{13}C$ (18.01 g, 180 mmol) and zinc iodide (10 mg) was cooled in an ice bath under nitrogen as 2-furaldehyde (17.30 g, 180 mmol) was added dropwise. The reaction was exothermic and instantaneous. The product obtained was used without further purification in the next step. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.20 (s, 9H), 5.54 (d, J=7.8 Hz, 1H), 6.40, 6.41 (dd, J=1.8, 3 Hz, 1H), 6.55 (d, J=3.6 Hz, 1H), 7.46, 7.46 (dd, J=1.8, 3 Hz, 1H).

**α-(Aminomethyl-$^{13}$C)-2-furanmethanol (3)** This compound was prepared by the same procedure described for the preparation of 3-$^{14}$C. The product was obtained as a yellow crystalline solid (15.0 g, 68.4%, m.p 84-86°C), and was used in the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.90 (bs, 2H), 2.66, 3.12 (dd, J=1.8, 138 Hz, 1H), 2.19 (d, J=138 Hz, 1H), 4.46 (s, 1H), 4.47-4.51 (m, 1H), 6.13 (d, J=3 Hz, 1H), 6.18-6.20 (m, 1H), 7.23 (bs, J=1.8, 1H).

**5-(2-Furanyl)-2,2-dimethyloxazolidine-4-$^{13}$C (4)** This compound was prepared by the same procedure described for the preparation of 4-$^{14}$C. The reaction mixture was used in the next step without isolation or purification of the oxazolidine 4-$^{13}$C.

**3-(Dichloroacetyl)-5-(2-furanyl)-2,2-dimethyloxazolidine-4-$^{13}$C (5)** This compound was prepared by the same procedure described for the preparation of 5-$^{14}$C. This procedure after recrystallization gave a white crystalline product (10.91 g, 48.6%). The chemical purity of this sample was determined by GLC to be 100% and by HPLC to be 99% by comparison with an unlabeled analytical standard of 5. The $^{13}$C isotopic enrichment was found to be 97 atom % by GLC/MS analysis, which also gave the expected parent peaks and isotopic cluster. $^1$H NMR (300 MHz, $CDCl_3$) δ.1.66 (s, 3H), 1.71 (s, 3H), 3.75, 4.24 (dt, J=9.6, 147 Hz, 1H), 3.92, 3.95, 4.40, 4.43 (ddd, J=5.7, 9.6, 144 Hz, 1H), 5.18-5.24 (m, 1H), 6.06 (s, 1H), 6.39, 6.40 (dd, J=2.1, 3 Hz, 1H), 6.48 (d, J=3 Hz, 1H), 7.46-7.47 (m, 1H).

## ACKNOWLEDGMENTS

The author would like to thank H. Fujiwara for obtaining mass spectral data and for his help in the interpretation of the mass spectral data.

## REFERENCES

1. Breaux, E. J., Patanella, J. E., and Sanders, E. F. - J. Agric. Food Chem. 35: 474 (1987).
1. Voronkov, M. G., Roman, V. K., and Maletina, E. A. - Synthesis: 277 (1982).
2. Evans, D. A., Carroll, G. L., and Truesdale, L. K. - J. Org. Chem. 39: 914 (1974).
3. Duboudin, F., Cazeau, Ph., Moulines, F., and Laporte, O. - Synthesis: 212 (1982).