

NOTE

PREPARATION OF 2-CHLORO-6-(2-FURANYLMETHOXY)-4-TRICHLOROMETHYLPYRIDINE-2,6-¹⁴C

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SUMMARY

A 16.7 mCi sample of 99+% radiochemically pure 2-chloro-6-(2-furanylmethoxy)-4-trichloromethylpyridine-2,6-¹⁴C with a specific activity of 13.2 mCi/mole was prepared from trimethyl citrate-1,5-¹⁴C in a 44% yield via a three-step process.

Key Words: 2-Chloro-6-(2-furanylmethoxy)-4-trichloromethylpyridine-2,6-¹⁴C, citrazinic acid-2,6-¹⁴C, 2,6-dichloro-4-trichloromethylpyridine-2,6-¹⁴C.

INTRODUCTION

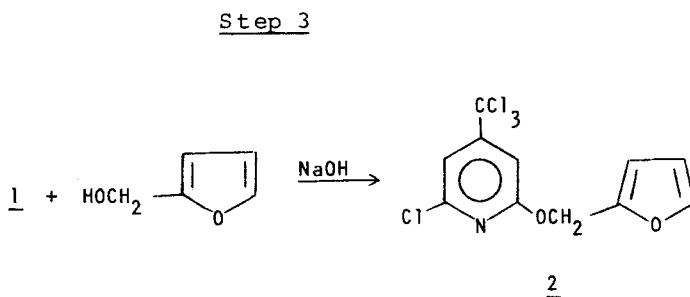
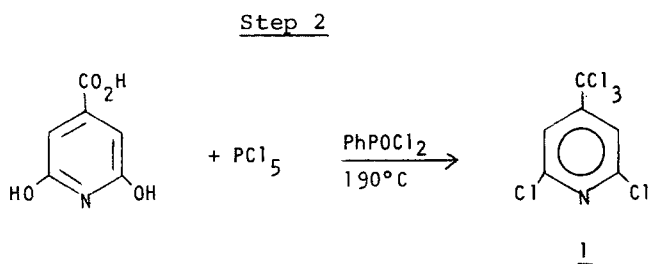
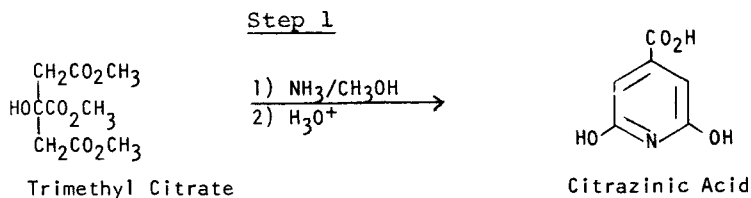
2-Chloro-6-(2-furanylmethoxy)-4-trichloromethylpyridine 2,6-¹⁴C (2) is a promising new Dow experimental systemic fungicide and a carbon-14 labeled sample was required for plant and soil metabolism studies.

DISCUSSION

The radiolabeled 2 was prepared via the process depicted in Scheme I.

The conversion of citric acid and its esters to citrazinic acid as depicted in Step 1 has been extensively investigated (1-4) and therefore the chemistry only required adaptation for the radiotracer synthesis. The modified process afforded

Scheme I



55-60% yields of 95% pure citrazinic acid in the pilot runs and a 63% yield in the tracer synthesis.

W. J. Sell and F. W. Dootson(5) had previously attempted the second step of the sequence using phosphorous pentachloride in phosphoryl chloride. They observed that only a small quantity of 2,6-dichloro-4-trichloromethylpyridine was produced. In the present study, the reaction was conducted in phenylphosphonic dichloride which affords high yields of desired product. Utilization of 99+% pure citrazinic acid (Eastman Chemicals) afforded 80-95% yields of 1 whereas the technical grade acid produced in Step 1 afforded 76% and 88% yields of 1 respectively in the pilot and tracer syntheses.

Step 2 must be conducted as described in the experimental section. The initial reaction of citrazinic acid in refluxing phenylphosphonic dichloride in the absence of phosphorous pentachloride presumably affords the intermediate 2,6-dichloro-isonicotinic acid chloride. If the phosphorous pentachloride is added prior to this conversion, ring chlorination occurs resulting in low product yields. The subsequent conversion of the acid to the trichloromethylpyridine using phosphorous pentachloride in phenylphosphonic dichloride has general applicability towards aromatic carboxylic acids and is the subject of a recent patent(6).

Synthesis of 2-chloro-6-(2-furanylmethoxy)-4-trichloromethylpyridine-2,6-¹⁴C (Step 3) was conducted in excess furfuryl alcohol to afford a 92% yield of 2 in the pilot run and a 79% yield of 99+% radiochemically pure 2 in the tracer synthesis. Thus, the tracer synthesis afforded a 44% overall yield of radiolabeled 2 from trimethyl citrate-1,5-¹⁴C.

EXPERIMENTAL

All GLC analyses were conducted on a Hewlett Packard 5830A instrument using a 2' x 4 mm glass column containing 10% SE 30 on 80/100 Chromasorb WHP. The following conditions were used unless otherwise stated: Inj. Temp: 175°C, FID Temp: 300°C, Temperature Program: 100° to 250°C at 10°/min, Time at 100°: 2.0 min, Time at 250°C: 5.0 min, N₂ flow: 60 ml/min; Rt 2 = 14.0 min. The percentages represent the GLC area % of the volatile components. No internal standards were used. The retention times were compared with those of authentic samples.

Citrazinic Acid-2,6-¹⁴C. A 434.8 mg (2.080 mmole) sample of trimethyl citrate-1,5-¹⁴C (Pathfinder Laboratories, Lot #81004, 49.83 mCi at 24.12 mCi/mmmole) was diluted with 353.0 mg of unlabeled trimethyl citrate affording ester with a specific activity of 13.9 mCi/mmmole. The solid was transferred to a 30-ml glass ampul with 15 ml of MeOH. The ampul was cooled to -78°C under N₂ and 5 ml of anhydrous NH₃ added.

The ampul was sealed, placed in a S.S. reactor and the reactor pressurized to 1250 psi with N_2 . The reactor was heated in a rocker-heater at 135-145°C for 7.0 hr and allowed to cool overnight.

The ampul was removed, cooled to -78°C, opened, and the contents allowed to warm over a 0.5 hr period which removed the excess NH_3 . The ampul was cooled to -78°C and the MeOH removed from the precipitate via a filter stick. The precipitate was treated with 5 ml of MeOH, allowed to warm to ca 24°C, and the mother liquor removed in the above manner. The washing was repeated with 2 x 2 ml of MeOH. Three ml of hot H_2O was added to the ampul and the mixture placed in a 95°C oil bath which caused complete dissolution. The solution was transferred to a tared 100-ml round-bottomed flask and the ampul rinsed with six 1-ml portions of hot H_2O .

The solvent was removed from the aqueous solution at 50°C and 30 mm and the residue treated with 3 ml of 70% H_2SO_4 . The mixture was heated at 120°C for 1.0 hr, cooled, and 5 ml of H_2O slowly added. The mixture was again heated at 120°C for 0.75 hr, allowed to cool to 24°C, and finally cooled to 5°C. The mother liquor was removed from the precipitate and the precipitate washed with 3 x 2 ml of H_2O and 3 x 2 ml of acetone. It was dried initially at 24°C and 30 mm and finally at 0.5 mm to afford 346.8 mg (2.236 mmole, 62.6% yield) of citrazinic acid-2,6- ^{14}C as a reddish brown solid.

2,6-Dichloro-4-trichloromethylpyridine-2,6- ^{14}C . Five ml of $PhPOCl_2$ was added to the flask containing the citrazinic acid-2,6- ^{14}C . The mixture was heated at 195°C under N_2 with stirring for 22.5 hr. The resultant black solution was cooled and 4.6 g of PCl_5 added. The flask was equipped with a Dean Stark trap and again heated at 195°C for 22.5 hr. The $POCl_3$ produced in the reaction was collected in the trap.

The mixture was cooled in an ice bath, treated slowly with ice until the excess PCl_5 and $PhPOCl_2$ had reacted, and diluted with 25 ml of n-pentane and 20 ml of H_2O . The phases were mixed well and extracted continuously with 15 ml of

n-pentane over a 6 hr period. The extraction flask was replaced with a second flask containing 25 ml of n-pentane and the extraction continued for 17 hr. The solvent was removed from each extract in vacuo and the residues chromatographed through 200 g of Brinkman Silica Gel G60 with 3:7 (v/v) CHCl₃:n-hexane. Product was first observed (GLC, isothermal at 170°C, Rt 1 = 2.53 min) after 625 ml of solvent had eluted and was isolated in 450 ml of solution.

Solvent removal afforded 521.6 mg (1.965 mmole, 87.9% yield) of 1 as a white crystalline solid which was 99.6 GLC area % pure (Rate = 20°/min, Rt 1 = 6.24 min).

2-Chloro-6-(2-furanylmethoxy)-4-trichloromethylpyridine-2,6-¹⁴C. To a 3-dram vial containing a stirring bar and 425.8 mg (1.604 mmole) of 2,6-dichloro-4-trichloromethylpyridine-2,6-¹⁴C (22.3 mCi at 13.9 mCi/mmole) was added 197.6 mg (4.94 mmole) of pulverized NaOH and 1.3 ml (15.0 mmole) of furfuryl alcohol. The mixture was stirred at ca 24°C for 18.5 hr. The black solution was treated with 5 ml of 20% NaOH and extracted with 10 x 2 ml of n-hexane. Each extract was transferred to a column containing 100 g of Brinkman Silica Gel G60. The product was chromatographed using 3:7 (v/v) CHCl₃:n-hexane and was first observed (GLC, Isothermal at 220°C, Rt 2 = 2.6 min) after 225 ml of solvent had eluted. It was isolated in 250 ml of solution. The solvent was removed in vacuo to afford 414.9 mg (1.269 mmole, 79.1% yield) of 2 as a colorless oil.

The oil was dissolved in 1 ml of C₆H₆ and transferred to a 10-ml Volumetric flask. The round-bottomed flask was rinsed with several portions of C₆H₆ and the Volumetric flask diluted to volume (Solution A). A 0.5 ml aliquot of Solution A was diluted to 50 ml (Solution B). A 1.0 ml aliquot of Solution B was diluted to 100 ml (Solution C).

The solutions were analyzed as described below to afford 16.7 mCi of 99+% radiochemically pure 2 with a specific activity of 13.2 mCi/mmole.

RADIOMETRIC DETERMINATION

The radioactivity was determined in a Packard Tri-Carb Liquid Scintillation Spectrometer using New England Nuclear Aquasol universal liquid scintillation cocktail. Triplicate assays of Solution C were taken.

The radiochemical purity was determined by spotting six - 5 x 20 cm - Merck silica gel 60F-254 plates with 6 μ l aliquots of Solution B along with standard samples of 1 and 2. The plates were developed in the solvent systems listed below:

Plate	Solvent System	Ratio (v/v)	R _f Values of	
			<u>1</u>	<u>2</u>
1	C ₆ H ₆ : <u>n</u> -hexane	25:25	0.35	0.46
2	CHCl ₃ : <u>n</u> -hexane	15:35	0.23	0.33
3	CH ₂ Cl ₂ : <u>n</u> -hexane	15:35	0.23	0.36
4	Acetone: <u>n</u> -hexane	5:45	0.51	0.47
5	EtOAc: <u>n</u> -hexane	5:45	0.51	0.47
6	CH ₃ OH: <u>n</u> -hexane	5:45	0.61	0.61

The plates were subsequently scanned using a Vanguard radioscanner connected to a Hewlett Packard 5830A integrator. Except for artifacts at the origin, no detectable impurities were observed.

Plates 2 and 4 were scraped in 5 mm sections and the sections counted. Histogram analyses of the data afforded product of 99+% radiochemical purity.

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