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On-line Synthesis of [¹¹C]Nitroalkanes

KARL-OLOF SCHOEPS,^{1,2} SHARON STONE-ELANDER¹ and CHRISTER HALLDIN^{1*}

¹Karolinska Pharmacy, Box 60024, S-10401 Stockholm, Sweden and ²Department of Neuroradiology, Karolinska Institute, S-10401 Stockholm, Sweden

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The on-line synthesis of ¹¹C-labelled nitroalkanes [nitromethane (I), nitroethane (II) and nitropropane (III)], from their corresponding ¹¹C-labelled alkyl iodides, by use of a heated silver nitrite column is described. The radiochemical yields of I, II and III were of the order of 40–70%, based on the corresponding [¹¹C]alkyl iodides. The total radiochemical yields, starting from [¹¹C]carbon dioxide, were of the order of 25–55% with an overall synthesis time of 8–15 min.

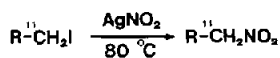
Introduction

A wide range of suitable labelled precursors is necessary in order to synthesize and label compounds with short-lived positron-emitting radionuclides, such as ¹¹C. A number of such precursors are available directly from target irradiations or by rapid on-line synthesis (for a review see Fowler and Wolf, 1986).

The synthetic importance of nitroalkanes in organic synthesis has been demonstrated by their action as nucleophiles in condensation and substitution reactions. Nitroalkanes can also be converted to other functionalities such as carbonyl compounds (Nef's reaction) and to amines.

The one-pot preparation of [¹¹C]nitromethane from [¹¹C]methyl iodide and its use in the condensation with benzaldehyde to produce [¹¹C]nitrostyrene was recently reported (Halldin *et al.*, 1987; Schoeps *et al.*, 1988). An on-line method for the production of ¹¹C-labelled nitroalkanes (I, II and III) from their corresponding [¹¹C]alkyl iodides has since been developed and is described here.

Problems encountered in the one-pot method regarding practical handling, reproducibility and the constrictions placed on solvents available for further synthesis were eliminated by using a heated column with silver nitrite as the stationary phase. The [¹¹C]alkyl halides (methyl-, ethyl- and propyl iodide), synthesized utilizing a one-pot reaction set-up from [¹¹C]carbon dioxide similar to that reported in detail elsewhere (Långström *et al.*, 1986), were passed through the heated column by carrier nitrogen. The [¹¹C]nitroalkanes produced were trapped in a medium suitable for further synthesis (Scheme 1 and Fig. 1).



R = H, Me, Et

Scheme 1

*Author for correspondence.

Experimental

General

Nitromethane and nitropropane were obtained from Merck, nitroethane from Riedel-de Haen and silver- and sodium nitrite from Fluka. [¹¹C]Carbon dioxide was produced at the Karolinska Hospital with a Scanditronix RNP 16 cyclotron using 16 MeV protons in the ¹⁴N(p, x)¹¹C reaction. The gas target was irradiated in a batch production. The [¹¹C]carbon dioxide produced was first trapped in a stainless steel coil cooled with liquid nitrogen and subsequently carried into the one-pot [¹¹C]alkyl halide system.

The radiochemical purity of I, II and III was analyzed by reversed-phase HPLC using an LDC Constametric III pump, a Rheodyne injector (7125 with a 100 μ L loop), a Waters μ -Bondapak C-18 column (10 μ m, 300 $\times$ 7.8 mm) and an ERMA u.v. detector (254 nm) coupled in series with a Berthold LB 503 detector. The mobile phase was acetonitrile and 0.01 M phosphoric acid (50/50) at a flow rate of 3.5 mL/min.

[¹¹C]Nitroalkanes (I, II and III)

The [¹¹C]alkyl halides (methyl-, ethyl- and propyl iodide) produced by the one-pot system were carried by the nitrogen gas (flow = 20–30 mL/min) through a soda-glass column (i.d. 3 mm, length 4 cm, oven temp. 80°C) containing silver nitrite (0.4 g). I, II and III, which eluted with the same retention times as standard reference compounds (4.0, 4.4, and 4.8 min, respectively (for more details see Schoeps *et al.*, 1988)), were trapped in a medium suitable for further synthesis.

Results and Discussion

Both silver- and sodium nitrite packed glass columns have been investigated with different temperatures and lengths but with the same internal diameter. Conversions with the silver nitrite were directly dependent on the operating temperature but were essentially insensitive to the length of the column. A shorter column was selected to minimize pressure build-up in the system. The product distribution was not significantly affected by different flow rates. By increasing the temperature from room temperature to 100°C the conversion of [¹¹C]methyl iodide to [¹¹C]nitromethane was increased by a factor of 3.5 (Table 1). No decrease in the activity of the column was observed, except when temperatures higher than 100°C were used. The column was easily packed at normal pressure by use of commercially available silver nitrite and glass wool stoppings (same column was used in all experiments in this investigation). In the case of sodium nitrite, [¹¹C]nitromethane was only obtained by use of a 12 cm column at 100°C (20%).

The trapping efficiency of the [¹¹C]nitroalkanes in dimethylsulphoxide (300 μ L) was better than 95%. The radiochemical yields of I, II and III were 70, 50 and 65%, respectively, (based on [¹¹C]alkyl iodide) and 55, 30 and 40%, respectively, (based on [¹¹C]carbon dioxide) (Table 2). The overall synthesis times calculated from [¹¹C]carbon dioxide ranged from 8 to 15 min. Under these no-carrier-added conditions, the specific activities of the nitroalkanes should be on the same order as those of the corresponding alkyl iodides (1000–5000 Ci/mmol).

The on-line synthesis of [¹¹C]nitromethane has been used in the preparation of D-[1-¹¹C]glucose, as has been preliminarily reported (Halldin *et al.*, 1988).

In conclusion, [¹¹C]nitroalkanes can now be prepared in an on-line extension of the one-pot [¹¹C]alkyl halide production system. Compared to the method previously re-

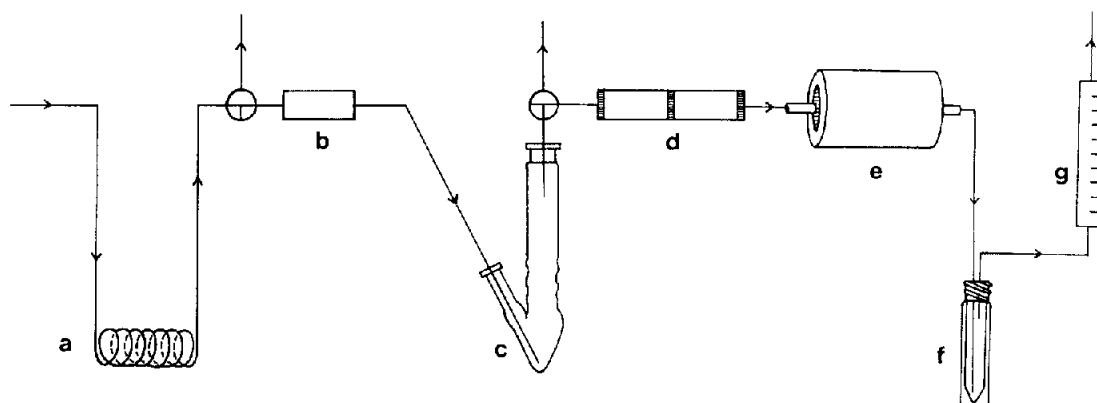


Fig. 1. System used for on-line preparation of 1-[^{14}C]nitroalkanes from [^{14}C]carbon dioxide. (a) Loop for trapping [^{14}C]carbon dioxide in liquid N_2 ; (b) P_2O_5 ; (c) reaction vessel; (d) $\text{NaOH}/\text{P}_2\text{O}_5$; (e) furnace containing AgNO_2 ; (f) collection vessel; (g) flowmeter.

Table 1. Effects of silver nitrite column temperature on product distributions*

Temp. (°C)	[^{14}C]CH $_3$ NO $_2$	Product distribution (%)		
		[^{14}C]CH $_3$ ONO	Unident. prod.	[^{14}C]CH $_3$ I
r.t.	27	5	30	38
40	42	3	29	26
60	77	4	19	0
80	88	3	9	0
100	95	2	3	0

*Product distributions determined by analytical HPLC of the ^{14}C -products trapped in 300 μL DMSO. (80% of the total radioactivity from the column).

Table 2. Radiochemical yields of 1- ^{14}C -labelled nitroalkanes*

[^{14}C]Nitroalkane	Radiochemical yield† (%)	Radiochemical yield‡ (%)
Nitromethane	70	55
Nitroethane	50	30
Nitropropane	65	40

*Silver nitrite column at 80°C.

†Based on [^{14}C]alkyl iodide and expressed in percent of total trapped radioactivity.

‡Based on [^{14}C]carbon dioxide.

ported, this on-line modification increases ease of handling and reproducibility and decreases constraints placed on solvent systems available for subsequent radiolabeling experiments.

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