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A convenient synthesis of [2,6-^{14}C]-2-chloroisonicotinic acid

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Summary

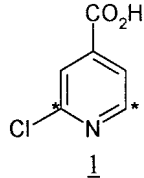
[2,6-^{14}C]-2-chloroisonicotinic acid (1) was prepared by kinetically controlled lithiation and carbonation of [2,6-^{14}C]-2,6-dichloropyridine, followed by reduction using hydrazine and potassium hydroxide. Copyright © 2001 John Wiley & Sons, Ltd.

Key Words: kinetic control; lithiation; [2,6-^{14}C]-2,6-dichloropyridine; [2,6-^{14}C]-2-chloroisonicotinic acid

Introduction

[2,6-^{14}C]-2-Chloroisonicotinic acid (1) was required for the preparation of a ^{14}C-labeled herbicide to be used in seasonal field testing.

A literature survey revealed no short syntheses useful for preparing material labeled with ^{14}C in the pyridine ring, and the more easily accessible ^{14}C-carboxyl-labeled material was not acceptable. Most



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literature preparations of 2-chloroisonicotinic acid have involved the conversion of isonicotinic acid or a derivative thereof to its N-oxide, followed by introduction of chlorine at the 2-position using $POCl_3$ or PCl_5.[1] This route would technically be feasible for preparation of

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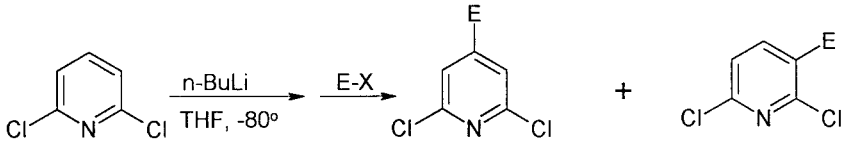
radiolabeled material, since [2-^{14}C]-isonicotinic acid can be prepared from ^{14}C-potassium cyanide via [2-^{14}C]picoline.[2] However, in our hands, the preparation of ^{14}C-labeled isonicotinic acid by this route has proved difficult and time-consuming. Other literature syntheses have utilized pyridine precursors not readily available with ^{14}C labels.[3–5]

Results and Discussion

Radinov and coworkers.[6] have shown that 2,6-dichloropyridine can be lithiated with kinetic control at the 4-position at low temperatures. (By contrast, lithiation occurs predominantly at the 3-position under equilibrating conditions.) Low-temperature quenching of the kinetic reaction mixture with electrophiles (Me_3SiCl, MeI) afforded mixtures in which products substituted in the 4-position predominated.

Since [2,6-^{14}C]-2,6-dichloropyridine (2) can be prepared readily as described by McKendry, Muelder and Wass,[7,8] it appeared to us that it should be possible to prepare ^{14}C-labeled 2,6-dichloroisonicotinic acid (3)



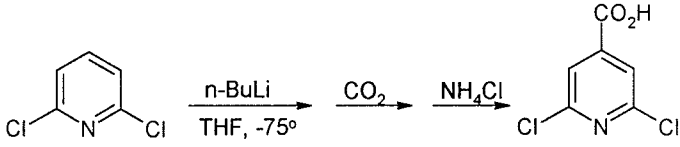
E = $SiMe_3$, 74:26

E = Me, 72:28

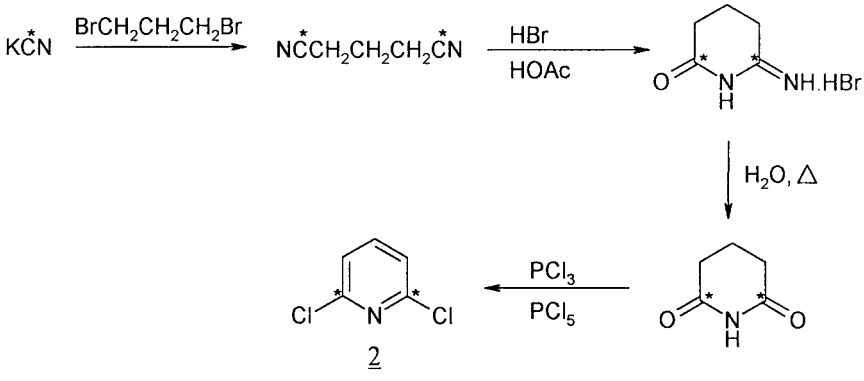
by means of kinetic lithiation of this material followed by quenching with carbon dioxide; and since 2,6-dichloroisonicotinic acid can be reduced to 2-chloroisonicotinic acid by a modified Wolff–Kishner reduction,[9] we felt that we should be able to prepare the desired ^{14}C-labeled product.

Since the above transformation has not been reported with carbon dioxide as electrophile, a lithiation/carbonation reaction was attempted on unlabeled material. Treatment of 2,6-dichloropyridine with n-butyllithium in tetrahydrofuran at -75°C for 30 min, followed by treatment with excess carbon dioxide and subsequent acidification gave a mixture of 2,6-dichloro-isonicotinic and nicotinic acids. Recrystallization of the crude mixture from ethanol/water afforded a 52% yield of

the desired 2,6-dichloroisonicotinic acid, 97% pure by ^{1}H NMR. Purification appeared to be facilitated by the relatively high solubility of the isomeric 2,6-dichloronicotinic acid present in the crude material.



[2,6-^{14}C]-2,6-dichloropyridine (2) was therefore prepared conveniently from ^{14}C-potassium cyanide.[7,8] The radiochemical yield (four steps) was 73%. Very little overchlorination was observed in the last step and the crude radiochemical purity of the product was 97%.



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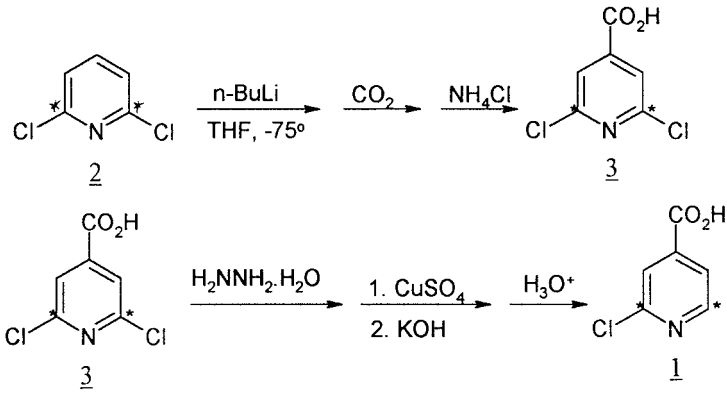
Lithiation and carbonation of [2,6-^{14}C]-2,6-dichloropyridine followed. A 57% yield of [2,6-^{14}C]-2,6-dichloroisonicotinic acid (3) was obtained, 99% pure by TLC after recrystallization. Reduction with hydrazine hydrate followed by heating with aqueous cupric sulfate and potassium hydroxide[9] afforded crude [2,6-^{14}C]-2-chloroisonicotinic acid (1). The product was purified by flash column chromatography to afford a 22% yield of the desired product, 99% radiochemically pure by HPLC (yield unoptimized).



Conclusion

Kinetically controlled lithiation and carbonation of [2,6-^{14}C]-2,6-dichloropyridine (2) followed by hydrazine reduction provided a convenient method of preparing the desired [2,6-^{14}C]-2-chloroisonicotinic acid (1) in satisfactory yield and in a timely manner.

Experimental

General

^{1}H NMR spectra were obtained on a Bruker AC-E 300 spectrometer. TLC analyses were performed on Analtech Uniplate™ Silica Gel GHLF 5×20 cm plates. HPLC analysis was performed on a Waters System (717 Autosampler, 600E pump, 2487 Dual X absorbance detector) with Zorbax® SB-C18 column and Canberra radiodetector. Flash chromatography was performed on Merck silica gel (230–400 mesh, 60 A) supplied by Aldrich Chemical Company.

[2,6-^{14}C]-2,6-Dichloroisonicotinic acid (3)

Anhydrous tetrahydrofuran (8.8 ml) was stirred under argon in a 50 ml 3 neck flask equipped with magnetic stirbar, rubber septum and air condenser connected to a vacuum line. The solution was cooled to -75°C (external bath temperature) and treated, dropwise, with *n*-butyllithium (1.6 M in hexanes, 8.8 mmol, 5.5 ml) After stirring for 10 min, a solution of [2,6-^{14}C]-2,6-dichloropyridine[7,8] (2, 802 mCi, 91.3 mCi/mmol, 8.78 mmol, 1.30 g) in 8.8 ml of anhydrous tetrahydro-

furan was added dropwise by syringe with rapid stirring. An orange–red color developed. The solution was stirred at −75°C for 30 min and the flask was then immersed in liquid nitrogen. The system was evacuated and excess carbon dioxide (approx. 20 mmol) was condensed in. The reaction mixture was thawed in the −75°C bath, whereupon the orange-red color disappeared and a milky white precipitate formed. After stirring at −75°C for a further 20 min, 2.8 ml of saturated aqueous ammonium chloride solution was added dropwise with rapid stirring and the mixture was warmed slowly to room temperature. A clear solution with a flocculent precipitate resulted. Solvent was removed on the rotary evaporator and the residue was partitioned between ether and water. Solid potassium carbonate was added to pH 11 and the layers were separated. The aqueous layer was washed 2 × 5 ml of ether and the ether extracts were discarded. The aqueous layer was cooled in ice and acidified to pH 2.5 with hydrochloric acid. Nitrogen was bubbled through for a few minutes to remove any ether remaining and the mixture was cooled in ice to complete precipitation of the product. The product was collected by vacuum filtration and pumped dry to afford 1.03 g of an off-white solid. TLC (Silica gel GHLF, hexane : ether : acetic acid, 50 : 50 : 1) showed approximately 90% pure product, with approximately 5% of isomeric [2,6-^{14}C]-2,6-dichloroisonicotinic acid present. Unlabeled 2,6-dichloronicotinic acid (Aldrich, 1.03 g) was added and the product was recrystallized from 12 ml of ethanol:water (1 : 2) to afford 1.875 g of off-white crystals.

TLC (Silica gel GHLF, hexane : ether : acetic acid, 50 : 50 : 1) showed 99% radiochemistry purity.

Radioassay (ethanol): 457 mCi at 46.8 mCi/mmol (57% radiochemical yield).

[2,6-^{14}C]-2-Chloroisonicotinic acid (1)

[2,6-^{14}C]-2,6-Dichloroisonicotinic acid (3, 9.76 mmol, 457 mCi, 46.8 mCi/mmol, 1.875 g) and unlabeled 2,6-dichloroisonicotinic acid (Aldrich, 7.17 mmol, 1.377 g) were placed in a 100 ml flask with a stirbar and reflux condenser. Water (325 mmol, 5.85 g) and hydrazine (325 mmol 10.43 g) were added and the mixture was stirred at 53° for 2.5 h. The mixture was cooled and volatiles were removed on the rotary evaporator to afford a pale yellow solid. Water (10 ml) was added and the mixture was heated to boiling. Ten percent aqueous cupric sulfate solution (54 ml) was added slowly while the mixture was still hot and a

thick, dark gelatinous precipitate formed. The mixture was refluxed for 30 min and transferred to a larger flask. Boiling was continued and a solution of potassium hydroxide (10 g) in water (10 ml) was added carefully. Vigorous gas evolution resulted. The mixture was refluxed for a further 15 minutes and then cooled in ice. Filtration through Celite® afforded a clear solution. The pH was adjusted to 2 with hydrochloric acid and a precipitate formed. The precipitate was collected by vacuum filtration and washed with two small portions of ice-cold water. Small amounts of water trapped in the solid were removed before flash chromatography by evaporation with methanol.

The crude product was slurried with a minimal volume of CH_2Cl_2 : CH_3OH : conc. NH_4OH (80 : 20 : 4) and loaded onto a column of flash silica (18 cm × 4 cm) packed in the same solvent mixture. The same solvent mixture was used for elution. After an early-eluting impurity, pure fractions were obtained. The pure fractions were combined and evaporated to afford a white solid. The solid was dissolved in a minimal volume of water and filtered through Celite® to clarify it. The solution was concentrated to a volume of approximately 15 ml on the rotary evaporator, cooled in ice, and acidified to pH 1 with concentrated hydrochloric acid. The precipitate was collected by vacuum filtration, washed with ice-cold water and pumped dry to afford 0.613 g of a creamy white solid.

HPLC (Zorbax SB-C18, 0.1% TFA/CH_3CN, 75 : 25): 99% radiochemical purity. Co-elution with cold standard was demonstrated.

Radioassay (ethanol with 2% conc. NH_4OH): 102.8 mCi at 26.4 mCi/mmol (22% radiochemical yield).

Acknowledgements

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