Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXV, No. 7

PREPARATION OF ^{11}C-NITROMETHANE AND AN EXAMPLE OF ITS USE AS A RADIOLABELING PRECURSOR

Karl-Olof Schoeps[1,2], Christer Halldin*[,1,3], Sharon Stone-Elander[1], Bengt Långström[4] and Torgny Greitz[2]

[1]Karolinska Pharmacy,Box 60024, S-104 01 Stockholm, Sweden

[2]Department of Neuroradiology, Karolinska Hospital, S-104 01 Stockholm, Sweden

[3]Department of Psychiatry and Psychology, Karolinska Hospital, S-10401 Stockholm, Sweden

[4]Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala Sweden

SUMMARY

No-carrier-added ^{11}C-nitromethane has been prepared from ^{11}C-methyl iodide in a one-pot reaction by use of silver or sodium nitrite in different solvents. A conversion of up to 87% was obtained within 3 min. It could easily be distilled from high-boiling solvents to another reaction vessel (140°C, 3 min). Its potential as a radiolabeling precursor in condensations with aldehydes was shown in the synthesis of ^{11}C-β-nitrostyrene (85% conversion after 3-5 min).

Key Words: ^{11}C-nitromethane, ^{11}C-nitroalkane, ^{11}C-β-nitrostyrene

* To whom correspondence should be addressed

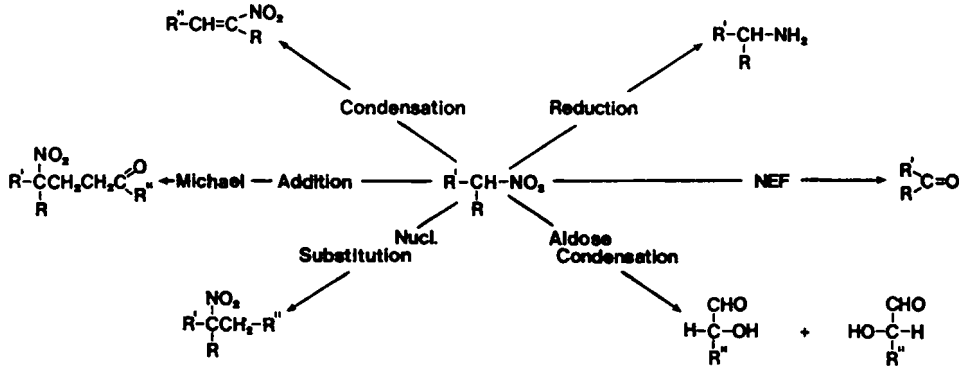
0362–4803/88/070749–10$05.00

Received October 22, 1987
Revised November 16, 1987

INTRODUCTION

To utilize the dynamic regional information obtained by positron emission tomography (PET) for monitoring specific biochemical processes, it is important to select appropriate radiolabeled compounds. In order to synthesize and label a desired compound with a short-lived positron-emitting radionuclide such as carbon-11 in a certain position, a wide range of suitable labeled precursors is necessary for synthetic flexibility. A number of such precursors may be available directly from target irradiations or by rapid on-line synthesis. Examples of these "primary" precursors are $^{11}CO_2$, ^{11}CO, $H^{11}CN$ and $^{11}CH_4$.[1] "Secondary" precursors may also be obtained from a "primary" precursor in batchwise or on-line productions. Examples of such "secondary" precursors are $R\text{-}^{11}CH_2I$,[2-4] $R\text{-}^{11}CHO$,[5-7] $^{11}COCl_2$,[8] $^{11}CH_3Li$[9] and $^{11}CH_2N_2$.[10] The development of these primary and secondary precursors has played a decisive role in the synthesis of new positron-emitting radiopharmaceuticals.

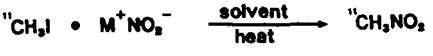
The synthetic versatility of nitroalkanes in organic synthesis has received a considerable amount of attention. With a pK_a=10.2, it can readily be converted to a nucleophile by the addition of base. In addition to undergoing condensation and nucleophilic substitution



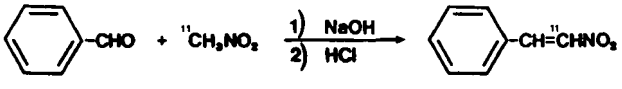
Scheme 1

reactions, nitroalkanes can be converted to other functionalities such as carbonyl compounds (Nef's reaction) and to amines (Scheme 1). One especially important application of the Nef reaction is in carbohydrate chemistry where nitromethane can be used to increase the number of carbon atoms in an aldose by one.

To investigate the possibility of extending these reactions to radiolabeling with positron-emitting radionuclides, emphasis has been placed on the synthesis of nitromethane labeled with carbon-11, as previously briefly reported.[11] ^{11}C-Nitromethane was prepared via a nucleophilic substitution reaction employing ^{11}C-methyl iodide in a one-pot reaction by use of silver or sodium nitrite in six different solvents (Scheme 2). A Simplex optimization method[12] was used to optimize the radiochemical conversion of ^{11}C-methyl iodide in dimethylformamide (DMF) and methanol. The utility of ^{11}C-nitromethane as a radiolabeling precursor was demonstrated by condensation with benzaldehyde[13] to yield ^{11}C-β-nitrostyrene (Scheme 3).



Scheme 2



Scheme 3

RESULTS AND DISCUSSION

^{11}C-Nitromethane can thus rapidly be prepared by the reaction of ^{11}C-methyl iodide with silver- or sodium nitrite. The yields obtained after 3 min reaction time varied between 0-87% in no-carrier-added experiments. Initial studies focused on the influence

of experimental factors on the product distribution. As summarized in Table 1, an investigation was performed on the effect of varying solvent, metal nitrite (silver and sodium) and reaction temperature (room temperature and 100°C) while the amount of salt and volume of solvent were held constant. The conversion of ^{11}C-methyl iodide to ^{11}C-nitromethane proceeded readily in the aprotic polar solvents dimethylsulfoxide (DMSO) and DMF. Good yields were also obtained in the protic polar solvent methanol but higher temperatures were required. In the less polar diethyl ether appreciable amounts of ^{11}C-nitromethane were only observed with silver nitrite at the higher temperature. In general higher yields were obtained with the silver than with the sodium nitrite salt. Likewise, yields of ^{11}C-nitromethane were generally higher at 100°C than at room temperature.

Table 1. Summary of results regarding the product distribution in six different solvents, two nitrite salts and two reaction temperatures.

			Product Distribution (%)		
Solvent	M^+	T	$^{11}CH_3NO_2$	$^{11}CH_3ONO$	$^{11}CH_3I$
Dimethylsulfoxide	Na	RT	54	46	-
		100	51	49	-
	Ag	RT	46	54	-
		100	49	51	-
Dimethylformamide	Na	RT	54	46	-
		100	53	47	-
	Ag	RT	54	46	-
		100	87	13	-
Acetonitrile	Na	RT	-	-	100
		100	19	17	65
	Ag	RT	70	30	-
		100	74	26	-
Isocapronitrile	Na	RT	-	-	100
		100	-	-	100
	Ag	RT	16	7	75*
		100	40	36	0*
Methanol	Na	RT	-	-	100
		100	26	6	68
	Ag	RT	20	7	73
		100	74	6	10*
Diethyl Ether	Na	RT	-	-	100
		100	-	-	100
	Ag	RT	4	-	93*
		100	51	4	0*

Solvent volume = 0.5 ml; MNO_2 = 100 mg; Trapping temperature = RT; Reaction time = 3 min; *Remainder of radioactivity is an unidentified by-product

^{11}C-Methyl nitrite, a major by-product of this reaction, was in some cases, found to be 51% of the total activity. Generally, however, the ratio of ^{11}C-nitromethane to ^{11}C-methyl nitrite increased with increasing temperatures. Another labeled product was observed in isocapronitrile, methanol and diethyl ether. Though unidentified, it might be a nitrate ester arising from the reaction of the alkyl halide with silver nitrate which may be formed during the thermal decomposition of silver nitrite.[14]

By use of the optimization method (Simplex), the influence of temperature and amount of silver nitrite was investigated in DMF and methanol (Tables 2 and 3, respectively). In both cases yields seem to be more influenced by maintaining a favourable reaction temperature than by increasing the amount of silver nitrite. For example in DMF, ^{11}C-nitromethane was obtained in 80% radiochemical yield with 10 mg

Table 2. Summary of results regarding the radiochemical yield in dimethylformamide.

$AgNO_2$ (mg)	Temp. (°C)	$^{11}CH_3NO_2$ (%)	$^{11}CH_3ONO$ (%)	$^{11}CH_3I$ (%)
10	0	23	5	72
10	80	81	19	0
10	100	80	20	0
10	123	80	20	0
20	175	68	32	0
50	64	82	18	0
100	25	54	46	0
100	80	85	15	0
100	100	87	13	0
100	123	76	24	0
100	175	68	32	0

Solvent volume = 0.5 ml; Trapping temp. = RT; Reaction time = 3 min

Table 3. Summary of results regarding the radiochemical yield in methanol.

$AgNO_2$ (mg)	Temp. (°C)	$^{11}CH_3NO_2$ (%)	$^{11}CH_3ONO$ (%)	$^{11}CH_3I$ (%)
2	123	60	25	0*
2	152	78	22	0
2	175	45	30	17*
5	120	79	16	5
10	50	3	0	97
50	120	86	13	0*
70	64	33	3	64
80	152	78	22	0
100	25	20	7	73
100	100	74	6	10*
100	175	69	31	0
102	100	75	12	0*
170	100	80	6	2*
190	48	40	2	48*
190	123	75	9	0*

Solvent volume = 0.5 ml; Trapping temp. = RT; Reaction time = 3 min; *Remainder of radioactivity is an unidentified by-product

silver nitrite at 80°C (Table 2). In methanol a radiochemical conversion of 79% can be obtained with 5 mg silver nitrite at 120°C (Table 3).

The trapping efficiency of ^{11}C-methyl iodide in the six solvents used was investigated by measuring the distribution of radioactivity in three vessels connected in series to the methyl iodide system. The flow rate was maintained at 29 mL/min (20°C), and 85-98% of the methyl iodide was trapped in the first reaction vessel (Table 4).

Table 4. Trapping efficiency of ^{11}C-methyl iodide in the reaction mixtures studied.

Solvent	Trapping eff. (%)**
DMSO	85
DMF*	96
Acetonitrile	96
Isocapronitrile*	98
Methanol*	92
Diethyl Ether*	92

Temperature = RT; Flow = 29 ml/min; Solvent volume = 0.5 ml; Amount of $AgNO_2$ = 50 mg; *undissolved; **Calculated from the trapped- and total amount of ^{11}C-methyl iodide

The total synthesis time from EOB (^{11}C-carbon dioxide) was 13 min (including preparation of ^{11}C-methyl iodide). ^{11}C-Nitromethane could easily be distilled to another reaction vessel (140°C, 3 min) from DMF or isocapronitrile. ^{11}C-β-Nitrostyrene was prepared via a condensation reaction between benzaldehyde and ^{11}C-nitromethane (85% conversion after 3-5 min). Further examples of the synthetic utility of ^{11}C-nitromethane as a radiolabeling precursor are presently under investigation as well as the development of an on-line production method.

EXPERIMENTAL

GENERAL

The ^{11}C-carbon dioxide was produced at the Karolinska Hospital with a Scanditronix RNP 16 cyclotron using 16 MeV protons in the ^{14}N(p,α)^{11}C reaction. The gas target was irradiated in a batch production. The ^{11}C-carbon dioxide produced was trapped in a stainless steel

coil cooled with liquid nitrogen before being transferred to the one-pot ^{11}C-methyl iodide system.[15] Analytical reversed-phase HPLC was performed using an LDC Constametric I pump, a Rheodyne injector (7125 with a 100 µL loop), a Waters µ-Bondapak C-18 column (300 x 7.8 mm) and an ERMA UV detector (254 nm) coupled in series with a Berthold LB 503 detector. Acetonitrile and 0.01 M phosphoric acid (50/50) was used as the mobile phase with a flow rate of 3.5 mL/min. Integration of the UV absorbance and radioactivity was accomplished using a Shimadzu C-R2AX two channel data processor. Silver and potassium nitrite were obtained from Fluka, benzaldehyde, nitromethane and methyl iodide from Merck and β-nitrostyrene from Aldrich. Methyl nitrite was synthesized by a literature method.[16] All other solvents and reagents used were available commercially and of analytical grade.

^{11}C-NITROMETHANE (Scheme 2)

^{11}C-Methyl iodide was trapped in a reaction vessel (1.0 mL mini-vial, Alltech) at room temperature, containing a magnetic stirrer, 0.5 mL solvent and a metal nitrite salt . After stirring for 3 min at the desired temperature, an aliquot was removed, added to 1 mL of the mobile phase precooled in dry ice/ethanol/water mixture (-10° to -30°C), and stored as such until the LC analysis was performed. The radioactive components eluted with same retention times as standard reference samples of methyl nitrite, nitromethane, and methyl iodide (3.2, 4.0, and 5.6 min, respectively). The unidentified product eluted at 4.6 min. A typical LC chromatogram (UV-absorbance/radioactivity) is shown in Figure 1.

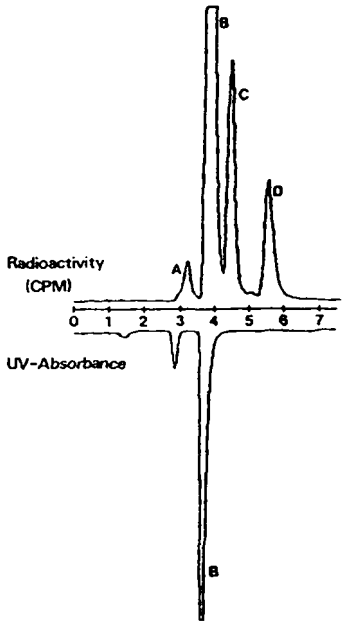


Figure 1. Analytical HPLC chromatogram (Radioactivity CPM and UV- Absorbance) A= $^{11}CH_3ONO$, B= $^{11}CH_3NO_2$, C= unident. D= $^{11}CH_3I$

^{11}C-β-NITROSTYRENE (Scheme 3)

^{11}C-Methyl iodide was trapped in a two-necked reaction vessel (10 mL, connected with a Vigreux column) containing a magnetic stirrer and a suspension of 30 mg silver nitrite in 0.5 mL isocapronitrile at room temperature. The mixture was heated at 100° C for 3 min for conversion of the methyl iodide. Under a stream of nitrogen the ^{11}C-nitromethane was subsequently distilled within 3 min at 140°C to a 5 mL conical vessel (at -10° to -20°C with dry ice/ethanol/water) containing 0.5 mL methanol and a magnetic stirrer. Benzaldehyde (106 mg, 1.0 mmol) and sodium hydroxide (25 µL, 10 M) were added. A yellow color appeared after addition of ice-water (200 µL) and hydrochloric acid (1 mL, 6.0 M). An aliquot was removed and stored for LC analysis as described above. At a flow of 3.5 mL/min ^{11}C-β-nitrostyrene eluted after 8.9 min with the same retention time as the reference sample.

ACKNOWLEDGEMENTS

The authors would like to thank Mr Göran Printz for assistance with the radionuclide production and Ms Camilla Falk and Ms Lena Lindberg for technical assistance. This work has been supported by grants from the Swedish Medical Research Council, the Bank of Sweden's Tercentenary fund, the Karolinska Institute, the National Institute of Mental Health and the Swedish Natural Science Research Council which is gratefully acknowledged.

REFERENCES

1. Christman D.R., Finn R.D., Karlstrom K.I. and Wolf A.P. Int. J. Appl. Radiat. Isot. 26: 435 (1975)

2. Comar D., Maziere M. and Crouzel C. - Radiopharmaceuticals and Labelled Compounds Vol. 1. IAEA, Vienna, (1974)

3. Långström B., Antoni G., Gullberg P., Halldin C., Någren K., Rimland A. and Svärd H. - Appl. Radiat. Isot. 37: 1141 (1986)

4. Crouzel C., Långström B., Pike V.W. and Coenen H.H. - Appl. Radiat. Isot. 38: 601 (1987)

5. Berger G., Maziere M., Sastre J. and Comar D. - J. Lab. Comp. Radiopharm. 17: 59 (1980)

6. Tang D.Y., Lipman A., Meyer G.J., Wan C.N. and Wolf A.P. - J. Lab. Comp. Radiopharm. 16: 435 (1979)

7. Halldin C. and Långström B. - Acta Chem. Scand. 38: 1 (1984)

8. Roeda D. and Westera G. - Int. J. Appl. Radiat. Isot. 32: 931 (1981)

9. Reiffers S., Vaalburg W., Wiegman T., Wynberg H. and Woldring M.G. - Int. J. Appl. Radiat. Isot. 34: 535 (1980)

10. Crouzel C., Amano R. and Fournier D. - Appl. Radiat. Isot. 38: 669 (1987)

11. Halldin C., Schoeps K-O., Stone-Elander S., Långström B. and Thorell J-O. - J. Nucl. Med. 28: 636 (1987)

12. Rimland A., Bergson G., Obenius U., Sjöberg S. and Långström B. Appl. Radiat. Isot. 38: 651 (1987)

13. Worrall D.E. - Org. Syn., Coll. Vol. 1, 413 (1941)

14. Kornblum N. - Org. Reactions, 12: 101 (1962)

15. Johnström P., Ehrin E., Stone-Elander S. and Nilsson J.L.G. - Acta Pharm. Suec. 21: 189 (1984)

16. Slater W.K. - J. Chem. Soc. 117: 587 (1920)