Tetrahedron Letters 51 (2010) 5908–5911

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Tetrabutylammonium fluoride-promoted α-[^{11}C]methylation of α-arylesters: a simple and robust method for the preparation of ^{11}C-labeled ibuprofen

Koichi Kato *, Tatsuya Kikuchi, Nobuki Nengaki, Takuya Arai, Ming-Rong Zhang

Department of Molecular Probes, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

ARTICLE INFO

Article history:
Received 24 August 2010
Accepted 1 September 2010
Available online 9 September 2010

Keywords:
Carbon-11
Isotopic labeling
Ibuprofen
Tetrabutylammonium fluoride
Positron emission tomography

ABSTRACT

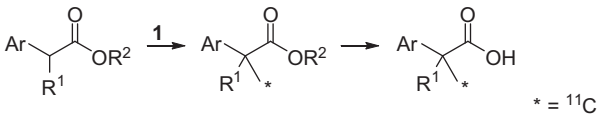
Tetrabutylammonium fluoride-promoted α-[^{11}C]methylation of α-arlylesters was developed. The method was amenable to the remote-controlled synthesis of ^{11}C-labeled ibuprofen.

Positron emission tomography (PET) can be used for non-invasive imaging of tracers and their metabolites labeled with positron-emitting radionuclides. PET images provide metabolic and biochemical information that describes enzyme activities, receptor interactions, and transporter regulations. This molecular information is useful for clinical diagnosis and helps to promote the importance of PET as a tool for drug research and development.[1,2] The use of an adequate tracer is crucial for simplifying the interpretation of PET images. The development of labeling methodology as well as the structure of the tracer itself is the key to the success of PET.

Since carbon is a ubiquitous element in organic molecules, carbon-11 ($T_{1/2}$ = 20.3 min) is the most viable of the positron-emitting isotopes for incorporating into a variety of molecules. Carbon-11 is produced via the ^{14}N(p, α)^{11}C nuclear reaction by a cyclotron as [^{11}C]O_2 or [^{11}C]H_4. These are converted into more reactive ^{11}C-labeling agents, such as iodo[^{11}C]methane (**1**), [^{11}C]cyanide, and [^{11}C]carbon monoxide.[3] Among these agents **1** is used most frequently, and is a rational starting point for other ^{11}C-labeling agents that can be exploited to develop ^{11}C-labeling methodology. To date, this strategy has been utilized for [^{11}C]methyl triflate, nitro[^{11}C]methane, and [^{11}C]formaldehyde.[4] Another approach is to use **1** to design a new ^{11}C-labeling methodology that affords a common structural framework of biologically active compounds. For this purpose, we incorporated the [^{11}C]methyl group into activated methylenes of carbon acids to yield potential building blocks for PET research.

2-Arylpropionates are integral structural components that are found in nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and flurbiprofen among others. NSAIDs are used in the treatment of cancer and Alzheimer's disease, both of which can be diagnosed using PET.[5] The pharmacological effects of NSAIDs are dependent on or independent of cyclooxygenases (COX-1 or COX-2). Regulation of COX activities is related to the progression of various diseases, therefore, in vivo imaging of COX enzymes is an emerging topic in PET research.[6] Assessment of uridine diphosphate glucuronosyltransferase (UGT)-catalyzed glucuronide conjugation is a significant issue in pharmacological research because these enzymes can act to elevate the withdrawal of carboxylic acid containing drugs.[7] The direct measurement of the pharmacokinetics of 2-arylpropionates by in vivo PET will help to advance this field of study. However, the use of 2-arylpropionates as potential PET tracers requires the incorporation of carbon-11 into their common structure.

α-[^{11}C]Methylation of α-arylesters using **1** yields a variety of ^{11}C-labeled esters of 2-arylpropionates, which are components of ^{11}C-labeled NSAIDs (Scheme 1). Using organolithium bases such as alkyl lithium or lithium diisopropylamide for the activation of the α-CH is not adequate because of their moisture sensitivity.[8]



Scheme 1. Plan for the preparation of ^{11}C-labeled α-arylesters.

* Corresponding author.
E-mail address: katok@nirs.go.jp (K. Kato).

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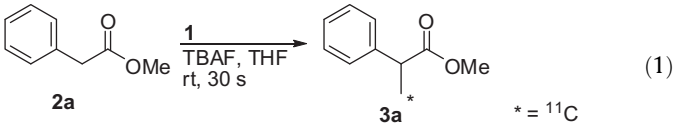
doi:10.1016/j.tetlet.2010.09.007

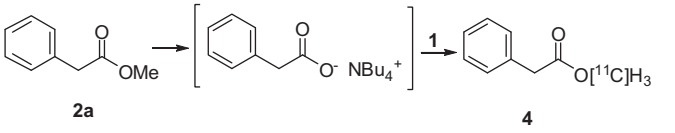
As well, the requirement for strict stoichiometry of these reagents is technically cumbersome for the radiolabeling synthesis. Phase-transfer conditions rely on the strong basic activity of the metal hydroxide; however, vigorous stirring reactions are difficult for ^{11}C-labeling reactions.[9] In addition, their latent saponification will become an obstacle for the formation of α-anions. Recently, α-[^{11}C]methylation of α-arylesters using metal hydride and **1** was reported.[10] However, metal hydrides are not well solubilized in organic solvents. The method using the homogeneous conditions is preferable to ^{11}C-labeling synthesis because of its suitability for remote-controlled synthesis. Therefore, we attempted to identify another type of base that could activate the α-CH under homogeneous conditions.

We focused on the use of fluoride ion as a base.[11,12] Fluoride-mediated ^{11}C-labeling reactions using **1** have been employed for the [^{11}C]methylation of hetero-atoms, such as oxygen and nitrogen.[11b] Fluoride-mediated ^{11}C–C bond formation via the nitroaldol reaction and the Michael addition reaction using nitro[^{11}C]methane have also been reported.[13] Nitromethane is more acidic than α-arylesters and there are no reports of fluoride-mediated ^{11}C-labeling into active methylenes using **1**.[14] In contrast to ^{11}C-labeling, Hammond and co-workers recently reported a C–C bond-forming reaction using tetrabutylammonium fluoride (TBAF), where an aldol reaction of a propargyl or allenyl ester and a variety of aldehydes yielded the thermodynamic-favored product selectively.[11c,d] The TBAF-promoted activation of carbon acids is suitable for ^{11}C-labeling because it can be carried out under homogeneous conditions. Therefore, we decided to explore the TBAF-promoted α-[^{11}C]methylation of α-arylesters.



(1)

We first investigated the TBAF-promoted [^{11}C]methylation of methyl phenylacetate (**2a**) yielding methyl 2-phenyl-[3-^{11}C]propionate (**3a**). The reactions started with the addition of 37–555 MBq (1–15 mCi) of **1** to a mixture of 20 μmol of **2a** and 20 μmol of TBAF (method A). Treatment of **1** and **2a** with TBAF at room temperature (rt) yielded **3a** efficiently.[15] The ^{11}C-labeling agent **1** was consumed within 30 s and the radiochemical conversion of **3a** was more than 95% (Eq. (1)). Because the [^{11}C]methylation at rt was very rapid and efficient and the radiochemical conversion of **3a** was not largely different at other reaction temperatures (0 °C and 50 °C, data not shown), we selected rt for further investigation. It was also expedient to use a commercial solution of TBAF·3H$_2$O in THF for the [^{11}C]methylation. Landini et al. reported that the basicities of the quaternary ammonium fluorides were lowered by increasing the number of solvated H$_2$O molecules.[12a] They found that fluoride-mediated Hofmann-like elimination of hexyl group of tetrahexylammonium fluoride did not occur at hydration states higher than six. In consideration of their results, we used dry solvent for the TBAF-promoted α-[^{11}C]methylation, but we did not use an inert atmosphere for preparing the reaction solutions or conducting the reactions.



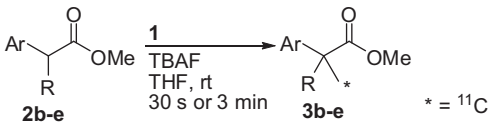
(2)

Because of the use of TBAF·3H$_2$O, hydroxide might promote the α-[^{11}C]methylation reaction instead of fluoride.[12b] To confirm the activity of fluoride, we investigated the hydroxide-promoted α-[^{11}C]methylation of **2a** by the treatment of **1** and **2a** with tetrabutylammonium hydroxide. The reaction yielded **3a** in 6.8 ± 3.5% radiochemical conversion while more than 50% of **1** remained unreacted. This result indicates that fluoride is an active base for the α-[^{11}C]methylation of **2a** even in a hydrated form. Moreover, the ester hydrolysis of **2a** was a considerable side reaction, which was promoted by hydroxide during the [^{11}C]methylation reaction.[12b] We also observed [^{11}C]methyl phenylacetate (**4**), which might be derived from the hydrolysis of **2a** following [^{11}C]methyl ester formation (Eq. (2)). However, the radiochemical conversion of **4** was negligibly low (<2%). In addition to the hydrolysis, a further side reaction occurred involving nucleophilic substitution of **1** by hydroxide to form [^{11}C]methanol. In this case, [^{11}C]methanol was also observed but the radiochemical conversion was only around 1%.

[^{11}C]Methylation promoted by TBAF was extended to other α-arylesters and the results are summarized in Table 1. The influence of fluoro and methoxy substitutions was investigated as representatives of electron-withdrawing and donating groups, respectively, because these functional groups have been identified in biologically active 2-arylpropionates. The [^{11}C]methylation of 4-fluoro compound **2b** gave a similar result to **2a** (entry 1). In contrast to **2a** and **2b**, [^{11}C]methylation of **2c** (entry 2) was slower, although, it had a slightly higher pK_a and its corresponding anion had increased nucleophilicity.[16] Thus, unreacted **1** was observed from the treatment of **1** and 4-methoxyphenyl compound **2c** with TBAF for 30 s with a corresponding decrease in radiochemical conversion. An extended reaction time improved the radiochemical conversion of **2c** (entry 3). Increasing the amounts of both **2c** and TBAF yielded **3c** more efficiently after 30 s of reaction time (entry 4). Therefore, the slower [^{11}C]methylation of **2c** may be attributed to the low concentration of the corresponding anion of **2c**, which is the result of small differences between the pK_a of **2c** and the basicity of the fluoride. In addition, we consider that the formation of hydrogen bifluoride from HF and TBAF might contribute to lowering the concentration of active fluoride over the course of time (Scheme 2).[12c,d] In this regard, the radiochemical conversion of **3c** was decreased considerably (less than 30%) when we prepared a mixture of **2c** and TBAF approximately 30 min before the [^{11}C]methylation of **2c** was carried out.

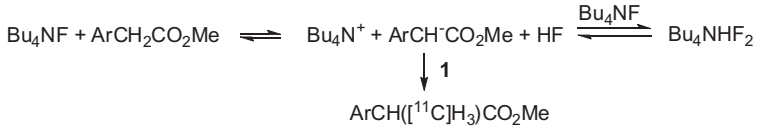
Ibuprofen is a representative of 2-arylpropionate NSAIDs and its 4-isobutyl analog **2d** can be used in the synthesis of ^{11}C-labeled ibuprofen. This analog was also incorporated by the [^{11}C]methyl

Table 1
TBAF mediated α-[^{11}C]methylation[a]



Entry	2 (μmol)	Ar	R	TBAF (μmol)	Method	**3** ARC[b] (%)
1	**2b** (20)	*p*-F–C$_6$H$_4$	H	20	A	91.1 ± 4.0
2	**2c** (20)	*p*-MeO–C$_6$H$_4$	H	20	A	57.1 ± 0.2
3[c]	**2c** (20)	*p*-MeO–C$_6$H$_4$	H	20	A	63.9 ± 0.7
4	**2c** (40)	*p*-MeO–C$_6$H$_4$	H	40	A	65.7 ± 1.1
5	**2d** (20)	*p*-Bu*i*–C$_6$H$_4$	H	20	A	89.3 ± 3.3
6	**2e** (20)	C$_6$H$_5$	Me	20	A	2.2 ± 1.0
7	**2e** (20)	C$_6$H$_5$	Me	20	B	32.8 ± 4.3
8	**2e** (40)	C$_6$H$_5$	Me	40	B	45.5 ± 2.6

[a] Each reaction was carried out more than three times.
[b] Average radiochemical conversion (ARC) was determined by radiochromatogram of analytical HPLC after decay correction.
[c] Reactions were carried out for 3 min.



Scheme 2. Summarized reaction scheme forming HF_2^-.

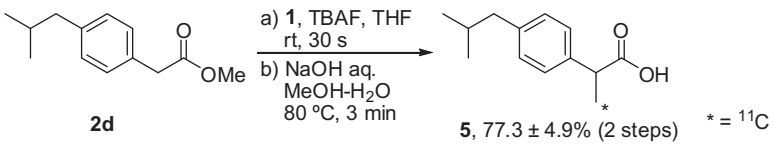


Figure 1. Synthesis of ^{11}C-labeled ibuprofen.

group with an 89.3 ± 3.3% radiochemical conversion (entry 5). [^{11}C]Methylation into methyl 2-phenylpropionate (**2e**) affording dimethyl analog **3e** was investigated because further incorporation of a methyl group at the α-position might provide a better substrate for the glucuronidation catalyzed by UGT2B7, a major UGT isoform for acylglucronidation.[7b] Moreover, routes for the preparation of α,α-dimethyl compounds are necessary to avoid future problems regarding the enantiomeric center at the 2-position of arylpropionates. Although, an isotopically substituted (3-^{11}C)-dimethyl analog still has an enantiomeric center at the α-position, the behavior of both enantiomers is not expected to largely influence the pharmacokinetic analyses under PET scan conditions.[17] The α-methyl group has increased nucleophilicity through an inductive effect and decreased steric hindrance. Because of the positive and negative effects of an additional methyl group, [^{11}C]methylation of **2e** was expected to give a similar result to that of **2a**.[16a] However, there were other factors affecting the [^{11}C]methylation of **2e** and the reaction gave very different results from the [^{11}C]methylation of 2-arylacetates. Thus, the order of addition of the reactants was essential for yielding **3e**, and a minimal amount of **3e** was obtained by the addition of **1** to a mixture of **2e** and TBAF (entry 6). In this manner, the ^{11}C-labeling agent **1** was converted primarily to an unidentified radioactive compound whose retention time was similar to that of **2e**. The desired α-anion of **2e** might be transient and a considerable amount of the α-anion may be transferred to other species that reacted with **1**. In contrast, measurable [^{11}C]methylation of **3e** was observed by the addition of TBAF to a mixture of **1** and **2e** (method B, entry 7). In this case, we believe that some of the desired α-anions of **2e** immediately react with **1** yielding **3e** before other reactive species are generated. Finally, improved radiochemical conversion of **3e** was obtained by the treatment of increased amounts of both **2e** and TBAF (entry 8).

We chose **2d** to complete Scheme 1. Thus, the test synthesis of 2-(4-isobutyl)phenyl-[3-^{11}C]propionic acid ([^{11}C]ibuprofen, **5**) started with approximately 370 MBq (10 mCi) of **1**, which was reacted via alkaline hydrolysis of **3d** by the addition of a 1:1 mixture of an aqueous solution of 1 M NaOH and MeOH at rt. The resulting mixture was heated to 80 °C and stored at the same temperature for 3 min. The ester hydrolysis of **3d** was completed and the overall radiochemical conversion of **5** was 77.3 ± 4.9% in two steps (Fig. 1). The synthetic preparation of **5** can be completed in a one-pot manner for both the methylation and hydrolysis and does not require a strictly inert atmosphere. The homogeneity of the reaction mixture throughout the entire process results in a decreased failure rate. Finally, the method was amenable to the remote-controlled synthesis of **5**, which started from approximately 11.1 GBq (300 mCi, calculated amount) of [^{11}C]O_2 and resulted in >1 GBq of **5** within 30 min from the end of bombardment. According to Takashima-Hirano et al., methyl ester **3d** was labile and significant radiolysis of **3d** was observed in the synthesis starting with >15 GBq of [^{11}C]O_2.[10] In addition, they found that acid form **5** was stable against radiolysis. The target of our PET studies was acid form **5,** and we obtained a sufficient amount of this via hydrolysis of **3d** starting with <15 GBq. Therefore, we did not encounter any serious problems in our remote-controlled synthesis of **5**.

We demonstrated a TBAF-mediated α-[^{11}C]methylation of α-arylesters and the synthesis of ^{11}C-labeled ibuprofen as a representative example of the success of the methodology. Compared with the former report, our method can be performed under homogeneous conditions throughout the entire process and is advantageous for remote-controlled tracer synthesis.[18] These improvements will facilitate the development of PET tracers of ^{11}C-labeled arylpropionate NSAIDs.

The procedure for the remote-controlled synthesis of **5**.

The ^{11}C-labeled precursor **1** was prepared and transferred in a N_2 gas stream (flow rate 30 mL/min) to the reaction vessel containing a solution of **2d** (20 μmol) in THF (300 μL) and TBAF (20 μmol) at rt. After 90 s, the radioactivity of the vessel reached a plateau and then the gas stream was stopped. After 30 s, a 1:1 mixture of aqueous 1 M NaOH and MeOH (400 μL) was added to the reaction mixture. The resulting solution was heated to 80 °C and stored for 3 min while maintaining the temperature. After cooling by air flow, a 9:1 mixture of eluent and AcOH (500 μL) was added and then the resulting mixture was injected into the semi-preparative HPLC (Waters XBridge C18, 5 μm, 7.5 × 250 mm I.D.; eluent, 60/40/0.2 CH_3CN/30 mM NH_4OAc/AcOH; flow rate, 4 mL/min; and retention time, 9 min).

Acknowledgments

This work was supported in part by a consignment grant for the Molecular Imaging Program on Research Base for PET Diagnosis from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We thank the staff of the Cyclotron Operation and Radiochemistry sections for technical support using radio isotopes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.007.

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14. The same authors of Ref.[10] briefly described that TBAF in THF was useful for the α-[^{11}C]methylation in the footnote of a table about NaH-mediated α-[^{11}C]methylation of α-arylacetates on a poster presented at the joint symposium between NIRS and RIKEN on the 21–22 January, 2011. No abstract is available for this presentation and further details are not found in Ref..[10]
15. A solution of TBAF was added to a solution of α-arylacetate approximately 10 min before starting the [^{11}C]methylation reaction, followed by the remote-controlled synthesis.
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18. A referee points out that the results described by Takashima-Hirano et al. are well established, and the method described herein does not improve the yield or provide better results for difficult substrates than their method. However, a solution-based method can avoid the technical troubles and mechanical problems associated with using insoluble materials. These are important aspects for both ^{11}C-labeling syntheses and in vivo and in vitro experiments. We believe that these improvements are valuable for this method.