ONE STEP CONVERSION OF GLUTARIMIDE-2,6-^{14}C TO PENTACHLOROPYRIDINE-2,6-^{14}C AND ITS SUBSEQUENT USE IN THE SYNTHESIS OF 2-OCTYL (4-AMINO-3,5-DICHLORO-6-FLUORO-2-PYRIDINYLOXY-2,6-^{14}C)ACETATE

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SUMMARY

A convenient method of preparing 2-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy-2,6-^{14}C)acetate from glutarimide-2,6-^{14}C is described. The process includes a novel one-step conversion of glutarimide-2,6-^{14}C to pentachloropyridine-2,6-^{14}C.

Key Words: Carbon-14, glutarimide, pentachloropyridine, 3,5-dichloro-2,4,6-trifluoropyridine, 4-amino-3,5-dichloro-2,6-difluoropyridine, 2-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy)acetate.

INTRODUCTION

2-octyl (4-amino-6-fluoro-2-pyridinyloxy)acetate (6) is a post emergence broadleaf herbicide[1-4] selective to grains and is currently sold in Europe under the common name of fluroxypyr-methylheptyl and the trade name of STARANE*. A radiolabeled sample was prepared in order to complete the metabolism studies required for its registration. Although general procedures from which 6 can be derived have been published, a specific process for 6 has not been reported.

DISCUSSION

The procedure used for the synthesis of 6 is depicted in Scheme I.

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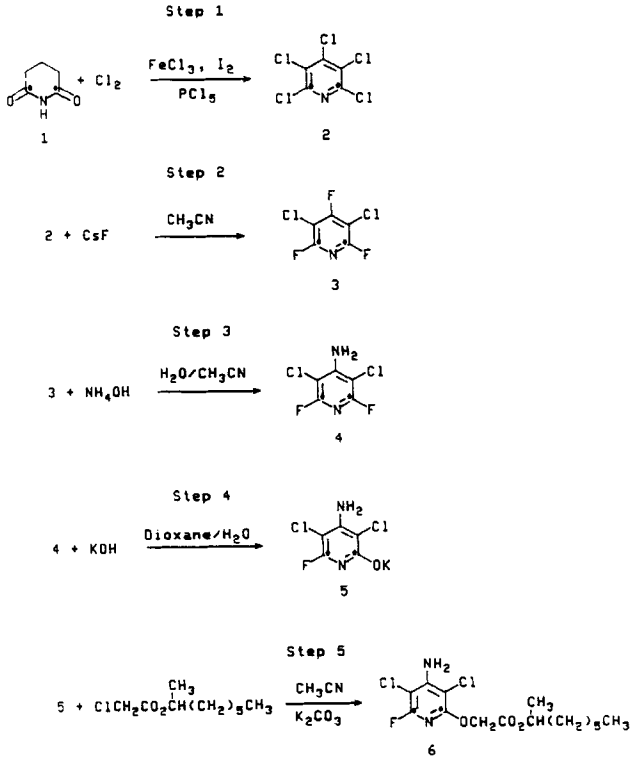
SCHEME I



Gutarimide-2,6-^{14}C (1) was prepared from KCN-^{14}C as previously described[5]. Step 1 represents a unique method of preparing pentachloropyridine-2,6-^{14}C (2) directly from glutarimide. The previous syntheses of 2 involved the conversion of 1 to a mixture of lower chlorinated pyridines. The mixture was then chlorinated via a technique similar to that previously described for 2,3,5,6-tetrachloropyridine[5] except that the reaction temperature was maintained at 250°C. The present approach eliminates the conversion of 1 to the lower chlorinated pyridines and affords 2 in a 91% yield.

It would a priori appear that the lower chlorinated pyridines could be prepared by a similar procedure if one appropriately modified the reaction temperature. Unfortunately at temperatures in the range of 24°C-200°C, a polychlorinated adduct is produced. The adduct has been tentatively identified as 2,2,3,3,5,5,6-heptachloro-2,3,4,5-tetrahydropyridine based upon its mass spectral (7 Cl) and NMR data (singlet at δ4.05).

The process described herein for the synthesis of 3,5-dichloro-2,4,6-trifluoropyridine (3, Step 2) is much more convenient to conduct on a laboratory scale and is more amenable to the tracer synthesis than that previously reported[6]. Trifluoropyridine 3 is volatile and, therefore, was not isolated in the milligram scale synthesis. However, GLC analysis of the reaction mixture indicated quantitative conversion of 2 to 3 which was substantiated by the high yields of 4-amino-3,5-dichloro-2,6- difluoropyridine (4) obtained when NH_4OH was subsequently added (Step 3). Steps 2 and 3 afforded 95% and 83% yields of 4 in the pilot run (unlabeled reactants) and tracer synthesis respectively. Care must be taken to add only two equivalents of NH_4OH since an excess will result in the formation of 2,4-diamino-3,5-dichloro-6-fluoropyridine.

The potassium salt 5 produced in Step 4 was not purified. The aqueous dioxane solvent was removed *in vacuo* and the crude 5 used to produce 2-octyl ester 6. The reaction was conducted in refluxing acetonitrile using potassium carbonate as the base as depicted in Step 5. The ester was purified via silica gel chromatography. The process afforded 18.16 mCi (83% yield for Step 5, 63% overall yield) of 99+% radiochemically pure 6 with a specific activity of 22.7 mCi/mmole.

EXPERIMENTAL

All GLC analyses were performed using a Hewlett Packard 5830A instrument under the following conditions: (A) 2' x 4 mm glass column containing 10% SE 30 on Chromosorb WHP, Inj. Temp=190°C, FID Temp=300°C, Temp 1=100°C, Time 1=2 min, Rate=20°C/min, Temp 2=250°C, Time 2=5 min; (B) 4' x 2 mm glass column containing 0.35% Silar 10C over bonded methyl silicone on 80/100 Chromosorb W-AW, Temp 1=50°C, Time 1=2 min, Temp 2=200°C, Time 2=5 min. The results are given as area%. No internal standards were used. The thin layer chromatographic (TLC) analyses were conducted on 5 x 20 cm Merck silica gel F-254 plates. The plates were radioscanned using a Vanguard radioscanner

connected to a Hewlett Packard integrator. Liquid scintillation counting was performed in a Packard Tri-Carb liquid scintillation spectrometer using New England Nuclear Aquasol liquid scintillation cocktail.

Pentachloropyridine-2,6-^{14}C (2)

A 10-ml glass ampul was purged with N_2 and a CH_2Cl_2 solution containing 1.798 mmole (ca. 41 mCi) of glutarimide-2,6-^{14}C added. The solvent was removed under a stream of N_2 at 50°-55°C. The ampul was cooled to room temperature and 11.4 mg of $FeCl_3$, 15.9 mg of I_2, and 1.91 g (9.17 mmole) of PCl_5 added. The ampul was cooled to -78°C and 1.0 ml of Cl_2, previously collected in a calibrated trap at -78°C, was transferred. The ampul was sealed, placed in a stainless steel reactor, and the reactor pressurized to 1500 psi with N_2. The reactor was placed in a rocker-heater and heated at 250-260°C for 28.5 hr. The ampul was cooled to -78°C, opened, and the excess Cl_2 allowed to escape while the ampul warmed to room temperature. The remaining contents were cooled in an ice bath and treated slowly with ice-water. The aqueous mixture was transferred to a 50-ml flask containing ca. 20 g of ice. The ampul was rinsed with H_2O (4 x 2 ml) and Et_2O (10 x 2 ml) which were transferred to the flask. The phases were mixed and extracted continuously with 15 ml of Et_2O over a 4.5 hr period. The solvent was removed from the Et_2O extract in vacuo and the residue purified via silica gel chromatography using n-hexane: benzene (1:1, 210 ml; 4:1, 420 ml) affording 411.9 mg (1.639 mmole, 91.2% yield) of 2 as a white solid; GLC (A) Rt 6.24 min, 99%; TLC radioscan (2:8 benzene:h-hexane) 100% .

4-Amino-3,5-dichloro-2,6-difluoropyridine-2,6-^{14}C (4)

A stirred mixture consisting of 411.9 mg (1.639 mmole) of 2, 3.1 mg (20.41 mmole) of CsF (dried at 120°C/0.5 mm), and 5 ml of CH_3CN was heated at reflux under a N_2 atmosphere for 24 hr to afford a mixture containing 3,5-dichloro-2,4,6-trifluoropyridine-2,6-^{14}C (3). The mixture was cooled in

an ice bath, and 465 μl of conc. NH_4OH (28%, 0.897 mg/μl, 3.34 mmole) was added dropwise. The mixture was stirred at 5°C (15 min) and room temperature (15 min), respectively. The mixture was filtered through $MgSO_4$ into a tared flask. The reaction flask and filter were rinsed with Et_2O. The solvents were removed from the filtrate in vacuo and the residual solid purified via silica gel chromatography (200 g) using $CHCl_3$ for elution. The solvent was removed from the fractions containing product in vacuo and the solid recrystallized from 6 ml of n-hexane to afford 270.0 mg (1.357 mmole, 82.8% yield) of 4 as a white solid; GLC (B) 11.37 min, 100%.

Potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinoate-2,6-^{14}C (5)

A stirred solution consisting of 191.2 mg (0.9608 mmole) of radiolabeled 4, 155.6 mg (2.380 mmole) of powdered KOH (85.8% pure), 5 ml of p-dioxane, and 2 ml of H_2O was heated in a 105°C oil bath for 21.5 hr. The solution was cooled, and the solvents removed in vacuo affording crude 5 as a solid.

2-Octyl (4-Amino-3,5-dichloro-6-fluoro-2-pyridinyloxy-2,6-^{14}C)acetate (6)

To the flask containing pyridinoate 5 was added 211.6 mg (1.024 mmole) of 2-octyl chloroacetate (98.5% pure) and 5 ml of CH_3CN. The mixture was refluxed under a N_2 atmosphere for 11.5 hr, cooled, and the solvent removed in vacuo. The residue was purified via silica gel chromatography using $CHCl_3$ for elution. The purification afforded 293.8 mg (0.8001 mmole, 83.8% yield from 4) of 6 as a colorless oil which was dissolved in 10 ml of benzene, GLC (A) Rt 11.71 min (100%), Rt standard 11.6 min; GLC (B) Rt 26.37 min (100%). The solution was counted to afford 18.16 mCi of 6 with a specific activity of 22.7 mCi/mmole. Radiolabeled and standard samples of 6 were spotted on seven 5 x 20 cm SiO_2 plates. The plates were developed in the following solvent systems and radioscanned: (1) CH_2Cl_2, Rf: 0.42, 100%; (2) $CHCl_3$, Rf: 0.36, 100%; (3) C_6H_6, Rf: 0.19, 99.9%; (4) Acetone:hexane (30:70), Rf: 0.34, 100%; (5) EtOAc:hexane (30:70), Rf: 0.40, 100%; (6) CH_3OH:C_6H_6 (5:95), Rf: 0.56,

99.2%; (7) HOAc:C_6H_6 (10:90), Rf: 0.42, 100%. The tracer and standard possessed the same Rf values[7].

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