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Synthesis of [^{11}C]Am80 via Novel Pd(0)-Mediated Rapid [^{11}C] Carbonylation Using Arylboronate and [^{11}C]Carbon Monoxide

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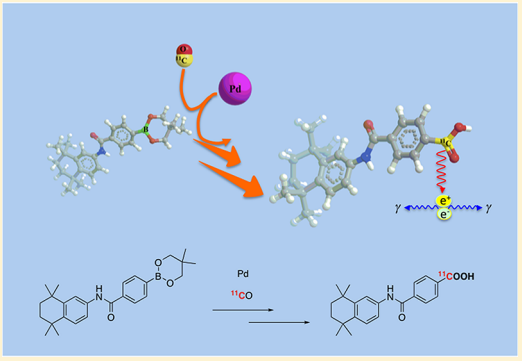
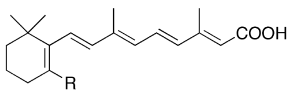
Supporting Information

ABSTRACT: ^{11}C-labeled methylbenzoates [^{11}C]**4a**−**d** were synthesized using Pd(0)-mediated rapid cross-coupling reactions employing [^{11}C] carbon monoxide and arylboronic acid neopentyl glycol esters **3a**−**d** under atmospheric pressure in methanol−dimethylformamide (MeOH−DMF), in radiochemical yields of 12 ± 5−26 ± 13% (decay-corrected based on [^{11}C]O). The reaction conditions were highly favorable for the synthesis of [^{11}C]Am80 ([^{11}C]**2**) and [^{11}C]methyl 4-((5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl)benzoate ([^{11}C]**2**-Me) using 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-*N*-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide (**5**), both of which produced a decay-corrected radiochemical yield (RCY) of 26 ± 13%, with >99% radiochemical purity and an average specific radioactivity of 44 GBq/μmol. The yields of [^{11}C]**4a**, [^{11}C]**2**-Me, and [^{11}C]**2** were improved by the use of a 2-fold excess of the solvents and reagents under the same conditions to give respective yields of 66 ± 8, 65 ± 7, and 48 ± 2%.



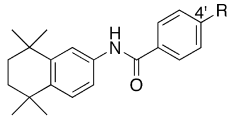
KEYWORDS: *Am80, tamibarotene, methoxycarbonylation, [^{11}C]carbon monoxide*

Positron emission tomography (PET), which uses specific probes radiolabeled with short-lived positron-emitting radionuclides, is one of the most powerful noninvasive tools for modern clinical diagnosis of diseases such as cancer, heart disease, and Alzheimer's disease.[1] PET also allows for microdose clinical assessment of drug distribution and action at the molecular level in living systems. Because most biological compounds contain carbon atoms, the development of synthetic methods that enable ^{11}C-radionuclide labeling is an important requirement for PET probe synthesis. However, the preparation of ^{11}C-radiolabeled probes is hampered by certain challenges because of the short half-life ($t_{1/2}$ = 20.4 min) of ^{11}C; consequently, rapid and efficient methods remain necessary. In this context, we have developed several Pd(0)-mediated rapid ^{11}C-labeling reactions,[2] which have recently been applied to the synthesis of [^{11}C]all-*trans*-retinoic acid[3] ([^{11}C]ATRA, **1**) (Figure 1). ATRA (**1**), a member of the retinoid family, is a ligand for the retinoic acid receptors (RAR-α, -β, and -γ) and is well-known as a useful drug for differentiation therapy for acute promyelocytic leukemia (APL).[4] The binding of ATRA to RAR causes degradation of the promyelocytic leukemia protein (PML)/RAR fusion protein, resulting in terminal differentiation of APL.[5] Although ATRA induces complete remission (CR) in the majority of patients, relapse resulting from ATRA-resistant cells has frequently been observed during maintenance therapy with ATRA.[6] The synthetic retinoid Am80 (**2**)[7] is an active agent for APL patients who have relapsed from ATRA-induced CR[8] and binds tightly to RAR-α but does not bind with the RAR-γ receptor, which is the major RAR in the dermal epithelium.[9] Moreover, ATRA and Am80 induce strong suppression of interleukin (IL)-6 production in IL-1-stimulated synovial fibroblasts. Therefore, both of these drugs may be applicable in therapies for psoriasis, multiple myeloma, and rheumatoid arthritis, although their exact function is still unknown.[10] Accordingly, we have sought to synthesize ^{11}C-labeled Am80 and its ester derivative for comparison of the biodistribution and pharmacodynamics of these compounds with those of [^{11}C]ATRA (**1**).



ATRA (**1**), R = CH_3

[^{11}C]ATRA ([^{11}C]**1**), R = $^{11}CH_3$



Am80 (tamibarotene) (**2**), R = COOH

[^{11}C]Am80 ([^{11}C]**2**), R = ^{11}COOH

Figure 1. Structures of ATRA (**1**), [^{11}C]ATRA (**1**), Am80 (**2**), and [^{11}C]Am80 ([^{11}C]**2**).

The straightforward synthesis of [^{11}C]**2** involves carboxylation of the corresponding Am80 precursor at the 4′-position.[11] Classically, carboxylation of the corresponding Grignard or organolithium reagents with [^{11}C]carbon dioxide ([^{11}C]O_2) represents the simplest method. However, because

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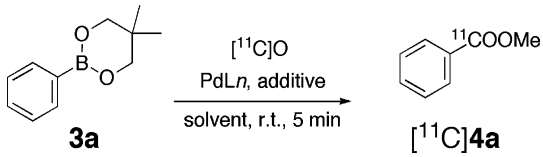
of the high sensitivity of these organometallic reagents to traces of moisture and the non-negligible contamination by atmospheric carbon dioxide, maintaining a constant high radiochemical yield and high specific radioactivity is generally very difficult.[12] On this basis, Pike et al. have very recently reported [^{11}C]carboxylation using the copper(I)-mediated reaction of an arylboronate and [^{11}C]O_2 in the presence of KF/Kryptofix 222.[13] Alternatively, carbonylation using a transition metal in conjunction with [^{11}C]carbon monoxide ([^{11}C]O) does not require such dry conditions and is applicable even in the presence of a wide range of functional groups. Moreover, the presence of [^{12}C]O in the atmosphere is generally negligible; thus, [^{11}C]carbonyl compounds may be obtained with high specific radioactivity.

However, as a result of the low solubility of CO in most common solvents,[14] carbonylation is still typically performed by a general organic synthesis method using [^{12}C]O with a Pd catalyst under high pressure for long periods.[15] Recently, Yamamoto et al. elaborated the methoxycarbonylation of an arylboronic acid or ester, which proceeds under atmospheric pressure at ambient temperature for several hours, using a catalytic amount of Pd(II) acetate/triphenylphosphine [Pd(OAc)$_2$/PPh$_3$] in the presence of *p*-benzoquinone (pbq) as a stoichiometric oxidant in methanol (MeOH) solvent.[16]

The incorporation of [^{11}C]O via Pd(0)-mediated rapid cross-coupling has been extensively developed over the last two decades.[12] To overcome the solubility problem, most of these reactions have been conducted with the use of special equipment such as high-pressure vessels,[17] recirculation systems,[18] and microfluidic reactor systems[19] to facilitate the incorporation of [^{11}C]O into the reaction. Chemical [^{11}C]O-fixation techniques have recently been developed as an alternative, with the aim of increasing the concentration of [^{11}C]O in solution.[20] The development of the advanced technique of Pd(0)-mediated [^{11}C]carbonylation has enabled the execution of the reaction under atmospheric pressure using xenon as a carrier gas, an aryl iodide as a substrate, and an amine and an alcohol as trapping nucleophiles for the synthesis of ^{11}C-incorporated amides, ureas, and carbamates.[21] Along a similar line, we have made an attempt to explore a novel reaction that is promoted under mild and advantageous conditions (ambient temperature and atmospheric pressure) and is adaptable to the synthesis of [^{11}C]Am80 ([^{11}C]**2**). In this paper, we described the efficient syntheses of ^{11}C-labeled **2** and its ester derivative via novel, rapid Pd(0)-mediated methoxy[^{11}C]carbonylation using arylboronate **5** and [^{11}C]O using conventional helium gas as a [^{11}C]O carrier.

The synthesis of [^{11}C]benzoic acid methyl ester ([^{11}C]**4a**) was undertaken, using the reaction of phenylboronic acid 2,2-dimethylpropane-1,3-diol ester (**3a**) and [^{11}C]O as a model reaction (Table 1). First, the [^{11}C]O-fixation method[20] was conducted in the presence of MeOH at 100 °C. The desired product was obtained in very low yield (Table 1, entry 1). Changing the phosphine ligand of the Pd complex to the bulky arylphosphine group with the objective of enhancing the reactivity also gave the same poor yield (Table 1, entry 2). Under these [^{11}C]O-fixation reaction conditions, it was found that as soon as the reaction temperature increased to 100 °C, [^{11}C]O gas was vigorously emitted from the reaction vessel. Therefore, further trials of the reaction were performed at a lower temperature. At ambient temperature, the original [^{11}C]O-fixation reaction[20] yielded the desired product in very low yield (Table 1, entry 3). With this information in mind,

Table 1. Examination of Methoxy[^{11}C]carbonylation Reaction



3a [^{11}C]**4a**

entry	conditions	solvent	temperature: trap	temperature: reaction	RCY[a] (%)
1	1. CuCl, K[Tp*], THF 2. Pd(PPh$_3$)$_4$, PPh$_3$	THF–MeOH–DMF (10:1:4)	rt	100 °C	<1
2	1. CuCl, K[Tp*], THF 2. Pd(OAc)$_2$, P(*o*-tolyl)$_3$	THF–MeOH–DMF (10:1:4)	rt	100 °C	<1
3	1. CuCl, K[Tp*], THF 2. Pd(PPh$_3$)$_4$, PPh$_3$	THF–MeOH–DMF (10:1:4)	rt	rt	<1
4	1. CuCl, K[Tp*], THF 2. Pd(OAc)$_2$, PPh$_3$, pbq	THF–MeOH–DMF (10:1:4)	rt	rt	3
5	Pd(OAc)$_2$, PPh$_3$, pbq	MeOH	rt	rt	2
6	Pd(OAc)$_2$, PPh$_3$, pbq	MeOH–DMSO (1:1)	rt	rt	<1
7	Pd(OAc)$_2$, PPh$_3$, pbq	MeOH–THF (1:1)	rt	rt	<1
8	Pd(OAc)$_2$, PPh$_3$, pbq	MeOH–DMF (1:1)	rt	rt	25
9	Pd(OAc)$_2$, PPh$_3$, pbq	MeOH–DMF (1:1)	−15 °C	rt	26 ± 13, 66 ± 8[b]
10	Pd(OAc)$_2$, PPh$_3$	MeOH–DMF (1:1)	−15 °C	rt	20 ± 10
11	Pd(OAc)$_2$, PPh$_3$, CsF	MeOH–DMF (1:1)	−15 °C	rt	<5
12	Pd$_2$(dba)$_3$, P(*o*-tolyl)$_3$	MeOH–DMF (1:1)	−15 °C	rt	4

[a]Isolated RCY based on trapped [^{11}C]O after purging. Mean value ± range for n = 3, determined by isolated yield. [b]Two-fold excesses of solvents and reagents were used.

Yamamoto's methoxycarbonylation conditions[16] were then introduced, in combination with the [^{11}C]O-fixation, to shorten the reaction time. However, unexpectedly, the cross-coupling product was also obtained in only very low yield (Table 1, entry 4). Performing the reaction under Yamamoto's original methoxycarbonylation conditions (the use of only MeOH solution) also gave a similarly poor result (Table 1, entry 5). A solvent mixture containing dimethyl sulfoxide (DMSO) or tetrahydrofuran (THF) with MeOH was also ineffective as a reaction medium. Here, it was surprisingly found that rapid methoxy[^{11}C]carbonylation was facilitated simply by using the combination of MeOH and dimethylformamide (DMF), giving the product [^{11}C]**4a** in 25% decay-corrected radiochemical yield (RCY) (Table 1, entry 8). Furthermore, [^{11}C]O trapping was more efficient at lower temperature (−15 °C), furnishing [^{11}C]**4a** in 26 ± 13% RCY (Table 1, entry 9). The use of a 2-fold excess of the solvents and reagents under the same conditions greatly improved the RCY, up to 65 ± 7% (Table 1,

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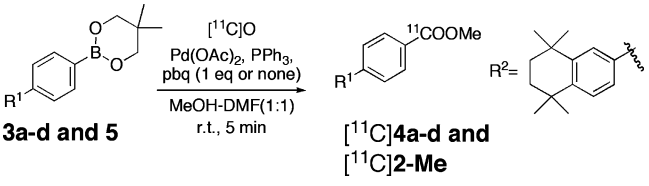
entry 9). In contrast, the removal of pbq greatly decreased the yield (Table 1, entry 10). Interestingly, the addition of CsF instead of pbq, with the aim of activating the carbon−boron bond, retarded the reaction strongly (Table 1, entry 11). The use of the bulky arylphosphine was also not effective in the reaction (Table 1, entry 11). Thus, it was concluded that the reaction was effectively promoted by a combination of the [^{11}C]O trap at −15 °C, followed by reaction at ambient temperature under atmospheric pressure using conventional helium carrier gas.[21] To confirm the generality of the reaction, we further examined the methoxy[^{11}C]carbonylation reaction using several *p*-substituted neopentyl glycol arylboronic acid esters ([^{11}C]**4b−d**); the results are summarized in Table 2.

Table 2. Generality of the Methoxy[^{11}C]carbonylation Conditions

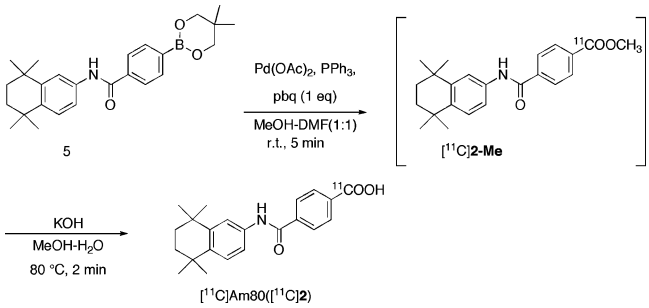


entry	R	pbq	RCY (%)[a]
1	H (**3a**)	1	26 ± 13, 66 ± 8[b]
2	H (**3a**)	0	20 ± 10
3	OMe (**3b**)	1	27 ± 5
4	OMe (**3b**)	0	3 ± 4
5	F (**3c**)	1	25 ± 3
6	F (**3c**)	0	6 ± 6
7	COOEt (**3d**)	1	12 ± 7
8	COOEt (**3d**)	0	<1
9	CONHR^2 (**5**)	1	27 ± 10, 65 ± 7[b] ([^{11}C]**2**-Me)
10	CONHR^2 (**5**)	0	<1

[a]Isolated RCY based on trapped [^{11}C]O after purging. Mean value ± range for n = 3, determined by isolated yield. [b]Two-fold excess amounts of solvents and reagents were used.

In all cases, the methoxy[^{11}C]carbonylation proceeded with moderate yields without any effects of electron-withdrawing (Table 2, entries 5 and 7) or electron-donating groups (Table 2, entry 3). In these reactions, pbq greatly influenced the reaction efficiency, and its absence resulted in much lower yields of the product. The improved conditions shown in Table 1, entry 9, were also effective for the reaction of **5**, as shown in Table 2, entry 9. It is likely that the reaction efficiency of entries 3, 5, and 7 could also be enhanced by using the same improved conditions. Finally, the conditions shown in Table 2, entry 9, were applied to the synthesis of [^{11}C]Am80 ([^{11}C]**2**). The synthesis was conducted in a one-pot manner without isolation of [^{11}C]**2**-Me. Thus, after methoxy[^{11}C]carbonylation of boronate precursor **5**, [^{11}C]**2**-Me underwent rapid hydrolysis with potassium hydroxide at 80 °C over 2 min to afford the desired acid [^{11}C]**2** in 26 ± 13% radiochemical yield based on [^{11}C]O (Scheme 1). The total synthesis time for formulation of [^{11}C]**2** was 36 min. The isolated radioactivity was as high as 1.4 GBq at the end of the synthesis, and the specific radioactivity was up to 44 GBq/μmol. The chemical identity of [^{11}C]Am80 was confirmed via coinjection analytical high-performance liquid chromatography (HPLC) using an authentic Am80 (column: Waters XBridge, 4.6 mm i.d. × 150 mm, 5 mm; mobile phase, CH_3CN:0.2% HCOOH in water = 60:40; flow rate, 1 mL/min; UV detection, 254 nm; and retention time, 8.2 min). The radiochemical purity was greater than 99%. The use of 2-fold excesses of solvents and reagents under the same conditions outlined above improved the yield of [^{11}C]**2** to 48 ± 2% (n = 3) RCY with 99% radiochemical purity.

Scheme 1. One-Pot Synthesis of [^{11}C]Am80 ([^{11}C]2)



In summary, Pd(0)-mediated rapid methoxy-[^{11}C]-carbonylation was successfully achieved under mild conditions using a phenylboronic acid neopentyl ester as a model precursor, and the reaction conditions were highly applicable to the synthesis of [^{11}C]esters([^{11}C]**4a−d**) and [^{11}C]Am80 methyl ester ([^{11}C]**2**-Me) and, eventually, the corresponding acid **2** by subsequent rapid hydrolysis. The novel PET probe **2** and its methyl ester will be used as specific PET probes for investigating the receptor functions involved in serious diseases such as APL in in vivo vital systems.[22] The rapid methoxy-[^{11}C]carbonylation should be applicable not only to the synthesis of [^{11}C]**2** but also to a variety of biologically important [^{11}C]carboxylic acids and their methyl esters. Furthermore, this first example of a simple methoxy[^{11}C]-carbonylation method at ambient temperature and under atmospheric pressure should be highly attractive to organic chemists who desire to synthesize [^{11}C]carbonyl compounds such as ^{11}C-labeled amides, ureas, isocyanates, oxazoles, and carbamates directly.[23]

■ ASSOCIATED CONTENT

Supporting Information

Experimental methods for the preparation of **5**, generation of [^{11}C]O, standard procedure for rapid methoxy[^{11}C]-carbonylation, and synthesis of [^{11}C]Am80 ([^{11}C]**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

PET, positron emission tomography; ATRA, all-*trans*-retinoic acid; CR, complete remission; PML, promyelocytic leukemia protein; MeOH, methanol; DMF, dimethylformamide; RAR, retinoic acid receptors; APL, acute promyelocytic leukemia; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; [^{11}C]O_2, [^{11}C]carbon dioxide; [^{11}C]O, [^{11}C]carbon monoxide; pbq, *p*-benzoquinone; RCY, decay-corrected radiochemical yield

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NOTE ADDED AFTER ASAP PUBLICATION

This paper published ASAP on August 27, 2012 with typographical errors in the title and keywords. The corrected version was reposted on August 31, 2012.