Palladium-mediated synthesis of [*carbonyl*-^{11}C]amides and hydrazides using [^{11}C]carbon monoxide

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Low concentrations of [^{11}C]carbon monoxide, a palladium complex, aryl halides and ammonia or hydrazine were used for the synthesis of five benzamides and seven hydrazides. Some of the selected compounds (*e.g.* nicotinamide and benzamide) are biologically active. The reactivity of the bromo- and iodoheteroaryls was studied for similar ^{11}C-carbonylation reactions. Furthermore, the impact of tetrabutylammonium iodide on the reactivity of 2-bromo-5-nitrofuran has been investigated. The radiochemical yield of the ^{11}C-labelled compounds was in the range of 40–90% and the specific radioactivity was up to 1700 GBq μmol^{-1}. The radiochemical purity of the target compounds was determined by analytical HPLC and exceeded 95%. In a typical experiment starting with 7.0 GBq [^{11}C]carbon monoxide, 2.1 GBq of HPLC-purified thiophene-2-[*carbonyl*-^{11}C]carbohydrazide were obtained within 27 minutes of the start of the carbonylation reaction (75% decay-corrected radiochemical yield). (*carbonyl*-^{13}C)Benzohydrazide was produced to verify the position of the label (δ 165.9 ppm) using ^{13}C NMR.

Introduction

Positron emission tomography (PET) is a powerful technique in drug development [1,2] and clinical research.[3] The demand for new radiotracers labelled with short-lived positron emitters requires new synthetic procedures and chemical pathways in order to prepare radiotracers with high specific radioactivity. The potential of [^{11}C]carbon monoxide as a precursor for ^{11}C-carbonylation reactions has been limited due to its low reactivity and solubility, and it has therefore rarely been used in labelling chemistry until recently.[4] With the development of a micro-autoclave based system these problems have been overcome.[5] The synthesis of a number of different ^{11}C-amides [5] and ^{11}C-imides [6] has subsequently been reported using this new technical approach. Due to the time-limitation for incorporation of a short-lived radionuclide into target molecules,[7] rapid and one-pot reactions used for labelled products with high specific radioactivity are of interest.

One way to obtain a primary ^{11}C-amide is through cyanation with [^{11}C]cyanide. This synthetic procedure was previously employed for the synthesis of ^{11}C-labelled benzamide with specific radioactivity in the range of 100–150 GBq μmol^{-1}.[8]

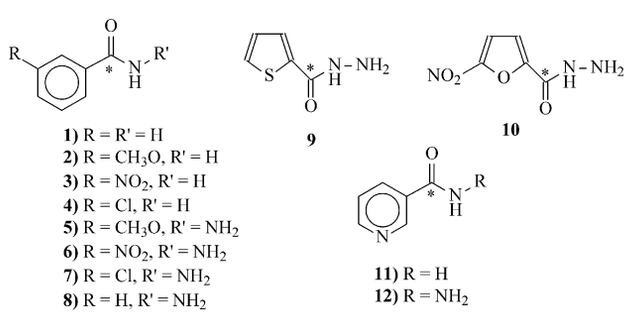
In the present paper a selection of different types of iodoaryls or bromoheteroaryls/iodoheteroaryls were used as precursors in carbonylation reactions to explore their utility under the specific conditions used for ^{11}C-labelling for the preparation of [*carbonyl*-^{11}C]amides and hydrazides with high specific radioactivity. To our knowledge [*carbonyl*-^{11}C]hydrazides have not been reported before.

The following biological active compounds were ^{11}C-labelled using this method: benzamide **1**, 3-methoxybenzamide **2**, 3-nitrobenzamide **3**, 3-chlorobenzamide **4** and nicotinamide **11**. Benzamide is an inhibitor of poly(ADP-ribose) synthetase,[9] and **2**, **3** and **4** have previously been studied for their anti-hypoxic and antispasmodic activities.[10] Nicotinamide has β-cell protection activity [11,12] and is an inhibitor of paraquat (1,1′-dimethyl-4,4′-bipyridylium dichloride) toxicity.[13]

Results and discussion

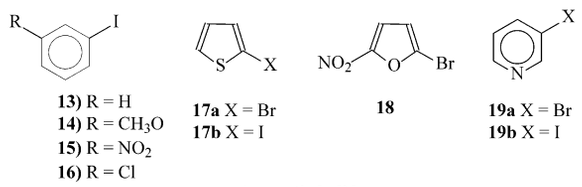
[^{11}C]Benzamides and -nicotinamide have previously been synthesised *via* cyanation followed by treatment with H_2O_2.[8] This method is potentially problematic, as it does not allow the presence of sensitive functional groups. Furthermore, the reported specific radioactivity (100–150 GBq μmol^{-1}) might be considered as a drawback.

The carbonyl ^{11}C-labelled amides were synthesised in a micro-autoclave (200 μl). The reaction mixture containing tetrakis(triphenylphosphine)palladium(0), an aryl halide/heteroaryl halide and ammonia/hydrazine was transferred in anhydrous THF into the micro-autoclave at high pressure (35 MPa) and the reaction was allowed to take place. The target compounds and the corresponding substrates are presented in Figs. 1 and 2. The results are shown in Tables 1–4.



Target compounds (* = ^{11}C)

Fig. 1



Aromatic halides

Fig. 2

The influence of temperature was investigated for the synthesis of ^{11}C-primary amides, using [^{11}C]carbon monoxide, palladium(0) and ammonia in dioxane (1 M). As expected, a higher reaction temperature improved the yield of the desired

Table 1 Radiochemical yields and specific radioactivity for the ^{11}C-labelled amides shown in Fig. 1

Compound	Trapping efficiency (%)[a]			Analytical RCY[b] (isolated)[c] (%)			Specific radioactivity/ GBq μmol^{-1}
	150 °C	170 °C	180 °C	150 °C	170 °C	180 °C	
1	88% (2)	96% (2)	97% ± 1 (4)	28%	41 (29%)	66 (53% ± 2)	389[d]
2	97%	—	98% ± 1 (2)	39(27%)	—	57 (47% ± 3)	412[d]
3	—	—	97% ± 2 (3)	—	—	57 (45% ± 2)	—
4	—	—	95% ± 1 (2)	—	—	56 (41% ± 2)	—
11[f]	—	—	98% ± 1 (4)	—	—	66 (54% ± 4)	1600[e]
11[g]	—	—	93% ± 2 (3)	—	—	21 (11% ± 1)	—

[a] Decay-corrected, the fraction of radioactivity left in the crude product after purging with nitrogen. Values in parenthesis show the number of runs. [b] Analytical radiochemical yield (RCY) determined by LC. [c] Calculated from the amount of radioactivity in the LC-purified product. [d] 10 μA h bombardment. [e] 37.4 μA h bombardment. [f] Using 3-iodopyridine. [g] Using 3-bromopyridine.

Table 2 Synthesis of compound **5** by heating at 150 °C for 5 min

Concentration/M[a]	1	0.4	0.1	0.04
Trapping efficiency (%)[b]	95	96	99	99
Analytical RCY (%)[c]	86	88	87	87

[a] Concentration of hydrazine (1 M solution in THF). [b] Decay-corrected, the fraction of radioactivity left in the crude product after purging with nitrogen. [c] RCY = radiochemical yield determined by HPLC.

compounds (Table 1). The need for a high temperature is most probably due to the poor nucleophilic properties of ammonia compared to hydrazine.

In order to increase the reaction rate higher concentrations of ammonia were used. In one variation of the method, tris(dibenzylideneacetone)palladium(0), $Pd_2(dba)_3$, and excess tri-*o*-tolylphosphine, $(o\text{-tol})_3P$, at 100 °C were used instead of tetrakis(triphenylphosphine)palladium(0) and yielded 20% of benzamide **1**.

In the study of the reactivity of hydrazine, the effect of its concentration was investigated in the synthesis of compound **5** using 3-iodoanisole (Table 2). The trapping efficiency and analytical radiochemical yield were in the same range in all cases.

The effect of temperature was studied for compound **12** and the data are shown in Table 3. Repeated experiments using hydrazine (0.04 M) at 180 *vs.* 150 °C showed that the yield decreased due to decomposition of hydrazine or ^{11}C-hydrazide. However, by increasing the concentration of hydrazine to 0.1 M the yield was increased to 57%.

In the synthesis of compound **11**, the use of 3-bromopyridine instead of 3-iodopyridine at 180 °C resulted in a reduced radiochemical yield. This was unexpected in light of a previous report[5] using aryl bromides.

Table 4 Relationship between particle bombardment [^{14}N(P,α)^{11}C] and specific radioactivity

Compound	Bombardment/μA h[b]	Specific radioactivity[a]/ GBq μmol^{-1}
1	3.0 (4)[c]	125 ± 4
1	10 (1)	389
2	1.2 (3)	50 ± 5
2	10 (1)	412
9	1.0 (2)	63 ± 3
9	7.0 (2)	426 ± 8
11	1.0 (3)	42 ± 3
11	37.4 (1)	1609
12	2.0 (3)	387 ± 13
12	3.0 (3)	532 ± 9
12	10 (1)	1760

[a] Based on concentration measurements determined by LC-MS analysis. [b] Bombardment is expressed as beam current (μA h). [c] Number of runs.

In order to investigate the scope and limitations of the reactivities of bromo/iodoheteroaryls, we synthesised compound **9** using the corresponding halides **17a** and **17b** under comparable conditions. The result showed that the radiochemical yield of **9** was increased from 20 to 88% using 2-bromo- and 2-iodothiophene, respectively. The scope of the iodoheteroaryls was further investigated for compound **12**. The results are illustrated in Tables 1 and 3.

One possible explanation might be that the resulting palladium complex generated after insertion of ^{11}CO is less reactive, since trapping efficiency was in the range of 90% when bromoheteroaryls were used. Using the described synthetic method trace amounts of **10** were obtained. We assumed that the bromide in $R^{11}COPd(PPh_3)_2Br$ might be exchanged with

Table 3 Radiochemical yields and specific radioactivity for the ^{11}C-labelled hydrazides using hydrazine (10 μl) at 150 °C, unless otherwise stated

Compound	Trapping efficiency (%)[a]	Isolated RCY[b] (%)[c]	Specific radioactivity[d]/GBq μmol^{-1}
5	98 ± 2 (6)	90 ± 3 (81 ± 3)	—
6	98 ± 1 (4)	78 ± 2 (63 ± 3)	—
7	98 ± 1 (2)	95 ± 2 (75 ± 6)	835[e]
8	99 ± 1 (6)	85 ± 3 (72 ± 2)	—
9[f]	90 ± 2 (2)	20 ± 4 (10 ± 1)	—
9[g]	98 ± 1 (2)	88 ± 2 (78 ± 3)	426[k] ± 8
10[f]	95 ± 1 (2)	7 ± 2	—
10[fj]	96 ± 3 (3)	38 ± 5	—
12[f]	89 ± 1 (2)	20 ± 5	—
12[g]	98 ± 1 (7)	90 ± 2 (78 ± 2)	1760[e]
12[gh]	94	15	—
12[ghi]	95 ± 1 (2)	57 ± 2	—

[a] Decay-corrected, the fraction of radioactivity left in the crude product after purging with nitrogen. Values in parenthesis show the number of runs. [b] Analytical radiochemical yield determined by LC. [c] Calculated from the amount of radioactivity in the LC-purified product. [d] Based on concentration measurements determined by LC-MS analysis. [e] 10 μA h bombardment. [f] Using the corresponding bromo compound. [g] Using the corresponding iodo compound. [h] Run at 180 °C. [i] Using 25 μl of hydrazine. [j] Tetrabutylammonium iodide. [k] 7.0 μA h bombardment.

iodide to some extent. Therefore, tetrabutylammonium iodide was added to the reaction mixture. This increased the yield of **10** to 40%.

Another aspect that we investigated was the influence on the specific radioactivity of the amount of radioactivity produced described in terms of radionuclide production.

Specific radioactivity is a key property of the labelled compounds for application in biological studies. Therefore, the different sources causing isotopic dilution should be minimized starting with the amount of [^{11}C]carbon produced at the nuclear reaction tube place in target. The maximum theoretically calculated specific radioactivity for ^{11}CO is 3.5×10^5 GBq μmol^{-1}, but, in practice, this value is in the range of 1000–2000 GBq μmol^{-1} when full bombardment (about 35 μA h) has been employed. In the study of the relation between radionuclide production and specific radioactivity, a linear correlation was observed between the degree of irradiation and the specific radioactivity (Table 4). The fluctuations seen in these values were due to the variation in the daily radionuclide production.

Conclusions

The use of low concentrations of [^{11}C]carbon monoxide (10^{-4} M) and palladium(0) constitutes a one-pot method for carbonylation using various aromatic halides. Iodoheteroaryls are preferred to bromoheteroaryls in carbonylation reactions of this type. Using aromatic and heteroaromatic halides in combination with hydrazine or ammonia the scope and limitations of this procedure have been illustrated. Notably, when bromoheteroaryls were used instead of iodoheteroaryls, only low amounts of the desired labelled compounds were obtained.

The specific radioactivities obtained were higher than for the previously reported synthesis of benzamides by cyanation.

Experimental

General

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

[^{11}C]Carbon dioxide was trapped on a Porapak Q column at −196 °C. The concentrated gas was released by heating in a slow stream of helium gas (10 ml min^{-1}). The gas flow was passed through a small tube containing zinc at 400 °C.[14] The [^{11}C]carbon monoxide produced was trapped again on a short silica column at −196 °C.[15] The [^{11}C]carbon monoxide was later released by putting the silica column in warm water. Then the gas was transferred into a high-pressure micro-autoclave.[16,17]

Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV-detector (Fullerton, CA, USA) in series with a β$^+$-flow detector.[18] The following mobile phases were used: 0.05 M ammonium formate pH 3.5 (A), acetonitrile–water (50 : 7) (B), acetonitrile (C) and 0.01 M formic acid (D). For analytical LC, a Jones Chromatography Genesis C_{18}, 4 μm, 250 × 4.6 mm ID column was used at a flow rate of 1.5 ml min^{-1}. For semi-preparative LC, a Jones Chromatography Genesis C_{18}, 4 μm, 250 × 10 mm (ID), column was used at a flow rate of 4 ml min^{-1}. Synthia, an automated synthesis system,[19] 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 (USA).

Radioactivity was measured in an ion chamber (Veenstra Instrumenten bv, VDC-202, Holland). For approximate estimations of radioactivity during synthesis, a portable dose-rate meter was used (Långenäs eltekniska AB, Sweden).

In the analysis of the ^{11}C-compounds, reference substances were used for comparison in all the LC runs. The identities of the synthesised compounds were determined using ^{1}H and ^{13}C NMR and LC-MS. NMR spectra were recorded on a Varian XL 300 (300 MHz). Chloroform-d_1 was used as internal standard. LC-MS was performed using a Micromass VG Quattro with electrospray ionisation using mobile phases C and D. A Beckman 126 pump, a CMA 240 autosampler and an xTerra™ MS C_{18} 3.5 μm, 4.6 × 100 mm column were used.

THF was distilled under nitrogen from sodium–benzophenone.

All chemicals were purchased from Aldrich or Chemtronica (Sweden).

Method A

Tetrakis(triphenylphosphine)palladium(0) and the halide were placed in a vial (1 ml). The vial was flushed with nitrogen gas and dry dioxane (50 μl) was added. The resulting mixture was heated at 70 °C for 1 min and kept at room temperature for 10–15 min. A volume of 0.5 M NH_3 (200 μl) in anhydrous dioxane was added and the reaction mixture was shaken just before injection into the micro-autoclave pre-charged with [^{11}C]carbon monoxide. The mixture was heated at the desired temperature for 5 min. The crude product was transferred to a pre-evacuated vial (5 ml). The micro-autoclave was washed with THF (250 μl) and the washings were collected in the vial. The radioactivity was measured before and after purging with nitrogen. The solvent was reduced to 0.1 ml by heating at 100 °C and flushing with nitrogen. The crude mixture was dissolved in acetonitrile–water and injected into the semi-preparative LC [solvent A and C (90 : 10), linear gradient to 0 : 100] during 10 min, then 3 min at 100%, flow 4 ml min^{-1}. The identity and radiochemical purity of the collected fraction were determined by analytical LC and LC-MS.

Method B

A vial (1 ml) was charged with tetrakis(triphenylphosphine)-palladium(0), the halide and THF (240 μl). The solution was heated at 70 °C for 1 min and kept at room temperature for 10–15 min. Hydrazine (1 M in THF, 10 μl) was added just before injection into the micro-autoclave. The resulting mixture was treated as described under method A.

[*carbonyl*-^{11}C]Benzamide (1)

Iodobenzene **13** (1.0 μl, 8.9 μmol) and tetrakis(triphenylphosphine)palladium (3.0 mg, 2.6 μmol) were used as described in method A. The crude product was dissolved in acetonitrile (0.8 ml) and water (1.2 ml) and injected into the semi-preparative LC (t_R = 9.0 min). Analytical LC: solvent A–B (95 : 5), linear gradient to 0 : 100 during 20 min, flow 1.5 ml min^{-1}, wavelength 254 nm (t_R = 6.4 min). LC-MS (ESI$^+$) m/z = 122 [M + H]$^+$.

3-Methoxy[*carbonyl*-^{11}C]benzamide (2)

3-Iodoanisole **14** (1.0 μl, 8.4 μmol) and tetrakis(triphenylphosphine)palladium (2.9 mg, 2.5 μmol) were used as described in method A. The collected fraction was dissolved in acetonitrile (0.8 ml) and water (1.0 ml) and injected into the semi-preparative LC (t_R = 9.4 min). Analytical LC: solvent A–B (95 : 5), linear gradient to 0 : 100 during 10 min, flow 1.5 ml min^{-1}, wavelength 254 nm (t_R = 5.9 min). LC-MS (ESI$^+$) m/z = 152 [M + H]$^+$.

3-Nitro[*carbonyl*-^{11}C]benzamide (3)

1-Nitro-3-iodobenzene **15** (2.0 mg, 8.0 μmol) and tetrakis-(triphenylphosphine)palladium (3.0 mg, 2.6 μmol) were used as described in method A. The crude product was dissolved in acetonitrile (0.8 ml) and water (1.0 ml) and injected into the

semi-preparative LC (t_R = 9.6 min). Analytical LC was performed as described for **2** (t_R = 6.1 min). LC-MS (ESI^+) m/z = 167 $[M + H]^+$.

3-Chloro[*carbonyl*-^{11}C]benzamide (4)

1-Chloro-3-iodobenzene **16** (1.0 μl, 8.1 μmol) and tetrakis-(triphenylphosphine)palladium (3.2 mg, 2.8 μmol) were used as described in method A. The crude product was dissolved in acetonitrile (1.0 ml) and water (1.0 ml) and purified by the semi-preparative LC (t_R = 10.4 min). Analytical LC was performed as described for **2** (t_R = 6.8 min). LC-MS (ESI^+) m/z = 156 $[M + H]^+$.

3-Methoxy[*carbonyl*-^{11}C]benzohydrazide (5)

3-Iodoanisole **14** (1.0 μl, 8.4 μmol) and tetrakis(triphenylphosphine)palladium (3.5 mg, 3.0 μmol) were used as described in method B. The collected fraction was dissolved in acetonitrile (0.5 ml) and water (1.5 ml) and injected into the semi-preparative LC (t_R = 9.1 min). Analytical LC was performed as described for **2** (t_R = 5.3 min). LC-MS (ESI^+) m/z = 167 $[M + H]^+$.

3-Nitro[*carbonyl*-^{11}C]benzohydrazide (6)

1-Nitro-3-iodobenzene **15** (2.1 mg, 8.4 μmol) and tetrakis-(triphenylphosphine)palladium (3.2 mg, 2.8 μmol) were used as described in method B. The crude product was dissolved in acetonitrile (0.8 ml) and water (1.0 ml) and injected into the semi-preparative LC (t_R = 6.2 min). Analytical LC was performed as described for **2** (t_R = 5.4 min). LC-MS (ESI^+) m/z = 182 $[M + H]^+$.

3-Chloro[*carbonyl*-^{11}C]benzohydrazide (7)

1-Chloro-3-iodobenzene **16** (1.0 μl, 8.1 μmol) and tetrakis-(triphenylphosphine)palladium (3.1 mg, 2.7 μmol) were used as described in method B. The crude product was dissolved in acetonitrile (1.0 ml) and water (1.0 ml) and purified by the semi-preparative LC (t_R = 10.2 min). Analytical LC was performed as described for **2** (t_R = 6.1 min). LC-MS (ESI^+) m/z = 171 $[M + H]^+$.

[*carbonyl*-^{11}C]Benzohydrazide (8)

Iodobenzene **13** (1.0 μl, 8.9 μmol) and tetrakis(triphenylphosphine)palladium (3.0 mg, 2.6 μmol) were used as described in method B. The crude product was dissolved in acetonitrile (0.5 ml) and water (1.5 ml) and injected into the semi-preparative LC (t_R = 8.6 min). Analytical LC was performed as described for **2** (t_R = 4.8 min). LC-MS (ESI^+) m/z = 137 $[M + H]^+$.

(*carbonyl*-^{13}C)Benzohydrazide (8)

A vial (1 ml) containing tetrakis(triphenylphosphine)-palladium(0) (8 mg, 6.9 μmol), halide **14** (4.0 μl, 35.6 μmol) dissolved in anhydrous THF (200 μl) and hydrazine (40 μl, 40 μmol), as described in method B. The resulting reaction mixture and [^{13}C]carbon monoxide (1 ml) were transferred to the micro-autoclave, which was pre-charged with [^{11}C]carbon monoxide. The micro-autoclave was heated at 130 °C for 20 min. The crude product was transferred to a vial under reduced pressure and the volatile fraction was removed by heating at 50 °C and purging with nitrogen. Acetonitrile (0.8 ml) and water (1.2 ml) were added and the resulting solution was injected into the semi-preparative LC. Analytical LC was performed as described for **2**. The radioactive fraction was collected and evaporated under reduced pressure to yield the desired compound (79 %). ^{13}C NMR (300 MHz, $CDCl_3$): 165.9.

Thiophene-2-[*carbonyl*-^{11}C]carbohydrazide (9)

Method B. 2-Iodothiophene **17b** (1.0 μl, 9.0 μmol) and tetrakis-(triphenylphosphine)palladium (3.0 mg, 2.6 μmol) were used as described in method B. The crude product was dissolved in acetonitrile (0.8 ml) and water (1.2 ml) and injected into the semi-preparative LC, t_R = 6.0 min. Analytical LC: solvent A–B (99 : 1), isocratic at 1% for 3 min, linear gradient to 0 : 100 during 5 min, flow 1.5 ml min^{-1}, wavelength 254 nm (t_R = 7.2 min). LC-MS (ESI^+) m/z = 143 $[M + H]^+$.

5-Nitro-2-[*carbonyl*-^{11}C]furohydrazide (10)

2-Bromo-5-nitrofuran **18** (1.9 mg, 10 μmol) and tetrakis-(triphenylphosphine)palladium (3.5 mg, 3.0 μmol) were dissolved in anhydrous THF (190 μl). The resulting mixture was heated (70 °C, 1 min) and kept at room temperature for 10–15 min. To this was added a solution of tetrabutylammonium iodide (33.0 mg, 45 μmol) in DMSO (50 μl). The resulting mixture was kept at room temperature for an additional 5 min then hydrazine (1 M in THF, 10 μl) was added. The collected fraction was dissolved in acetonitrile (0.8 ml) and water (1.2 ml) and injected into the semi-preparative LC (t_R = 5.2 min). Analytical LC was performed as described for **9** (t_R = 7.1 min). LC-MS (ESI^+) m/z = 172 $[M + H]^+$.

[*carbonyl*-^{11}C]Nicotinamide (11)

3-Iodopyridine **19b** (1.8 mg, 8.8 μmol) and tetrakis(triphenylphosphine)palladium (2.8 mg, 2.4 μmol) were used as described in method A. The collected fraction was dissolved in acetonitrile (0.8 ml) and water (1.2 ml) and injected into the semi-preparative LC (t_R = 6.2 min). Analytical LC: solvent A–B (99 : 1), isocratic at 1% for 5 min, linear gradient to 80 : 20 during 10 min then ramped up to 0 : 100 over 5 min, flow 1.5 ml min^{-1}, wavelength 254 nm (t_R = 5.7 min). LC-MS (ESI^+) m/z = 123 $[M + H]^+$.

[*carbonyl*-^{11}C]Nicotinohydrazide (12)

3-Iodopyridine **19b** (1.8 mg, 8.8 μmol) and tetrakis(triphenylphosphine)palladium (2.8 mg, 2.4 μmol) were used as described in method B. The collected fraction was dissolved in acetonitrile (1 ml) and water (1 ml) and injected into the semi-preparative LC (t_R = 6.2 min). Analytical LC was performed as described for **11** (t_R = 4.7 min). LC-MS (ESI^+) m/z = 138 $[M + H]^+$.

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