JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2003; **46**: 1279–1285.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.787

Note

Purification of [^{11}C]nitromethane for use in asymmetric nitroaldol reactions

Sven Åke Gustavsson, Koichi Kato and Bengt Långström*
Department of Organic Chemistry, Institute of Chemistry, Uppsala University and Uppsala Imanet, P.O. Box 967, Uppsala 751 09, Sweden

Summary

[^{11}C]Nitromethane was prepared by modifying previously published procedures. Nitrogen oxides contaminating the [^{11}C]nitromethane were removed by a heated sodium carbonate plug. An asymmetric nitroaldol reaction was performed using a lanthanum–lithium–(*R*)-binol (LLB) complex as catalyst. 1-Nitro-4-phenylbutan-2-ol was produced in a reaction between [^{11}C]nitromethane and 3-phenyl-propionaldehyde in 16% enantiomeric excess (e.e.) and a radiochemical yield of 23%. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: [^{11}C]nitromethane; asymmetric nitroaldol reaction; LLB

Introduction

Several compounds having the β-aminoalcohol structure are potentially interesting as PET tracers e.g. norepinephrine.[1] Secondary β-aminoalcohols are chiral molecules and the two enantiomers can have different pharmacological properties. If a β-aminoalcohol is labelled with ^{11}C and used as a PET tracer, the two enantiomers may display different binding affinities, selectivities or metabolism. Using a racemic tracer in PET studies may result in complex data due to the two enantiomers. An enantiomerically pure tracer is preferred.[1] Therefore, the use of

*Correspondence to: B. Långström, Department of Organic Chemistry, Institute of Chemistry, Uppsala University and Uppsala Imanet, P.O. Box 967, Uppsala 751 09, Sweden. E-mail: bengt.langstrom@uppsala.imanet.se

Received 30 July 2003
Revised 8 August 2003
Accepted 5 September 2003

asymmetric catalysis was explored in the synthesis of ^{11}C-labelled chiral β-aminoalcohols.

The synthetic route to ^{11}C-labelled β-aminoalcohol contains a reduction of the labelled β-nitroalcohol[2] formed by the Henry reaction between an aldehyde and [^{11}C]nitromethane in the presence of a base. Since [^{11}C]nitromethane is rapidly produced in good radiochemical yields[3] it is a valuable route to ^{11}C-labelled β-nitroalcohols.

The use of bases, such as tetrabutylammonium fluoride (TBAF), yields racemic β-nitroalcohols. When the reaction was performed with the Shibasaki catalyst[4] (LLB complex) an asymmetric nitroaldol reaction gave β-nitroalcohols in low e.e. The Shibasaki catalyst, however, is sensitive to acidic substances and special precautions had to be taken in order to remove acidic nitrogen oxides.

Results and discussion

Production of [^{11}C]nitromethane

The previously described nitroaldol reactions with [^{11}C]nitromethane using TBAF were insensitive to small impurities[2] and therefore no problems were then observed regarding the [^{11}C]nitromethane production. The LLB metal complex, however, was sensitive to contaminations such as water and acidic compounds.

[^{11}C]Nitromethane was produced by passing [^{11}C]iodomethane through a column containing a plug of silver nitrite kept at 80°C. A schematic presentation of the system is shown in Figure 2. In initial experiments it was observed that the colourless THF solution of LLB quickly turned red during the trapping of [^{11}C]nitromethane. The breakdown products of this reaction were however basic enough to catalyse a racemic nitroaldol reaction. 1-Nitro-4-phenyl-[1-^{11}C]butan-2-ol was obtained in 5–10% decay-corrected radiochemical yield but with no enantiomeric excess. In control experiments when only the carrier-gas helium was passed through the silver nitrite, the same colour change took place. It was thus confirmed that the silver nitrite was the source of contamination. Silver nitrite decomposes during heating and forms, among other things, nitrogen oxides[5] that quickly destroy the LLB-complex. To overcome this problem, a method for the purification of [^{11}C]nitromethane was developed.

The first attempt to remove the nitrogen oxides was made by passing the formed [^{11}C]nitromethane through sodium hydroxide on a silica support (i.e. Ascarite^{TM}). However, with this material both the formed

nitrogen oxides and [^{11}C]nitromethane were absorbed. Finely ground sodium hydrogen carbonate at ambient temperature was also used unsuccessfully since large amounts of the radioactivity were trapped on the material while nitrogen oxides still leaked through. The large absorption of [^{11}C]nitromethane could be due to condensation of nitromethane on the surface of the particles. This problem was overcome by putting the sodium hydrogen carbonate column partly inside the oven at 80°C, Figure 1. It was found that the column material efficiently absorbed the nitrogen oxides, without trapping [^{11}C]nitromethane, if a low flow rate of helium (10–20 ml/min) was used. This method was successful but reproducibility was poor. To improve the trapping of nitrogen oxides a stronger base, sodium carbonate, was used. This gave reproducible production of [^{11}C]nitromethane free from nitrogen oxides. It allowed a higher flow rate of the carrier helium gas; up to 50 ml/min. Sodium carbonate can, however, release water that decomposes the LLB-complex. The [^{11}C]nitromethane was therefore passed through an extra Sicapent^{TM} drying tower before it was trapped in the LLB-solution, Figure 2.

Parameters influencing the process are the helium flow rate, the column temperature, the particle size and the basicity of the column. The process gave reproducible production of contaminant free [^{11}C]nitromethane with the parameters set as mentioned above.

Synthesis of 1-nitro-4-phenyl-[1-^{11}C]butan-2-ol

The 1-nitro-4-phenyl-[1-^{11}C]butan-2-ol was selected as a target molecule due to its stability towards elimination or racemisation. 3-Phenyl-

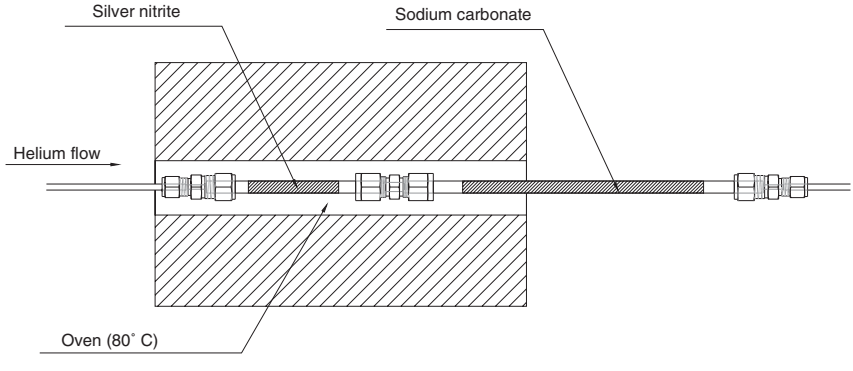


Figure 1. The nitromethane reactor with a sodium carbonate plug for absorption of nitrogen oxides

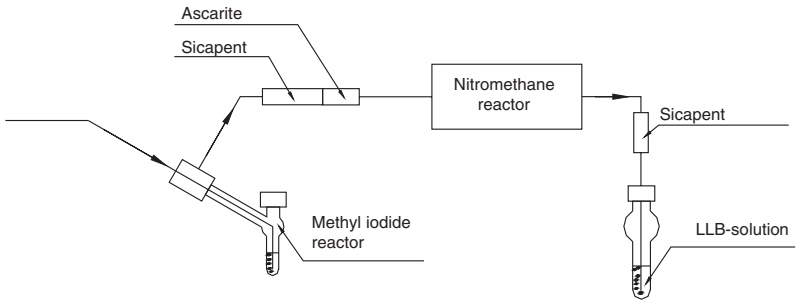
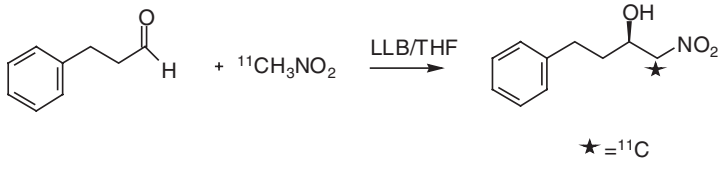


Figure 2. Schematic picture of the [^{11}C]iodomethane and [^{11}C]nitromethane system including the trapping vial containing the LLB-catalyst solution



Scheme 1. The synthesis of 1-nitro-4-phenyl-[1-^{11}C]butan-2-ol

propionaldehyde and [^{11}C]nitromethane were reacted in the presence of the LLB-complex in order to obtain the corresponding labelled *β*-nitroalcohol (Scheme 1). 1-Nitro-4-phenyl-[1-^{11}C]butan-2-ol was obtained in 23% decay-corrected radiochemical yield and with 16% e.e.

Experimental

General

[^{11}C]Carbon dioxide was produced by the ^{14}N(p, α)^{11}C nuclear reaction using a gas target containing nitrogen (AGA 6.0) and 0.05% oxygen (AGA 6.0) bombarded with 17 MeV protons produced by the Scanditronix MC-17 cyclotron of Uppsala Research Imaging Solutions. Solid phase extraction was performed with 3 ml C18 SPEC® columns with 15 mg of sorbent (Ansys Diagnostics, Inc., Lake Forrest, CA).

Chemicals

Lanthanum isopropoxide and (*R*)-(+)-1,1′-bi-2-naphtol (BINOL) were of 99% purity. Butyl lithium 2.5 M in hexane was obtained from Lancaster. Silver nitrite (P.A., Fluka), acetonitrile (Chromasolv®,

Riedel-deHaën) and 2-propanol (HPLC grade, Sigma-Aldrich) were used. Trifluoroacetic acid (Uvasol), phosphorous pentoxide (Sicapent™) and hexane (LiChrosolv®) were purchased from Merck. Sodium carbonate was of P.A. quality.

Chromatography

Analytical liquid chromatography separations were performed using a Beckman (Fullerton, CA, USA) System (a 126 pump and a 166 UV detector) with a flow γ-detector (Bio-scan Flow-count, Washington, DC, USA) in series.

The following eluents and methods were used:

Method 1: Luna C18(2) HPLC column (Phenomenex) 75 × 4.6 mm, 3 µm, flow 1 ml/min, A = 10 mM KH_2PO_4 + 10 mM K_2HPO_4, B = acetonitrile, linear gradient 5–60% B 0–15 min, 15–25 min 60% B.

Method 2*:* Chiracel OD-H (Daicel) 250 × 4.6 mm, isocratic flow 0.8 ml/min, hexane with 10%(V/V) 2-propanol.

Semi-preparative HPLC was performed using equipment from Waters (Milford, MA, USA); a modified M 6000A pump, a 440 UV detector with a flow β-detector in series using the following method:

Method 3: Ultrasphere C18 (Beckman) 250 × 10 mm, 5 µm, flow 4 ml/min, isocratic water with 40% (V/V) acetonitrile.

La–Li–BINOL (LLB) complex

The synthesis of LLB was performed according to published procedures[4] under an argon atmosphere in Schlenk flasks. (R)-(+)-1,1′-Bi-2-naphthol (211.8 mg, 0.74 mmol) and lanthanum isopropoxide (78.5 mg, 0.248 mmol) was dissolved in 20 ml THF. Butyl lithium (0.3 ml, 3 mmol) was added at 0°C and the mixture was left at ambient temperature overnight. Water (18 µl, 1 mmol) and butyl lithium (133 µl, 1 mmol) was then added.

[^{11}C]Nitromethane

[^{11}C]Iodomethane was prepared by reduction of [^{11}C]carbon dioxide with lithium aluminium hydride and a subsequent reaction with hydrogen iodide.[6] The formed [^{11}C]methyl iodide was passed through tubes containing Sicapent™ and Ascarite™, respectively, in order to remove water and hydroiodic acid. [^{11}C]Nitromethane was obtained by

passing the [^{11}C]methyl iodide through a 4 cm silver nitrite plug held at 80°C in a 4 mm I.D. glass tube.[7] In the same tube, after the silver nitrite, a 10 cm plug of finely ground and dried sodium carbonate was placed. The formed [^{11}C]nitromethane was also passed through a tube (I.D. 10 mm, length 50 mm) containing Sicapent™. The synthesis time of [^{11}C]nitromethane counted from the release of $^{11}CO_2$ was about 15 min and most radioactivity was transformed to [^{11}C]nitromethane.

1-Nitro-4-phenyl-[1-11c]butan-2-ol

The LLB-solution (300 µl) was placed in a 2 ml V-shaped vial. [^{11}C]Nitromethane was transferred in a helium stream and trapped in the LLB-solution. The trapping vial was then placed in a cooling bath (−40°C) and 3-phenyl-propionaldehyde (1 µl, 7.6 µmol) was added. After 3 min, a saturated solution of ammonium chloride (100 µl) was added to quench the reaction and the vial was removed from the cold bath. Acetonitrile (1 ml) was added to the reaction mixture, which was then passed through a C-18 SPEC® disc. An aliquot from the filtrate was analysed by analytical LC (method 1). The reference compound 1-nitro-4-phenylbutan-2-ol had a retention time of 10 min (method 1). The rest of the filtrate was diluted with 1 ml of water and injected on to the semi-preparative LC (method 3). The fraction with a retention time of approximately 13 min was collected. This fraction, approximately 6 ml, was diluted with water to a total volume of 10 ml. The diluted fraction was passed through a SPEC® disc and the labelled 1-nitro-4-phenylbutan-2-ol was retained. The disc was flushed with helium (200 ml/min) and was eluted with 300 µl of the mobile phase from HPLC method 2. This eluate was used for the determination of the enantiomeric excess (e.e.) by chiral HPLC (method 2).

Conclusions

[^{11}C]Nitromethane was purified from nitrogen oxides by using a plug of sodium carbonate. The method was dependent on several parameters such as the helium flow, the column temperature, the particle size of the solid base and the basicity of the absorbent material. Appropriate values of these parameters enabled reproducible synthesis of contami-

nant free [^{11}C]nitromethane. The removal of the nitrogen oxides was important in order not to decompose the LLB used as the metal mediator in the asymmetric nitroaldol reaction. The reaction between [^{11}C]nitromethane and 3-phenyl-propionaldehyde in an LLB solution yielded 1-nitro-4-phenylbutan-2-ol with 16% enantiomeric excess (e.e.) and a decay-corrected radiochemical yield of 23%.

Acknowledgement

The Japan Society for the Promotion of Science (JSPS) is gratefully acknowledged for a Postdoctoral Fellowship for Research Abroad.

References

1. Farde L, Halldin C, Någren K, Suhara T, Karlsson P, Schoeps K-O, Swahn C-G, Bone D. *Eur J Nucl Med* 1994; **21**: 345–347.
2. Någren K, Schoeps KO, Halldin C, Swahn CG, Farde L. *Appl Radiat Isot* 1994; **45**: 515–521.
3. Schoeps KO, Stone-Elander S, Halldin C. *Appl Radiat Isot* 1989; **40**: 261–262.
4. Shibasaki M, Yoshikawa N. *Chem Rev (Washington, DC, US)* 2002; **102**: 2187–2209.
5. Oza TM, Oza VT, Thacker RH. *J Chem Soc* 1955; 2457–2465.
6. Långström B, Lundqvist H. *Appl Radiat Isot* 1976; **27**: 357–363.
7. Schoeps KO, Halldin C, Stone-Elander S, Långström B, Greitz T. *J Label Compd Radiopharm* 1988; **25**: 749–758.

