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Synthesis of ^{11}C-labeled 2-aminoethanol via a nitroaldol reaction using nitro[^{11}C]methane

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ABSTRACT

The nitroaldol reaction of nitro[^{11}C]methane and formaldehyde using EtOH and EtONa efficiently provided 2-nitro[^{11}C]ethanol in 3 min. The nitro group reduction in the presence of $NiCl_2$ and $NaBH_4$ in MeOH followed by purification using semi-preparative HPLC using 10% EtOH aqueous solution as an eluent proved to be a practical and accessible method for the synthesis of 2-amino[2-^{11}C]ethanol.

Recent progress of tumor imaging by positron emission tomography (PET) plays a crucial role for cancer diagnosis. 2-Deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is well recognized as a PET tracer for cancer diagnosis and FDG-PET is utilized at every PET center. However, the usefulness of FDG-PET for cancer diagnosis is limited as FDG is not a tumor selective tracer. Therefore, new tracer molecules that provide tumor selective images are always required. There are many factors to consider when identifying potentially new PET tracer molecules. Development of new labeling methodology is important because only a limited number of labeling reactions are available for tracer syntheses due to the short half-life of the radionuclide.[1] As a result, a number of promising molecules have not yet been labeled as potential PET tracers.

Phospholipid metabolism is a significant target for analysis and detection of tumor cells. 2-Aminoethanol (AE) and choline are the primary components of phospholipids and their uptake is increased in accordance with the rapid proliferative rate of the tumor cell.[2] In fact, [*N*-^{11}C]methyl-choline has been used for tumor imaging in cancers that are not well imaged by FDG such as brain cancer, prostate cancer, and any cancers less than 1 cm in size. Recently, Ponde et al. reported that AE showed a 2–7-fold better uptake than choline using ^{14}C-labeled AE and ^{14}C-labeled choline against a diverse group of cancer cell lines, including glioblastoma, prostate, melanoma, colorectal cancer, and lymphoma.[3] In addition to radioisotope labeled experiments, an uptake of AE that is higher than choline has been suggested by MRS experiments.[4] AE is a potential tumor imaging probe, however there are no reports of in vivo tumor imaging using AE by PET. Even the synthesis of AE labeled with a positron emitting radionuclide has not reported yet. The structure of AE permits incorporation of ^{11}C, ^{13}N, and ^{15}O as radiolabels, with ^{11}C being the most suitable due to its relatively long half-life. However, the half-life of ^{11}C is 20.3 min and several constraints which are involved in ^{11}C-labeling make it difficult to synthesize ^{11}C-labeled AE. In this context, our interests were directed toward elucidating the synthetic methodology of 2-amino[2-^{11}C]ethanol (**1**). Herein we describe the efficient and practical synthesis of **1** via a rapid and regulated nitroaldol reaction between nitro[^{11}C]methane (**2**) and formaldehyde affording 2-nitro[^{11}C]ethanol (**3**) as a key product.

A carbon-11-labeled nitroaldol reaction of nitromethane and formaldehyde followed by the reduction of the nitro group is the most feasible for the synthesis of ^{11}C-labeled AE. Although both ^{11}C-labeled **2** and [^{11}C]formaldehyde are available, [^{11}C]formaldehyde is not commonly used in the synthesis of PET tracers. Recently facile production of [^{11}C]formaldehyde was reported, however the method was a 'wet' production.[5] Wet production usually requires another process such as removal of solvent and residual chemicals before the reaction is completed, resulting in a time-consuming step compared with on-line synthesis. On the other hand, the agent **2** is prepared using an on-line synthesis via nitration of iodo[^{11}C]methane, the most frequently used compound for ^{11}C-labeling (Eq. 1).[6] The synthesis of **1** using **2** is more technically accessible, however the constraints placed on the reaction because of the use of a short-lived radionuclide necessitate special requirements for producing **3**. These include, first, the carbon-11-labeling reactions should be terminated within a few minutes of initiation owing to the competing decay of both the ^{11}C-labeling agent and the ^{11}C-labeled product. Second, the nitroaldol reaction between the no-carrier added **2** and formaldehyde should take place in

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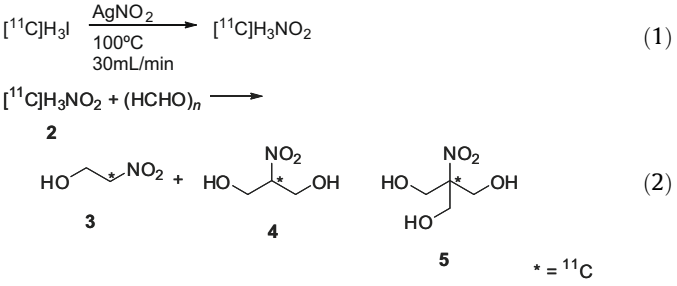
the presence of a large excess of formaldehyde. Contamination of ^{11}C-labeling precursors with ^{12}C is inevitable and unregulated, and specific activities of ^{11}C-labeled compounds for PET studies are in the range of 37–370 GBq/μmol. Hence, the total amount of ^{11}C-labeling agents (**2** in this study) is mostly in the low nanomol range. Thus, more than 1 μmol of precursor (10 μmol in this study) is usually introduced. As a result, it is important to suppress any successive nitroaldol reactions that form nitrodiol **4** and nitrotriol **5** while keeping rapid formation of **3** (Eq. 2). It is also important for the practical synthesis of **1** to avoid any time-consuming processes throughout the entire procedure.



The labeling agent **2** was prepared via nitration of iodo[^{11}C]methane by passing it through a plug of $AgNO_2$ with heating at 100 °C. Gaseous **2** was collected in the reaction vessel at 0 °C. Results of reaction **2** and formaldehyde are summarized in Table 1. All reactions were carried out for 3 min at 0 °C. Treatment of **2** and paraformaldehyde with EtONa in THF afforded the low radiochemical conversion of **3**, leaving most of **2** intact (entry 1). The low solubility of EtONa in THF was the major reason for the slow reaction. We investigated the additive effect of EtOH for enhancing the formation of **3** while retarding the successive reaction which formed **4**. The former effect occurred because of the increased solubility of EtONa. We expected the latter effect on the basis of the nitroalkane anomaly that was observed particularly in protic solvents. Thus, nitroalkanes act as slow acids compared with other carbon acids with regard to rate versus pK_a and the anomaly becomes more noticeable with the alkyl group substitution at the α-position.[7] Thus, the addition of EtOH enhanced the reactions which used EtONa to give the higher radiochemical conversion into **3** (entries 2–5). Furthermore, increasing the amount of additive EtOH afforded **3** with a relative low conversion into **4**. The best results were obtained by the addition of 10 μL of EtOH. Under these conditions, the radiochemical conversions of **3** and **4** were 64.4 ± 3.1% and 17.0 ± 3.9%, respectively (entry 4). However, treatment of **2** and paraformaldehyde with EtONa in EtOH gave low radiochemical conversion of **3** (entry 6). In general, the intramolecular hydrogen-bond is an important determinant factor for the selective formation of **3**. Under the non-labeled conditions, Herman and ApSimon reported the efficient formation of **6** by the reaction of

Table 1
Nitroaldol reaction of **2** and paraformaldehyde using EtONa[a,b]

Entry	solvent	EtOH (μL)	Radiochemical conversion[c] (%)		
			3	**4**	**5**
1	THF	0	<9	0	0
2	THF	2	33.9 ± 1.6	27.9 ± 2.6	0
3	THF	5	51.3 ± 3.9	37.2 ± 2.5	0
4	THF	10	64.4 ± 3.1	17.0 ± 3.9	0
5	THF	50	57.2 ± 6.6	17.8 ± 1.6	0
6	EtOH	—	<10	0	0

[a] Reaction conditions were 0 °C, 3 min, **2** (37–370 MBq), paraformaldehyde (10 μmol), EtONa (15 μmol) and solvent (300 μL).
[b] Each reaction was carried out more than three times.
[c] Determined by radiochromatogram of analytical HPLC after decay correction.

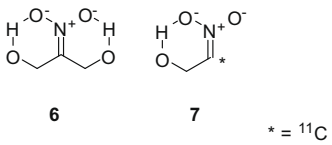
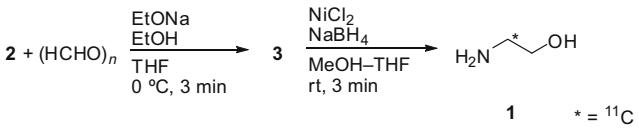


Figure 1. Structure of **6** and **7**.

nitromethane and formaldehyde (Fig. 1).[8] Stabilization of the intramolecular hydrogen-bond of **6** can retard the third addition of formaldehyde resulting in slow conversion to nitrotriol. The formation of a similar intramolecular hydrogen-bond complex like **7** was considerable and could assist the selective formation of **3** by retarding the second addition (Fig. 1). Acetalization of formaldehyde and EtOH might modulate the reaction rate of each nitroaldol reaction, resulting in predominant formation of **3**. Furthermore, we believe that the addition of EtOH assists the selective formation of **3**. An increased amount of EtOH affected the nitronate formation more seriously for **3** than **2** and the second addition to form **4** became relatively slow, resulting in the selective formation of **3** (Eq. 2 and Table 1).

Several reagents are available for the reduction of a nitro group to the corresponding amine. Although hydrogenation using Pt or Pd on carbon is usually chosen for the reduction of a nitro group in non-radiolabeled synthesis,[9] these methods need to be converted to special equipment for performing a ^{11}C-labeling reaction under a H_2 atmosphere. A system which is easily assembled with all necessary reactants accessible for automation is another important requirement for PET tracer synthesis therefore a method other than hydrogenation is preferable for the reduction of **3**. We chose Ni_2B–$NaBH_4$ for the conversion of **3** to **1** because the reducing agent could be prepared by treatment of $NiCl_2$ and $NaBH_4$ in situ in MeOH.[10] Moreover, this method has the advantage of THF as the solvent for the nitroaldol reaction because the procedure does not require a separation process between the nitroaldol reaction and the following reduction. In fact, MeOH was added to the reaction mixture of entry 4 in Table 1 and the resulting solution was transferred directly to the reaction vessel with $NiCl_2$ and $NaBH_4$ to give the desired amine **1** in 52.4 ± 1.7% radiochemical conversion (2 steps) (Scheme 1).[11] The HPLC method for the analysis of the reduction reaction of **3** used aqueous EtOH as an eluent and



Scheme 1. Synthesis of **1**.

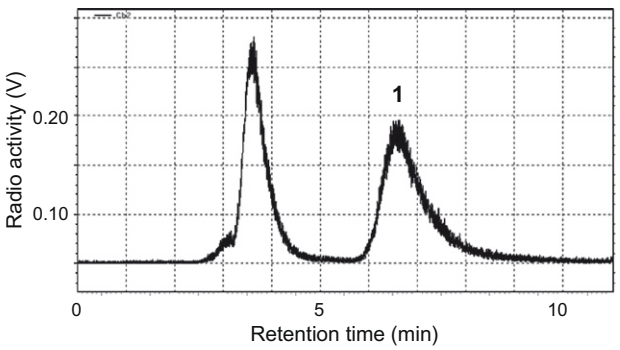


Figure 2. HPLC chromatogram of the reduction reaction of **3**. HPLC conditions: column J'sphere ODS-H80 (4.6 × 150 mm, 4 μL, YMC Co. Ltd), flow rate 0.6 mL/min, eluent 15/85 (EtOH/ammonium phosphate buffer pH 9.4), detector NaI scintillator.

provided excellent separation of **1** (Fig. 2). Semi-preparative HPLC is frequently introduced for purification of PET tracers and similar conditions as described above is applicable for the synthesis of **1**.[12] Use of aqueous EtOH as an eluent is advantageous because the fraction containing **1** can be directly utilized for the PET studies after dilution with water. Thus, a time-consuming evaporation process of the HPLC fraction can be omitted and the estimated total synthetic time after the end of the bombardment is less than 25 min. Moreover the loss of volatile **1** by evaporation can be avoided.

We have demonstrated an efficient method for the ^{11}C-labeling synthesis of **1** via a rapid and regulated nitroaldol reaction affording **3**. All reagents including the ^{11}C-labeling agent **2** are accessible and commercially available and the synthetic procedures are robust and practical. We anticipate that our method can be applied to the synthesis of **1** for use in PET studies for further development of cancer diagnosis tools.

Acknowledgments

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11. Gaseous **2** was collected by a reaction vessel containing EtONa (15 μmol), EtOH (10 μL), and paraformaldehyde (10 μmol) in THF (300 μL) with 30 mL/min flow rate at 0 °C. After 3 min at 0 °C, MeOH (500 μL) was added to the reaction mixture. The mixture was transferred to a next reaction vessel containing $NiCl_2$ hexahydrate (2.5 μg) and $NaBH_4$ (14 μg). After 3 min at room temperature, ammonium phosphate buffer (pH 9.4, 500 μL) was added to the reaction mixture. The contents of the resulting mixture were analyzed by HPLC.
12. Retention times from semi-preparative HPLC were 4.5 and 8.8 min for serinol and 2-aminoethanol respectively. Conditions: column J'sphere ODS-H80 (10 × 250 mm, 8 μm, YMC Co. Ltd), flow rate 3 mL/min, eluent 10/90 (EtOH/ammonium phosphate buffer pH 9.4), detector UV (210 nM).