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Difunctional Two-Carbon Molecules Derived From [^{11}C]Cyanide

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Summary

A synthetic strategy for producing new difunctional molecules for potential use as radiolabelling precursors derived from [^{11}C]cyanide is presented. No-carrier-added [^{11}C]CN^- was reacted with chloromethyl pivalate to generate the nitrile [^{11}C]cyanomethyl pivalate, **1**, which was subsequently converted to ethyl [1-^{11}C]glycolate, **2**, with acid and alcohol, or to [1-^{11}C]glycolic acid, **4**, using aqueous acid. [1-^{11}C]Ethylene glycol, **3**, and [2-^{11}C]2-aminoethanol **5**, were obtained by reduction of **2** and **1**, respectively, with lithium aluminum hydride. Conditions for obtaining conversions *ca.* 90% are described. By using a microwave wave-guide cavity to speed up transformations requiring elevated temperatures, all five carbon-11 labelled compounds were synthesized in less than a total of 3 min.

Key words: microwaves, ethyl [1-^{11}C]glycolate, [1-^{11}C]ethylene glycol, [1-^{11}C]glycolic acid, [2-^{11}C]2-aminoethanol

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Introduction

The synthesis of radiolabelled molecules depends on the ready availability of appropriate radiolabelled precursors. Due to their short half-lives, positron-emitting radionuclides (^{15}O, ^{13}N, ^{11}C, ^{18}F) must be produced directly prior to the start of the tracer synthesis and the chemical forms of these accelerator-produced primary precursors are very simple.

A considerable amount of effort has been made by PET radiochemists to develop methods for the conversion of [^{11}C]CO_2 to small molecules of differing functionalities. A few examples are carbon-11 labelled alkyl halides (1,2), formaldehyde (3), acid halides (4,5), methyl lithium (6), nitroalkanes (7) and methyl triflate (8). [^{11}C]Cyanide (CN^-), a secondary precursor produced on-line from [^{11}C]CO_2, has been used in the syntheses of ^{11}C-labelled carbohydrates, amino acids, amines and carboxylic acids (9). The synthetic flexibility potentially accessible via the

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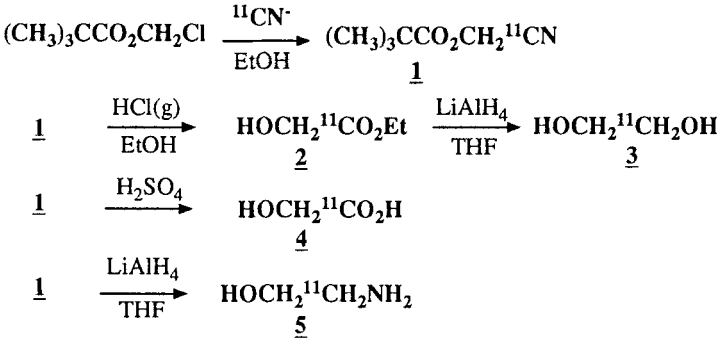
intermediate nitriles has also been exploited in the syntheses of other precursors (for example, cyanate (10); urea (11); butanediol (12); acrylonitriles (13); halonitriles (14); cyanogen bromide (15); diethyl oxalate and oxalic acid (16). However, due to the time requirements for good conversions, such procedures are usually limited to a few reaction steps. The application of microwave technology to radiolabelling procedures (see references in 17) not only has reduced reaction times thereby making multi-step syntheses more feasible, (16, 18-19) but, in some cases, has also provided the only means of reliably accomplishing a desired radiolabelling (20).

This paper presents the syntheses of four difunctional small molecules derived from $[^{11}C]CN^-$ that potentially can function as two-carbon radiolabelling precursors. The strategy chosen, as outlined below, was based on the reaction of $[^{11}C]CN^-$ with chloromethyl pivalate. The labelled nitrile **1** could subsequently be converted to a number of functionalities, depending on the reagents chosen. For reactions requiring elevated temperatures a microwave wave-guide cavity (21) was used to shorten the reaction time.



Experimental

General

Chloromethyl pivalate (ClMePiv) was obtained from Aldrich, glycolic acid from Janssen Chimica, lithium aluminum hydride ($LiAlH_4$), ethylene glycol and 2-aminoethanol from Merck. The solvents, acids and bases were all of analytical grade and commercially available. Reference cyanomethyl pivalate was synthesized by a literature method (22). Reference ethyl glycolate was synthesized by the esterification of glycolic acid and by the alcoholysis of cyanomethyl pivalate.

Gas chromatographic analysis indicated that both routes gave one product (IR: 3600-3100 cm^{-1}, OH and 1750 cm^{-1}, ester carbonyl).

Analytical HPLC was performed using an LDC Constametric III pump, a Rheodyne injector (7125 with a 250 µL loop), an Erma ERC-7510 refractometer connected in series with a Beckman 170 β-flow radiodetector. Integration of the peaks was performed using a Shimadzu C-R2AX integrator. The columns used for HPLC analyses were µ-Bondapak C-18 (300 X 3.9 mm, 10 µm, Waters) (A), Aminex HPX 89-H (300 X 7.8 mm, 9 µm, Biorad) (B) and a Partisil SAX (250 X 4.6 mm, 10 µm, Jones) (C). Mobile phases were for (A) CH_3CN:H_3PO_4 (0.01 M) = 60:40 at a flow rate of 1.5 mL/min, (B) 0.01 N H_2SO_4 at 1.0 mL/min and (C) 5 mM K_3PO_4 at 2 mL/min. The retention times for the radiolabelled products are given in Table 1.

Table 1. The retention times for the different carbon-11 labelled intermediates and products on HPLC columns A, B and C

Comp. | Column	A	B	C
[^{11}C]CN^-	3.7 min	-	2.8 min
1	4.5 min	29 min	3.3 min
2	6.5 min	-	-
3	-	10 min	-
4	-	8 min	-
5	-	-	5 min

The microwave cavity used is a prototype whose performance in radiolabelling reactions with ^{11}C-labelled alkyl halides and cyanide has been demonstrated (21 and 16, respectively). Briefly, the microwaves are delivered to the sample in a waveguide-type cavity. This single-mode equipment allows placement of the sample in the maximum of the electromagnetic field. Much lower input magnetron power and shorter reaction times than in a conventional microwave oven are thus required to effect the desired transformations. The vessels used for the microwave reactions were Pyrex tubes (total volume *ca* 10 mL) equipped with a screw cap and teflon septum for insertion of needles through which reagents were added. The sample volume did not exceed 1/10th the total volume of the tube in order to allow sufficient head space for pressure developed during the microwave treatment.

$[^{11}C]CO_2$ was produced batchwise using the Scanditronix MC 16 cyclotron at the Karolinska Hospital/Institute by bombardment of a nitrogen gas target with 17 MeV protons in the $^{14}N(p,\alpha)^{11}C$ reaction. $[^{11}C]CN^-$, produced in a two-step on-line conversion from $[^{11}C]CO_2$ (23), was bubbled through H_2SO_4 (2 mL, 50 %) heated at 80 °C (24). The $[^{11}C]HCN$ flowed through a tube containing P_2O_5 (1.5 g) and finally was trapped in ethanol (0.5 mL, 0-5 °C) containing NaOH (5 μL, 5 M).

Radiolabellings

[^{11}C]Cyanomethyl pivalate **1**

ClMePiv (50 μL, 35 μmol) was added to the alcoholic solution of $[^{11}C]CN^-$. The solution was heated at 80 °C for 2 min or treated with a microwave input power of 100 W for 15 sec. Conversions (%, according to analyses by radio-HPLC)=91±4%.

Ethyl [1-^{11}C]glycolate **2**

HCl (0.5 mL, 4 M in EtOH) was added to the alcoholic solution of **1**. The solution was heated at 80 °C for 10 min or treated with a microwave input power of 75 W for 30 sec. Conversions=93±7%.

[1-^{11}C]Ethylene glycol **3**

The alcoholic solution of **2** was evaporated to dryness and $LiAlH_4$ (0.5 mL, 0.2 M in THF) was added. The solution was stirred at room temperature for 2 min. Conversions=89±2%.

[1-^{11}C]Glycolic acid **4**

H_2SO_4 (0.5 mL, 50%) was added to the alcoholic solution of **1**. The solution was heated at 120 °C for 5 min or treated with a microwave input power of 75 W for 15 sec. Conversions=90±13%.

[2-^{11}C]2-Aminoethanol **5**

The alcoholic solution of **1** was evaporated to dryness and $LiAlH_4$ (0.5 mL, 0.2 M in THF) was added. The solution was stirred at room temperature for 2 min. Conversions=90±2%.

Results and Discussion

Use of the substrate ClMePiv required the removal of the ammonia added to the gas from the target during the processing to $[^{11}C]CN^-$. This was accomplished using the on-line procedure

described by Maeda *et al.* (24). No additional processing time was required for this method and only small losses of radioactivity in the sulfuric acid and P_2O_3 traps were observed (10-15%).

Formation of the ^{11}C-labelled nitrile **1** proceeded readily under no-carrier-added conditions through the nucleophilic displacement of chloride by [^{11}C]CN$^-$. Although appreciable amounts of **1** were formed at room temperature, conversions on the order of 85-95% were obtained after 2 min at 80°C. With microwave treatment only 15 sec with 100 W was required for comparable yields.

The nitrile group in **1** was subsequently converted to four different functionalities: the ester in **2** by alcoholysis, the primary alcohol in **3** by reduction of the ester **2**, the carboxylic acid in **4** by hydrolysis and the amine in **5** by reduction. The pivalate protecting group was removed by either solvolysis or reduction, thereby generating the second (alcohol) functionality.

The conversion of a [^{11}C]nitrile to a [^{11}C]ester was recently demonstrated in the synthesis of diethyl [1-^{11}C]oxalate (16). Similar to those studies, the conversion of **1** to **2** required elevated temperatures. Conversions of *ca.* 70 and 90% were obtained after 5 and 10 min, respectively, at 80 °C. As previously demonstrated (16), microwave treatment was especially favorable for alcoholysis: *ca.* 90% conversions after 30 sec with 75 W.

The transformation nitrile to alcohol producing [1-^{11}C]ethylene glycol **3** could, in principle, be performed via either **2** or **4**. However, since anhydrous conditions are required for the reduction, it was easier to evaporate the alcoholic solution of **2** than try to isolate **4** from the aqueous media used. Subsequent reaction of **2** with $LiAlH_4$ proceeded readily at room temperature (*ca.* 90% after 2 min) when all the previous alcoholic solvent had been removed. However, some losses of radioactivity (10-15%) were observed during the evaporation.

[1-^{14}C]Glycolic acid has been previously synthesized from acetic acid via the α-halo acid (25) or, more recently, by the reaction of labelled carbon dioxide with a protected methyl lithium anion and subsequent catalytic reduction (26). The procedure presented here is much faster and avoids problems with poisoned catalysts previously reported (26). The hydrolysis of **1** to **4** was performed using H_2SO_4 (50%). Other mineral acids such as HCl could also be used although the

results were more consistent with H_2SO_4. For the thermal procedure good conversions were obtained after 5 min at 120 °C. The use of microwaves shortened the reaction times to 15 sec for comparable results.

The transformations of **1** to **5** was accomplished after evaporation of the alcoholic trapping media. By using $LiAlH_4$ to reduce the nitrile and simultaneously remove the pivalate protecting group, the reaction was essentially complete after 2 min at room temperature.

Conclusions

The times of preparation and conversions for **1** to **5** are given below in Table 2. For reactions with slow kinetics the advantages of using microwave treatment as a complement to thermal treatment are obvious. Not only are the reactions speeded up, but the same equipment can be used for different reaction conditions: for example, the conversion of $[^{11}C]CN^-$ to **4** would require 80 °C first to obtain **1** and then 120 °C to generate **4** under thermal conditions. For microwave treatment, different reaction conditions are achieved by simply changing the input microwave power or slightly increasing the time of treatment.

Table 2. The reaction conditions and the conversions for the different steps

	Microwave		Thermal		
	Time	Effect	Time	Temp	Conversion (%)*
Reaction	(min)	(W)	(min)	(°C)	
$[^{11}C]CN^- \rightarrow$ **1**	0.25	100	2	80	91±4
1 → **2**	0.5	75	10	80	93±7
2 → **3**	-	-	2	r.t.	89±2
1 → **4**	0.25	75	5	120	90±13
1 → **5**	-	-	2	r.t.	90±2

*At least 3 repeated experiments

To our knowledge none of these ^{11}C-labelled precursors have previously been synthesized. Subsequent labelling procedures may preferentially use one of the functional groups. The difunctionality of these molecules presents new possibilities for introducing a carbon-11 label in, for example, heterocyclic rings. The use of combined microwave and conventional thermal

procedures makes such multi-step procedures feasible in the time available for radiolabelling with short-lived radionuclides.

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References

(1) Crouzel C., Långström B., Pike V.W. and Coenen H.H. -Appl. Radiat. Isot. **38** 601 (1987) and refs therein.

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

(3) Berger G., Maziere M., Sastre J. and Comar D. -J. Label. Cmpds. Radiopharm. **17** 59 (1980)

(4) Roeda D., Crouzel C. and van Zanten B. -Radiochem. Radioanal. Lett. **33** 175 (1978)

(5) Luthra S.K., Pike V.W. and Brady F. -J. Chem. Soc. Chem. Commun. 1423 (1985)

(6) Reiffers S., Vaalburg W., Wiegman T., Wynberg H. and Wolding M.G. -Int. J. Appl. Radiat. Isot. **31** 535 (1980)

(7) Schoeps K.-O., Stone-Elander S. and Halldin C. -Appl. Radiat. Isot. **40** 261 (1989)

(8) Jewett D.M. -Appl. Radiat. Isot. **43** 1383 (1992)

(9) Fowler J.S. and Wolf A.P. -"Positron Emission Tomography and Autoradiography: Principles and applications for the Brain and Heart. (Eds. Phelps M.E., Mazziotta J.C. and Schelbert H.R.) Raven Press, New York pp 391 (1986)

(10) Winstead M.B., Chern C.I., Lin T.H., Khentigan A., Lamb J.F. and Winchell H.S. -Int. J. Appl. Radiat. Isot. **29** 443 (1978).

(11) Emran A.M., Boothe T.E., Finn R.D., Vora M.M. and Kothari P.J. -Appl. Radiat. Isot. **37** 1033 (1986).

(12) Hassan M., Thorell J.-O., Warne N. and Stone-Elander S. -Appl. Radioat. Isot. 40: 1055 (1991)

(13) Antoni G. and Långström B. -Appl. Radiat. Isot. **43** 903 (1992).

(14) Hörnfelt K., Antoni G. and Långström B. -Acta Chem. Scand. **46** 87 (1992).

(15) Westerberg G., Malmborg P. and Långström B. -J. Label. Cmpds. Radiopharm. **30** 126 (1991)

(16) Thorell J.-O., Stone-Elander S. and Elander N. -J. Label. Cmpds. Radiopharm. **33** 995 (1993)

(17) Stone-Elander S. and Elander N. -Appl. Radiat. Isot. **44** 889 (1993)

(18) Thorell J.-O., Stone-Elander S. and Elander N. -J. Label. Cmpds. Radiopharm. **31** 207 (1992)

(19) Hwang D.-R., Moerlein S.M., Dence C.S. and Welch M.J. -J. Label. Cmpds. Radiopharm. **26** 391 (1989)

(20) Zijlstra S., Visser G.M., Korf J. and Vaalburg W. -Appl. Radiat. Isot. **44** 651 (1993)

(21) Stone-Elander S. and Elander N. -J. Label. Cmpds. Radiopharm. **32** 154 (1993)

(22) Daub G.H., Kerr V.N., Williams D.L. and Whaley T.W. - "Organic synthesis with stable isotopes", *Proceedings of the third international conference on stable isotopes, Argonne National Laboratory*. Klein E.R. and Klein P.D. Eds., Academic Press New York, pp 7 (1979)

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

(24) Maeda M., Nishimura S., Fukumora T. and Kojima M. -J. Label. Cmpds. Radiopharm. **25** 233 (1988)

(25) Ramamurthy T.V. and Viswanathan, K.V. -J. Label. Cmpds. Radiopharm. **24** 995 (1983)

(26) Clizbe L.A. and Reist E.J. -J. Label. Cmpds. Radiopharm. **31** 951 (1992)