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# Nitroaldol reaction of nitro[$^{11}$C]methane to form 2-(hydroxymethyl)-2-nitro[2-$^{11}$C]-propane-1,3-diol and [$^{11}$C]Tris

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**The nitroaldol reaction of nitro[$^{11}$C]methane and formaldehyde, which yields 2-(hydroxymethyl)-2-nitro[2-$^{11}$C]propane-1,3-diol, is explored. The fluoride-ion-assisted nitroaldol reaction using $(C_4H_9)_4NF$ was rapid and provided the desired nitrotriol in more than 97% radiochemical conversion (decay-corrected) in 3 min at room temperature. Neither 2-nitro[2-$^{11}$C]ethanol nor 2-nitro[2-$^{11}$C]propane-1,3-diol was observed under the reaction conditions. The preparation of 2-amino-2-(hydroxymethyl)-[2-$^{11}$C]propane-1,3-diol ([$^{11}$C]Tris) was described, which was followed by the nitro-group reduction using $NiCl_2$ and $NaBH_4$ in aqueous MeOH. The decay-corrected radiochemical conversion to [$^{11}$C]Tris was 68.0 $\pm$ 6.5% in two steps.**

**Keywords:** isotopic labeling; carbon-11; nitroaldol reaction; fluoride ion; Tris

## Introduction

The nitroaldol reaction is an important route to C–C bond formation in organic syntheses. Nitroaldol products are used as synthetic intermediates of versatile pharmaceuticals, including $\beta$-aminoalcohols, which are structural components of $\beta$-blockers.[1] In general, the nitroaldol reaction is performed in the presence of excess nitroalkane to carbonyl compounds in order to suppress multiple addition reactions and compensate for the low reactivity of nitroalkanes. Methods that utilize the multiple adduct as a synthetic building block are also being developed.[2]

Carbon-11 is a positron-emitting radionuclide that can be used for positron emission tomography (PET) research. Iodo[$^{11}$C]-methane ([$^{11}$C]$H_3$I, **1**) is a frequently used $^{11}$C-labeling agent for PET tracer synthesis.[3] Carbon-11-labeled nitromethane ([$^{11}$C]$H_3NO_2$, **2**) is prepared via on-line nitration of **1**.[4] In contrast to the electrophilic character of **1**, **2** can be used as a nucleophile by furnishing the stabilized carbanion under mild basic conditions. Thus, the umpolung strategy is available for $^{11}$C-labeling methodologies, although there are several constraints of using a short-lived radioisotope. When we consider the use of **2** as an $^{11}$C-labeling agent, the development of an efficient method for the nitroaldol reaction using **2** becomes a challenging issue in $^{11}$C-labeling chemistry. Because of the short half-life of $^{11}$C, the development of rapid reaction conditions that overcome the considerably low reactivity of **2** is required. It is difficult to regulate the multiple additions and the dehydration of nitroaldol products because $^{11}$C-labeling reactions involve a large excess of carbonyl compounds and bases.[5,6] With the exception of the reaction with formaldehyde, controlling the chiral center of nitroaldol products is a primary concern.[7]

The nitroaldol reaction of **2** and formaldehyde provides us opportunities to develop appropriate $^{11}$C-labeling methodologies that overcome the major differences in the reaction conditions between radiolabeling and nonradiolabeling reactions. Thus, the reaction can afford three nitroaldol products, 2-nitro[2-$^{11}$C]ethanol (**3**), 2-nitro[2-$^{11}$C]propane-1,3-diol (**4**), and 2-(hydroxymethyl)-2-nitro[2-$^{11}$C]propane-1,3-diol (**5**), by mono- and multiple additions in the presence of a large excess of formaldehyde [Equation (1)]. In our previous research, we encountered the obstacle of regulating the formation of **3.** The low steric hindrance of formaldehyde promoted multiple reactions, yielding **4** by treatment of **2** and paraformaldehyde with EtONa in the presence of EtOH at 0°C.[5] We optimized the reaction conditions to give **3** in good radiochemical conversion by adjusting the amount of EtONa and EtOH.[5] Besides optimizing the mono-adduct formation, we also found another difficulty relating to the third addition to form nitrotriol **5**. We did not observe the multiple adduct yielding **5** during our previous attempt of $^{11}$C-labeled nitroaldol reactions, in contrast to the facile formation of **4**. The intra-molecular hydrogen bonding of nitronate that renders the isolation of nitrodiol feasible under nonradiolabeling conditions would require a longer reaction time for the formation of **5** (Figure 1).[8] Thus, we explored reaction conditions to produce **5** rapidly for use in $^{11}$C-labeling synthesis.

2-Amino-2-(hydroxymethyl)-[2-$^{11}$C]propane-1,3-diol ([$^{11}$C]Tris, **6**), which can be prepared by nitro-group reduction, becomes a target of synthetic applications of **5** because Tris is a pharmaceutical product used for treatment of acidosis.[9] Acidosis is worthy of comment in relation to PET research because it is

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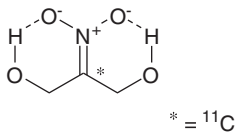



**Figure 1.** A structure of intra-molecular hydrogen bonding.

accompanied by inflammation. Inflammation is a common target for diagnosis by PET as it is observed across several diseases. In addition, the reduction of aliphatic nitro compounds to corresponding amines is a difficult process under $^{11}$C-labeling conditions. Therefore, the development of nitroaldol reaction as well as efficient nitro-group reduction provides new synthons for use in $^{11}$C-labeling. In this context, the reaction of **2** with formaldehyde to yield nitrotriol **5** and the synthesis of **6** become topics of interest from the viewpoint of the $^{11}$C-labeling nitroaldol reaction. We describe herein the synthesis of **6**, including simple preparation of **2**, rapid nitroaldol reaction, and the nitro-group reduction of **5**.

## Experimental section

### General information

Reagents EtONa, 1.0 M THF solution of TBAF, paraformaldehyde, $AgNO_2$, and aqueous 57% HI solution were purchased from WAKO Co. Ltd. 2-Hydoroxymethyl-2-nitropropane-1,3-diol was purchased from Aldrich Co. Ltd. A 0.05 M THF solution of lithium aluminum hydride (LAH) was prepared by diluting a 1.0 M THF solution purchased from Aldrich. The reaction solvents used, THF, EtOH (used as an additive), and MeOH, were of dehydrated grade purchased from WAKO Co. Ltd. Solvents used for HPLC, hexane, 1,4-dioxane, MeOH, and acetonitrile, were of HPLC grade purchased from WAKO Co. Ltd.

A CYPRIS HM-18 cyclotron (Sumitomo Heavy Industry, Tokyo) was used for the $^{11}$C production by a $^{14}$N(p, $\alpha$)$^{11}$C nuclear reaction. Purification and analysis of radioactive mixtures was performed by HPLC with an in-line UV (210 nm) detector in series with a NaI crystal scintillation detector.

### Nitro[$^{11}$C]methane (2)

[$^{11}$C]Carbon dioxide was produced by the $^{14}$N(p,$\alpha$)$^{11}$C nuclear reaction in a nitrogen gas containing 0.01% oxygen with 18 MeV protons. After bombardment, [$^{11}$C]$O_2$ was transferred to the reaction vessel where a 0.05 M THF solution of LAH (500 μL) was placed at 0°C. After evaporating THF, an aqueous 57% HI solution (400 μL) was added to the vessel. The resulting mixture was heated to 150°C to produce gaseous iodo[$^{11}$C]methane (**1**). The precursor **1** was passed through $P_2O_5$, and Ascarite then converted to nitro[$^{11}$C]methane (**2**) by passing at a flow rate of 30 mL/min through a plug of $AgNO_2$ attached to a column filled with $NaHCO_3$. The column of $AgNO_2$ was wound with a prior tube line to preheat the gas stream. Both of the column and wound tube line were covered by foil and robber heater and heated at 100°C.

### Nitroaldol reaction by treatment of 2 and paraformaldehyde with EtONa and EtOH

Gaseous **2** was collected by a reaction vessel containing EtONa (15 μmol), EtOH (10 μL), and paraformaldehyde 10 μmol) in THF (300 μL) with a 30 mL/min flow rate at RT. After reaching a plateau of radioactivity in the reaction vessel, a gas stream was suspended and the solution was heated up to 40 or 100°C. After 3 min, the reaction was quenched by the addition of $CH_3COOH$ (100 μL). The reaction mixture was analyzed by HPLC under the following conditions: column, Silica AG 80 (Shiseido Ltd., 4.6 × 250 mm, 5 μm); flow rate, 2 mL/min; eluent, hexane/1,4-dioxane (65/35). The retention times for **3** and **4** were 3.6 and 5.2 min, respectively.

### 2-(Hydroxymethyl)-2-nitro[2-$^{11}$C]propane-1,3-diol (5)

Gaseous **2** was collected by a reaction vessel containing TBAF (5 μmol) and paraformaldehyde 10 μmol) in THF (300 μL) with a 30 mL/min flow rate. After reaching a plateau of radioactivity in the reaction vessel, a gas stream was suspended and the solution was placed at RT. After 3 min, the reaction was quenched by the addition of $CH_3COOH$ (100 μL). The reaction mixture was analyzed by HPLC under the following conditions: column, Silica AG 80 (Shiseido Ltd., 4.6 × 250 mm, 5 μm); flow rate, 2 mL/min; eluent, hexane/1,4-dioxane (65/35). The retention time for **5** was 8.1 min.

### 2-Amino-2-(hydroxymethyl)-[2-$^{11}$C]propane-1,3-diol (6)

To an unquenched reaction mixture of **5**, a 6:4 mixture of MeOH and $H_2O$ (500 μL) was added. The resulting solution was transferred to the next reaction vessel containing $NiCl_2$ (2 mg) and $NaBH_4$ (12 mg) by gas flow. The reaction mixture immediately became black and bubbled vigorously, and then it was placed for 1 min at RT and then $CH_3COOH$ (100 μL) was added. The resulting mixture contained black precipitation and a part of supernatant (approximately 10 μL) was mixed with the eluent of analytical HPLC (approximately 100 μL). The resulting clear solution was analyzed by HPLC under the following conditions: column, J'sphere L80 (YMC Ltd., 4.6 × 150 mm, 5 μm); flow rate, 0.5 mL/min; eluent, MeOH/50 mM ammonium phosphate buffer (pH = 4) (15/85). The retention time for **6** was 4.0 min under the reverse-phase condition. The mixture was also analyzed by liquid chromatography-mass spectrometry (LCMS) and the retention time of **6** of radiochromatogram corresponded with that of ion intensity chromatogram of MS spectrum for nonlabeled Tris contaminated in **6**. LC conditions used were as follows; column, Atlantis® HILIC (Waters Ltd., 4.6 × 150 mm, 3 μm); flow rate, 0.3 mL/min; eluent, 5 mM $NH_4OAc$ solution of $CH_3CN$–$H_2O$ (70/30); LC-MS/MS *m/z* 122 (M+H) and 56.

## Results and discussion

According to a previous report by Shoeps *et al.*, the $^{11}$C-labeling agent [$^{11}$C]$H_3NO_2$, **2**, is prepared via nitration of [$^{11}$C]$H_3I$, **1,** by passing through a heated plug of $AgNO_2$ in a furnace at 80–100°C.[4] At lower temperatures, **1** is converted into other radioactive compounds and the radiochemical yield of **2** is decreased.[4] Therefore, a whole glass column of $AgNO_2$, including joints, should be placed in a furnace to allow the nitration reaction to achieve better conversion while maintaining the desired high reaction temperature. Using a furnace is a reasonable approach; however, sometimes it can prove to be cumbersome spatially. In contrast, the use of a rubber heater makes the reaction system smaller, although it is not suitable for covering the entire glass column and joints. This means that the gas stream containing **1** passes through the front part of a plug

of $AgNO_2$ without being heated sufficiently by the rubber heater. As a result, the actual reaction temperature of the nitration reaction becomes partially lower by using a rubber heater, resulting in the poor conversion of **2**. In fact, the radiochemical conversion of **2** was 40–70% when a rubber heater covered the glass tube directly and heated it to 100°C. To overcome the problem of insufficient heating of the gas stream, we introduced preheating of the tube line. Thus, we wound a prior tube line on to the glass column of $AgNO_2$, covered both of them with foil and rubber heater (Figure 2), and then heated at 100°C. After this treatment, the radiochemical conversion of **2** became similar to that achieved using a furnace (around 90% conversion). The pyrolysis of $AgNO_2$ under nitration conditions is also a problematic issue because it affords several types of acidic nitrogen oxides that retard base-promoted reactions.[10] To overcome this, a column containing $NaHCO_3$ was attached following the $AgNO_2$ column to remove these products.[11,12]

The choice of solvent for the nitroaldol reaction plays an important role both chemically and technically because the synthesis of [$^{11}$C]Tris **6** requires two steps. For a multistep synthesis of an $^{11}$C-labeled compound, a shorter total synthetic time should be considered in order to increase the radioactivity of the final product. Besides the short reaction time of $^{11}$C-labeling, avoiding time-consuming processes such as evaporation, distillation, and isolation between every reaction step helps to reduce total synthetic time. For this purpose, we selected THF as the solvent for the nitroaldol reaction because the nitro-group reduction reaction of **5** would not be influenced by contamination of THF.

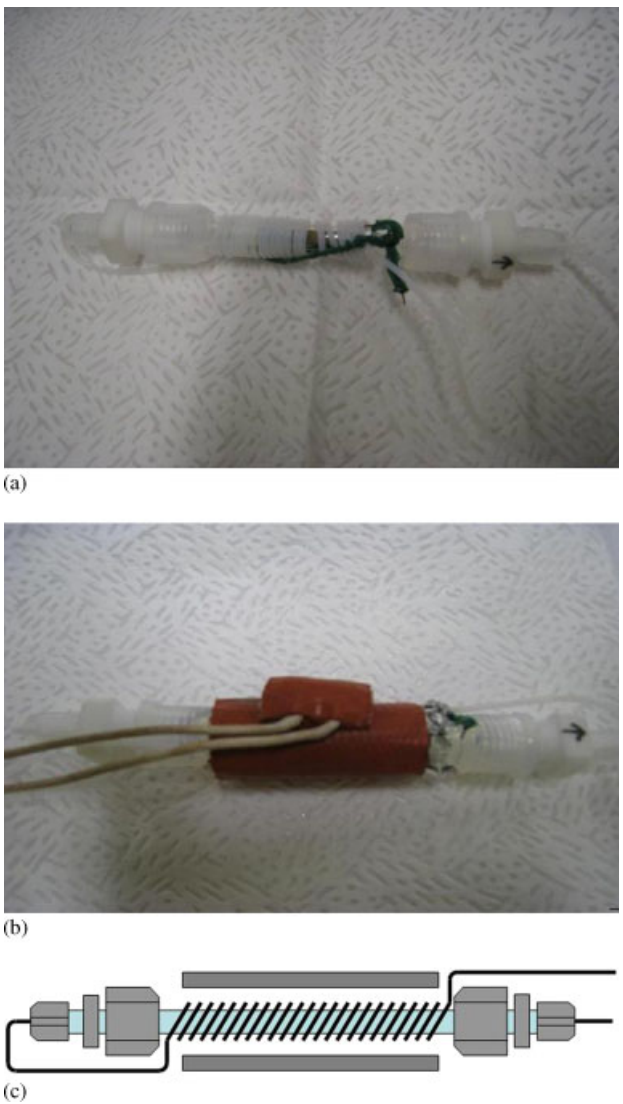
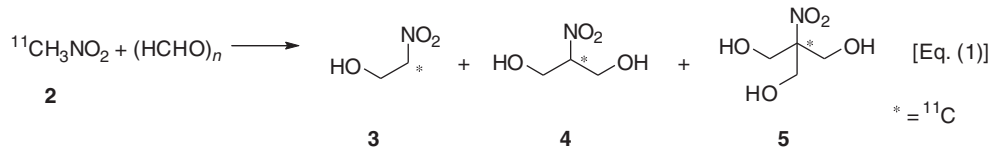



**Figure 2.** Pictures and a drawing of $AgNO_2$ column: (a) a glass column wound with a prior tube; (b) a glass column covered with foil and a rubber heater; and (c) a drawing of a glass column wound with a prior tube.

In our previous study, the addition of EtOH with EtONa enhanced the nitroaldol reaction of **2** and paraformaldehyde yielding $^{11}$C-labeled nitroethanol **3** at 0 °C.[5] The radiochemical conversion of **3** was 64.4±3.1% (Table 1). The reaction also yielded $^{11}$C-labeled nitrodiol **4** in 17.0±3.9% radiochemical conversion but nitrotriol **5** was not obtained at the reaction temperature. From the viewpoint of the multiple additions reactions, pseudo-first-order conditions of the $^{11}$C-labeling reaction using **2** to formaldehyde could assist the rapid formation of **5**. Thus, we first decided to introduce higher reaction temperatures to the above reaction conditions in order to increase the total reaction rate for the formation of each nitroaldol product. The reaction was carried out by treating **2** and paraformaldehyde (10 μmol) with EtONa (15 μmol), and EtOH (17 μmol) at 40°C. As a result, nitroaldol reactions forming **4** were enhanced and radiochemical conversion was increased to 67.0±5.9% (entry 1). However, the desired nitrotriol **5** was not obtained. Even though a higher temperature was introduced (100°C), no improvement in the formation of **5** was observed (entry 2). Stabilization by intra-molecular hydrogen bonding in the reaction using EtONa and EtOH was too strong to allow the formation of **5** even under two different high temperatures. Our efforts in the preparation of **5** thus directed us toward another approach, which was focused on the disruption of intra-molecular hydrogen bonding of nitroaldol intermediates.

Ionic fluoride assists nucleophilic substitution of alkyl halides by hetero atoms such as N, O, and S. The presence of strong hydrogen bonds between fluoride and hydrogen on hetero atoms promotes these reactions.[13] We considered that the hydrogen-bonding ability of fluoride might induce the disruption of the stabilized nitronate of **4** (Figure 3). By the way, the strong HF bond energy allows the potential of ionic fluoride to act as a base. Therefore, potential properties of basic fluoride direct us toward the investigation of fluoride-promoted rapid formation of **5**. We chose tetrabutylammonium fluoride (TBAF) as a base because of its high solubility in THF. We carried out the reaction by treatment of **2** and paraformaldehyde (10 μmol) with TBAF (5 μmol). The reaction gave **5** very efficiently even at RT. The radiochemical conversion of **5** was more than 97% after 3 min (Table 1, entry 3). As the formation of **5** was sufficient for $^{11}$C-labeling syntheses and 5 μmol TBAF would not affect the reduction of the nitro-group, we did not investigate the TBAF-mediated reaction further. It should be noted that TBAF used in this study was a commercially available trihydrate solution in THF and that the reaction proceeded without any additives to enhance nonradiolabeling reactions.[14] Någren *et al.* reported the nitroaldol reaction of **2** and aromatic aldehyde using solid TBAF.[6] They pointed out the increased selectivity for the formation of nitroaldol against dehydrated products using TBAF. However, they did not observe the multiple addition products. In our laboratory, we observed neither **3** nor **4,** nor the dehydrated products. Compared with the reaction using aromatic aldehydes, both the nitroaldol products and the aldehyde of the reaction using formaldehyde are sterically less

**Table 1.** Nitroaldol reaction of **2** and $(HCHO)_n$ [a,b]




| Entry | Base (μmol) | Temp | EtOH (μL) | Radiochemical conversion (%)[c,d] 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| 1 | 15 | 40°C | 10 | 29.2±5.2 | 67.0±5.9 | 0 |
| 2 | 15 | 100°C | 10 | 2.9±1.4 | 85.3±2.1 | 0 |
| 3 | 5 | rt | — | 0 | 0 | 97> |
| 4[e] | 15 | 0°C | 10 | 64.4±3.1 | 17.0±3.9 | 0 |

[a]Reaction conditions: **2** (37–370 MBq); paraformaldehyde (10 μmol); THF (300 μL); reaction time (3 min).
[b]Each reaction was carried out more than three times.
[c]Determined by a radiochromatogram of analytical HPLC after decay correction.
[d]Significant amount of radioactivity was not remained in the column after each analysis.
[e]Reference[4].

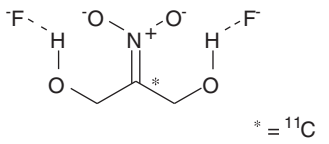
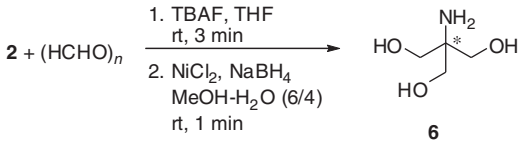



**Figure 3.** Hypothesis of fluoride-assisted disruption.




**Scheme 1.**

hindered. Therefore, hydrogen-bond-free nitronate and paraformaldehyde reacted immediately after second and third additions in the presence of fluoride, as compared with the reaction of **2** and aromatic aldehyde. The rapid nitrotriol formation also retards the dehydration of nitroaldols because there are no acidic α-protons in **5**. The amount of TBAF used for the nitroaldol reactions we used (5 μmol) was different from that used by Någren (100 μmol). We consider that removing the acidic nitrogen oxides derived from the preparation of **2** by $NaHCO_3$ contributes to reducing the required amount of TBAF.

The reduction reaction of $^{11}$C-labeled aliphatic nitro compounds to the corresponding amines was difficult to perform when we applied it to the remote-controlled automation for PET tracer syntheses. Raney Ni in HCOOH and Zn in acidic EtOH are effective for the reduction of a nitro group under $^{11}$C-labeling conditions.[6,15] Hydrogenation under an $H_2$ atmosphere using Pd or Pt on carbon is usually chosen under nonradiolabeling conditions.[16] However, a more accessible method that assembles all the necessary reactants easily under mild conditions would be preferable for the reduction of the nitro group under the $^{11}$C-labeling conditions. Recently, we reported that the reduction of a nitro group using $Ni_2B$-$NaBH_4$ could yield amines efficiently under $^{11}$C-labeling conditions.[5,17] The reagent $Ni_2B$–$NaBH_4$ is prepared by mixing $NiCl_2$ and $NaBH_4$ *in situ*, and gaseous $H_2$ is not required.[18] In addition, the reduction reaction is carried out under neutral conditions and is robust against the contamination of water. In fact, any isolation process of the reaction mixture of the nitroaldol reaction was not necessary for the nitro group reduction of **5**.[6,19] Thus, the reduction reaction was performed by the addition of MeOH to the nitroaldol reaction and then transferred to the next reaction vessel containing $NiCl_2$hexahydrate and $NaBH_4$. The black precipitation and gas evolution were observed in the reaction mixture and the nitro-group reduction of **5** yielded the corresponding amine **6** after 1 min at room temperature in 61.3±6.3% radiochemical conversion (decay-corrected, two steps).[20] The less polar radioactive byproducts, which may have been derived from the reductive amination or acetalization of 1,3-diol or incomplete reduction of nitro-group, were obtained. These side reactions arise from an excess of formaldehyde. Reducing the amount of formaldehyde in the nitroaldol reaction could suppress these side reactions. However, this treatment is likely to affect the conversion of the nitroaldol reaction, leading to the contamination of **4**. The reduction of a mixture of **4** and **5** would afford $^{11}$C-labeled serinol and **6**, but the efficient separation of serinol and **6** by high-performance liquid chromatography was difficult to achieve. It was better to keep the amount of formaldehyde and therefore another treatment was required. We alternatively carried out the nitro-group reduction in aqueous methanol[14] because we considered that the addition of water might assist the conversion of **6** by the hydrolysis of imine and acetal or by increasing the stability of $Ni_2B$-$NaBH_4$. In fact, the nitro-group reduction of **5** with $Ni_2B$-$NaBH_4$ using 60% aqueous MeOH instead of 100% MeOH improved the decay-corrected radiochemical conversion of **6** to 68.0±6.5% in two steps (Scheme 1).[20,21]

## Conclusion

The fluoride-assisted nitroaldol reaction of **2** and formaldehyde was rapid and yielded nitrotriol **5** efficiently. Carbon-11 labeling synthesis of Tris was carried out as an application of **5**. The preparation of **2** using a rubber heater is convenient compared

with that using a furnace. The reduction by $Ni_2B$–$NaBH_4$ is facile and yields the corresponding amine very efficiently under $^{11}$C-labeling conditions. We believe that the technical and synthetic improvements described in this paper solve the problems that hamper the utility of **2** as an $^{11}$C-labeling agent. We anticipate that the procedures described in this paper will allow $^{11}$C-labeling synthesis using **2** to become more accessible.

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## References

[1] G. Rosini, in *Comprehensive Organic Synthesis*, Vol. 2 (Eds: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon Press, Oxford, **1991**, pp. 324–340.
[2] D. Seebach, P. Knochel, *Helv. Chim. Acta* **1984**, *67*, 261–283.
[3] G. Antoni, T. Kihlberg, B. Långström, in *Handbook of Radiopharmaceuticals* (Eds: M. J. Welch, C. S. Redvanly), Wiley, West Sussex, **2003**, pp. 141–194.
[4] a) K.-O. Schoeps, S. Stone-Elander, C. Halldin, B. Långström, *J. Label. Compd. Radiopharm*. **1988**, *25*, 749–758; b) K.-O. Schoeps, S. Stone-Elander, C. Halldin, *Appl. Radiat. Isot*. **1989**, *40*, 261–262.
[5] K. Kato, M.-R. Zhang, K. Minegishi, K. Suzuki, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3439–3441.
[6] a) K. Någren, K.-O. Schoeps, C. Halldin, C.-G. Swahn, L. Farde, *Appl. Radiat. Isot.* **1994**, *45*, 515–521; b) K.-O. Schoeps, C. Halldin, *J. Label. Compd. Radiopharm*. **1992**, *31*, 891–901; c) K.-O. Schoeps, C. Halldin, K. Någren, C.-G. Swahn, P. Karlsson, H. Hall, L. Farde, *Nucl. Med. Biol.* **1993**, *20*, 669–678.
[7] K. Kato, S. Å. Gustavsson, B. Långström, *Tetrahedron Lett.* **2008**, *49*, 5837–5839.
[8] a) L. W. Herman, J. W. ApSimon, *Tetrahedron Lett*. **1985**, *26*, 1423–1424; b) C. A. Sprang, Ed. F. Degering, *J. Am. Chem. Soc*. **1943**, *65*, 628.
[9] a) R. H. Kallet, R. M. Jasmer, J. M. Nuce, L. H. Lin, J. D. Marks, *Am. J. Respir. Crit. Care. Med*. **2000**, *161*, 1149–1153; b) M. Okauchi, N. Kawai, T. Nakamura, M. Kawanishi, S. Nagao, *J. Neurotrauma*, **2002**, *19*, 741.
[10] T. M. Oza, V. T. Oza, R. H. Thacker, *J. Chem. Soc*. **1955**, 2457–2465.
[11] In a former report, attaching a column containing $K_2CO_3$ was effective for trapping nitrogen oxides. However, most of radioactivity was absorbed in $K_2CO_3$ and we could not obtain 1 in this institute.
[12] S. Å. Gustavsson, K. Kato, B. Långström, *J. Label. Compd. Radiopharm.* **2003**, *46*, 1279–1285.
[13] a) J. H. Clark, *Chem. Rev*. **1980**, *80*, 429–452; b) M. J. Adam, S. Jivan, J. M. Huser, J. Lu, *Radiochim. Acta*. **2000**, *88*, 207–209.
[14] a) R. Fernández, C. Gasch, A. Gómez-Sánchez, J. E. Vĭchez, *Tetrahedron Lett*. **1991**, *32*, 3225–3228; b) A. G. M. Barrett, C. Robyr, C. D. Spilling, *J. Org. Chem*. **1989**, *54*, 1233–1234.
[15] K. Kato, M.-R. Zhang, K. Suzuki, *Mol. BioSyst*. **2008**, *4*, 53–55.
[16] M. Hoogenraad, J. B. Van der Linden, A. A. Smith, *Org. Process Res. Rev.* **2004**, *8*, 469–476.
[17] K. Kato, M.-R. Zhang, K. Suzuki, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6222–6224.
[18] J. O. Osby, B. Ganem, *Tetrahedron Lett.* **1985**, *26*, 6413–6416.
[19] Y.-S. Ding, J. S. Fowler, J. Gatley, S. L. Dewey, A. P. Wolf, D. J. Schlyer, *J. Med. Chem*. **1991**, *34*, 861–863.
[20] Each reaction was carried out more than three times and significant amount of radioactivity was not remained in the column after each analysis.
[21] We have not yet completed the remote-controlled synthesis of **6**. However, we did not observe significant loss of radioactivity when the reaction mixture was recovered by filtration using a plug of glass wool after the addition of a 10% aqueous solution.