Biologically Active ^{11}C-Labeled Amides Using Palladium-Mediated Reactions with Aryl Halides and [^{11}C]Carbon Monoxide

Tor Kihlberg† and Bengt Långström*,†,‡

Department of Organic Chemistry, Institute of Chemistry, and Uppsala University PET Centre, Uppsala University, S-751 85 Uppsala, Sweden

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Using [^{11}C]carbon monoxide in palladium-mediated synthesis, six amides were labeled with ^{11}C. Phenyl and benzyl halides with halides as additional substituents were carbonylated and reacted with primary and secondary amines. Four of the selected amides were receptor ligands, one was a precursor to a receptor ligand, and one was a model compound. The ^{11}C-labeled amides were obtained with good to almost quantitative radiochemical yields with specific activities up to 1000 GBq/μmol. The radiochemical purity of the final products exceeded 98%. In one case, the corresponding ^{13}C-substituted compound was produced to verify the position of the label. In a typical experiment starting with 5.0 GBq of [^{11}C]carbon monoxide, 2.2 GBq of LC-purified *N*-(2-aminoethyl)-4-chloro-[carbonyl-^{11}C]benzamide was obtained within 15 min from the start of the carbonylation reaction (74% decay-corrected radiochemical yield). The presented approach gives significant new possibilities for ^{11}C-labeling and is seen to be valuable also for synthesis of ^{13}C- and ^{14}C-substituted compounds.

Introduction

Tracers labeled with short-lived positron emitting radionuclides (e.g., ^{11}C, $t_{1/2}$ = 20.3 min) are used in noninvasive in vivo studies in combination with positron emission tomography (PET).[1] Special synthetic procedures are required for the production of these tracers on account of their radioactivity, short half-lives, and the submicromole quantities involved.[2] The development of new ^{11}C-labeled precursors is important not only in order to increase the number of compounds that can be labeled with ^{11}C but also for increasing the possibility of labeling a given compound in different positions.[3] Throughout the development of a production method, the recognition of time as a parameter in the same category as chemical yield and purity is an important consideration.[4]

Although [^{11}C]carbon monoxide was one of the first ^{11}C-labeled compounds to be used in tracer experiments in man,[5] it has until recently rarely been applied as a precursor in labeling chemistry.[6] One reason for this stems from its low reactivity and solubility, which create difficulties in trapping [^{11}C]carbon monoxide in a reaction medium.[7] Two methods have been developed to overcome the trapping problem: (I) recirculation of the [^{11}C]carbon monoxide through the reaction media;[8] (II) concentration and enclosure of the [^{11}C]carbon monoxide in a micro-autoclave at high pressure. Method I has been described in a report on the synthesis of ^{11}C-labeled ketones.[8] In the present paper, method II has been used in the preparation of a selection of amides.

Carbonylation of organohalides with a zerovalent palladium reagent, carbon monoxide, and a nucleophile is a versatile method for synthesis of carbonyl compounds in high yields (i.e., amides, carboxylic acids, esters, aldehydes, and ketones).[7,9] Virtually all types of functionality seems to be tolerated, and the synthesis can usually be performed in a one-pot procedure. One limitation is encountered with organohalides having β-protons bound to sp^3 carbons; these usually give low yields due to the competing β-hydride elimination reaction.[10]

This work deals with the synthesis of ^{11}C-labeled amides according to Scheme 1. The target molecules (Figure 1) were selected using the following criteria: (1) to show that the presented method could be applied where the use of Grignard reagents would probably be obstructed; (2) to investigate substrates (**8** and **9**, Figure

* To whom correspondence should be adressed.
† Institute of Chemistry.
‡ Uppsala University PET Centre.

(1) Wagner, H. N.; Szabo, Z.; Buchanan, J. W. *Principles of Nuclear Medicine*; W. B. Saunders Co.: Philadelphia, 1995.

(2) Emran, A. *New Trends in Radiopharmaceutical Synthesis, Quality Assurance and Regulatory Control*; Plenum Press: New York, 1991.

(3) (a) Kihlberg, T.; Valind, S.; Långström, B. *Int. J. Appl. Radiat. Isot.*, Part B: *Nucl Med. Biol.* **1994**, *21*, 1067−1073. (b) Kihlberg, T.; Valind, S.; Långström, B. *Int. J. Appl. Radiat. Isot.*, Part B: *Nucl Med. Biol.* **1994**, *21*, 1053−1067. (c) Långström, B.; Andersson, Y.; Antoni, G.; Axelsson, S.; Bjurling, P.; Fasth, K. J.; Gee, A. D.; Kihlberg, T.; Ulin, J.; Watanabe, Y. *Acta Radiol. Suppl.* **1989**, *28*, 376, 31−36. (d) Bjurling, P.; Antoni, G.; Watanabe, Y.; Långström, B. *Acta Chem. Scand.* **1990**, *44*, 178−182. (e) Bjurling, P.; Watanabe, Y.; Oka, S.; Nagasawa, T.; Yamada, H.; Långström, B. *Acta Chem. Scand.* **1990**, *44*, 183−188. (f) Bjurling, P.; Watanabe, Y.; Tokushige, M.; Långström, B. *J. Chem. Soc., Perkin. Trans. 1* **1989**, 1331−1334. Halldin, C.; Bjurling, P.; Stålnacke, C. G.; Jossan, S.; Oreland, L.; Långström, B. *Appl. Radiat. Isot. A* **1989**, *40*, 557−560.

(4) Långström, B.; Bergson, G. *Radiochem. Radioanal. Lett.* **1980**, *43*, 47−54.

(5) Tobias, C. A.; Lawrence, J. H.; Roughton, F. J. W.; Rooth, W. J.; Gregerson, M. I. *Am. J. Physiol.* **1945**, *145*, 253−260.

(6) (a) Tang, D. Y.; Lipman, A.; Meyer, G.-J.; Wan, C.-N.; Wolf, A. P. *J. Labeled Compd. Radiopharm.* **1979**, *16*, 435−440. (b) Kothari, P. J.; Finn, R. D.; Vora, M. M.; Booth, T. E.; Emran, A. M.; Kabalka, G. W. *Int. J. Appl. Radiat. Isot.* **1985**, *36*, 412−413. (c) Kilbourne, M. R.; Jarabek, P. A.; Welch, M. J. *J. Chem. Soc., Chem. Commun.* **1983**, 861−862. (d) Andersson, Y.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 287−289. (e) Zeisler, S. K.; Nader, M.; Theobald, A.; Oberdorfer, F. *Appl. Radiat. Isot.* **1997**, *48*, 1091−1095.

(7) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991.

(8) Lidström, P.; Kihlberg, T.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, **1**, 2701−2706.

(9) Gyorkos, A. C.; Stille, J. K.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8465−8472.

(10) (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Cemistry*; University Science Books: Mill Valley, CA, 1987. (b) Yamamoto, A. *Organotransition Metal Chemistry*; John Wiley & Sons: New York, 1986. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.

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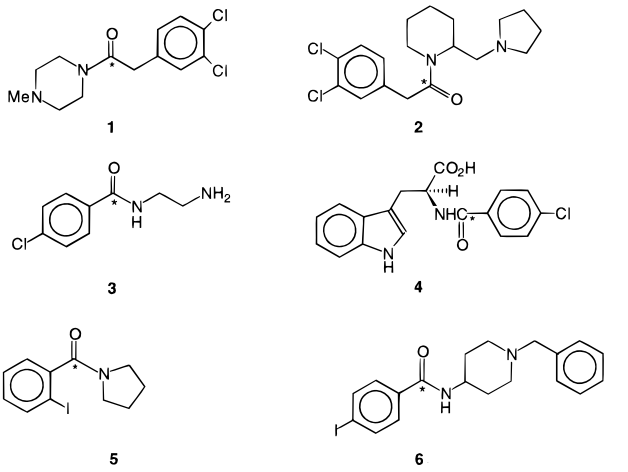
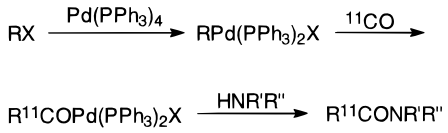


Figure 1. Target molecules. * = ^{11}C.

Scheme 1



2**),** which are unusual in the context of palladium-mediated carbonylation; and (3) to label compounds that were directly or indirectly of interest as PET tracers.[11−17]

The amides selected for this study constitute a fraction of the amides with potential as PET tracers that would be possible to ^{11}C-label using method II. This paper is the first in a series of papers dealing with the labeling of carbonyl compounds using [^{11}C]carbon monoxide.

Results and Discussion

The ^{11}C-labeled amides were synthesized in a microautoclave (200 μL) at pressures exceeding 35 MPa using tetrakis(triphenylphosphine)palladium(0), an aryl halide, an amine, and [^{11}C]carbon monoxide (Scheme 1). The results are presented in Table 1, and the corresponding organohalides and amines are shown in Figures 2 and 3, respectively. The specific radioactivity of the [^{11}C]-carbon monoxide was in the range 400−1300 GBq/μmol, which corresponds to a mass range of 0.3−0.8 μg.

In the cases of compounds **1**, **2**, and **3** (entries 1a,b, 2, and 3) the syntheses were without complications. The reagents were dissolved in 1,4-dioxane, and the resulting mixture was heated with [^{11}C]carbon monoxide at 130−150 °C. The conversion of [^{11}C]carbon monoxide to labeled products (the trapping efficiency) was nearly quantitative, and the radiochemical purities of the crude products of **1** and **3** were high. The reason for the lower radiochemical yield of **2** was primarily the low purity (75%) of the amine **11**.

Compound **4** (entry 4) is an amide of tryptophan. Tryptophan, however, is nearly insoluble in most organic solvents, and its primary nitrogen lacks nucleophilicity due to protonation. It was found that the tetrabutylammonium salt of tryptophan (**16**) was both reactive and soluble in DMSO. Good radiochemical yields were obtained when the palladium complex of **10**, made in 1,4-dioxane, was mixed with a solution of **16** in DMSO.

Compound **5** (entry 5) was synthesized from **8** and **12** with a 20% radiochemical yield. Although this radiochemical yield was lower than for the other target compounds, it is still good enough for production of a PET tracer. The reason for this low radiochemical yield was not low trapping efficiency but the formation of several side products that were not identified. The radiochemical

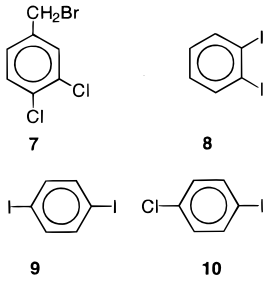


Figure 2. Substrates for palladium-mediated carbonylation.

Table 1. Radiochemical Yields and Specific Radioactivitys for the ^{11}C-Labeled Amides Shown in Figure 1

no.	organo halide	amine	product	trapping efficiency[a] (%)	isolated rcy[b] (%)	specific radioact[c] (GBq/μmol)
1a	**7**	**15**	**1**	98 ± 2 (6)[d]	78 (1)	107
1b[f]	**7**	**15**	**1**	97 ± 1 (2)	76 ± 3 (2)	600, 1000
2	**7**	**11**	**2**	93 ± 2 (3)	43 (1)	48
3	**10**	**13**	**3**	97 (1)	75 (1)	115
4	**10**	**16**	**4**	89 ± 3 (3)	55 ± 3 (2)	105
5	**8**	**12**	**5**	91 ± 3 (3)	20 ± 2 (2)	24
6	**9**	**14**	**6**	92 (1)	54 (1)	120

[a] Decay-corrected, the fraction of radioactivity left in the crude product after purge with nitrogen. [b]Decay-corrected, calculated from the amount of radioactivity in the crude product before nitrogen purge, and the radioactivity of the LC purified product. [c]Based on concentration measurements determined by LC−MS analysis. [d]Values in parentheses shows number of runs. [e]Runs using 10−20 times larger bombardments (22−24 μAh).

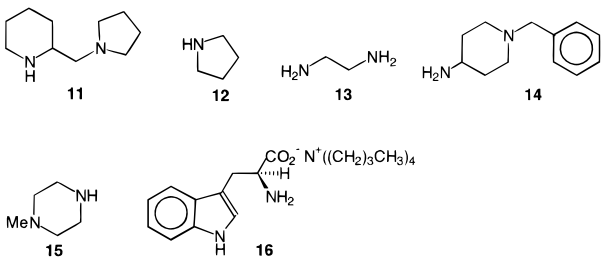


Figure 3. Amines used in the ^{11}C-labeling reactions.

(11) The corresponding amine of **1** (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine) is a σ_1 receptor antagonist.[12] Compound **2** ((±)-1-(3,4-dichlorophenyl)[carbonyl-^{11}*C*]acetyl-2-(1-pyrrolidinyl)methylpiperidine) is a very κ/μ-selective and potent κ ligand.[13] Compound **3** (*N*-(2-aminoethyl)-4-chloro[carbonyl-^{11}*C*]benzamide) is a monoamine oxidase-B inhibitor.[14] Compound **4** (Benzotript, *N*-(4-chloro[carbonyl-^{11}*C*]benzoyl)-L-tryptophan) is a selective cholecystokinin receptor antagonist.[15] Compound **5** is a model for *cis*-2-(difenylmethyl)-*N*-[(2-iodophenyl)methyl]-1-azabicyclo[2.2.2]octan-3-amine, a potent and selective nonpeptide NK_1 tachykinin receptor antagonist.[16] Compound **6** (*N*-(2-iodo[carbonyl-^{11}*C*]benzoyl)pyrrolidine) is a receptor ligand that combines high affinity for σ_1 and moderate affinity for σ_2 sites.[17]

(12) Masumoto, R. R.; Bowen, W. D.; Tom, M. A.; Vo, V. N.; Truong, D. D.; De Costa, B. R. *Eur. J. Pharmacol.* **1995**, *280*, 301−310.

(13) Vecchietti, V.; Giordani, A.; Giardina, G.; Colle, R.; Clarke, G. D. *J. Med. Chem.* **1991**, *34*, 397−403.

(14) Cesura, A. M.; Imhof, R.; Muggli-Maniglio, D.; Picotti, G. B.; Da Prada, M. *Biochem. Parmacol.* **1990**, *39*, 216−220.

(15) Magous, R.; Bali, J. P. *Regul. Pept.* **1983**, *7*, 233−241.

(16) Snider, R. M.; Constantine, J. W.; Lowe, J. A.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H. J. *Science* **1991**, *251*, 435−437.

(17) John, C. S.; Vilner, B. J.; Bowen, W. D. *J. Med. Chem.* **1994**, *37*, 1737−1739.

yield of **6** (entry 6) was considerably higher than for **5**. In the synthesis of **6**, the conditions for making the oxidative addition of palladium to **9** were crucial. Good radiochemical yields were obtained only when a solution of tetrakis(triphenylphosphine)palladium(0) was slowly added to a solution of **9** in more than 15-fold excess.

After semipreparative LC, compounds **1**−**6** were obtained with radiochemical purity exceeding 98%.

As expected, the specific radioactivities (i.e., the ratio of radioactivity to mass) for compounds **1**−**6** were high, most probably in the same range as the [^{11}C]carbon dioxide produced in the target using the described radio nuclide production. The variations in specific radioactivity are likely to reflect variations in the nuclide production rather than variations in the syntheses. Determination of the specific radioactivity of the [^{11}C]carbon monoxide used in the carbonylation reactions is currently unfeasible. Usually small bombardments (1−2 μAh), about a tenth of the maximal amount for [^{11}C]carbon dioxide, were used. Since larger bombardments give larger amounts of radioactivity without a corresponding increase in mass, two experiments using bombardments in the range 22−24 μAh were performed. As expected, exceptional high levels of specific radioactivity were observed (entry 1b). The amounts of LC-purified ^{11}C-labeled product were in most cases in the range 10−20 nmol.

The identities of compounds **1**−**6** were assessed using LC−MS. Preliminary identifications were performed using analytical LC with co-injection of nonradioactive reference material. The identity of compound **3** was further confirmed by ^{13}C NMR analysis of *N*-(2-aminoethyl)-4-chloro(carbonyl-^{13}C)benzamide synthesized as **3**. The ^{13}C NMR signal at 167.4 ppm corresponded to the ^{13}C signal from the carbonyl carbon of authentic *N*-(2-aminoethyl)-4-chlorobenzamide.

Amides labeled with ^{11}C in the carbonyl group have previously been synthesized with high radiochemical yields and short reaction times using Grignard reagents.[18] The use of Grignard reagents, however, implies several limitations and drawbacks. Compounds containing additional iodo or bromo atoms, carbonyl groups, nitrile, or groups with acidic protons cannot be used in Grignard synthesis. Many nitrogen-containing compounds, other than those mentioned, are excluded due to problems with complex formation.[19] These limitations are greatly diminished in the synthetic approach where palladium(0) and carbon monoxide are used (Scheme 1). As exemplified by the preparations of **5** and **6**, some of the limitations present in palladium-mediated carbonylation can be further reduced in applications using [^{11}C]-carbon monoxide.

When [^{11}C]carbon monoxide is used in labeling chemistry, an important and problematic issue is the determination of radiochemical yield. The reasons for this are that [^{11}C]carbon monoxide can only be trapped in a solution if it is consumed by a reaction and that it is difficult to perform exact measurements of the radioactivity located inside a radioprotected synthesis system. The efficiency of the system and the use of the following procedure made it possible to accurately determine the radiochemical yields. At the end of the reaction, the contents of the micro-autoclave (250 μL) were transferred to an evacuated, septum-fitted collection vial (5 or 20 mL). The micro-autoclave was then rinsed with THF. During this procedure, and the following radioactivity measurement, a reduced pressure was maintained in the collection vial. The amount of the residues of [^{11}C]carbon monoxide and labeled products left in the system, roughly estimated using a portable dose−rate meter, was always less than 1%. Thus, the measurement of radioactivity in the collection vial before and after nitrogen purge was sufficient for accurate calculations of the conversion of [^{11}C]carbon monoxide (trapping efficiency).

When compounds are labeled with ^{11}C, it is usually important to maximize specific radioactivity. To achieve this, the isotopic dilution and the synthesis time must be minimized. Isotopic dilution from atmospheric carbon dioxide may be substantial when [^{11}C]carbon dioxide is used in a labeling reaction. Due to the low reactivity and atmospheric concentration of carbon monoxide (0.1 ppm vs 3.4×10^4 ppm for CO_2), this problem is reduced with reactions using [^{11}C]carbon monoxide.

The aryl halides **8** and **9** are interesting substrates since they contain two iodide atoms where palladium may react. Synthesis of iodo bensoyl amides from compounds **8** and **9** would probably not be useful if the yield was based on the conversion of organo halide to product. However, when the yield is based on the conversion of carbon monoxide (e.g., [^{11}C], (^{13}C), or (^{14}C)) to product, and the unlabeled reagents can be used in excess, new options arise. This situation makes it possible to utilize reaction paths that otherwise would be neglected.

The labeling reactions were run at temperatures in the range 130−150 °C. In most cases, when the precursors had good thermal stability and high concentrations of the amine could be used the reaction temperature was not of crucial importance. For example, the radiochemical yields of **1** or **3** were almost quantitative in the temperature range 110−160 °C.

An important result from the use of the micro-autoclave technique with ethereal solvents (e.g., 1,4-dioxane) is that temperatures up to 200 °C may be used without significant problems from side products. One reason is that the micro-autoclave technique precludes air contact with the reaction mixture and that ethers are usually chemically inert. In this paper, the influence of temperature on radiochemical yield was not systematically studied. However, in situations where the amines used in the labeling reaction are thermal unstable or applicable only in low concentrations (e.g., due to high molecular weight), the choice of temperature for radiochemical yield optimization will be more important.

With the development of a fully automated version of this micro-autoclave system, the value of [^{11}C]carbon monoxide as a precursor for ^{11}C-labeled tracers should be comparable with [^{11}C]methyl iodide. Currently, [^{11}C]-methyl iodide[20] is the most frequently used ^{11}C-precursor due to ease in production and handling and since groups suitable for labeling with [^{11}C]methyl iodide (e.g., het-

(18) (a) McCarron, J. A.; Turton, D. R.; Pike, V. W.; Poole, K. G. *J. Labeled Compd. Radiopharm.* **1996**, *38*, 941−953. (b) Scripko, J. G.; Huang, C. C.; Kilbourne, M. R. *J. Labeled Compd. Radiopharm.* **1994**, *35*, 141.

(19) (a) Kihlberg, T. Development of Methods for ^{11}C−C Bond Formation. *Acta Univ. Ups.* **1994**, 24−25. (b) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36−56.

(20) (a) Långström, B.; Antoni, G.; Gullberg, P.; Halldin, C.; Malmborg, P.; Någren, K.; Rimland, A.; Svärd, H. *J. Nucl. Med.* **1987**, *28*, 1037−1040. (b) Reference 1, S. 166−178.

eroatom-bound methyl groups) are common among biologically active substances. Carbonyl groups, which can be conveniently labeled with [^{11}C]carbon monoxide, are also common among biologically active substances. In many cases, due to metabolic events in vivo, a carbonyl group may even be more advantageous than a methyl group as labeling position. The use of [^{11}C]carbon monoxide for production of PET tracers may thus become an interesting complement to [^{11}C]methyl iodide. Furthermore, through the use of similar technology, this method will most likely be applicable for synthesis of ^{13}C- and ^{14}C-substituted compounds. This paper provides only one example using (^{13}C)carbon monoxide, since our focus has been on the development of methods for synthesis of ^{11}C-labeled compounds, where time constrains are crucial.

Conclusions

The use of [^{11}C]carbon monoxide at very low concentrations in palladium-promoted carbonylative coupling of aryl halides with amines has been shown to be a versatile method for the production of amides ^{11}C-labeled in the carbonyl moiety. Using this approach, arylic ^{11}C-labeled amides were synthesized in good to quantitative radiochemical yields with high specific radioactivity. The presented method is rapid, mild, general, and conducted in a one-pot procedure suitable for automation. The method holds promise for routine production of ^{11}C-labeled amides. The use of (^{13}C)carbon monoxide in a similar method enables the synthesis of different carbonyl ^{13}C-labeled amides.

Experimental Section

General Methods. [^{11}C]Carbon dioxide production was performed using a Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. The ^{14}N(p,α)^{11}C reaction was employed in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA. Oxygen 4.8), which was bombarded with 17 MeV protons.

[^{11}C]Carbon monoxide was produced as described previously.[8]

Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable-wavelength UV detector in series with a β^+-flow detector. The following mobile phases were used: 0.5% triethylamine in water (A), 0.5% triethylamine in acetonitrile (B), 0.05 M ammonium formate pH 3.5 (C), and acetonitrile (D). For analytical LC, a Beckman Ultrasphere ODS C_{18}, 5 μm, 250 × 4.6 mm i.d. column was used at a flow of 1.5 mL/min. For semipreparative LC, a Beckman Ultrasphere ODS C_{18}, 5 μm, 250 × 10 mm (i.d.), column was used at a flow rate of 4 mL/min. Synthia, an automated synthesis system,[21] was used for LC injection and fraction collection. Data collection and LC control were performed with the use of a Beckman System Gold chromatography software package.

Radioactivity was measured in an ion chamber, Veenstra Instrumenten bv, VDC-202. For coarse estimations of radioactivity during production, a portable dose−rate meter was used, Långenäs eltekniska AB.

In the analysis of the ^{11}C-labeled compounds, unlabeled reference substances were used for comparison in all the LC runs. Identities of synthesized materials were determined using ^{1}H and ^{13}C NMR and GC−MS and LC−MS. NMR spectra were recorded on a Varian XL 300 (300 MHz). As internal standard tetramethylsilane or chloroform-d_1 was used. LC−MS was performed using a Micromass VG Quattro with electrospray ionization. A Beckman 126 pump, a CMA 240 autosampler and a Beckman Ultrasphere ODS C_{18} (5 μm, 100 × 4.6 mm i.d.) column were used. Mobile phases were A and B.

THF was distilled under nitrogen from sodium/benzophenone.

The reference compounds for **2**, **3**, and **6** were purchased from Tocris Cookson Ltd. The reference compound for **4** was purchased from Research Biochemicals International. The reference compound for **1** was synthesized from 3,4-dichlorobensoyl chloride and *N*-methylpiperazine.[22] The reference compound for **5** was synthesized from 2-iodobensoyl chloride and pyrrolidine.[22] Compound **11** was prepared according to the literature procedure.[10] All other chemicals were purchased from Sigma-Aldrich except **7** and **9**, which were purchased from Lancaster.

Preparation of Reagents and Reference Compounds. Tetrabutylammonium Tryptophan (16). Tetrabutylammonium hydroxide (0.98 mL, 1 M in H_2O), H_2O (5 mL) and L-tryptophan (200 mg, 0.98 mmol) were mixed. The resulting solution was concentrated under reduced pressure and the residue dried in a vacuum.

***N*-(2-Aminoethyl)-4-chloro(carbonyl-^{13}*C*)benzamide ([^{13}C]-3).** A vial (5 mL) was charged with tetrakis(triphenylphosphine)palladium(0) (10 mg, 9 μmol), 1-chloro-4-iodobenzene (**10**) (35 mg, 147 μmol), 1,4-dioxane (3 mL), and ethylenediamine (**13**) (20 μL, 300 μmol) and flushed with nitrogen. The vial was evacuated and charged with (^{13}C)carbon monoxide (10 mL). The mixture was heated at 110 °C and stirred vigorously for 1 h. The mixture was concentrated under reduced pressure, and acetonitrile (1 mL) was added followed with water (1 mL). A sufficient amount of the corresponding ^{11}C-labeled compound was added and the resulting solution injected on the semipreparative LC. The chromatography was performed as described for **1**. The radioactive fraction was collected and evaporated under reduced pressure, yield 55% calculated from 1-chloro-4-iodobenzene.

Synthesis of Carbonyl-^{11}*C*-Labeled Amides. 1-[2-(3,4-Dichlorophenyl)[carbonyl-^{11}*C*]acetyl-4-methylpiperazine (1). A vial (1 mL) was charged with tetrakis(triphenylphosphine)palladium(0) (2 mg, 1.8 μmol) and 1,4-dioxane (200 μL). The vial was capped, flushed with nitrogen, and shaken until the solution was homogeneous. 3,4-Dichlorobenzyl bromide (**7**) (1 μL, 6.7 μmol) and *N*-methylpiperazine (**15**) (5 μL, 45 μmol) were added. The resulting mixture was transferred with pressure (35 Mpa) to the micro-autoclave (200 μL), precharged with [^{11}C]carbon monoxide. The micro-autoclave was heated (130 °C) for 5 min. The crude product was transferred to a preevacuated, septum-fitted vial (5 mL). The micro-autoclave was filled with THF (250 μL) and emptied into the collection vial. The radioactivity was measured before and after the vial was purged with nitrogen. The solvent volume was reduced to less than 0.2 mL by heating at 130 °C and purging with nitrogen. Acetonitrile/water 1:1 (2 mL) was added, and the resulting solution was injected on the semipreparative LC. Solvent A/B (60:40) linear gradient to 0:100 10 min, flow 4 mL/min, t_R = 8.4 min. The identity and radiochemical purity of the collected fraction were assessed by analytical LC: solvent A/B (70:30) linear gradient to 0:100 8 min, flow 1.5 mL/min, wavelength 254 nm, t_R = 5.4 min. LC−MS: *m*/*z* 291/290/289/288/287 ($M^+ + 1$).

(±)-1-(3,4-Dichlorophenyl)[carbonyl-^{11}*C*]acetyl-2-(1-pyrrolidinyl)methylpiperidine (2). The synthesis was performed as described for **1** except that 1-pyrrolidinylmethylpiperidine (**11**) was used instead of **15**. Semipreparative LC: t_R = 16.3 min. Analytical LC: t_R = 6.6 min. LC−MS: *m*/*z* 359/358/357/356/355 ($M^+ + 1$).

***N*-(2-Aminoethyl)-4-chloro[carbonyl-^{11}*C*]benzamide (3).** The synthesis was performed as described for **1** with the following differences: ethylenediamine (**13**) was used instead of **15**; 1-chloro-4-iodobenzene (**10**) was used instead of **7**; and **10** was added before the 1,4-dioxane. Semipreparative LC: t_R

(21) Bjurling, P.; Reineck, R.; Westerberg, G.; Gee, A. D.; Sutcliffe, J.; Långström, B. *Proceedings of the VIth workshop on targetry and target chemistry*, Vancouver, Canada, 1995; pp 282−284.

(22) Marvel C. S.; Lazier W. A. *Org. Synth.* **1941**, *I*, 99−101.

= 8.5 min. Analytical LC: t_R = 3.5 min. LC−MS: *m*/*z* 201/200/199 ($M^+ + 1$).

***N*-(4-Chloro[carbonyl-^{11}*C*]benzoyl)-L-tryptophan (4).** A vial (1 mL) was charged with tetrakis(triphenylphosphine)-palladium(0) (2.0 mg, 1.8 μmol), 1-chloro-4-iodobenzene (**10**) (2.0 mg, 8.4 μmol), and 1,4-dioxane (100 μL). The vial was capped, flushed with nitrogen, and shaken until the solution was homogeneous (vial A). In a second vial, tetrabutylammonium tryptophan (**16**) (5.0 mg, 11 μmol) was dissolved in DMSO (100 μL) and flushed with nitrogen (vial B). The contents of vial A were added to vial B, and the resulting mixture was transferred to the micro-autoclave, precharged with [^{11}C]carbon monoxide. The micro-autoclave was heated (130 °C) for 5 min. The crude product was collected, and the radioactivity was measured as described for **1**. Saline (1 mL) was added, and the resulting solution was injected on the semipreparative LC. Solvent C/D (60:40) linear gradient to 0:100 10 min, flow 4 mL/min, t_R = 9.1 min. The identity and radiochemical purity of the collected fraction were assessed by analytical LC: solvent C/D (70:30) linear gradient to 0:100 8 min, flow 1.5 mL/min, wavelength 265 nm, t_R = 6.3 min. LC−MS: *m*/*z* 346/345/344/343 ($M^+ + 1$).

***N*-(2-Iodo[carbonyl-^{11}*C*]benzoyl)pyrrolidine (5).** The synthesis was performed as described for **1** with the following differences: pyrrolidine (**12**) was used instead of **15**, and 1,2-diiodobenzene (**8**) was used instead of **7**. Semipreparative LC: t_R = 8.5 min. Analytical LC: t_R = 4.9 min. LC−MS: *m*/*z* 303/302 ($M^+ + 1$).

***N*-(*N*-Benzylpiperidin-4-yl)-4-iodo[carbonyl-^{11}*C*]benzamide (6).** A vial (1 mL) was charged with tetrakis(triphenylphosphine)palladium(0) (1.0 mg, 0.9 μmol) and 1,4-dioxane (100 μL), capped, flushed with nitrogen, and shaken until the solution was homogeneous. In a second vial, 1,4-diiodobenzene (5.0 mg, 15 μmol) was dissolved in 1,4-dioxane (100 μL) and flushed with nitrogen. The contents of the first vial were added to the second vial during 20 s, and 4-amino-*N*-benzylpiperidine was added. The resulting mixture was transferred to the micro-autoclave, precharged with [^{11}C]carbon monoxide. The micro-autoclave was heated (150 °C) for 5 min. The crude product was collected, and the radioactivity was measured as described for **1**. Semipreparative LC: t_R = 9.0 min. Analytical LC: t_R = 7.3 min. LC−MS: *m*/*z* 422/421 ($M^+ + 1$).

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