JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2006; **49**: 263–267.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1024

Note

Simple synthesis of [1-^{11}C]acetate

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Summary

[1-^{11}C]Acetate is prepared by carboxylation of a Grignard reagent, CH_3MgBr, on a simple polyethylene loop with cyclotron-produced [^{11}C]carbon dioxide, followed by hydrolysis and purification on solid-phase extraction cartridges. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: acetate; loop synthesis; solid-phase extraction; carbon 11

Introduction

[1-^{11}C]Acetate is a well-known tracer entering the Krebs cycle, reflecting cell oxidative metabolism. Besides cardiology, a new interest is arising for [1-^{11}C]acetate in oncology mainly for the study of prostate and liver tumors.

[1-^{11}C]Acetate is prepared by carboxylation of a Grignard reagent, CH_3MgBr or CH_3MgCl, with cyclotron-produced [^{11}C]carbon dioxide, followed by hydrolysis and purification. The original synthesis[1] requires solvent extraction, a difficult step for automation; simplified methods have been reported to avoid phase separation, mostly making use of SPE (solid-phase extraction) techniques.[2–5] New techniques for ^{11}C-carboxylation, based on immobilization or containment of Grignard reagent on the inner surface of various tubing, have greatly improved the production of [1-^{11}C]acetate[6] and have been applied to other compounds such as WAY100635[7] and other syntheses (^{11}C-methylations[8]).

For a new automated system, we aimed at a combination of these techniques to achieve 'the simplest system': loop method for Grignard carboxylation, based on results from Davenport *et al.*[6] and SPE techniques for purification, as reported for [1-^{11}C]acetate by Kruijer *et al.*[3] and Roeda *et al.*[4]

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Received 19 May 2005
Revised 3 October 2005
Accepted 15 October 2005

Experimental

Materials and methods

Reagents: Methyl magnesium bromide 3 M solution in diethyl ether, THF and other chemicals were obtained from Sigma Aldrich Fluka. Sodium bicarbonate for IV perfusion, $NaHCO_3$ 1.4% (0.16 mmol ml^{-1}), is obtained from Aguettant.

Acetate carrier solution is 1 mmol l^{-1}. The loop was made from 1 m of 3.20 mm OD PE tubing (1.6 mm ID), washed before each run with 10 ml water, 10 ml THF and dried with 100 ml min^{-1} nitrogen for 20–30 min. The solid-phase cartridges were Alltech Maxi-clean IC-H, IC-OH and IC-Ag, 0.5 ml cartridges. H^+/Ag column was obtained by mixing the contents of two of each SPE cartridges in a 2 ml syringe, equipped with rubber cap. Carbon 11 was obtained as [^{11}C]carbon dioxide via the $^{14}N(p,\alpha)^{11}C$ reaction on N5.6 nitrogen with 0.5% N5.6 oxygen, with 18 MeV protons (IBA Cyclone 18/9 cyclotron). $^{11}CO_2$ was concentrated in a stainless steel loop/cryogenic trap (liquid nitrogen).

Analytical HPLC was performed on a Beckman Gold system, with a Raytest GABI for radioactivity detection, or a Beckman RI detector on an Aminex HP-87H (organic acids) 7.8 × 300 mm column eluted with 0.004 M H_2SO_4 in water at 0.6 ml min^{-1}, at room temperature. Radiochemical yields were determined with a Capintec CRC-120 dose calibrator.

[1-^{11}C]Acetate production

The loop is loaded under nitrogen through a 3-way stopcock with 100 µl of CH_3MgBr solution, freshly prepared from 1 ml of methyl magnesium bromide 3 M solution in diethyl ether diluted with 1 ml of distilled THF. A 5 ml min^{-1} nitrogen flow is then established through the system, and cyclotron-produced $^{11}CO_2$ is recovered from the target and released from the cryogenic trap through the loop less than 2 min after Grignard introduction.

Further, 2 ml of 1 mM carrier acetate solution is pushed through the loop and passed on the combination of SPE cartridges (mixed H^+/Ag, OH^-). Then 5 ml water and 10 ml air are used to rinse the loop and the cartridges, and then the anionic IC-OH SPE cartridge is washed with 10 ml of water before elution with 5 ml 0.9% NaCl solution in a vial containing 0.5 ml of 2 N HCl. A 200 ml min^{-1} nitrogen flow (from an independent line) is established for 2 min for [^{11}C]carbonate elimination.

The injectable [^{11}C]acetate solution is obtained after neutralization with 6 ml $NaHCO_3$ 1.4%, filtration through 0.22 µm millipore filter, and dilution with sterile isotonic saline (Figure 1).

Results and discussion

This simple setup produces [1-^{11}C]acetate in good yields (60–70% decay corrected to EOB). The amount of Grignard in this synthesis is similar to the amounts used by Kruijer *et al.* (0.3 mmol)[3] or Roeda *et al.* (0.1 mmol),[4] but higher than the amount (0.03 mmol) reported by Davenport *et al.* in their system based on a smaller teflon loop.[6] As shown by HPLC (Figure 2), by-products such as [^{11}C]acetone and [^{11}C]*t*-butanol are present in the waste fraction, with a minor amount of [1-^{11}C]acetate. SPE techniques afford an easy

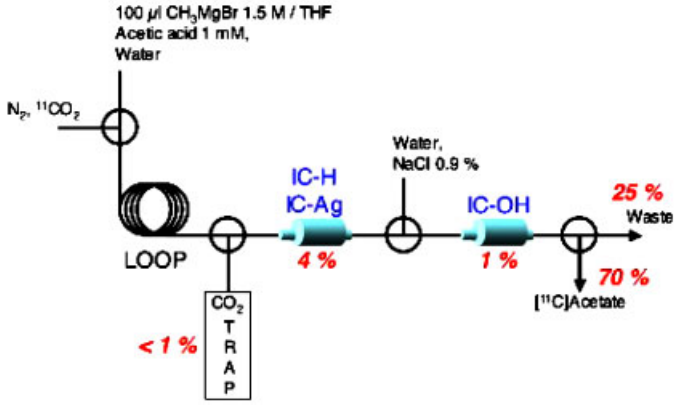

Figure 1. Synthesis apparatus and radioactivity distribution

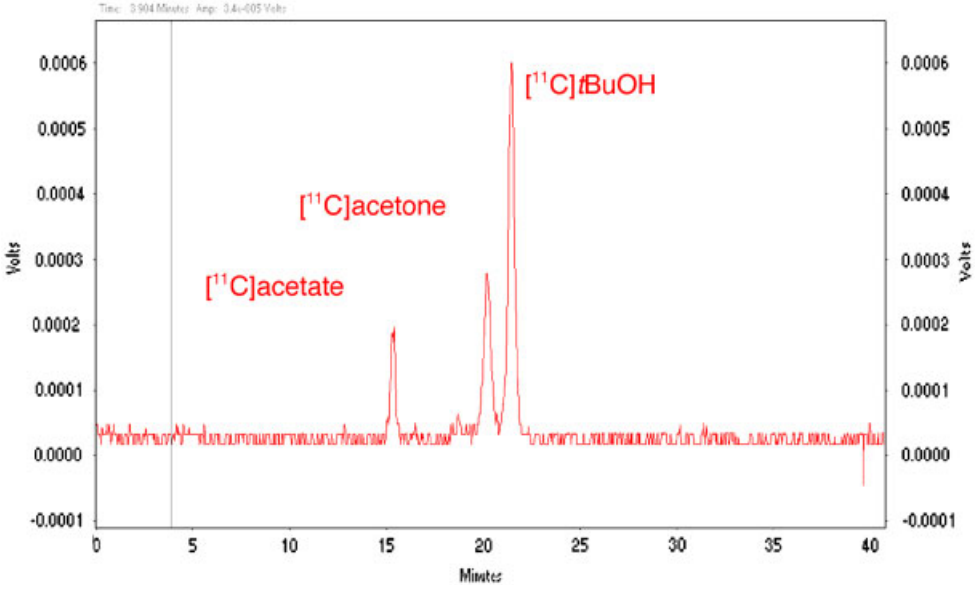

Figure 2. HPLC radiochromatogram of waste fraction

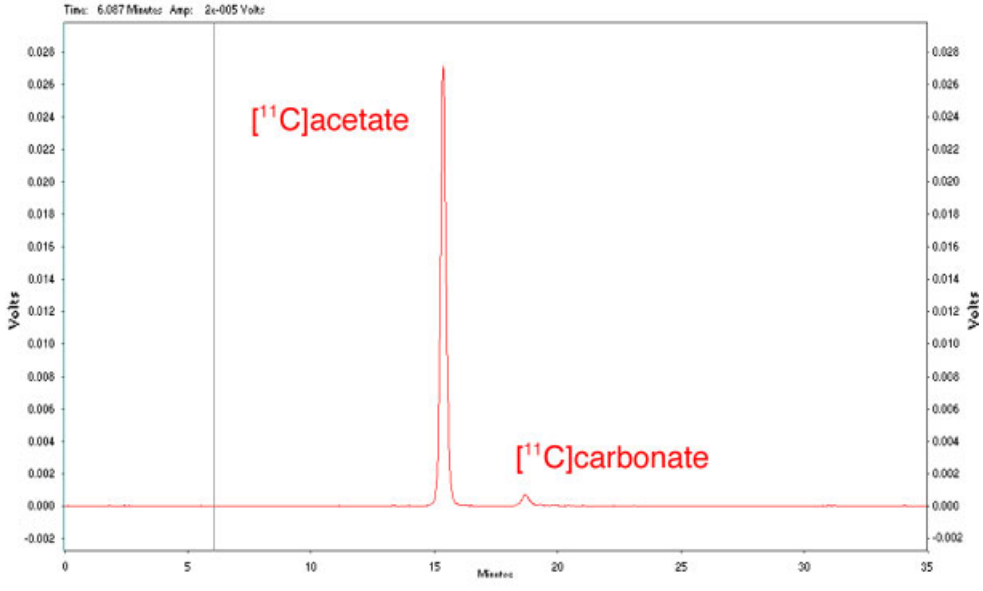

Figure 3. HPLC radiochromatogram of eluted fraction (NaCl 0.9%)

purification step, carrier acetate is added to ensure efficient and reproducible trapping and elution from the anion exchange column as shown by Kruijer *et al.*[3] In contrast to this similar purification process, we found that physiologic saline was sufficient to elute acetate from the anionic column. [^{11}C]Carbonate amounted to 5–10% of radioactivity (Figure 3) and had to be removed with nitrogen flow in acidic solution. Analytical HPLC on Aminex HP 87-H reported the excellent chemical and radiochemical purities; HPLC analyses with refractive index detection did not show the unidentified contaminant reported by the Orsay group, with a different $^{11}CO_2$ production system.[4] During the setup phase of the synthesis, preparative HPLC has been investigated: the carboxylation of the Grignard reagent can take place in a stainless-steel HPLC loop, and the reaction mixture can be directly injected on a C18 column to achieve HPLC purification (see Davenport *et al.*,[6] Kihlberg *et al.*[9] for HPLC use); this approach opens the possibility of acetate radiosynthesis in automated 'loop systems'.

Conclusion

Radiosynthesis has been automated with a programmable logic controller (PLC), a motor-driven syringe and electrovalves; the reaction is processed in less than 12 min and is afforded in a typical run of around 500 mCi, 18.5 GBq EOS-injectable [1-^{11}C]acetate from an 18 µAh 36 µA beam, in low specific radioactivity due to carrier-added purification, with excellent radiochemical and chemical purities.

Acknowledgements

Thanks to V.W. Pike, H. Tochon-Danguy and V. Tadino for fruitful discussions.

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