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Preparation of No-carrier-added [1-^{11}C]Ethylene and [1-^{11}C]1,2-Dibromoethane as New Labelling Agents

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A method is described for the preparation of NCA [1-^{11}C]ethylene based on the passage of [1-^{11}C]ethanol over heated (500°C) quartz glass in a stainless steel tube (in preference to dehydration by catalysis on γ-alumina or pyrolysis). The [1-^{11}C]ethanol is prepared from cyclotron-produced NCA [^{11}C]carbon dioxide by ^{11}C-carboxylation of methylmagnesium bromide, freshly prepared in dibutyl ether, and reduction of the adduct with lithium aluminium hydride in diglyme. The use of involatile solvents avoids the formation of carrier ethylene and radioactive and stable diethyl ether by cracking processes over the heated catalyst. The preparation takes 21 min from the end of radionuclide production and has a radiochemical yield of 44%, decay-corrected from [^{11}C]carbon dioxide. NCA [1-^{11}C]ethylene is converted quantitatively into [1-^{11}C]1,2-dibromoethane when collected in a solution of bromine in carbon tetrachloride. The NCA [1-^{11}C]ethylene and [1-^{11}C]1,2-dibromoethane may serve as new and useful labelling agents. © 1997 Elsevier Science Ltd

Introduction

Clinical research with positron emission tomography (PET) requires a wide range of organic molecules to be labelled with the short-lived positron-emitter, carbon-11 ($t_{1/2} = 20.4$ min; $\beta^+ = 99.8\%$). In PET centres carbon-11 is mainly produced as no-carrier-added (NCA) [^{11}C]carbon dioxide by the ^{14}N(p,α)^{11}C reaction on nitrogen (Qaim *et al.*, 1993). ^{11}C-Carboxylations of organometallic reagents, especially organolithiums and Grignard reagents, are generally very efficient reactions and by choice of conditions may be controlled to give various ^{11}C-labelled products, including carboxylic acids, alcohols and ketones (Ehrenkaufer and Scripko, 1991). Reduction of the initially formed ^{11}C-carboxylated adducts with lithium aluminium hydride is also an efficient route to ^{11}C-labelled alcohols (Raichle *et al.*, 1976; Del Fiore *et al.*, 1986). However, the conversion of no-carrier-added (NCA) [^{11}C]ethanol into NCA [^{11}C]ethylene and its derivatives, which are potentially useful labelling agents, has not hitherto been addressed.

Here we report* our investigations on the preparation of NCA [^{11}C]ethylene via the ^{11}C-carboxylation of methylmagnesium bromide, reduction with lithium aluminium hydride and dehydration over heated catalysts. This culminates in an effective procedure for the preparation of NCA [1-^{11}C]ethylene and [1-^{11}C]1,2-dibromoethane (Fig. 1).

*For preliminary reports of this work see Shah *et al.* (1994) and Shah and Pike (1995).

Experimental

Materials

Methylmagnesium bromide in diethyl ether (3M), lithium aluminium hydride in 2-methoxyethyl ether (diglyme) (0.5M), tetrahydrofuran (THF) and dibutyl ether (99%) were all obtained in "Sure/Seal™" bottles from Aldrich Chemical Co. Ltd (Gillingham, U.K.). Alumina (Al_2O_3;100 mesh, 99.9%), bromine, bromine in carbon tetrachloride (1M), bromomethane, ethylene (10% in helium), propylene (>99%), 2-methylpropene (>99%), 1,2-dibromoethane, 1,2-dibromopropane and 1,2-dibromo-2-methylpropane were also obtained from Aldrich Chemical Co. Ltd (Gillingham, U.K.). Lithium aluminium hydride (>95%) was obtained from Fisons Ltd (Loughborough, U.K.). γ-Alumina (0.015 μm for polishing), alumina (Brockmann grade 2, 100 mesh), acetone, ethanol (HPLC grade), *t*-butanol, di-isopropyl ether, iodine and magnesium turnings were obtained from BDH Merck Ltd (Poole, U.K.). Magnesium turnings were cleaned with diethyl ether and oven-dried. Activated alumina (sold as packing material for GC columns, 60–80 mesh) was

obtained from Alltech Associates Inc. (Carnforth, U.K.). Quartz glass rod (2 mm diameter) was obtained from Goodfellows Ltd (Cambridge, U.K.). GC columns (60/80 Carbopack B with 1% SP 1000 support) were purchased from Supelco Ltd (Poole, U.K.). All gases were obtained from Linde (Redditch, U.K.).

Experimental radiochemistry apparatus

The apparatus constructed and used for experimental radiochemistry featured facilities for (i) entrapment of dry cyclotron-produced [^{11}C]carbon dioxide in a spiral stainless steel tube (o.d. 1.6 mm; i.d. = 0.76 mm; diameter of spiral *ca* 5 cm, 3 turns) immersed in liquid argon; (ii) release of the trapped radioactivity from the warmed spiral tube in a slow stream of nitrogen; (iii) ^{11}C-carboxylation of methylmagnesium bromide in solution under nitrogen; (iv) reduction of the radioactive adduct under nitrogen with lithium aluminium hydride solution; (v) hydrolysis of the reduced adduct with water; and (vi) heating of the reaction vessel to transfer the volatile radioactive products in a controlled stream of nitrogen through a heated tube and into a collection vial (Fig. 2). For the construction of the apparatus solenoid valves (Bio-chem Valve Inc.) were obtained from (PD Marketing; Chichester, U.K.) and stainless steel needle valves from South London Valve and Fitting (Burgess Hill, U.K.). The apparatus was controlled externally via a programmable logic controller (Hitachi; H.T. Electrical, Croydon, U.K.),

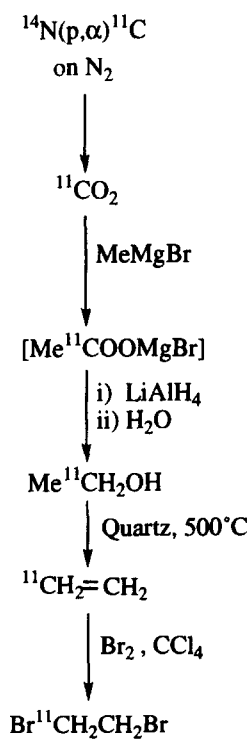

Fig. 1. The preparation of [1-^{11}C]ethylene (and conversion into [1-^{11}C]1,2-dibromoethane).

as described in principle by Clark *et al.* (1990). The controller was re-programmed as necessary for variations in procedure. The temperatures of the glass reaction vessel (internal volume, 3.5 mL), contained in an oil bath, and the heated tube, contained in a small furnace (MTF 9/15/130; Carbolite, Sheffield, U.K.), were each controlled by a thermocouple unit (Cal 9900). The apparatus was shielded from personnel by 2 cm thick lead.

Analytical gas chromatography

Analytical gas chromatography (GC) was performed on a Carlo-Erba instrument (Fisons; Croydon, U.K.) equipped with a thermal conductivity (TCD) or flame ionisation detector (FID) in series with a radioactivity detector (Bioscan, NaI, 20 mm diameter; Lablogic; Sheffield, U.K.), with each detector linked to a data acquisition and analysis module (Perkin-Elmer, Beaconsfield, U.K.). This instrument was equipped with a 60/80 Carbopack B column (1% SP 1000, 1/8"o.d.), either 2.44 m long for use with the TCD detector or 3.05 m long for use with the FID detector.

The TCD was operated with helium (30 p.s.i; 30 mL/min through column) and calibrated for mass of ethanol and 1,2-dibromoethane (10–500 μg of analyte). The following temperature programmes were used for analysis with the TCD:

Programme 1. 70°C for 10 min, rising by 20°C/min to 190°C and held for 20 min. Retention times: methanol, 2.5 min; ethanol, 5.0 min; 2-propanol, 10.6 min.

Programme 2. 70°C for 12 min, rising by 40°C/min to 190°C and held for 28 min. Retention times: ethylene, 0.81 min; propylene, 2.69 min; methanol, 2.31 min; ethanol, 5.0 min; acetone, 9.7 min; 2-propanol, 14.0 min; *t*-butanol, 15.4 min; diethyl ether, 15.5 min; carbon tetrachloride, 17.3 min; di-isopropyl ether, 19.6 min; 1,2-dibromoethane, 20.3 min; 1,2-dibromopropane, 24.4 min; 1,2-dibromo-2-methylpropane, 28.9 min.

The FID was run with helium (20 p.s.i., 20 mL/min through column), air (14.5 p.s.i.) and hydrogen (7 p.s.i.) and the following temperature programme.

Programme 3. 70°C for 12 min, rising by 40°C/min to 190°C and held for 54 min. Retention times: ethylene, 1.65 min; ethane, 1.80 min; propylene, 3.23 min; methanol, 3.57 min; ethanol, 5.5 min; 2-propanol, 14.8 min; *t*-butanol, 15.9 min; carbon tetrachloride, 17.5 min; 1,2-dibromoethane, 21.0 min; 1,2-dibromopropane, 26.1 min.

GC–MS analysis

GC–mass spectrometry (GC–MS) was performed with a Varian gas chromatograph, equipped with a capillary column (25 mm × 0.33 mm i.d.; B.P.1 type; Thames Chromatography, Maidenhead, U.K.) run isothermally at 25°C with helium carrier (5 p.s.i.) and coupled to a Nermag quadrupole mass spectrometer operating in electron impact mode.

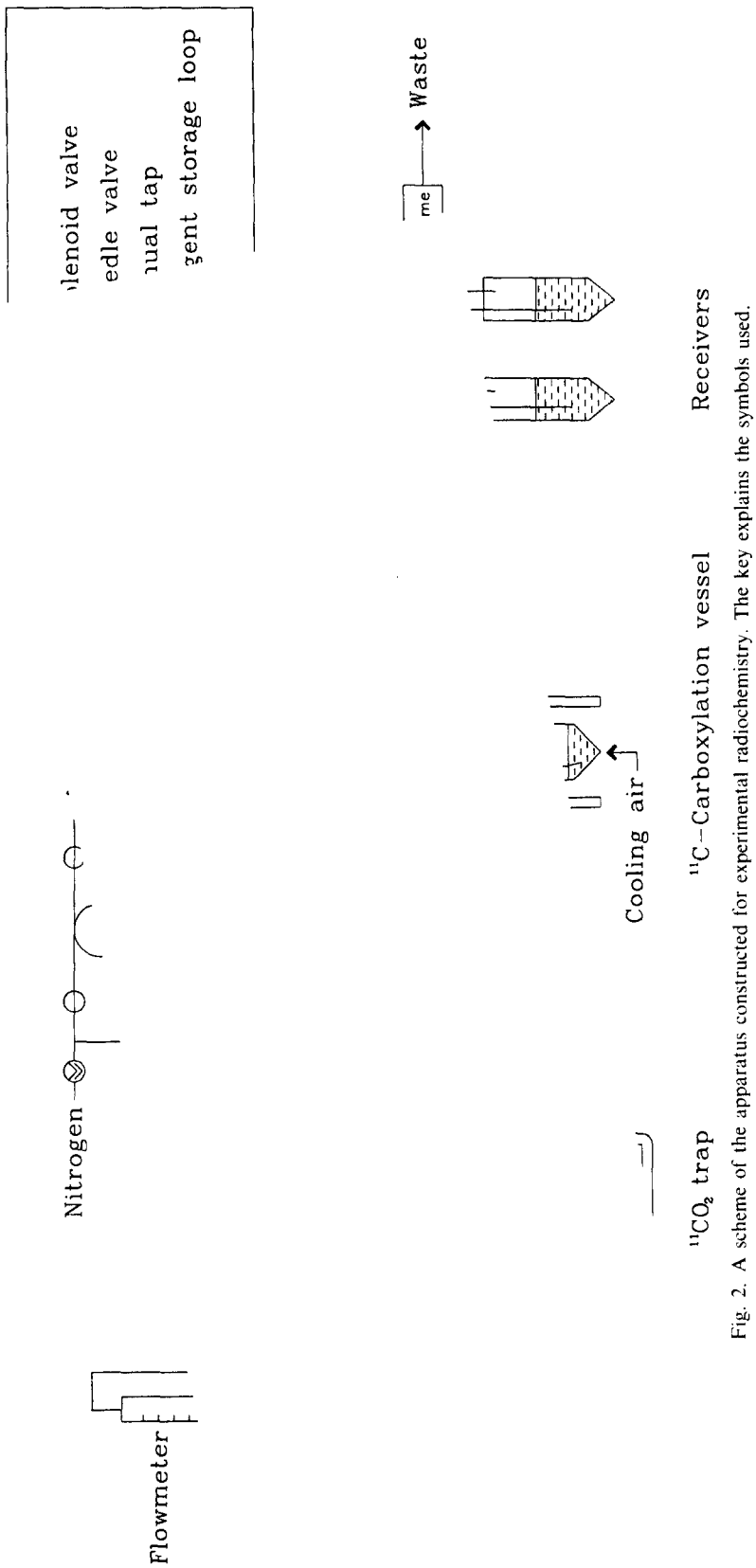

Fig. 2. A scheme of the apparatus constructed for experimental radiochemistry. The key explains the symbols used.

Preparation of methylmagnesium halides

Methylmagnesium bromide in diethyl ether (1M) was prepared from bromomethane and magnesium turnings under nitrogen as described by Pike *et al.* (1981). Methylmagnesium bromide in dibutyl ether (0.5M) was prepared similarly. Sonication was used to accelerate the latter preparation (Tuulmets *et al.*, 1986). Methylmagnesium bromide solutions were stored under nitrogen at room temperature and used within 1 week of preparation.

Production of NCA [^{11}C]carbon dioxide

NCA [^{11}C]carbon dioxide (*ca* 27 mCi; 1 GBq) was prepared with a Scanditronix MC40 (Mk II) cyclotron by the irradiation of dry nitrogen gas (99.95% purity, 15 bar) or nitrogen containing 0.1% oxygen (15 bar) with protons (19 MeV, 30 μA) for 1 min. The [^{11}C]carbon dioxide was passed over anhydrous magnesium perchlorate and into the experimental radiochemistry apparatus where it was trapped and concentrated in a spiral of stainless steel immersed in liquid argon (Fig. 2).

Preparation of NCA [1-^{11}C]ethanol

Using commercial methylmagnesium bromide in diethyl ether. The method was adapted from those in the literature (Raichle *et al.*, 1976; Del Fiore *et al.*, 1986), as follows. The reaction pot of the apparatus (Fig. 2) was loaded with commercial methylmagnesium bromide in diethyl ether (1M; 0.35 mL) under nitrogen. Trapped [^{11}C]carbon dioxide was released from the stainless steel spiral by allowing its temperature to rise to ambient while passing a slow stream of pure nitrogen (6 mL/min) through the spiral and into the Grignard reagent for 3 min at room temperature. Lithium aluminium hydride in THF (20 mg/mL; 0.53M; 0.45 mL) was then added from a pre-loaded loop under nitrogen and the reaction mixture heated to 75°C for 6 min under a stream of nitrogen to remove diethyl ether. The reaction mixture was cooled and water (0.4 mL) added from another pre-loaded loop. A slow stream of nitrogen (6 mL/min) was then passed through the reaction mixture while it was heated to 100°C to carry volatile radioactive products into a trap of methanol (0.2 mL). The trap was monitored for maximal accumulation of radioactive product using a Geiger-Müller detector (Minalarm) linked to a chart recorder. The trapped radioactive products were analyzed by GC (programme 1).

Using freshly prepared methylmagnesium bromide solution in dibutyl ether. The procedure was the same as for the preparation using commercial Grignard reagent, except that (i) the [^{11}C]carbon dioxide was transferred for 6 min by a slower stream of nitrogen (1 mL/min) into freshly prepared methylmagnesium bromide in dibutyl ether (0.5M; 1 mL) under nitrogen at room temperature; (ii) lithium aluminium hydride in diglyme (0.5M; 0.7 mL) was then added under nitrogen and left for 1 min; (iii) the reaction mixture was cooled to less than 10°C and water (0.3 mL) added; and (iv) a slow stream of nitrogen (6 mL/min) was then passed through the reaction mixture while it was heated to 120°C for 10 min to carry volatile radioactive products into a trap of methanol (2 mL). The trapped products were analyzed by GC (programme 1).

Preparation of NCA [1-^{11}C]ethylene

NCA [1-^{11}C]ethanol was carried from the synthesis pot (Fig. 2) in a stream of nitrogen (*ca* 6 mL/min) through a furnace tube (0.5 mm i.d. × 20 cm; quartz

Table 1. Performance of catalysts for conversion of NCA [1-^{11}C]ethanol into [1-^{11}C]ethylene

Catalyst	n[a]	Temperature (°C)	Retentioin of activity[b] (%)	[1-^{11}C]Ethylene in effluent[c] (%)	[^{11}C]Et_2O in effluent[d] (%)
Alumina (100 mesh	7	400	73–89	30.5–90	0–32
in auartz glass tube)	2	550	42	66	21.7
	2	650	90	50	50
Alumina (γ, Grade 2)	5	400	52–75	71–90	10–29
Alumina (GC grade)	4	400	54	36	41
	7	450	57–82	90–98	2–10
Quartz glass tube	2	700	51	67	22
	2	800	68	99.4	0
Stainless steel tube	4	700	0.3–9	26–46.5	20–46
Quartz tube (within	8[e]	700	8–14	57–81	0–1.4
stainless steel tube)	50[e]	500	< 5	100	0

[a] n = number of experiments.
[b] % of initially trapped radioactivity retained by furnace tubes or catalysts.
[c] % of initially trapped radioactivity in furnace effluent as [1-^{11}C]ethylene (usually detected after conversion into [1-^{11}C]1,2-dibromoethane) derived from [1-^{11}C]ethanol, as measured by radio-GC.
[d] % of initially trapped radioactivity in furnace effluent as [2-^{11}C]diethyl ether derived from [1-^{11}C]ethanol as measured by radio-GC.
[e] These experiments were performed using freshly prepared methylmagnesium bromide in dibutyl ether. All other experiments were performed using commercial methylmagnesium bromide in diethyl ether.

glass or stainless steel), which was either empty or containing particulate alumina (*ca* 0.5 g) or a quartz glass tube (30 cm × 2 mm i.d.), and held at a set external temperature (Table 1). The effluent was collected into syringes and analysed by GC (programme 2) and in some experiments by GC–MS.

Preparation of NCA [1-^{11}*C*]1,2-*dibromoethane*

Crude NCA [1-^{11}C]ethylene from the furnace effluent was trapped in a solution of bromine in carbon tetrachloride (1M; 3 mL). The trapped radioactivity was measured. This solution was heated

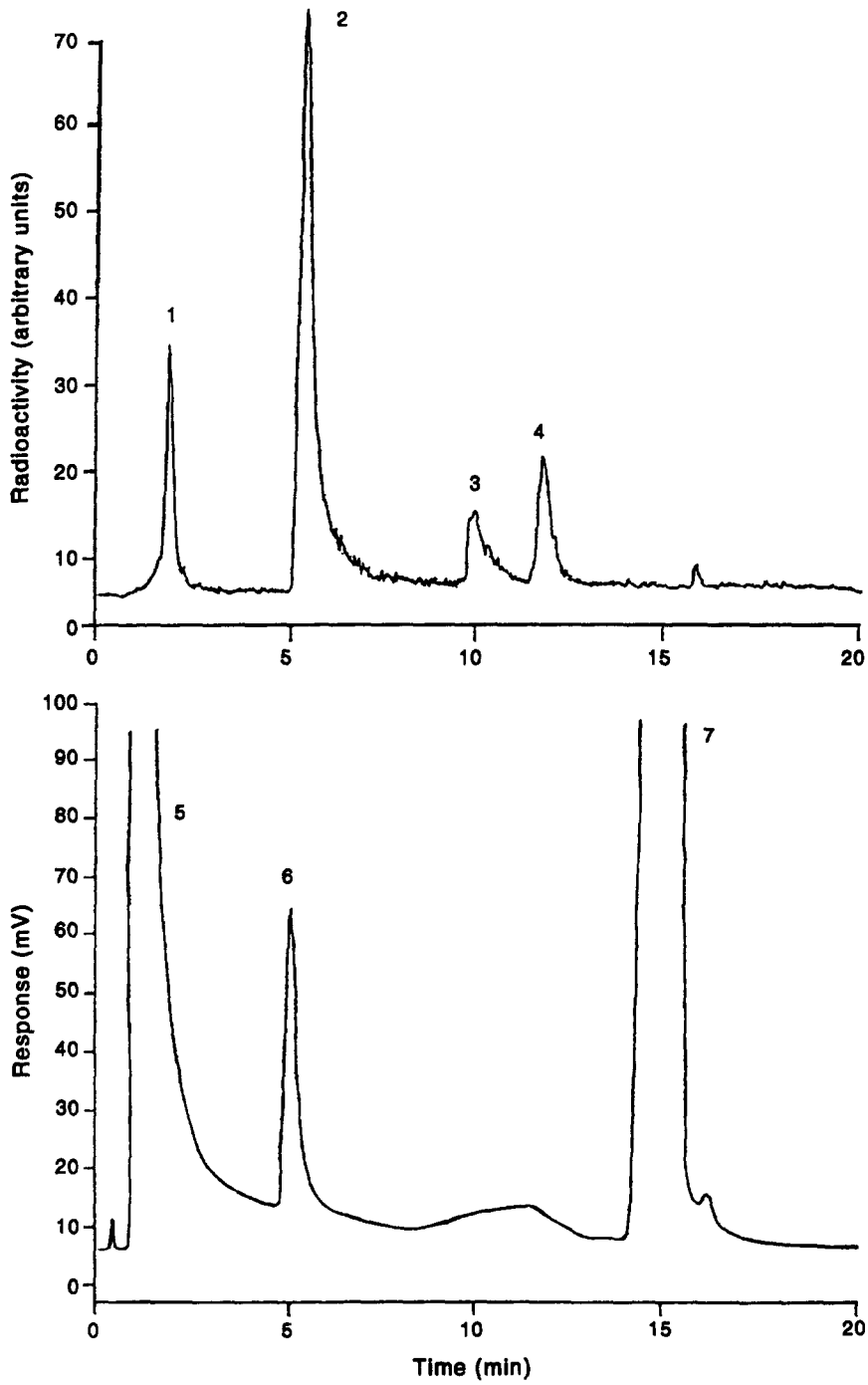

Fig. 3. GC-analysis (programme 1) of the volatile radioactive products from the ^{11}C-carboxylation-reduction of commercial methylmagnesium bromide in diethyl ether. The peaks are as follows. 1: [^{11}C]methanol; 2: [^{11}C]ethanol; 3: [^{11}C]isopropanol; 4: [^{11}C]butanol; 5: methanol; 6: ethanol; 7: carbon tetrachloride.

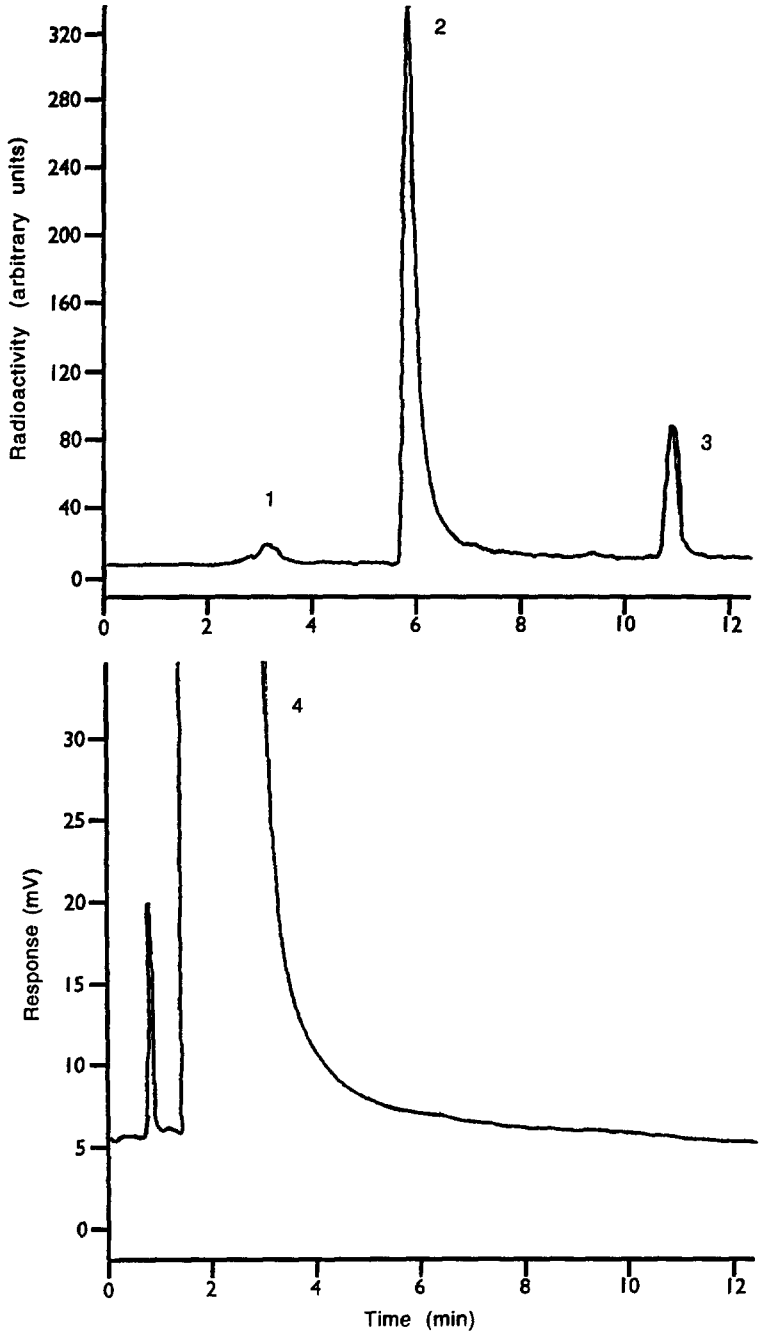

Fig. 4. GC-analysis (programme 1) of the volatile radioactive products from the ^{11}C-carboxylation-reduction of freshly prepared methylmagnesium bromide in dibutyl ether. The peaks are as follows. 1: [^{11}C]methanol; 2: [^{11}C]ethanol; 3: [^{11}C]isopropanol; 4: methanol.

at 80°C and purged with nitrogen to remove bromine before analysis by GC (programme 2 or 3). Any loss of radioactivity during evaporation was recorded. In some experiments two traps of bromine in carbon tetrachloride solution were used in series. In all experiments the apparatus was equipped with a sodalime trap on the gas outlet (Fig. 2).

Results

The efficiency with which cyclotron-produced [^{11}C]carbon dioxide was trapped from a stream of nitrogen (*ca* 6 mL/min) in methylmagnesium bromide (0.5 mmol) in diethyl ether (500 μL) at room temperature exceeded 94%. However, with the reagent in dibutyl ether, trapping was very inefficient

at this flow rate. Acceptably high trapping efficiency (82%, $n = 6$) was achieved by using a slower flow of nitrogen (*ca* 1 mL/min) in a larger volume of reagent (1 mL). Maximal radioactivity was trapped within 6 min.

The ^{11}C-carboxylation of commercial methylmagnesium bromide in diethyl ether followed by reduction with lithium aluminum hydride in THF and hydrolysis gave [1-^{11}C]ethanol as the main volatile radioactive product (> 83% of the radioactivity in the analyte), as assessed by GC method **1** (Fig. 3). The radiochemical yield of [1-^{11}C]ethanol from cyclotron-produced [^{11}C]carbon dioxide was 63%, decay-corrected. The main volatile radioactive byproduct was [^{11}C]methanol. [2-^{11}C]Isopropanol was also detected in the analyte. High amounts of carrier ethanol (*ca* 25 μg; 0.75 μmol) were detected in these preparations. The use of higher concentrations of reagent or longer reaction times lowered the radiochemical yield of [1-^{11}C]ethanol at the expense of forming greater proportions of [2-^{11}C]isopropanol and [2-^{11}C]*t*-butanol.

The ^{11}C-carboxylation of freshly prepared methylmagnesium bromide in dibutyl ether, followed by reduction with lithium aluminium hydride in diglyme and hydrolysis, gave NCA [1-^{11}C]ethanol as the main volatile radioactive product (>80% of the radioactivity in the analyte) as assessed by GC method 1 (Fig. 4). The radiochemical yield of [1-^{11}C]ethanol from cyclotron-produced [^{11}C]carbon dioxide was 44%, decay-corrected. The volatile radioactive byproducts were [2-^{11}C]isopropanol and [^{11}C]methanol. No stable ethanol was detected by GC, indicating that the amount of carrier ethanol in the whole preparation was below 2.5 μg (0.075 mmol). The preparation of [1-^{11}C]ethanol required 20 min from the end of radionuclide production.

Passage of NCA [1-^{11}C]ethanol, produced from commercial methylmagnesium bromide in diethyl ether, over various grades of γ-alumina or α-alumina in a quartz furnace tube heated at temperatures between 400 and 650 °C gave [1-^{11}C]ethylene as the major radioactive product in the effluent (Table 1), as assessed directly by GC–MS analysis ($m/z = 28$, $[M]^+$) or by GC analysis of the [1-^{11}C]1,2-dibromoethane formed by trapping the volatile radioactive products in a solution of bromine in carbon tetrachloride. The trapping of [1-^{11}C]ethylene in the bromine solution was nearly quantitative since in a large number of experiments (Table 1) no [1-^{11}C]ethylene was ever detected in the presence of [1-^{11}C]1,2-dibromoethane, and a second bromine trap in series produced less than 1% of the total [1-^{11}C]1,2-dibromoethane. [2-^{11}C]Diethyl ether was the main radioactive byproduct (Table 1). Radioactivity retained by the furnace tube and the alumina catalyst represented a high proportion of the volatile radioactivity retrieved from the reaction pot in these experiments (Table 1).

Passage of [1-^{11}C]ethanol, produced from commercial methylmagnesium bromide in diethyl ether, through an empty quartz glass tube heated at 700 °C gave [1-^{11}C]ethylene as the major radioactive product in the tube effluent, with [2-^{11}C]diethyl ether as the main byproduct (Table 1). A high proportion of the volatile radioactivity recovered from the reaction pot was retained by the quartz glass tube (average 51%). With the tube at 800 °C, the effluent consisted almost exclusively of [1-^{11}C]ethylene, but the proportion of volatile radioactivity retained by the tube was higher (68%).

Passage of [1-^{11}C]ethanol, produced from commercial methylmagnesium bromide in diethyl ether, through an empty stainless steel tube heated at 700 °C gave [1-^{11}C]ethylene as a significant proportion of radioactivity in the effluent, with [2-^{11}C]diethyl ether as the major byproduct. Unchanged [1-^{11}C]ethanol was also a significant proportion of the radioactivity in the effluent (Table 1). The percentage of volatile radioactivity retained by the stainless steel tube ranged from 0.3–9%.

Passage of [1-^{11}C]ethanol, produced from freshly prepared methylmagnesium bromide in dibutyl ether, through a stainless steel tube containing a quartz tube and heated at 700 °C gave [1-^{11}C]ethylene as the major radioactive product in the effluent, with [2-^{11}C]diethyl ether as a very minor byproduct (Table 1). The percentage of volatile radioactivity retained by the stainless steel tube ranged from 8–14%. At 500 °C the radioactive effluent from the furnace tube was found by GC to consist almost entirely of [1-^{11}C]ethylene (Fig. 5). No nonradioactive ethylene was detected in the GC analysis. In 50 preparations the percentage of volatile radioactivity retained by the furnace tubes was always less than 5% (Table 1). The radiochemical yield of [1-^{11}C]ethylene (measured as [^{11}C]1,2-dibromoethane) from [^{11}C]carbon dioxide was on average 44% decay-corrected ($n = 12$). The preparation time was 21 min from the end of radionuclide production. Under these conditions, generally only a small proportion of the total radioactivity (0.6%) passed through the bromine reagent and trapped on the sodalime. Each quartz glass tube was used for at least 10 successive preparations without noticeable detriment to the radiochemical yield or specific radioactivity of the NCA [1-^{11}C]ethylene.

Discussion

Well known laboratory methods for the preparation of ethylene include dehydration of ethanol by treatment with agents such as sulphuric acid or phosphorous pentoxide or by catalytic dehydration over heated alumina. [1-^{11}C]Ethanol has been prepared in high radiochemical yield by several groups, either as a radiopharmaceutical (Raichle *et al.*, 1976; Del Fiore *et al.*, 1986) or as a reaction intermediate (Långström *et al.*, 1986; Slegers *et al.*,

1986). This suggested that [1-^{11}C]ethylene might be prepared by the simple dehydration of [1-^{11}C]ethanol.

Preliminary attempts to prepare [1-^{11}C]ethylene by treating [1-^{11}C]ethanol in solution with sulphuric acid or phosphorous pentoxide were unwieldy and did not give encouraging results. We considered that the gas phase catalytic dehydration of no-carrier-added (NCA) [1-^{11}C]ethanol would be a more practical approach to the production of NCA [^{11}C]ethylene.

To explore catalytic dehydration as a route to NCA [1-^{11}C]ethylene it was necessary to establish the practical production of NCA [1-^{11}C]ethanol, which is based on the ^{11}C-carboxylation of methylmagnesium halide followed by reduction of the adduct with lithium aluminium hydride and hydrolysis (Fig. 1). Previous reports (Pike *et al.*, 1981, 1982; Raichle *et al.*, 1976; Någren and Långström, 1989) have highlighted several factors as being crucial in

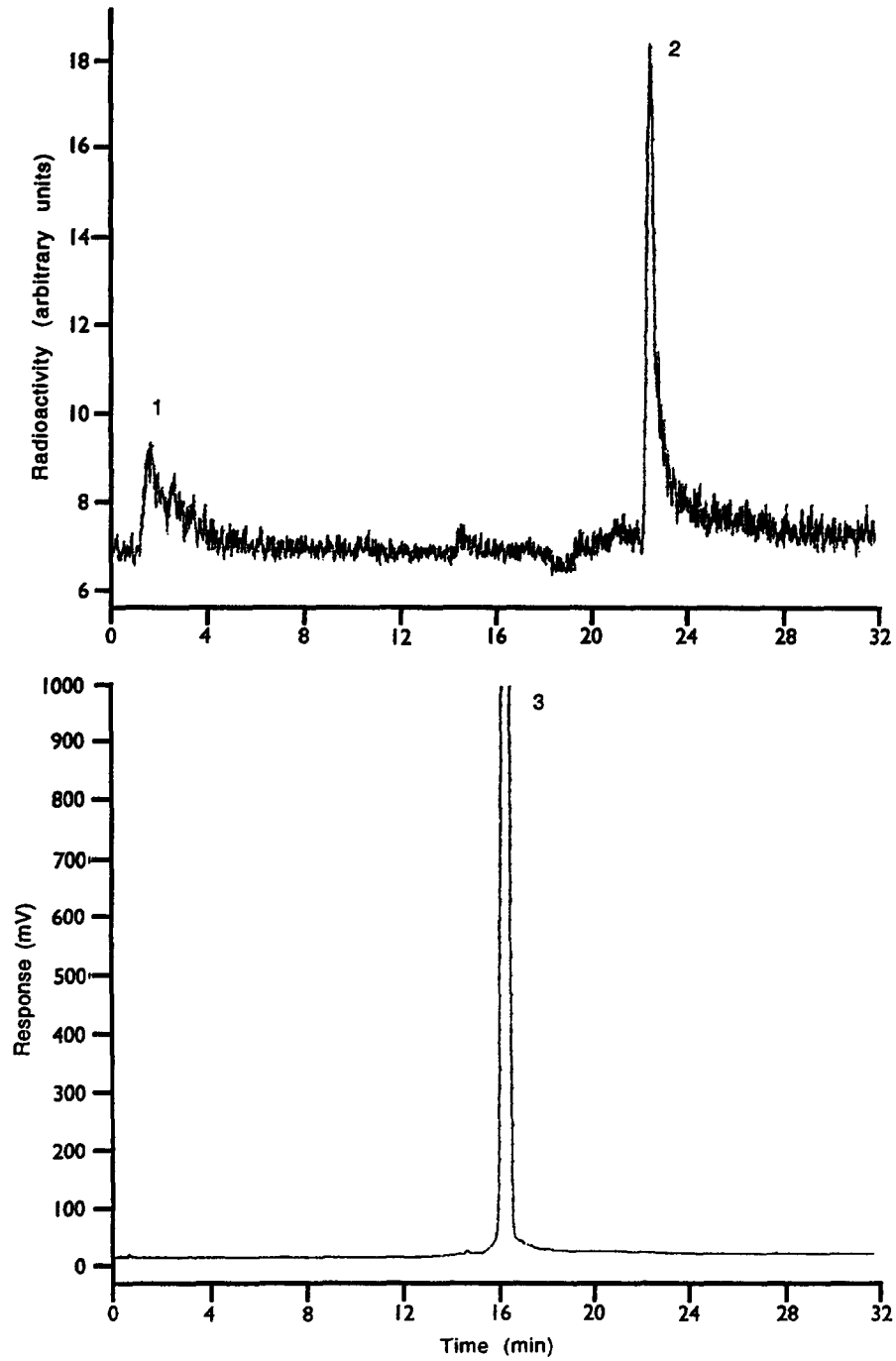

Fig. 5. GC analysis (programme 3) of NCA [1-^{11}C]1,2-dibromoethane prepared from NCA [1-^{11}C]ethylene prepared by the optimised procedure. The peaks are as follows. 1: [^{11}C]methanol; 2: [^{11}C]1,2-dibromoethane; 3: carbon tetrachloride.

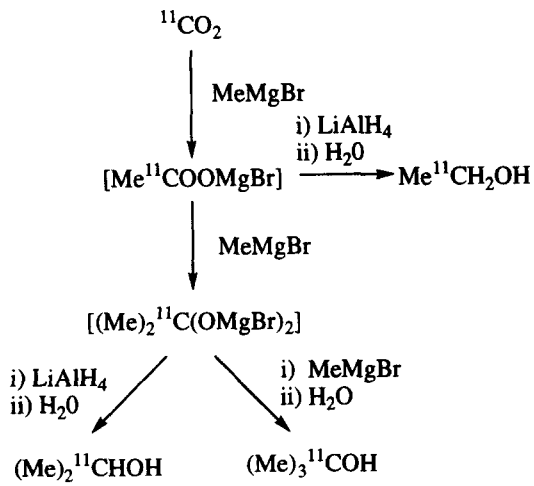

Fig. 6. Formation of [1-^{11}C]ethanol, [2-^{11}C]isopropanol and [2-^{11}C]*t*-butanol by the ^{11}C-carboxylation-reduction of methylmagnesium bromide.

determining the spectrum of radioactive products obtained from the ^{11}C-carboxylation of methylmagnesium halides, including the nature of the halide, reagent concentration, reaction temperature and reaction time. Increasing reagent concentration, reaction temperature and reaction time encourage further reaction of the ^{11}C-carboxylation adduct with excess reagent to form [2-^{11}C]acetone, which in turn may react further to form [2-^{11}C]*t*-butanol (Fig. 6). By appropriate choice of reaction parameters it is possible to limit the reaction of the ^{11}C-carboxylation product with excess methylmagnesium halide. Methylmagnesium bromide has reactivity between that of the less reactive iodide and the more reactive chloride. We chose methylmagnesium bromide as reagent because it is possible to achieve efficient ^{11}C-carboxylation in a brief time at room temperature without any significant further reaction of the ^{11}C-carboxylation adduct with excess reagent (Pike *et al.*, 1981, 1982).

Initially, we attempted to prepare [1-^{11}C]ethanol by using commercial solutions of methylmagnesium bromide in diethyl ether and commercial lithium aluminium hydride in THF as reducing agent. Under mild reaction conditions [1-^{11}C]ethanol was formed in good radiochemical yield; however [2-^{11}C]isopropanol was usually observed as a radioactive byproduct. [^{11}C]Methanol was also observed as a byproduct and must have arisen from the reaction of free [^{11}C]carbon dioxide with lithium aluminium hydride. The commercial Grignard reagent was also found to give significant amounts of carrier ethanol, leading to a very low specific radioactivity. Grignard reagents prepared freshly, with careful precautions against the ingress of carbon dioxide, gave product with much higher specific radioactivity. This implies that the used commercial reagent was contaminated by carbon dioxide during manufacture, transport or storage.

[1-^{11}C]Ethanol was removed from the reaction milieu by heating under a stream of nitrogen. The high temperature (100°C) required for the efficient removal of the [1-^{11}C]ethanol also led to the evaporation of traces of volatile organic solvent and the water used for final hydrolysis of the reduced ^{11}C-carboxylation adduct. Control experiments demonstrated the possibility to produce ethylene by the cracking of diethyl ether or tetrahydrofuran at 800°C. Hence, the procedure was modified to use less volatile solvents, namely dibutyl ether (b.p. 143°C) for the methylmagnesium bromide and diglyme (b.p. 163°C) for the lithium aluminium hydride. These solvents proved satisfactory except that [^{11}C]carbon dioxide appeared to be less soluble in dibutyl ether than in diethyl ether or THF. Under conditions in which the trapping of [^{11}C]carbon dioxide by Grignard reagent in diethyl ether was very efficient, trapping by the reagent in dibutyl ether was negligible. However, by using a slow stream of nitrogen for the introduction of the [^{11}C]carbon dioxide and a larger volume of dibutyl ether, an acceptably high trapping efficiency was obtained. Consequently, somewhat more time had to be allowed for this stage.

Various alternatives to the use of water were tried for the hydrolysis reaction, including the use of anhydrous citric acid at 130–140°C (McCarthy *et al.*, 1993) and the use of alcohols with high boiling points. However, none of these approaches gave satisfactory production and recovery of the [1-^{11}C]ethanol. The use of a small quantity of water did not cause difficulties in subsequent experiments and was thus retained in the radiosynthetic procedure.

γ-Alumina is the preferred catalyst for the conversion of ethanol into ethylene (see for example, Shintaro *et al.*, 1992; Gates, 1992). Initially we tried various aluminas, including γ-alumina in a quartz glass tube, heated at temperatures between 400 and 650°C, as catalysts for the dehydration of [1-^{11}C]ethanol to [1-^{11}C]ethylene (Table 1). The effluent from the heated tube was trapped in syringes or in a solution of bromine in carbon tetrachloride. A combination of GC–MS and GC analyses on

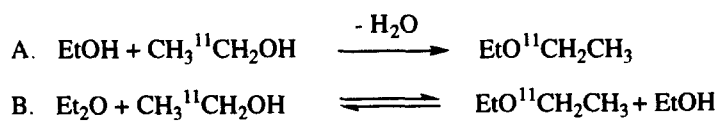

Fig. 7. Possible formation of [2-^{11}C]diethyl ether from [1-^{11}C]ethanol over heated catalysts; A from carrier ethanol and B from trace diethyl ether.

volatile radioactivity collected in a syringe identified the major radioactive product to be [1-^{11}C]ethylene, since this comigrated with reference ethylene and its associated carrier gave a mass spectrum matching that for ethylene in the reference library of the National Institute of Science and Technology. Analysis of radioactivity trapped in bromine solution revealed the presence of [^{11}C]1,2-dibromoethane, indirectly corroborating the formation of [1-^{11}C]ethylene.

Since the reaction of [1-^{11}C]ethylene with bromine in carbon tetrachloride was shown to be virtually instantaneous and quantitative, this presented a convenient means for trapping and measuring the [1-^{11}C]ethylene formed in experiments. For experiments using various grades of alumina as catalysts, [1-^{11}C]ethylene was always found to be present in the effluent by GC analysis (directly, or by conversion into its dibromo derivative with bromine in carbon tetrachloride). However, [2-^{11}C]diethyl ether was nearly always detected as a significant byproduct. These experiments used commercial Grignard reagent and hence the specific radioactivity was low. The low specific radioactivity would have provided opportunity for the dehydration of one molecule of radioactive ethanol in the presence of one molecule of nonradioactive ethanol to give the observed [2-^{11}C]diethyl ether. The formation of diethyl ether is a well-known side reaction in the γ-alumina-catalyzed dehydration of ethanol (see for example, Shintaro *et al.*, 1992). Moreover, a trace of diethyl ether from the reaction medium may have been carried over the catalyst, perhaps facilitating the labelling of diethyl ether by reversible exchange reactions with the [1-^{11}C]ethanol (Fig. 7).

In these experiments high proportions of the radioactivity entering the furnace tube were retained (Table 1). It is presumed that retention was by adsorption on the alumina or quartz. This adsorption of radioactivity rendered the production of [1-^{11}C]ethylene very inefficient (Table 1).

We considered that pyrolytic dehydration in the absence of a catalyst might achieve the necessary conversion of [1-^{11}C]ethanol into [1-^{11}C]ethylene and avoid the loss of radioactivity by adsorption. Passage of [1-^{11}C]ethanol through an empty quartz tube heated to 700 or 800°C always gave a high percentage of radioactivity as [1-^{11}C]ethylene in the tube effluent (Table 1). However, the retention of radioactivity by the quartz tube was substantial in all experiments. For this reason we replaced the quartz tube with a stainless steel tube heated to 700°C. This change had the desired effect of reducing the proportion of radioactivity retained by the heated tube. However, the conversion of [1-^{11}C]ethanol into [1-^{11}C]ethylene was markedly lower than with the quartz tube. Again, since commercial Grignard reagent was used for these experiments, the specific radioactivity was low and [2-^{11}C]diethyl ether was observed as a significant byproduct.

We found, by using a Geiger-Müller radioactivity detector, that adsorption of radioactivity onto the quartz glass tube occurred at "cold regions" projecting from each end of the furnace. We considered that the adsorption effect could be circumvented by placing all the quartz within the heated region of the furnace while retaining the apparently favourable ability of quartz to promote the conversion of [1-^{11}C]ethanol into [1-^{11}C]ethylene. Good conversions of [1-^{11}C]ethanol into [1-^{11}C]ethylene and low retentions of radioactivity on tubes were obtained in experiments using a quartz glass tube within a stainless steel tube heated to 800°C (Table 1). These experiments used freshly prepared Grignard reagent in dibutyl ether and lithium aluminium hydride in diglyme to minimise contact of organic solvent with the heated tube and its contents. In order to avoid any possibility for trace solvents to be cracked to carrier ethylene at very high temperatures we tried experiments at lower temperatures. At 500°C, virtually quantitative conversions of [1-^{11}C]ethanol into [1-^{11}C]ethylene were obtained, with only minor retention of radioactivity on furnace tubes and with no formation of [2-^{11}C]diethyl ether as byproduct. The level of carrier was below that detectable in GC analysis (Fig. 5), indicating that the level of carrier was below 0.1 μmol. The average radiochemical yield of [1-^{11}C]ethylene (measured as [1-^{11}C]1,2-dibromoethane) over 12 preparations was 44% from [^{11}C]carbon dioxide, decay-corrected. The preparation time is adequately fast for the efficient use of short-lived carbon-11. Hence, this became the preferred method for the preparation of NCA [1-^{11}C]ethylene and [1-^{11}C]dibromoethane.

In over 50 preparations of NCA [1-^{11}C]ethylene/[1-^{11}C]1,2-dibromoethane by the preferred method, it was found that a single quartz rod could be used for at least 10 successive preparations without detriment to radiochemical yield or specific radioactivity.

[1-^{11}C]Ethylene and [1-^{11}C]1,2-dibromoethane have potential for application as useful labelling agents, for example in ring closure reactions and in radiosyntheses requiring bifunctional labelling agents. Recently, for example, we have applied NCA [1-^{11}C]ethylene to the preparation of other bifunctional derivatives as intermediates in the radiosynthesis of new labelled anticancer agents (Prenant *et al.*, 1995). By appropriate choice of organometallic reagent and ^{11}C-carboxylation conditions, this approach also has potential for the preparation of higher [^{11}C]alkenes and their derivatives, such as [2-^{11}C]propene (Shah *et al.*, 1994).

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