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Synthesis of High Specific Activity [1-^{14}C] 3-N,N-Dimethylaminopropylamine

Zhigang Jian*, Crist Filer, and Terence P. Kelly

NEN Life Science Products, 549 Albany St., Boston, MA 02118

Summary

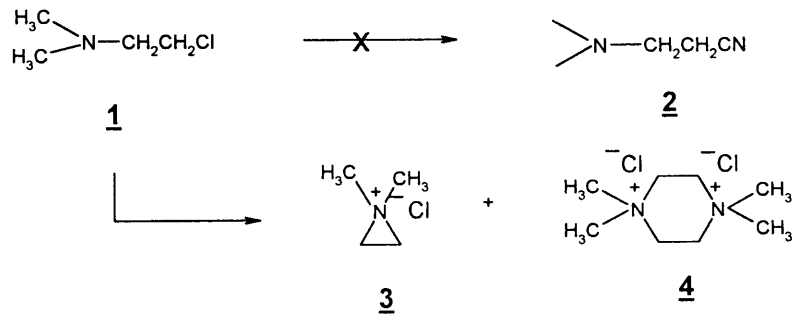
A convenient synthesis of high specific activity [1-^{14}C] 3-N,N-dimethylaminopropylamine 10 is described. The reaction between [^{14}C] KCN and N,N-dimethyl bromoacetamide 7 afforded [nitrile-^{14}C] N,N-dimethyl cyanoacetamide 8. Stepwise reduction of 8 provided 99% pure 10 in 59% overall radiochemical yield. The specific activity was 53.3 mCi/mmol.

Keywords: [1-^{14}C] 3-N,N-Dimethylaminopropylamine, [Nitrile-^{14}C] N,N-Dimethyl Cyanoacetamide, [3-^{14}C] N,N-Dimethyl 3-aminopropionamide.

Introduction

We needed to prepare [1-^{14}C] 3-N,N-dimethylaminopropyl amine 10 at high specific activity. This compound is made industrially by the addition of dimethylamine to acrylonitrile, followed by the reduction of the nitrile group (1). The preparation of low specific activity ^{14}C labeled 3-N,N-dimethylaminopropylamine was also carried out in the same way (2). Unfortunately, we could not apply this process because ^{14}C- labeled acrylonitrile is quite unstable at high specific activity. We initially tried to prepare this compound by the reduction of 3-N,N-dimethylaminopropionitrile 2, which in turn would be made from the reaction of N,N-dimethyl-3-chloroethylamine 1 and sodium cyanide (Scheme I). However, all the attempts to prepare nitrile 2 failed, probably due to the formation of aziridinium chloride 3 and piperazinium chloride 4 under a variety of reaction conditions (3).

Scheme I



A solution was implemented through the use of [nitrile-^{14}C] N,N-dimethyl cyano acetamide 8 prepared from [^{14}C] sodium cyanide and N,N-dimethyl bromoacetamide 7

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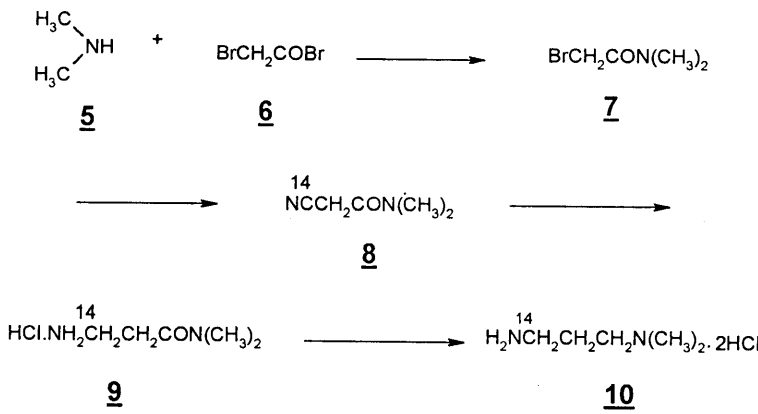
(Scheme II). This paper describes the successful synthesis of high specific activity [1-^{14}C] 3-N,N-dimethylaminopropylamine 10.

Results and Discussion

N,N-Dimethyl bromoacetamide 7 was prepared by reacting two equivalents of dimethylamine 5 and one equivalent of bromoacetyl bromide 6 in chloroform at low temperature in 79% yield. N,N-Dimethyl bromoacetamide 7 was then converted to [nitrile-^{14}C] N,N-dimethyl cyanoacetamide 8 in 82% radiochemical yield by treatment with [^{14}C] KCN in water/ethanol (1/2) at room temperature. Several attempts to reduce N,N-dimethyl cyanoacetamide 8 ($LiAlH_4$, $NaBH_4/AlCl_3$, $LiAlH_4/AlCl_3$, and diborane) in one step to the target compound 10 were unsuccessful. The stepwise reduction, however, provided the final product 10 in excellent yield. Thus, intermediate 8 was first hydrogenated at room temperature to afford N,N-dimethyl 3-aminopropionamide 9 in quantitative yield, which was then reduced with diborane in THF to give desired product 10. Recrystallization in ethanol/ether afforded 99% pure 10 in 72% radiochemical yield.

Scheme II



This process afforded high specific activity 10 in 59% overall radiochemical yield and can be used to label any of the 3 carbons in the chain with ^{14}C because of the easy access to both ^{14}C labeled cyanide and ^{14}C labeled bromoacetyl bromide.

Experimental

Evaporation was carried out on a Buchi rotary evaporator in vacuo at a bath temperature below 40°C. TLC was performed on Analtech 5x 20 cm (250 um) silica gel GF plates. Autoradiography was performed at 0°C after spraying with PPO (NEN Life Science Products) and exposing the TLC plates to Eastman Kodak SB-5 film. TLC plates were also scanned for radioactivity by using a Packard 7201 scanner. Proton NMR were obtained on a Bruker WP 300 MHz spectrometer and chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a Kratos MS25 Mass Spectrometer.

[Nitrile-^{14}C] N,N-Dimethyl Cyanoacetamide 8:

Dimethylamine 5 (4.7g 100 mmol) in chloroform (10 mL) was added dropwise to bromoacetyl bromide 6(10.2g, 50 mmol) in chloroform (40 mL) at 0^{0}C over 15 min. The reaction mixture was stirred at room temperature for 30 min. after the addition was completed and stored in a refrigerator overnight. It was then washed with water and dried over $MgSO_4$. Solvent removal left 7 as a colorless oil (6.57 g, 79%) which was used directly in the next step reaction without further purification. [^{14}C] Sodium cyanide (0.97 g, 1129 mCi, 19.8 mmol) in water (20 mL) was added dropwise over 15 min. at room temperature to N,N-dimethyl bromoacetamide 7 (3.32 g, 20 mmol) in ethanol (30 mL) with stirring. The stirring was continued overnight at room temperature and solvent was then removed. The residue was partitioned between water (15 mL) and chloroform (6 x 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and the solvent removed. Flash chromatography (silica gel, hexane/EtOAc 1/1) afforded [nitrile-^{14}C] N,N-dimethyl cyanoacetamide 8 (1.82 g, 929 mCi, 82% radiochemical yield). ^{1}H NMR ($CDCl_3$): 3.6 (s, 2H), 3.1 (s, 3H), 3.0 (s, 3H).

[1-^{14}C] 3-N,N-Dimethylaminopropylamine 10:

[Nitrile-^{14}C] N,N-Dimethyl cyanoacetamide 8 (1.82 g, 929 mCi, 16.3 mmol) in ethanol (25 mL) and conc. HCl (3 mL) was hydrogenated at 45 psi in a Parr shaker in the presence of PtO_2 (475 mg) at room temperature for 3 hr. Solvent was removed and the residue was basified with 10% NaOH, and the mixture was extracted with chloroform (4 x 25 mL). The combined extracts were dried over Na_2SO_4. Solvent removal afforded 9 which was then dissolved in 40 mL of anhydrous THF prior to adding dropwise, with stirring, diborane (1M, 100 mL) at 0^{0}C over 30 min. The reaction mixture was refluxed for 3 hr. Excess diborane was removed on a rotary evaporator and the residue was treated carefully with 10 mL of ethanol, followed by 10 mL of conc. HCl. The mixture was evaporated to dryness and basified with conc. NaOH. The product was distilled along with water into a trap cooled with liquid nitrogen. The aqueous solution was acidified with conc. HCl. Solvent removal left a white solid which was dissolved in a small volume of ethanol and precipitated by the addition of ether. The product was collected by filtration and washed with ether (2.01g, 72% radiochemical yield). ^{1}H NMR (D_2O): 3.25 (m,2H), 3.1 (t, 2H), 2.9 (s, 6H), 2.15 (m, 2H); MS (DCI) m/e 105(M^+). The specific activity of the product was found to be 53.3 mCi/mmol by weight assay.

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