Palladium-Mediated ^{11}C-Carbonylative Cross-Coupling of Alkyl/Aryl Iodides with Organostannanes: An Efficient Synthesis of Unsymmetrical Alkyl/Aryl [^{11}C-*carbonyl*]Ketones

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[^{11}C]Carbon monoxide in low concentration, palladium complexes, alkyl/aryl iodides, and organostannanes are utilized in the synthesis of twenty alkyl [carbonyl-^{11}C]ketones. The activated palladium(0) species [Pd{P(*o*-Tol)$_3$}$_2$] was generated in situ from tris(dibenzylideneacetone)palladium(0) [Pd$_2$(dba)$_3$] and a large excess of tri-*o*-tolylphosphane [P(*o*-Tol)$_3$]. The Stille coupling reactions were performed in a micro-autoclave system. Radiochemical yields of ^{11}C-labelled alkyl/aryl ketones were in the range of 37–98 % with specific radioactivity up to 300 GBq μmol^{-1}. Using this method, 4′-aminoacetophen[^{13}C-*arbonyl*]one **6** was synthesised in order to confirm the position of labelling (δ = 196.7 ppm, $CDCl_3$). The presented approach is an efficient way for synthesising ^{11}C-labelled alkyl/aryl ketones with acceptable radiochemical yield and is generally applicable in ^{13}C-labelling syntheses.

Introduction

The increasing application of positron emitting tomography (PET) has stimulated the development of rapid and efficient methods for the incorporation of positron-emitting radionuclides with a short half-life like ^{11}C ($t_{1/2}$ = 20.3 min)[1] into the target molecule. The most used precursors for the introduction of ^{11}C in a bioactive molecule are [^{11}C]iodomethane and [^{11}C]methyl triflate used in methylation reactions, [^{11}C]carbon dioxide in the Grignard reaction[2] and, more recently, [^{11}C]carbon monoxide in carbonylation reactions.

Due to the short half-life, low reactivity and solubility of [^{11}C]carbon monoxide,[3] one-pot carbonylation reactions using a micro-autoclave[4] are preferred, and various types of ^{11}C-carbonyl compounds have been synthesised by this approach.[5]

In this paper, [^{11}C]carbon monoxide at low concentration, palladium complexes, alkyl/aryl iodides and organostannanes are utilized in the synthesis of twenty alkyl [^{11}C-*carbonyl*]ketones.

Results and Discussion

The first published report on [^{11}C-*carbonyl*]ketones based on [^{11}C]carbon monoxide, tetrakis(triphenylphosphane)palladium(0) and the appropriate organostannanes resulted in 10% yield of the total amount of radioactivity.[6] This low efficiency was significantly improved by concentrating [^{11}C]carbon dioxide, followed by local reduction to [^{11}C]carbon monoxide, and then using a recirculation technique with [^{11}C]carbon monoxide. This approach increased the trapping efficiency to 70% but the radiochemical yields were still low. For example, 1-phenylethan[^{11}C-*carbonyl*]one (**1**) was obtained in a radiochemical yield of 36%.[7]

In another study using a micro-autoclave technique, the influence of various ligands and temperature on the radiochemical yield of ^{11}C-ketones was investigated.[8]

An alternative route to organostannanes, the use of organoboronic acid,[9] was studied recently. However, the radiochemical yield of these alkyl/aryl [^{11}C-*carbonyl*]ketones was in the range of 15 to 45% using triflates in a Suzuki cross-coupling reaction in a micro-autoclave system.[10]

[^{11}C]Carbon monoxide at low concentration, an aryl/alkyl iodide, [Pd{P(*o*-Tol)$_3$}$_2$] (formed in situ) and organostannanes have been used for the synthesis of alkyl/aryl [^{11}C-*carbonyl*]ketones with a micro-autoclave-based technique.[4] There is still, however, a need for a rapid efficient alternative method for ^{11}C-labelling of ketones owing to the variation in reported radiochemical yields. In our attempts to synthesis 1-phenylethan[^{11}C-*carbonyl*]one (**1**) from iodobenzene and tetramethyltin, a series of palladium complexes were used and all reactions were performed at 125 °C (Table 1). A standard reaction time of 5 min was selected. The results indicated that the choice of ligand and solvent have a major impact on the radiochemical yield. For instance, using DMSO instead of DMF increased the radiochemical yield from 8% to 49%. This may be due to the

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higher dielectric constant and solubility of DMSO.[11] The impact of the ligand ratio was further investigated for $[Pd_2(dba)_3]/AsPh_3$ and $[Pd_2(dba)_3]/P(o\text{-Tol})_3$ (Table 2). In the former case, increasing the amount of ligand resulted in a lower radiochemical yield. However, the opposite outcome was obtained using an excess of $P(o\text{-Tol})_3$. As the $P(o\text{-Tol})_3$ was not completely dissolved in DMSO (500 μL), a saturated solution was most probably obtained.

Table 1. Impact of the ligand nature on the radiochemical yield and trapping efficiency of 1-phenylethan[^{11}C-*carbonyl*]one. The reactions were performed at 125 °C for 5 min with iodobenzene and tetramethyltin.

	Ratio	Solvent	Trapping efficiency [%] [b]	RCY[a] [%] (*n*)[c]
$[PdCl_2(dppe)]$	–	THF/NMP	85 ± 3 (2)	5 ± 2 (2)
$[Pd(PPh_3)_4]$	–	THF	91 ± 2 (4)	7 ± 2 (4)
$[PdCl_2P(o\text{-Tol})_2]$	–	THF/NMP	92	6
$[Pd_2(dba)_3]/AsPh_3$	1:4	THF	95 ± 2 (2)	50 ± 3 (2)
$[Pd_2(dba)_3]/P(t\text{Bu})_3$	1:4	THF	75	1
$[Pd_2(dba)_3]$/dppe	1:4	THF/NMP	91	6
$[Pd_2(dba)_3]$/dppf	1:1	THF	92	40
$[Pd_2(dba)_3]$/TFP	1:4	THF	93	6
$[Pd_2(dba)_3]/P(o\text{-Tol})_3$	1:4	DMF	90	8
$[Pd_2(dba)_3]/P(o\text{-Tol})_3$	1:4	DMSO	95 ± 1 (2)	49 ± 1 (2)

[a] RCY = radiochemical non-isolated yield. [b] Decay-corrected trapping efficiency, the fraction of radioactivity left in the crude product after purge with nitrogen; the value in parentheses is the number of runs. [c] The value in parentheses is the number of runs.

Table 2. Impact of palladium/ligand ratio on radiochemical yield and trapping efficiency of 1-phenylethan[^{11}C-*carbonyl*]one. The reactions were performed at 125 °C for 5 min with iodobenzene and tetramethyltin.

Palladium complexes	Ratio	Solvent	Trapping efficiency [%][b]	RCY[a] [%] (*n*)[c]
$[Pd_2(dba)_3]/AsPh_3$	1:4	THF	95 ± 2 (2)	50 ± 3 (2)
$[Pd_2(dba)_3]/AsPh_3$	1:8	THF	95	46
$[Pd_2(dba)_3]/AsPh_3$	1:12	THF	89	15
$[Pd_2(dba)_3]/P(o\text{-Tol})_3$	1:4	DMSO	95 ± 1 (2)	49 ± 1 (2)
$[Pd_2(dba)_3]/P(o\text{-Tol})_3$	1:12	DMSO	99	67

[a] RCY = radiochemical non-isolated yield. [b] Decay-corrected trapping efficiency, the fraction of radioactivity left in the crude product after purging with nitrogen; the value in parentheses is the number of runs. [c] The value in parentheses is the number of runs.

The reaction between $[Pd_2(dba)_3]$ and $P(o\text{-Tol})_3$ generates the active Pd^0 species $[Pd\{P(o\text{-Tol})_3\}_2]$. The bulkiness of $P(o\text{-Tol})_3$ (cone angle = 194°) is assumed to contribute to the reactivity of the Pd^0 species formed.[12,13] Furthermore, the assumption was made that an excess of ligand $P(o\text{-Tol})_3$ may stabilise the activated palladium complex.

The scope and limitations of this system were explored by choosing various aliphatic/aromatic iodides and aliphatic organostannanes (Figure 1, Figure 2 and Figure 3). The results are shown in Table 3 and 4.

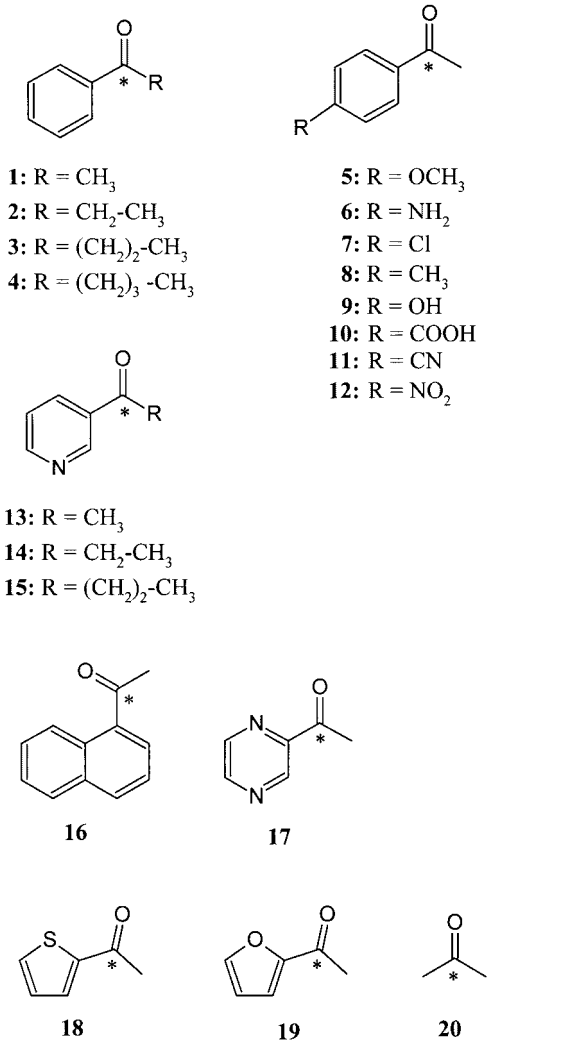

Figure 1. Target compounds (* = ^{11}C).

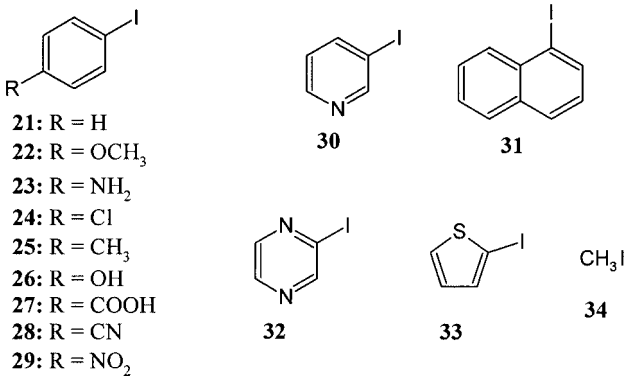

Figure 2. Halides.

1-Phenylethan[^{11}C-carbonyl]one (**1**) was synthesised from either iodobenzene (**21**) and tetramethyltin (**35**) or iodomethane (**44**) and tributylphenyltin (**36**). In the former case, the analytical radiochemical yield was in the region of 72% (isolated radiochemical yield 68%). However, in the

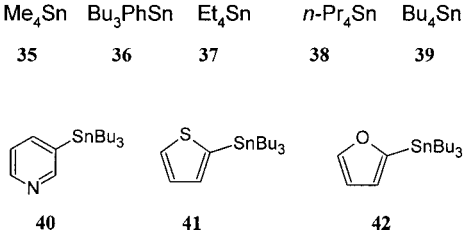

Figure 3. Organostannyl compounds.

latter case the radiochemical yield was increased to 91%. The analytical radiochemical yields of **2** and **3** were 60 and 65%, respectively. However, the yield of **4** was 37%. This may be due to the low purity of the tetrabutyltin used (93%). This study was further expanded by choosing various electron-donating and -accepting substituted iodobenzenes.

Table 4. Radiochemical yields for the [^{11}C]ketones shown in Figure 1.

Entry	Halide	Stannyl compound	Product	T [°C]	Trapping efficiency [%][b]	RCY[a] [%] (n)[c]
35	**30**	**35**	**13**	100	91 ± 3 (4)	61 ± 1 (4)
36	**34**	**40**	**13**	100	97 ± 1 (3)	93 ± 2 (3)
37	**30**	**37**	**14**	100	78 ± 1 (2)	45 ± 1 (2)
38	**30**	**37**	**14**	150	86 ± 1 (2)	59 ± 2 (2)
39	**30**	**38**	**15**	150	91 ± 1 (2)	47 ± 1 (2)
40	**31**	**35**	**16**	100	93	7
41	**31**	**35**	**16**	150	92 ± 1 (2)	63 ± 2 (2)
42	**32**	**35**	**17**	rt	53	48
43	**32**	**35**	**17**	50	68 ± 3 (5)	46 ± 10 (5)
44	**32**	**35**	**17**	100	93	18
45	**33**	**35**	**18**	100	98 ± 1 (3)	71 ± 1 (3)
46	**34**	**41**	**18**	100	95 ± 1 (4)	98 ± 1 (4)
47	**34**	**42**	**19**	100	96 ± 1 (4)	95 ± 1 (4)
48	**34**	**35**	**20**	100	95 ± 1 (2)	97 ± 1 (2)

[a] RCY = radiochemical non-isolated yield. [b] Decay-corrected trapping efficiency, the fraction of radioactivity left in the crude product after purging with nitrogen; the value in parentheses is the number of runs. [c] The value in parentheses is the number of runs.

Table 3. Radiochemical yields for the [^{11}C]ketones shown in Figure 1.

Entry	Halide	Organostannyl compound	Product	T [°C]	Trapping efficiency [%][b]	RCY[a] [%] (n)[c]
1	**21**	**35**	**1**	150	98	60
2	**21**	**35**	**1**	125	99	67
3	**21**	**35**	**1**	100	98 ± 1 (7)	72 ± 3 (7)
4	**34**	**36**	**1**	100	98 ± 1 (3)	91 ± 3 (3)
5	**21**	**37**	**2**	150	98	50
6	**21**	**37**	**2**	100	98 ± 1 (3)	60 ± 1 (3)
7	**21**	**38**	**3**	100	98	22
8	**21**	**38**	**3**	150	97 ± 1 (3)	65 ± 2 (3)
9	**21**	**39**	**4**	50	98	2
10	**21**	**39**	**4**	100	97 ± 1 (2)	8 ± 2 (2)
11	**21**	**39**	**4**	150	97 ± 1 (3)	37 ± 1 (3)
12	**22**	**35**	**5**	100	96 ± 2 (3)	68 ± 2 (3)
13	**23**	**35**	**6**	100	96 ± 1 (3)	75 ± 1 (3)
14	**23**[e]	**35**	**6**	100	95	48
15	**24**	**35**	**7**	100	98 ± 1 (3)	62 ± 5 (3)
16	**25**	**35**	**8**	100	95 ± 2 (3)	73 ± 2 (3)
17	**26**	**35**	**9**	100	93	1
18	**26**[d]	**35**	**9**	50	75	5
19	**26**[d]	**35**	**9**	100	96	7
20	**26**[d]	**35**	**9**	150	94	10
21	**26**[e]	**35**	**9**	100	91 ± 3 (3)	75 ± 4 (3)
22	**27**	**35**	**10**	150	90	48
23	**27**	**35**	**10**	100	94 ± 1 (3)	56 ± 1 (3)
24	**27**[d]	**35**	**10**	100	94	11
25	**27**[e]	**35**	**10**	100	92	21
26	**28**	**35**	**11**	150	89	9
27	**28**	**35**	**11**	100	88 ± 1 (2)	49 ± 1 (2)
28	**29**	**35**	**12**	140	82	40
29	**29**	**35**	**12**	100	87	41
30	**29**	**35**	**12**	80	92 ± 3 (2)	49 ± 1 (2)
31	**29**	**35**	**12**	60	88 ± 1 (2)	41 ± 4 (2)
32	**29**	**35**	**12**	30	66	40
33	**29**	**35**	**12**	30[f]	76 ± 4 (2)	28 ± 1 (2)
34	**29**	**35**	**12**	r.t.	41	65

[a] RCY = radiochemical non-isolated yield. [b] Decay-corrected trapping efficiency, the fraction of radioactivity left in the crude product after purging with nitrogen; the value in parentheses is the number of runs. [c] The value in parentheses is the number of runs. [d] Tetrabutylammonium salt of the corresponding halide. [e] HCl salt of the corresponding halide. [f] Reaction time: 8 min.

In the synthesis of compounds **5**–**8**, the use of halides **22**–**25** gave good radiochemical yields. In an attempt to increase the radiochemical yield of **6**, the HCl salt of halide **23** was used (entry 14). This resulted in a decrease of the radiochemical yield from 75% (isolated = 69%) to 48%.

When **26** was used, despite a good trapping efficiency, only a trace amount of **9** was obtained. The analytical radiochemical yield increased slightly on using the tetrabutylammonium salt of **26**. However, the radiochemical yield was increased to 75% when the HCl salt of **26** was used (entries 18–21).

The lower radiochemical yields of **10**–**12** may be due to the electron-accepting nature of the substituted halides **27**–**29**. The substituent effect on the aromatic ring may have an impact on the reactivity of the corresponding iodobenzene in the palladium-mediated ^{11}C-carbonylation reactions.

The investigation was further extended by studying the synthesis of **13**–**15** from 3-iodopyridine (**30**) and the corresponding organostannyl compound. The radiochemical yield of **13** was increased when iodomethane (**34**) and 3-(tributylstannyl)pyridine (**40**) were used (entry 36). This might be due to the higher reactivity of iodomethane than the aromatic halides (Table 4).

In the case of 1-pyrazin-2-ylethanone (**17**), a good radiochemical yield was obtained at rather low temperature (entry 42). The lower yield of **17** at higher temperature may indicate that the compound is unstable under these conditions.

A good radiochemical yield of **18** was obtained when performing the reaction at 100 °C (entry 44). However, the radiochemical yield increased considerably when iodomethane was used instead of **33** (entry 45).

These results (entries 4 and 36) indicate that iodomethane is more reactive towards ^{11}C-carbonylative cross coupling than aromatic or heteroaromatic iodides. The radiochemical yields of **19** (95%) and **20** (97%) confirmed this assumption.

The effective specific radioactivity value for the [^{11}C]carbon is below the theoretical figure (3.4×10^5 GBq μmol^{-1}) because of the dilution by stable isotopes originating from the target, delivery lines, chemical reagents, etc. However, when using [^{11}C]carbon monoxide, as described in the present approach, ^{11}C-labelled compounds with high specific radioactivity are obtained. Generally, the amount of labelled product is in the range of 10–100 nmol. The specific radioactivity of [^{11}C]4′-aminoacetophenone (**6**) was determined to be 298 GBq μmol^{-1} upon irradiation at 20 μAh.

The ^{11}C-labelled ketones were characterised by analytical HPLC (equipped with radio- and UV-detectors) with co-injection of non-radioactive reference compounds and comparing the retention times for the UV and radioactive peaks.

The identity and the confirmation of the labelling position were confirmed by ^{13}C NMR analysis of ^{13}C-labelled **6**. The ^{13}C NMR signal at δ = 196.7 ppm corresponds to the carbonyl carbon of authentic 4′-aminoacetophenone.

Conclusions

[^{11}C]Carbon monoxide at low concentration has been used in the palladium-mediated carbonylative coupling of organic iodides with organostannanes to form ^{11}C-labelled ketones. An excess of tri-*o*-tolylphosphane [P(*o*-Tol)$_3$] may be essential in order to increase the radiochemical yield of alkyl/aryl [^{11}C-carbonyl]ketones. It has been shown that iodomethane has a higher reactivity than aromatic iodides in the ^{11}C-carbonyl cross-coupling. The present method is rapid, mild, general and can be conducted in a one-pot procedure that is probably suitable for automation.

Experimental Section

General: [^{11}C]Carbon dioxide was produced at Uppsala Imanet 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 using a Scanditronix MC-17 cyclotron. [^{11}C]Carbon dioxide was trapped on a Silica column at –196 °C. The concentrated gas was released into a slow stream of helium gas (10 mL min^{-1}) by heating. 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. The [^{11}C]carbon monoxide was released by warming the silica column to about 60 °C and transferring the radioactivity into a micro-autoclave.

At the start of the experimental sessions, the stainless-steel micro-autoclave was washed with 10–15 mL of DMSO, followed by heating at 100–150 °C for 5 min, and then washed with an additional 5–10 mL of DMSO. It was also washed with 1–2 mL of DMSO after each experiment.

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.[15] The following mobile phases were used: 0.01 M formic acid (A), acetonitrile/water (50:7) (B), 0.01 M potassium hydrogen phosphate (C) and acetonitrile (D). For analytical LC, a Jones Chromatography Genesis C_{18} (4 μm, 250 × 4.6 mm i.d.) column was used with a flow of 1.5 mL min^{-1}. For semi-preparative LC, a Jones Chromatography Genesis C_{18} (4 μm, 250 × 10 mm i.d.) column was used with a flow of 4 mL min^{-1}. Synthia, an automated synthesis system,[16] was used for LC injection and fraction collection. Data collection and LC control were performed with the Beckman System Gold chromatography software package (USA).

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

In analyses of the ^{11}C-labelled compounds, unlabelled reference substances were used for comparison in all LC runs. The identity of the synthesised ^{13}C-labelled compound **6** was determined bby ^{13}C NMR spectroscopy. NMR spectra were recorded on a Varian XL 400 (400 MHz) and deuterated chloroform was used as internal standard. LC-MS was performed with a Micromass VG Quattro with electrospray ionisation, a Beckman 126 pump, a CMA 240 autosampler and a Beckman Ultrasphere ODS C_{18} (5 μm, 100 × 4.6 mm i.d.) column using mobile phases C and D.

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

General Method: A capped vial (1 mL) containing a solution of tris(dibenzylideneacetone)palladium(0) (2.1 mg, 2.3 μmol) and tri-*o*-tolylphosphane (16 mg, 52.6 μmol) in anhydrous DMSO (500 μL) was flushed with argon. The reaction mixture was kept at room temperature for 10 min. The appropriate halide (18 μmol) was added and the resulting mixture kept at room temperature for an additional 5 min. The reaction mixture was filtered (ThermoHypersil F2513-3, PTFE syringe filter 0.45 μm) before addition of the organostannane just before injection into the micro-autoclave precharged with [^{11}C]carbon monoxide. The micro-autoclave was heated at the desired temperature for 5 min. The crude product was transferred to a vial (3 mL) at reduced pressure. The radioactivity was measured before and after the vial was flushed with nitrogen. The identity of the crude product was determined by analytical LC using a reference compound.

Compounds **1**–**5**, **7**, **8**, **11**, **12**, **16** and **18** were analysed using the following HPLC method: Solvent A/B (70:30), linear gradient to 0:100 during 6 min, then 7 min at 100% B, flow 1.5 mL min^{-1}.

Compounds **6**, **9**, **10**, **13**–**15**, **17** and **19** were analysed using the following HPLC method: Solvent A/B (90:10), linear gradient to 0:100 during 8 min, then 5 min at 100% B, flow 1.5 mL min^{-1}.

Compound **20** was analysed using the following HPLC method: Solvent C/B (95:5), isocratic at 5% B for 5 min, linear gradient to 0:100 during 8 min, then 1 min at 100% B, flow 1.5 mL min^{-1}.

([^{13}C)4′-Aminoacetophenone (6): Tris(dibenzylideneacetone)palladium(0) (2.1 mg, 2.3 μmol), tri-*o*-tolylphosphane (16 mg, 52.6 μmol), 4-iodoaniline (**23**; 5 mg, 22.8 μmol) and tetramethyltin (140 μL, 1.01 mmol) were used. The reaction was performed as described before but the micro-autoclave was pre-charged with [^{11}C] carbon monoxide and (^{13}C)carbon monoxide, and then heated at 120 °C for 25 min. 4′-Aminoacetophenone was purified using the following preparative HPLC method: solvent A/D (70:30), isocratic at 30% B for 1 min, linear gradient to 0.100 during 7 min, then 9 min at 100% D. The radioactive fraction was collected and evaporated under reduced pressure to yield the desired compound (89%). ^{13}CNMR (400 MHz, $CDCl_3$): δ = 196.7 ppm.

Acknowledgments

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