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SHORT COMMUNICATION

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Improved Yields for the Palladium-Mediated ^{11}C-Carbonylation Reaction Using Microwave Technology

Kenneth Dahl,*[a] Magnus Schou,[b] Obaidur Rahman,[a] and Christer Halldin[a]

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Microwave heating technology was applied for the palladium-mediated ^{11}C-carbonylation of aryl halides and triflates at ambient pressure using xantphos as supporting ligand. Improved yields were observed for the ^{11}C-aminocarbonylation of electron-deficient aryl halides in comparison to thermal heating and the approach even allowed the use of an aryl chloride as substrate. The scope of this reaction was further extended to ^{11}C-labeled aryl acid and two ^{11}C-labeled aryl esters.

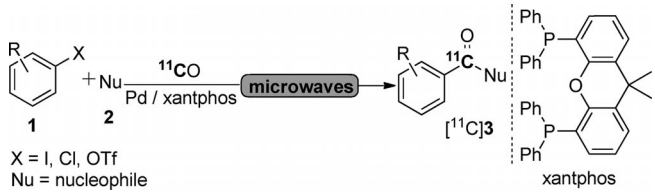
Introduction

Positron emission tomography (PET) is a powerful non-invasive imaging tool that uses radiolabeled compounds as molecular probes to investigate biological processes in vivo.[1] The synthesis of these biological probes presents a particular challenge, since the employed radionuclei in PET are short-lived, only present in minute chemical amounts and emit gamma radiation.[2]

[^{11}C]Carbon monoxide (^{11}CO), derived from the positron emitting isotope ^{11}C ($t_{1/2}$ = 20.4 min), has been increasingly recognized as an important ^{11}C-labeling reagent because it can provide access to a wide range of carbonyl-containing compounds through transition-metal-mediated ^{11}C-carbonylation.[3] Despite its versatility, the widespread use of ^{11}CO has long been hampered by the lack of a simple method for its efficient introduction. In our long-term objective to improve general access to this synthon, we recently reported a novel ^{11}C-carbonylation protocol in which ^{11}CO is trapped and incorporated as a part of the ^{11}CO-insertion procedure.[4] The method is general, simple, and has the potential to bring wide access to the attractive synthon [^{11}C]carbon monoxide.

The application of microwaves as an efficient heating source for organic synthesis was recognized in the mid-1980s.[5] Shortly thereafter microwaves were also applied in the synthesis of radiopharmaceuticals for PET[6] and, today, numerous examples exist in which radiosynthesis times have been reduced as a consequence of microwave heating.[7]

In an effort to widen the scope of our newly developed methodology we were thus led to examine the potential use of microwave-assisted heating as a possible means to reduce reaction time and improve selectivity for the ^{11}C-carbonylation reaction (Scheme 1). However, the application of microwave-enhanced carbonylation using gaseous carbon monoxide has been very little explore, and only a few papers have been published describing this approach.[8]



Scheme 1. Microwave-enhanced Pd-mediated [^{11}C]carbonylation route to form the [^{11}C]carbonyl-containing product.

Results and Discussion

Our initial efforts focused on establishing optimal microwave conditions for the ^{11}C-aminocarbonylation reaction. We selected [^{11}C]-3-nitro-benzyl benzamide ([^{11}C]**6**) as a target molecule, which was prepared by ^{11}C-aminocarbonylation of 3-nitro-iodobenzene (**4**) with benzylamine (**5**), using the Pd_2(π-cinnamyl)Cl_2–xantphos catalytic system in 0.7 mL of anhydrous tetrahydrofuran (THF; Scheme 2). In our previous studies using thermal heating conditions,[4] a five minute reaction gave [^{11}C]**6** in 73% ^{11}C-trapping efficiency (TE) and 46% radiochemical yield (RCY) (Figure 1, diagram A, entry 1), indicating significant room for im-

[a] Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatric Research, Karolinska Hospital, 17176 Stockholm, Sweden
E-mail: kenneth.dahl@ki.se
www.ki.se
[b] AstraZeneca Translational Sciences Centre, PET centre of Excellence, Department of Clinical Neuroscience, Karolinska Institutet, Karolinska Hospital, 17176 Stockholm, Sweden
www.astrazeneca.com
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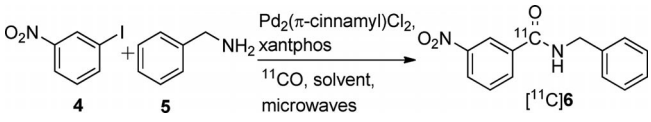
provement with regards to both TE and RCY. TE corresponds to the total amount of ^{11}CO that is converted into nonvolatile product at the end of reaction. In a typical experiment, the coupling reagents were prepared in a standard disposable glass vial commonly used for HPLC purposes (4 mL), and installed in the synthesis module approximately 5 min prior to the start of the synthesis. ^{11}CO was concentrated and introduced in a controlled stream of helium (20 mL/min) into a closed reaction vessel, and the sealed reaction vessel was manually transferred to the microwave cavity. In this work a single-mode microwave reactor equipped with temperature control was used.



Scheme 2. The model palladium-mediated [^{11}C]carbonylation reaction for the formation of 3-nitrobenzyl-[carbonyl-^{11}C]benzamide.

A series of experiments was thus conducted in which the TE and RCY of [^{11}C]**6** was investigated as a function of time and temperature. The microwave maximum power was kept fixed at 250 W to minimize the time required to reach the set temperature. The results are summarized in Figure 1. Under identical conditions (100 °C for 5 min), a relative 35% increase in RCY was observed with microwave heating compared with thermal heating (Figure 1, diagram A, entries 1 and 2). Heating at 120 °C for 5 min using active cooling (AC) resulted in quantitative TE with an improvement in RCY to 81% (Figure 1, diagram A, entry 4), which is a 78% increase in overall RCY compared with conventional heating.

The use of higher temperatures (140–160 °C) were tested with the aim of completing the reaction in shorter time, however, RCYs were decreased due to the formation of an unknown radioactive byproduct. For example, at 140 °C the RCY was decreased by 12% (Figure 1, diagram A, entry 5) and a similar result was observed when the reaction was conducted at 160 °C for 2 min (Figure 1, diagram A, entry 8). Attempts to run the reaction at 120 °C with a reduced reaction time resulted in decreased TE and thereby lower RCY. Therefore, 120 °C and a 5 min reaction time with active cooling was established as the preferred settings for the microwave-enhanced Pd-catalyzed [^{11}C]aminocarbonylation.

We continued our study by performing the reaction in different solvents. A series of commonly used solvents with different microwave properties was screened. The results are summarized in Figure 1 (diagram B). Quantitative TE was observed in eight of the ten examined solvents, with 1,4-dioxane and dimethyl sulfoxide (DMSO) being exceptions. Although we did notice a large variation in product distribution between the examined solvents (6–83%), it was noteworthy that the highly protic solvent MeOH exhibited a similar or better RCY of [^{11}C]**6** compared with the investigated aprotic solvents under microwave conditions. One would expect that the corresponding methyl [^{11}C]benzoate would be produced as the main product. On the other hand, a significant amount (85.5%) of an unidentified byproduct, likely to be the corresponding ethyl [^{11}C]benzoate, was produced when EtOH was used as solvent. Although MeOH showed promise as a reaction media, THF was selected as the solvent of choice for the continued study.

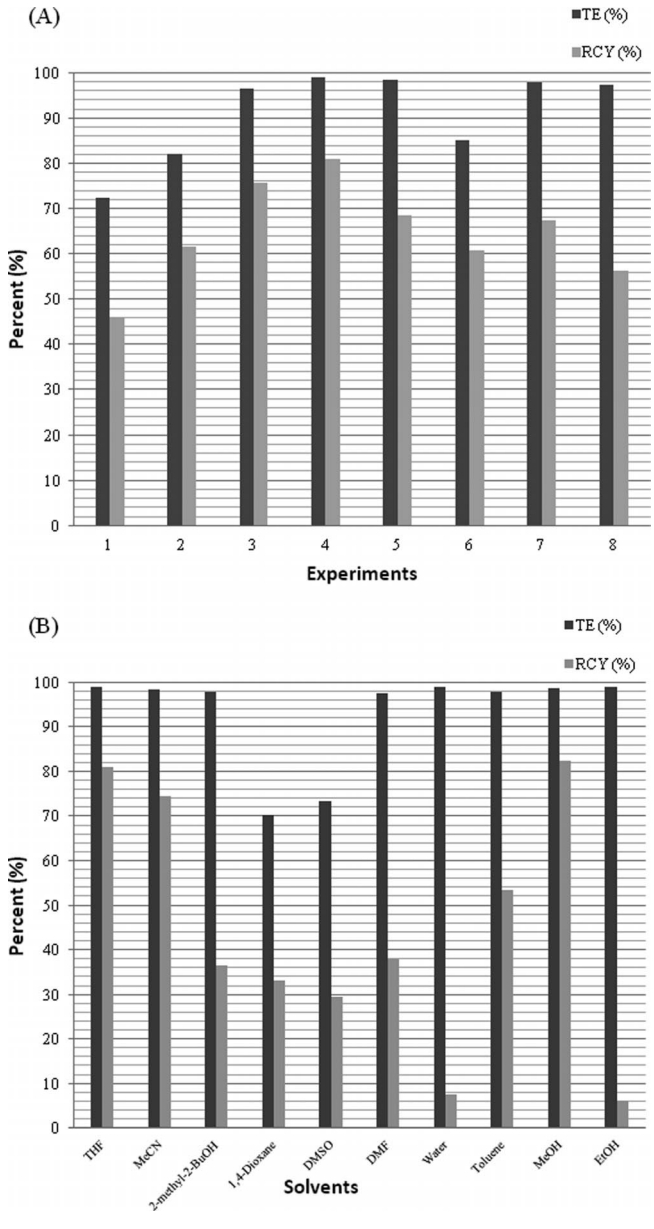
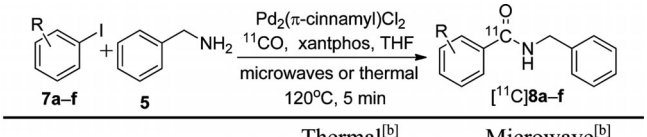


Figure 1. (A) Trapping efficiency (TE) and radiochemical yield (RCY) examined as a function of time and temperature. Reaction conditions: substrate (20 μmol), benzylamine (100 μL), xantphos (14 μmol), Pd$_2$[π-cinnamyl]Cl$_2$ (14 μmol). Thermal heating: [1] 100 °C/5 min.[4] MW heating: [2] 100 °C /5 min, [3] 100 °C/5 min/AC, [4] 120 °C/5 min/AC, [5] 140 °C/5 min/AC, [6] 120 °C/3 min/AC, [7] 140 °C/3 min/AC, [8] 160 °C/2 min/AC. (B) TE and RCY examined by using different solvents.

The optimal conditions were then applied to the ^{11}C-aminocarbonylation of a range of functionalized aryl iodides, an aryl triflate and an aryl chloride by using **5** as a model amine nucleophile. The selected substrates were first

investigated by using conventional heating to facilitate rapid comparison between the two conditions. The results are summarized in Table 1. The RCYs of substrates containing electron-withdrawing groups in the *meta*-position were generally increased under microwave-enhanced conditions (Table 1, entries 3–5), whereas the RCY for the disubstituted substrate, 3,5-nitro-iodobenzene, was not improved (Table 1, entry 6). Surprisingly, appreciable RCYs were obtained when chlorobenzene was used as substrate under both heating technologies, although a relative 21% increase in RCY was obtained with microwave heating compared with thermal heating (Table 1, entry 1). This is, to the best of our knowledge, the first example of a successful ^{11}C-carbonylation of an aryl chloride. In addition, a 16% improvement in product distribution was observed for substrate **7c** compared with reported results obtained with thermal heating, whereas the RCY was not improved when the nonhalide substrate **7b** was used as substrate. Thus, the increased yield observed for ^{11}C-aminocarbonylation of four of the six aryl substrates examined herein supports the view that microwave irradiation increases the efficiency of ^{11}C-amide formation for electron-deficient aryl halides.

Table 1. Difference in ^{11}CO trapping efficiency (TE) and radiochemical yield (RCY) was examined for six different aminocarbonylation reactions between microwave and thermal heating.[a]

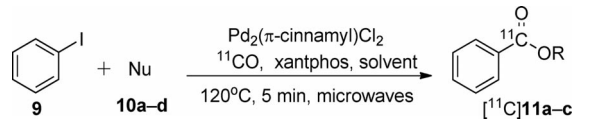


Entry	Substrate	Thermal[b]		Microwave[b]	
		TE [%]	RCY [%]	TE [%]	RCY [%]
1	**7a**	98±2	37±3	88±3	58±1
2	**7b**	>99	92±1	> 99	91±1
3	**7c**	>99	76±1	> 99	92±1
4	**7d**	83±5	51±4	> 99	81±3
5	**7e**	69±3	33±4	94±3	62±3
6	**7f**	30±3	12±1	44±1	13±2

[a] Reaction conditions: substrate (20 μmol), benzylamine (100 μL), xantphos (14 μmol), Pd_2[π-cinnamyl]Cl_2 (14 μmol), THF (0.7 mL), microwave (120 °C, 5 min, AC) or thermal (120 °C, 5 min) heating. [b] Average of two runs.

To further examine the scope of this methodology, we turned our attention to functional groups other than amides. Beside amides, carboxylic acids and esters are two of the most abundant functional groups in biologically important compounds and drug-like molecules. To this end, two esters and a carboxylic acid were produced by using iodobenzene as substrate (Table 2). However, in contrast to the conditions used for the aminocarbonylation, the hydroxy and alkoxy nucleophiles (water, methanol and ethanol) were also used as reaction media. When ^{11}C-hydroxycarbonylation was conducted in an equimolar mixture of aqueous sodium hydroxide and THF, the corresponding carboxylic acid [^{11}C]**11a** was produced in 97% RCY (Table 2, entry 1). Following the same protocol but using a 1:1 mixture of THF and alcohol, the corresponding alkyl [^{11}C]benzoates were produced with excellent and reproducible RCYs (Table 2, entries 2–3). Replacing ethanol with a solution of its lithium salt in anhydrous THF provided [^{11}C]**11c** in 73% RCY (Table 2, entry 4), with [^{11}C]-benzoic acid as the main byproduct. These encouraging results imply that the use of microwave-enhanced ^{11}C-carbonylation provides a facile route to ^{11}C-esters labeled in the carbonyl position. Traditionally, ^{11}C-labeled compounds with carbonyl functionality have been synthesized through multi-step protocols, typically using the direct application of [^{11}C]carbon dioxide in the carboxylation of Grignard reagent.[9] However, unlike the method describe in this paper, such methodologies are highly sensitive to trace amounts of moisture and oxygen, and therefore a high radiochemical yield is generally very difficult to maintain.

Table 2. Results for the Pd-mediated ^{11}C-carbonylation using O-centered nucleophiles.[a]



Entry	Nu	R	TE [%]	RCY [%][d]
1	H_2O[b]	H	> 99	97 ± 1
2	MeOH	Me	> 99	93 ± 1
3	EtOH	Et	> 99	82 ± 1
4	LiOEt[c]	Et	> 99	73 ± 6

[a] Reaction conditions: substrate (20 μmol), nucleophile (400 μL), xantphos (14 μmol), Pd_2[π-cinnamyl]Cl_2 (14 μmol), THF (400 μL), 120 °C, 5 min. [b] NaOH (70 μmol) was used as base. [c] Reaction was performed with LiOEt (100 μmol) in pure THF. [d] Average of two runs.

Conclusions

We herein described the first application of microwave heating to facilitate Pd-mediated ^{11}C-carbonylation of aryl substrates. By using microwave irradiation at ambient pressure in a disposable glass vial, we observed improved yields in the ^{11}C-aminocarbonylation of electron-deficient aryl halides, and the approach even allowed the use of an aryl chloride as substrate. The scope of this reaction was further extended to the synthesis of ^{11}C-labeled aryl acid and two ^{11}C-labeled aryl esters. These results further demonstrate the utility and potential of ^{11}CO as a labeling precursor for application in PET.

Experimental Section

General Procedure for the Microwave-Enhanced [^{11}C]Carbonylation Reaction: $^{11}CO_2$ was reduced online to ^{11}CO by using a pre-heated quartz column (850 °C) charged with Mo-powder. Unreacted $^{11}CO_2$ was subsequently removed by an ascarite trap and the ^{11}CO was concentrated on a silica gel trap immersed in liquid nitrogen. Upon complete entrapment, the trap was heated to release the ^{11}CO into a vial (4 mL) containing the coupling reagents (aryl halide, Pd-source, ligand and amine dissolved in appropriate solvent) equipped with a rubber septum. The sealed reaction vessel was manually transferred to the microwave cavity and heated at the desired temperature for 2–5 min, after which the vial was cooled to room temp. The radioactivity was measured before and after the vial was purged with nitrogen. Radiochemical purity (RCP) of the crude reaction mixture was established with radio-HPLC. For a more detailed description of the reaction procedure, see the Supporting Information.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, and radio-HPLC chromatograms.

Acknowledgments

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[1] M. P. Phelps, *Neurochem. Res.* **1991**, *16*, 929–940.
[2] P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem.* **2008**, *120*, 9136; *Angew. Chem. Int. Ed.* **2008**, *47*, 8998.
[3] a) B. Långström, O. Itsenko, O. Rahman, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 794; b) T. Kihlberg, B. Långström, *J. Org. Chem.* **1999**, *64*, 9201–9205; c) O. Rahman, T. Kihlberg, B. Långström, *J. Org. Chem.* **2003**, *68*, 3558–3562; d) O. Itsenko, T. Kihlberg, B. Långström, *J. Org. Chem.* **2004**, *69*, 4356–4360; e) H. Doi, J. Barletta, M. Suzuki, R. Noyori, Y. Watanabe, B. Långström, *Org. Biomol. Chem.* **2004**, *2*, 3063–3066; f) J. Eriksson, O. Åberg, B. Långström, *Eur. J. Org. Chem.* **2007**, 455–461; g) G. Buscemi, P. W. Miller, S. Kealey, A. D. Gee, N. J. Long, J. Passchier, R. Vilar, *Org. Biomol. Chem.* **2011**, *9*, 3499–3503; h) P. W. Miller, H. Audrain, D. Bender, A. J. deMello, A. D. Gee, N. J. Long, R. Vilar, *Chem. Eur. J.* **2011**, *17*, 460–463.
[4] K. Dahl, M. Schou, N. Amini, C. Halldin, *Eur. J. Org. Chem.* **2013**, 1228.
[5] a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279–282; b) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.
[6] D. R. Hwang, S. M. Moerlein, L. Lang, M. J. Welch, *J. Chem. Soc., Chem. Commun.* **1987**, 1799.
[7] a) N. Elander, J. R. Jones, S. Y. Lu, S. Stone-Elander, *Chem. Soc. Rev.* **2000**, *29*, 239; b) S. Stone-Elander, N. Elander, *J. Labelled Compd. Radiopharm.* **2002**, *45*, 715; c) N. Lazarova, F. G. Simeon, J. L. Musachio, S. Y. Lu, V. W. Pike, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 463–465.
[8] a) C. M. Kormos, N. E. Leadbeater, *Synlett* **2006**, 1663; b) C. M. Kormos, N. E. Leadbeater, *Org. Biomol. Chem.* **2007**, *5*, 65; c) J. Salvadori, E. Balducci, S. Zaza, E. Petricci, M. Taddei, *J. Org. Chem.* **2009**, *75*, 1841; d) E. Awuah, A. Capretta, *Org. Lett.* **2009**, *11*, 3210; e) B. Roberts, D. Liptrot, L. Alcaraz, *Org. Lett.* **2010**, *12*, 1264; f) D. Liptrot, L. Alcaraz, B. Roberts, *Adv. Synth. Catal.* **2010**, *352*, 2183.
[9] a) C. Aubert, C. Perrio-Huard, M. C. Lasne, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2837–2842; b) C. Perrio-Huard, C. Aubert, M. C. Lasne, *J. Chem. Soc. Perkin Trans. 1* **2000**, 311–316; c) M. Matarrese, F. Sudati, D. Soloviev, S. Todde, E. A. Turolla, M. G. Kienle, F. Fazio, *Applied Radiation Isotopes* **2002**, *57*, 675–679; d) S. Y. Lu, J. Hong, V. W. Pike, *J. Labelled Compd. Radiopharm.* **2003**, *46*, 1249–1259.

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